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Foreword

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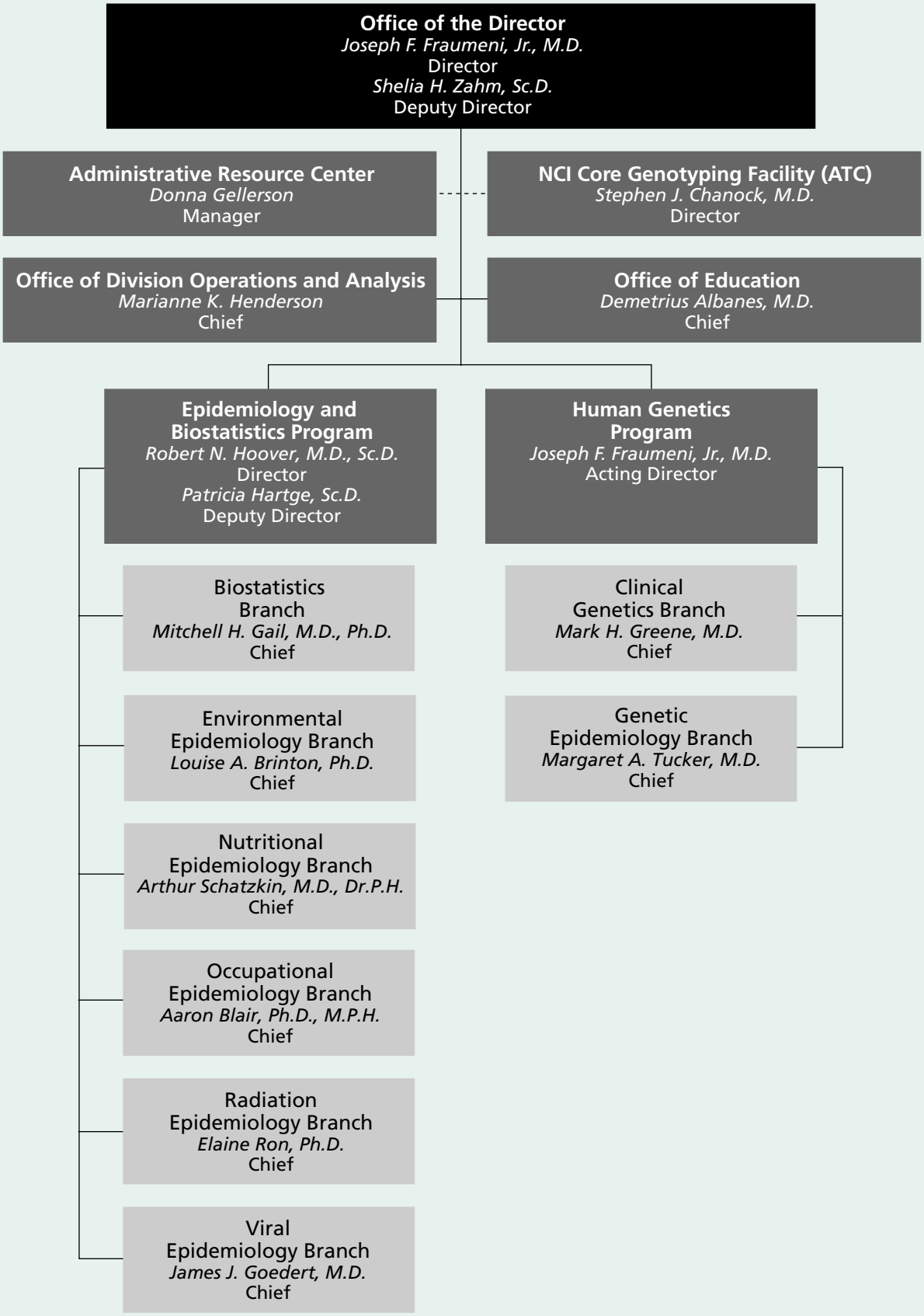
The paramount goal of the National Cancer Institute (NCI) is to develop the knowledge base that will ultimately lead to the prevention or cure of cancer. Among the important contributions to this base are the outstanding scientists in the Intramural Research Program of the NCI. Their curiosity and interests drive new discoveries that continue to advance the field of cancer research. The NCI supports these intramural scientists with resources and an intellectually stimulating and collegial environment to carry out their research. In addition, we are committed to supporting the next generation of scientists through carefully structured mentoring programs that include research training and didactic courses. The high quality of all aspects of the Intramural Research Program is maintained through peer review, using rigorous standards to assure its leadership in the cancer research community.

The Division of Cancer Epidemiology and Genetics (DCEG) is responsible for a national program of population-based studies to identify environmental and genetic determinants of cancer. In carrying out its mission, the Division is at the cutting edge of interdisciplinary research that integrates epidemiologic, laboratory, and clinical approaches to unravel complex gene-environment and gene-gene interactions in cancer etiology. Investigators at all levels of their careers work collaboratively to bring together the scientific disciplines needed to conduct these studies. This environment is exciting and productive, and presents extraordinary opportunities for young scientists who are launching their research careers.

The DCEG Research Directory provides a compendium of research activities illustrating the breadth and depth of the Division's 61 principal investigators. Their efforts contribute significantly to the NCI's goal of preventing cancer, since innovative research into the origins of cancer is our major route to effective prevention. The NCI is committed to strengthening a comprehensive intramural program of population-based research and its linkage to clinical and laboratory approaches that run the spectrum from discovery to practical applications, a research program that will benefit everyone. The American people can be proud of the dedicated efforts of the men and women in the DCEG that are reflected in the science summarized in this document.

Andrew C. von Eschenbach, M.D.
Director, National Cancer Institute

National Cancer Institute
Division of Cancer Epidemiology and Genetics



Division of Cancer Epidemiology and Genetics
Office of the Director

The Division of Cancer Epidemiology and Genetics (DCEG) is part of the Intramural Research Program of the National Cancer Institute (NCI) and carries out population-based and interdisciplinary research to discover the genetic and environmental determinants of cancer. Through its broadly based programs in epidemiology, genetics, statistics, and related areas, the primary mission of the DCEG is to conduct high-quality, high-impact research to uncover the causes of cancer and the means of prevention.

The Division was formed as part of a restructuring of the NCI in October 1995 in order to strengthen and expand programs in cancer epidemiology, genetics, and statistics, and to ensure that recent discoveries in molecular genetics and cancer biology are accelerated and broadened through population-based etiologic studies.

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The DCEG is uniquely positioned to conduct epidemiologic research projects that are high-risk in nature and require long-term commitments of scientific staff and funding support through contracts, a coordinated national programmatic approach, or a rapid response to emerging public health or scientific issues. The Division maintains a national and international perspective and gives priority to emergent issues identified through clinical, laboratory, and epidemiologic observations, as well as public health and policy concerns identified by the Institute, the Department, Congress, regulatory agencies, and other appropriate bodies. Recent areas of activity include studies of potential cancer risk associated with breast implants, cellular phone use, prenatal diethylstilbestrol (DES), radiation fallout from the Chornobyl accident in the Ukraine, benzene occupational exposures, diesel fume exposures, and pesticide exposures to farmers and their families.

While they are not a primary focus, the DCEG also conducts intervention trials in special circumstances, particularly when they are the logical extension of etiologic discoveries made by Division staff. Examples include a large phase III trial to determine the efficacy of two NCI-developed prophylactic vaccines against human papillomavirus, the etiologic agent of cervical cancer, that is now under way in Costa Rica, and a trial in Shandong, China, to determine whether supplementation with vitamins and minerals, garlic extract, or antibiotic treatment for *Helicobacter pylori* infection can retard the progression of precancerous gastric lesions that are ubiquitous in this population.

As part of its ongoing research efforts, the DCEG develops multidisciplinary infrastructures and resources for use throughout the scientific community. Examples include database management software for biospecimen inventories and family-based studies, a variety of software packages for exposure assessment and for estimation of dietary intake, and interactive cancer atlases to generate leads into the environmental determinants of cancer. All of these resources can be found on the NCI Research Resources Web site: **http://resresources.nci.nih.gov**.

The DCEG also has a firm commitment to training the next generation of scientists and has developed specialized tracks in genetic epidemiology, radiation epidemiology, molecular epidemiology, and biostatistics. The Division is currently exploring partnerships with various schools of public health to support pre- and postdoctoral training of young investigators in the fields of epidemiology, genetics, and statistics.

This publication is the third edition of the *DCEG Annual Research Directory* and is intended to provide an overview of the Division's mission and research activities. Currently, the DCEG has 61 principal investigators (tenured and tenure track) who direct wide-ranging projects, many of which are described in this directory. Another 21 staff scientists and 48 postdoctoral and predoctoral fellows with degrees in epidemiology, biostatistics, genetics, or related areas participate in overseeing and supporting a variety of studies. Most studies in progress are interdisciplinary in nature, involving biomarkers to assess precursor states, intermediate outcomes, exposures, susceptibility states, gene-environment interactions, and mechanisms of carcinogenesis.

Areas of Research

Epidemiologic studies into various forms of cancer are being carried out to evaluate the role of lifestyle factors, including diet and nutrition, environmental pollutants, occupational exposures, genetic susceptibility, hormonal and other endogenous factors, medicinal agents, infectious agents, and ionizing and nonionizing radiation. Particular emphasis is placed on interdisciplinary studies (biochemical and molecular epidemiology) to elucidate the environmental and genetic determinants of cancer and their interactions. The Division also emphasizes studies designed to identify the cancer risk factors responsible for the geographic and temporal patterns identified by the DCEG mapping project and by the SEER program, and for the racial, ethnic, and socioeconomic disparities of cancer incidence and mortality in the United States. This past year, specific approaches and risk factors included the following:

- Agricultural exposures
- Alcohol
- Alkylating agents
- Anthropometric factors
- Arsenic
- Benzene
- Biostatistics
- Breast implants
- Butadiene
- Chlorination byproducts
- Clinical genetics
- Cytotoxic drugs
- Descriptive patterns
- Diesel exhausts
- Diet and nutrition
- Diethylstilbestrol
- DNA viruses
- Electromagnetic fields
- Endogenous hormones
- Environmental contaminants
- Exposure assessment
- Familial syndromes
- Genetic susceptibility
- Geographic patterns
- Health disparities
- Helicobacter pylori
- Hepatitis B and C
- Heterocyclic amines
- Hormone replacement therapy
- Human immunodeficiency virus
- Human papillomavirus
- Human T cell lymphotropic viruses, I and II
- Immunodeficiency states
- Immunosuppressive drugs
- Ionizing radiation
- Kaposi's sarcoma herpesvirus
- Medicinal agents
- Menopausal hormones
- Methodologic research
- Molecular epidemiology
- Multiple primary cancers
- Nitrates and nitrosamines
- Occupational exposures
- Oral contraceptives
- Pesticides
- Pharmacogenetics
- Physical activity
- Population genetics
- Radon
- Retroviruses
- Risk assessment
- Simian virus 40
- Socioeconomic status
- Tobacco
- Ultraviolet light
- Viral epidemiology

Recent Scientific Highlights

Over the past year, DCEG investigators contributed over 300 publications to scientific journals and produced a number of key findings that have provided new insights into cancer etiology and potential preventive measures. Some examples are briefly summarized below:

- The role of human papillomavirus (HPV) in the etiology of cervical cancer was clarified through many studies, including an investigation in the high-risk province of Guanacaste, Costa Rica, where strong associations were found between certain "non-European" variants of HPV-16 and both cancer and high-grade precursors. These variants were associated with more than 10-fold increased risk of cancer and 3-fold risk of precursors above the several 100-fold increased risk from any HPV-16 infection. DCEG investigators are now leading a phase III HPV-16 vaccine trial in Costa Rica in collaboration with scientists from the NCI's Center for Cancer Research.

- A randomized trial of management strategies for women with mildly abnormal Papanicolaou (Pap) test results found that 45 percent of women with atypical squamous cells of undetermined significance were HPV-negative and did not need to undergo colposcopy. In another study, it was found that interobserver reproducibility is mediocre to poor for three colposcopy specimen types: thin-layer cytology, punch biopsy, and loop electrosurgical excision procedure. There is ongoing work to assess whether HPV testing is a more effective primary screening tool than the Pap smear in two large cohorts of women. It was also shown to be feasible for women to collect their own cervicovaginal cells using a Dacron swab for HPV DNA detection, particularly for the higher risk HPV genotypes.

- Study was made of cofactors that might influence the progression to high-grade squamous intraepithelial lesions and cervical cancer among HPV-infected women. Increased risk was associated with number of live births, cigarette smoking, and oral contraceptive use. Decreased risk was associated with current use of barrier contraceptives. Adenocarcinoma of the cervix appeared to have a different risk profile than squamous cervical cancer, with decreased risks associated with cigarette smoking. High levels of serum homocysteine were also found to predict risk of invasive cervical cancer, possibly reflecting folate or B6 deficiency or genetic polymorphism.

- An investigation of hormone replacement therapy revealed that postmenopausal women who take estrogen in combination with progestin have a 40 percent higher risk of developing breast cancer than women not on therapy, while women who take estrogen alone have a 20 percent greater risk. For women who take estrogen-progestin, the risk increases by 8 percent for each year of use, while the risk for those who take estrogen alone increases by 1 percent per year.

- A study of breast cancer among Swedish women who had breast reduction surgery found a dramatically reduced risk of breast cancer among women with at least 1,600 grams of tissue removed from both breasts (odds ratio of 0.24) compared to women with less than 800 grams removed. This result should be reassuring to women undergoing either cosmetic breast reduction or prophylactic mastectomy in high-risk settings. In another study, women who received cosmetic breast implants had no increased risk of breast cancer, but did have elevated risks for cancers of the cervix, respiratory tract, and brain.

- In a population-based case-control study of Jewish women in Israel, multiparity lowered the risk of ovarian cancer among carriers and noncarriers with founder mutations in *BRCA1* and *BRCA2*. However, oral contraceptive use was protective only among noncarriers, suggesting that it is premature to advise use of oral contraceptives as chemoprevention among mutation carriers.

- Studies of prostate cancer in China, where rates are exceptionally low but increasing, elevated risks were related to abdominal adiposity, high serum insulin levels, longer CAG repeats in the *AR* gene, insulin-like growth factor-I (IGF-I) and the IGF-I:IGFBP-3 molar ratio, but not serum leptin. Decreased risk was observed among men with both higher levels of IGFBP-3 and the ff genotype of the vitamin D receptor gene.

- The role of obesity and hypertension in kidney cancer was evaluated among a cohort of Swedish construction workers. Compared with men in the lowest range of body mass index, men in the middle range had a 30 to 60 percent greater risk of renal cell cancer, while men in the highest range had nearly

double the risk. Blood pressure levels were directly associated with renal cell cancer risk. At the sixth year of followup, the risk rose or fell with the change in blood pressure, after data were adjusted for baseline measurements. Current or former smokers had a greater risk than nonsmokers for both renal cell cancer and renal pelvis cancer. No relationship was found between body mass index or blood pressure and the risk of renal pelvis cancer.

- Reasons for the high incidence of multiple myeloma among blacks, compared to whites, were sought using data from a case-control study conducted in three areas of the United States. Inverse gradients in risk were associated with occupation-based socioeconomic status (SES), income, and education. Low SES contributed to a higher proportion of cases in blacks than whites, and accounted for about half of the excess incidence in blacks. The greater use of vitamin C supplements by whites and the higher frequency of obesity among blacks also appeared to contribute to the elevated risk of multiple myeloma among blacks.

- Similar findings were observed in relation to squamous cell esophageal cancer, which also occurs much more frequently among blacks than whites in the United States. Four major risk factors—low income, moderate to heavy alcohol intake, tobacco use, and infrequent consumption of raw fruits and vegetables—accounted for almost all of the cancers (98 percent for whites and 99 percent for blacks) and for 99 percent of the excess incidence among black men.

- Analyses of recent cancer incidence trends revealed dramatic increases in adenocarcinoma of the esophagus among men and women. In a series of projects, the major risk factor was shown to be acid reflux, which initiates a multistage process from esophagitis, to intestinal-type metaplasia (Barrett's esophagus), dysplasia, and adenocarcinoma. Other risk factors included obesity (which may promote reflux), smoking, and asthma. Decreased risks were associated with use of nonsteroidal anti-inflammatory drugs and with *Helicobacter pylori* infection (which colonizes the gastric mucosa and reduces gastric acid production and reflux).

- Studies in a high-risk area of China showed that *H. pylori* infection was associated with an increased cancer risk of progression from gastric atrophy to dysplasia or gastric cancer, and that *H. pylori* carriage may increase cancer risk at all gastric subsites. The risk of progression was increased also with the number of years of smoking cigarettes and with the number of cigarettes smoked. In contrast, the risk of progression was 80 percent lower among subjects with highest tertile of baseline ascorbic acid levels. A case-control study within a cohort of male Finnish smokers suggested that *H. pylori* carriage may also play a role in the development of pancreatic cancer as well as gastric cancer.

- It was found that genetic polymorphisms associated with overexpression of a cytokine that promotes inflammation predispose a person infected with *H. pylori* to develop gastric cancer instead of peptic ulcer or an asymptomatic, trouble-free infection. In particular, polymorphisms in the proinflammatory interleukin-1 *IL-1b* gene and in its receptor antagonist, the *IL-1RN* gene, were associated with risk of low acid production, gastric atrophy, and gastric cancer.

- In a high-risk area of China for esophageal and gastric cardia cancer, a protective effect was associated with high selenium levels in pretrial sera from participants in a randomized nutritional intervention trial. The proportion of these cancers attributable to low selenium levels was 26 percent. No evidence was found for a gradient of serum selenium associated with incidence of gastric noncardia cancer.

- A dietary intervention study in patients with colorectal adenomas found that adopting a diet low in fat and high in fiber, fruits, and vegetables does not influence the risk of recurrence. A similar percentage of subjects in the intervention and control groups had at least one recurrent adenoma. In addition, among subjects with such lesions, the mean number of adenomas did not differ significantly between the two groups. The rates of recurrence of large adenomas and advanced adenomas were also similar among the intervention and control groups.

- The roles of caloric intake and energy balance were investigated in two record-linkage studies in Scandinavia. In Denmark, the overall cancer incidence among women with anorexia nervosa was reduced by a factor of 80 percent. In Sweden, followup of hospital patients with any discharge diagnosis of obesity showed a 33 percent excess incidence of cancer. Significant risk elevations were observed for cancers of the

small intestine, colon, gallbladder, pancreas, larynx, renal parenchyma, bladder, cervix uteri, endometrium, ovary, brain, and connective tissue, as well as lymphomas. The relationships of obesity to the risk of breast, prostate, and pancreatic cancers were modified by age.

- In a multicenter cohort study, cancer risk was evaluated among women given diethylstilbestrol (DES) during pregnancy and among female and male offspring with prenatal DES exposure. The women given DES showed a modest increase in breast cancer risk, but there was no association with ovarian, endometrial, or other cancers. Elevated risks of clear-cell adenocarcinoma of the vagina and cervix among female offspring exposed in utero were quantified. In addition, there appeared to be elevated risks for higher grade squamous cell carcinoma of the cervix and vagina, but a role for increased screening could not be ruled out. Higher risks for infertility, primarily due to uterine and tubal problems, were also observed. Among DES-exposed male offspring, cancer rates were not elevated, except for testicular cancer, which was three times more common among exposed than nonexposed men.

- The long-term effects of radiation and chemotherapy were studied among leukemia cases and controls within cohorts of patients who were previously diagnosed with testicular cancer and with Hodgkin's disease (HD). Radiotherapy (mean dose to active bone marrow, 12.6 Gy) without chemotherapy was associated with a 3-fold elevated risk of leukemia after testicular cancer. The estimated relative risk of leukemia at a cumulative dose of 650 mg cisplatin, commonly administered in current treatment regimens, was 3.2; larger doses (1,000 mg) were linked with 6-fold increased risks. Among 1,000 patients given a treatment dose of 25 Gy and followed for 15 years, an excess of 9 leukemias was predicted; cisplatin-based chemotherapy (dose, 650 mg) might result in 16 cases of leukemia. A followup study of approximately 6,000 children with HD showed a 7-fold increase in solid tumors and a 27-fold increase in acute leukemias. The risk of solid tumors persisted even at 25 years of followup. Greater than 50-fold increased risks were observed for tumors of the thyroid and respiratory tract among children treated before age 10. After HD diagnosis at older ages (10 to 16 years), the largest number of second cancers occurred in the digestive tract (O/E=19.3) and breast (O/E=22.9). These results underscore the importance of lifelong followup of cancer patients who have been aggressively treated at young ages.

- The first study linking plutonium exposure to human cancer was published. Substantially increased risks of bone cancer (relative risk of 17.0) and liver cancer (relative risk of 7.9) mortality were observed among approximately 11,000 Russian workers who were exposed to internally deposited plutonium and external gamma radiation.

- A study of women who received repeated, small X-ray doses as scoliosis patients in the 1960s revealed a two-fold risk of dying from breast cancer as compared with women in the general population. Risk increased significantly in relation to the cumulative number and dosage of X-rays. Women who had 50 or more X-ray exams were four times more likely to die from breast cancer, while those who had received a dose of 20 centigrays were more than three times more likely to die from breast cancer.

- In a case-control study of brain tumors, no association was found with cell phone use, even among people exposed for more than 60 minutes per day or for 5 years or more. Nor did tumors occur more often on the side of the head where a phone was used. Furthermore, in a study of childhood leukemia, no association was found with any exposure to electromagnetic fields.

- Occupational and residential studies have been used to quantify the risk of lung cancer associated with exposure to radon gas. In a study of Chinese tin miners, the risk of lung cancer increased sharply with the measured activity of lead-210, a long-lived decay product of radon. Risk was higher if radon exposure and tobacco use overlapped. Exposure to radon in childhood did not impart any added lung cancer burden. Residential exposure to radon was also found to be a risk factor for lung cancer through studies in China, Missouri, and in analyses which pooled data from 9 North American studies and 11 European studies. In the Missouri study, cumulative radon exposure was estimated through use of novel surface monitors, which measure radon decay products embedded in glass objects that belonged to the subjects over their adult lives. Higher correlations between lung cancer risk and radon exposure were observed when lifetime exposures were estimated using the surface monitor than when using standard radon gas detectors, which measure recent exposure only.

• In China, indoor exposure to smoky coal with high levels of polycyclic hydrocarbons was linked to an excess risk of lung cancer, especially among women, nearly all of whom were nonsmokers. The effect was seen primarily among those with sputum samples positive for *p53* overexpression.

• Record-linkage studies involving population-based U.S. registries revealed that (in addition to AIDS-defining cancers) AIDS patients are prone to Hodgkin's disease (particularly the mixed cellularity and the lymphocytic depletion subtypes), T cell lymphoma, lip cancer, and testicular seminoma, in a pattern that appeared related to the advancing immunosuppression associated with HIV disease progression. Certain other cancers occurred in excess, but seemed related instead to heavy smoking (lung cancer), frequent exposure to HPV (penile cancer), or inaccurately recorded cases of Kaposi's sarcoma (soft tissue sarcoma). In addition, a survey of children with AIDS revealed an increased risk of non-Hodgkin's lymphoma, Kaposi's sarcoma, Hodgkin's disease, and leiomyosarcoma.

• Two genes, *CDKN2A* and *CDK4*, were implicated in the development of cutaneous malignant melanoma (CMM). Germline mutations of *CDKN2A*, a tumor suppressor gene that encodes *p16*, were detected in a series of melanoma-prone families, some of which were also prone to pancreatic cancer. Germline mutations in *CDK4*, a proto-oncogene, were also found, but in only three melanoma-prone families to date. Although many clinical features for CMM were otherwise indistinguishable between the *CDKN2A* and *CDK4* families, there was a significant difference in age-adjusted median numbers of nevi, with CMM case subjects from *CDKN2A* families having greater numbers of nevi. A separate study used a combined segregation/linkage analysis to examine the relationship between *CDKN2A* and dysplastic nevi, total nevi, and solar injury in 20 American melanoma-prone families, 13 of which had cosegregating *CDKN2A* mutations. Overall, the likelihood score improved when dysplastic nevi, total nevi, or both covariates were added to the base model, which included dominant transmission of the *CDKN2A* gene and a linear increase of risk with the logarithm of age on the logit scale.

• Incidence and mortality data were provided for 400 cases of chordoma, a rare tumor arising from notochordal remnants, using the Surveillance, Epidemiology, and End Results (SEER) program, 1973–1995. Within the axial skeleton, 32 percent of cases were cranial, 32.8 percent spinal, and 29.2 percent sacral. In a study of three high-risk families with chordoma (including one family with 10 affected individuals), genome-wide linkage analysis revealed a susceptibility locus mapped to chromosome 7q33.

• The tumor spectrum associated with germline *p53* mutations was evaluated in a series of 45 families, plus 140 other affected cases and kindreds reported in the literature. In addition to the six tumor types (breast and adrenocortical carcinomas, sarcomas of the bone and soft tissues, brain tumors, and leukemias) characteristic of the Li-Fraumeni syndrome, a variety of other cancers (carcinomas of the lung and gastrointestinal tract, lymphomas, and certain other neoplasms) occurred excessively at much earlier ages than expected in the general population. The findings suggest that germline *p53* mutations confer increased risk for a wider range of neoplasms than previously thought.

• A study in the Nordic countries followed 1,218 blood relatives of 56 patients with ataxia-telangiectasia (A-T), a recessive genetic neurologic disorder caused by mutation of the *ATM* gene. Among the patients with A-T, a total of 6 cancers (4 leukemias and 2 non-Hodgkin's lymphomas) were observed compared with 0.16 expected, while among the 1,218 relatives, 150 cancers were recorded with 126 expected. Invasive breast cancer occurred in 5 out of 50 mothers who were obligate *ATM* mutation carriers, but relatives who were less likely to be carriers had no significant increase in the risk of breast cancer.

• A mortality study of 1,604 one-year survivors of retinoblastoma diagnosed during 1914–1984 revealed an excess of early-onset lung cancers in heritable cases. The tumors were mainly small cell carcinoma, which often harbors somatic mutations of *RB1*. These findings suggest that carriers of *RB1* mutations in the germline are highly susceptible to smoking-induced lung cancers and should be targeted for smoking cessation efforts. Over 50 percent of heritable cases developed second cancers (especially sarcomas, melanomas, and brain tumors) by age 50 when treated with ionizing radiation, indicating a gene-environment interaction, while no excess of cancers was noted after sporadic (or nonfamilial) retinoblastoma.

• A number of methodologic advances that should enhance epidemiologic studies were described, including new ways to quantify bias due to population stratification, an examination of the time-dependent effects of exposure histories on disease risk, a study to determine the magnitude and variability in androgen assay results, a marginal likelihood approach for estimating penetrance from a kin-cohort design, and an alternative method for collecting buccal cell DNA.

Development of Resources

DCEG investigators have developed numerous epidemiologic resources, research tools, and improved methods that are used throughout the scientific community. Data management systems were developed to store and analyze family pedigree data (family studies data management system) and to track and report on biospecimen repositories (biospecimen inventory processing system). A series of computer programs were devised to integrate occupational exposure assessment information (exposure assessment program), to classify jobs using standardized government coding schemes (CodeSearch), to calculate observed versus expected events, to compute attributable risk in a variety of epidemiologic designs, and to calculate statistical power and sample size in epidemiologic studies of interactions. DCEG statisticians produced the STATLAB toolbox of the MATLAB program, updated and improved the Gail Model for breast cancer risk prediction, and updated the radioepidemiologic tables estimating the probability of causation. In addition, assays for Kaposi's sarcoma-associated herpesvirus and methods for obtaining DNA through buccal cell collection have been optimized by DCEG researchers.

The DCEG makes extensive use of the World Wide Web to make the research tools developed by the Division widely available to the scientific community. For example, the DCEG Cancer Mortality Maps and Graph Web Site represents an extension of the recently published U.S. cancer atlas and provides interactive maps, graphs (which are accessible to the blind and visually impaired), text, tables, and figures showing geographic patterns and time trends of cancer mortality for the time period 1950–1994 for more than 40 cancers. Another Web site contains questionnaire modules for a wide range of potential risk factors that have been used successfully in DCEG investigations and can be downloaded for use by interested researchers. Of special note are job-specific modules, which obtain detailed information on occupational exposures, and modules on meat cooking practices, which are linked to databases with information on levels of heterocyclic amines and polycyclic hydrocarbons. In collaboration with the National Institute for Occupational Safety and Health and the National Center for Health Statistics, the Division has developed a database containing information on mortality and occupation from death certificates from 24 U.S. states over 12 years. These data have been a valuable resource for examining relationships between occupational exposures and cancer, as well as exploring possible reasons for the geographic variation in cancer mortality.

The following is a list of selected DCEG Web Sites:

• DCEG Web Site: **http://dceg.cancer.gov**

• DCEG Annual Research Directory: Overview of Division's mission and research activities **http://www.qrc.com/nih/nci**

• Biospecimen Inventory Processing System: Downloadable repository tracking system **http://bsi-ii.cancer.gov**

• Cancer Atlases: Atlas maps for exploring associations between environmental/occupational factors **http://www.nci.nih.gov/atlasplus**

• Chronic Lymphocytic Leukemia (CLL) Family Registry: Registry information for families with chronic lymphocytic leukemia **http://dceg.cancer.gov/hgp/geb/CLL/CLLnewsletter.html**

• Computerized Occupational Referent Population System (CORPS): A referent population to be used for epidemiologic studies of employed persons **http://dceg.cancer.gov/ebp/oeb/doc.html**

• Datasets from Completed Occupational Epidemiology Studies: Any datasets not actively being used in studies by Occupational Epidemiology Branch **http://dceg.cancer.gov/ebp/oeb/datasets.html**

• Occupational Code Assignment System (CodeSearch): Dataset of occupation and industry job codes **http://dceg.cancer.gov/ebp/oeb/AvailRes.html#CodeSearch**

• Publications Database for the Division of Cancer Epidemiology and Genetics: **http://dceg.cancer.gov/Publications.html**

• Questionnaire Modules (QMOD): Collection of sample research questionnaires; includes a search function **http://dceg.cancer.gov/QMOD**

Newsletters

The DCEG actively communicates its research findings through the Web and documents produced for the scientific community and the public. The Division partners with the NCI Office of Communication to produce fact sheets on various facets of cancer risk and actively seeks new high-risk families to participate in DCEG research studies on the genetic susceptibility to cancer. The following is a list of selected DCEG newsletters:

• DCEG *Linkage Newsletter:* Newsletter covers topics of scientific and professional interest to the members of the Division **http://dceg.cancer.gov/Linkage.html**

• *Family Research Matters:* Newsletter for family members of the NCI Familial Breast-Ovarian Cancer Studies Registry

• *Familial Melanoma Study News:* Newsletter for the participants of the Melanoma Study

• *CLL Family Registry News:* Newsletter for families enrolled in the NCI-CLL study

• *An Update From The Retinoblastoma Followup Study:* The retinoblastoma study follows over 1,600 survivors

• *Radiologic Technologists Health Study:* A newsletter for participants in the study

• A *DES Research Update:* Report of the DES followup study from the National Cancer Institute

• *Waldenstrom's Macroglobulinemia Family Study:* Pamphlet for prospective participants

• *Living With Beckwith-Wiedemann Syndrome:* A brief overview of BWS, the care children need, and some of the resources that are available to help

• *The New England Study of Environmental Health:* Pamphlet for prospective participants

Workshops

The Division organized a number of workshops involving scientists from around the world to review and develop new approaches for problems facing epidemiology. A total of 275 attendees from 24 states and 8 foreign countries participated in a workshop on best practices for the creation and operation of biorepositories. A workshop was held to review what is known about iodine nutrition in Ukraine and Belarus, the site of fallout from the nuclear power station accident at Chornobyl, how iodine nutrition might affect the risk of thyroid tumor formation resulting from exposure to radioiodine, and how to monitor iodine nutrition. Consortium meetings of researchers investigating familial melanomas, familial leukemias, thyroid cancer among persons exposed to fallout from Chornobyl, adult brain cancer, and non-Hodgkin's lymphoma have also been held.

Training Programs

The Division provides extraordinary opportunities for young scientists who are launching their research careers. Fellows design, carry out, and analyze research aimed at elucidating the etiology and genetics of cancer in human populations, and participate in a broad range of educational experiences at the NCI and NIH. Specialized training is currently offered for genetic, molecular, and radiation epidemiology, and involves academic courses, laboratory rotations, clinical investigations, and other features. The Division seeks to foster partnerships with graduate programs at schools of public health and departments of

preventive medicine to establish research and training collaborations. The recent formation of the DCEG Office of Education has greatly enhanced the development of new fellowship and career development opportunities in the Division.

Future

The Division will continue to pursue a comprehensive, flexible, and balanced approach in seeking answers to critical questions in cancer etiology. Emphasis will continue to be given to interdisciplinary investigations that incorporate molecular and biochemical techniques into epidemiologic studies designed to identify the environmental and genetic determinants of cancer and to provide new insights into preventive measures.

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Biography: *Dr. Fraumeni received a B.A. from Harvard College, an M.D. from Duke University, and an M.Sc. in epidemiology from the Harvard School of Public Health. He completed a medical residency at Johns Hopkins Hospital and Memorial Sloan-Kettering Cancer Center. Dr. Fraumeni joined the NCI in 1962 as a Staff Associate. He became Head of the Ecology Studies Section in 1966, Chief of the Environmental Epidemiology Branch in 1975, Director of the Epidemiology and Biostatistics Program in 1979, and Director of the newly created Division of Cancer Epidemiology and Genetics in 1995. In recognition of his research on environmental and genetic determinants of cancer, Dr. Fraumeni has received numerous awards, including the Lilienfeld Award from the American College of Epidemiology, the John Snow Award from the American Public Health Association, the James D. Bruce Award from the American College of Physicians, the Dr. Nathan Davis Award from the American Medical Association, and the Charles S. Mott Prize from the General Motors Cancer Research Foundation. Dr. Fraumeni is an elected member of the National Academy of Sciences and the Institute of Medicine, and he serves as an Adjunct Professor of Epidemiology at the Harvard School of Public Health, the Uniformed Services University of the Health Sciences, and the George Washington University School of Public Health and Health Services.*

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Biography: *Dr. Zahm received an Sc.D. in epidemiology from the Harvard School of Public Health. She joined the NCI as a Staff Fellow in 1980, became a tenured member of the Occupational Studies Section in 1987, and was appointed the Deputy Chief of the Occupational Epidemiology Branch in 1996 and the Deputy Director of the Division of Cancer Epidemiology and Genetics in 1998. Dr. Zahm received the American Occupational Medical Association's Merit in Authorship Award for a paper on job-exposure matrices, the NIH Merit Award and the PHS Special Recognition Award for work on the relationship between pesticides and risk of non-Hodgkin's lymphoma, the NIH Director's Award for research on cancer among migrant and seasonal farm workers, the NIH Quality of Work Life Award, and the DCEG Mentoring Award. Dr. Zahm is a Senior Editor of the* American Journal of Epidemiology *and serves on editorial boards of the* American Journal of Industrial Medicine, Cancer Investigation, *and* Environmental Research. *She was also an Editor for the occupational health section of an award-winning book on women's health. Dr. Zahm chairs the DCEG Technical Evaluation of Protocols Committee and the Promotion and Tenure Review Panel. She also serves on numerous national and international committees and advisory groups, and chairs the United Auto Workers/General Motors Occupational Health Advisory Board. Dr. Zahm is an elected member of the American Epidemiology Society and is an adjunct faculty member at George Washington University. Her research interests include cancer risks associated with pesticide exposure, the etiology of non-Hodgkin's lymphoma, and occupational cancer among women.*

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Division of Cancer Epidemiology and Genetics
Office of Division Operations and Analysis

The Office of Division Operations and Analysis plans, initiates, develops, analyzes, and coordinates activities that broadly affect the Division. These activities include scientific narratives and periodic reports, special scientific planning and reporting documents, and responses to inquiries from Congress, other agencies, and the public. The Office advises on policy, structure, organization, personnel, and other matters affecting the Division's management and administrative operations. In addition, the Office develops and plans senior scientific staff retreats and serves as the focal point for information technology-related activities.

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The DCEG Office of Education (OE) was established in 1999 to promote the recruitment of high-caliber postdoctoral and predoctoral fellows, to provide oversight of fellows' training and career progression, to facilitate the retention of selected trainees and high-quality placement in the extramural community, and to develop and promote graduate program partnerships with public health and medical schools in the United States and abroad. The OE also coordinates the DCEG summer research program offering fellowships to high school, college, and graduate students interested in exploring careers in cancer epidemiology and genetics.

The OE coordinates special fellowship training programs that actively foster opportunities for interdisciplinary research in the following areas:

- **Genetic Epidemiology:** Fellows receive training in clinical, molecular, and quantitative genetics, and in genetic epidemiology, with a focus on identifying the genetic determinants of cancer. The training program seeks to expand the pool of investigators with the skills to bridge the population, clinical, and laboratory-based sciences in carrying out research leading to new strategies for cancer prevention.
- **Radiation Epidemiology:** Fellows are trained in radiation epidemiology, biostatistics, radiation biology, and risk assessment of cancer from radiation exposure. Academic courses are given in collaboration with Johns Hopkins University and the NCI's Center for Clinical Research. Fellows may spend up to two years at the Radiation Effects Research Foundation in Hiroshima.
- **Molecular Epidemiology:** Training focuses on integrating laboratory and clinical investigations with population research, including studies of biomarkers of genetic susceptibility, carcinogenic exposure and mechanisms, and intermediate endpoints.
- **Biostatistics and Informatics:** Fellows receive training in emerging biostatistical areas, including epidemiologic methods, statistical genetics, clinical trials, risk assessment, and informatics.

In addition to serving as a centralized coordination point for the recruitment, interviewing, hiring, and orientation of new fellows, the OE provides guidance to senior investigators for their continued professional development and represents the DCEG and the NCI interests at NCI and NIH meetings relevant to the coordination of training, recruitment, and educational activities.

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Biography: *Dr. Albanes received his B.S. in biology from the State University of New York at Stony Brook and his M.D. from the Medical College of Wisconsin. After completing his internship at the University of California, Irvine, he joined the Epidemic Intelligence Service of the Centers for Disease Control and Prevention (CDC), through which he began working in the Cancer Prevention Program of the NCI in 1982. Thereafter, Dr. Albanes completed a preventive medicine residency with the CDC and continued his research in the Cancer Prevention Studies Branch of the NCI from 1984 to 1990, when he became a tenured Senior Investigator. He was awarded the Public Health Service Commendation Medal in 1992 for his research and leadership in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, and joined the Division of Cancer Epidemiology and Genetics in 2000 as a Senior Investigator in the Nutritional Epidemiology Branch and as Chief of the Office of Education.*

Division of Cancer Epidemiology and Genetics
NCI Core Genotyping Facility

The NCI's Advanced Technology Center (ATC), established for the implementation of novel technologies to address biological, clinical, and genetic questions pertinent to human cancers, includes the NCI Core Genotyping Facility which is overseen by DCEG. Under the direction of Dr. Stephen Chanock, the aim of the CGF is to meet the genotyping and DNA sequencing needs of the DCEG and the NCI's Center for Cancer Research. The facility performs high-throughput genotyping and sequencing to support genetic analysis for a broad range of projects for the intramural research program of the NCI.

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Biography: *Dr. Chanock received his medical degree from Harvard Medical School in 1983 and completed training in pediatrics, infectious diseases, and pediatric hematology/oncology at Boston Children's Hospital and the Dana-Farber Cancer Institute. He joined the NCI in 1991, where he has been investigating the molecular, cellular, and clinical problems of infectious complications in patients with cancer and HIV infection. Dr. Chanock has been the Medical Director of Camp Fantastic since 1996 and recently became Chair of the Steering Committee for the NCI Genetics, Genomics, and Proteomics Faculty. Dr. Chanock has become an active collaborator with investigators in DCEG and in the NCI Cohort Consortium on projects devoted to understanding gene-environment interactions. As Director of the NCI Genotyping Facility, Dr. Chanock has responsibility for managing and supervising the facility, including the staff, equipment, and space required to fulfill the genotyping needs of the NCI's intramural scientists. He also holds a dual appointment as a Senior Investigator in the Pediatric Oncology Branch of the NCI's Center for Cancer Research.*

Division of Cancer Epidemiology and Genetics
Administrative Resource Center

The Administrative Resource Center is responsible for administratively supporting the DCEG's research and management activities. The ARC provides high quality service that is responsive, creative, and flexible. The professional and technical team provides support in the areas of finance and budget, personnel, procurement, contracts management, travel, property management, space utilization, and facilities management. The ARC works with DCEG staff in providing the highest levels of service in support of the Division's research mission.

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The Epidemiology and Biostatistics Program conducts independent and collaborative epidemiologic and biostatistical investigations to identify the distribution, characteristics, and causes of cancer in human populations. These aims are accomplished through a series of integrated programs of research, including studies of: (1) demographic variation in the occurrence of cancer by age, race, gender, geography, and over time (i.e., descriptive studies), (2) cancer related to occupational and environmental exposures, (3) drug-induced cancer (i.e., pharmacoepidemiology), (4) cancer induced by ionizing and nonionizing radiation, (5) the relationship of diet and nutrition to cancer risk, (6) microbial origins of cancer (e.g., viruses and bacteria), (7) metabolic and hormonal aspects of cancer risk, and (8) genetic susceptibility to cancer-causing exposures. The Program also develops biostatistical methods for family-based and population-based studies.

In carrying out research activities, we utilize national and regional statistics, conduct field studies involving the collection of risk-related information and biologic specimens, and collaborate with other governmental agencies, academic centers, and private sector groups. Emphasis is placed on interdisciplinary studies in which clinical and/or laboratory components are integrated into epidemiologic research designs (biochemical and molecular epidemiology). Studies are often national in scope, and some incorporate international components that involve the evaluation of unique exposures or unusual cancer risks.

A broad range of studies are undertaken to identify genetic and environmental factors contributing to the risk of cancer. These studies include investigations to determine the reasons for regional differences in breast cancer mortality, evaluate the possible role of pesticides and other environmental chemicals in risk of non-Hodgkin's lymphoma, examine the immune response to human papillomavirus infection, and explore the molecular epidemiology of benzene toxicity.

The Epidemiology and Biostatistics Program has established the Cancer Epidemiology and Biostatistics Training Program to provide unique training opportunities in the principles and methods of epidemiology and biostatistics and in their application to cancer etiology research, including interdisciplinary studies. The goal of the Training Program is to expand the pool of epidemiologists and statisticians with the expertise to identify the causes of cancer and open new avenues for cancer prevention strategies. The Training

Program is open to postdoctoral fellows, visiting scientists from around the world, predoctoral candidates conducting dissertation research, and master-level students seeking intensive practical training prior to entering a doctoral program. Trainees work under the supervision of a senior-level epidemiologist or statistician within the Program.

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Biography: *Dr. Hoover received a B.A. from the University of Notre Dame and an M.D. from Loyola University in Chicago. Following an internal medicine internship at Cook County Hospital, he completed a preventive medicine residency at the Harvard School of Public Health. During this period, Dr. Hoover received an S.M.Hyg. and Sc.D. in epidemiology from the School of Public Health. He joined the NCI in 1972, holding a series of positions before becoming Director of the Epidemiology and Biostatistics Program in 1996. Dr. Hoover serves on many national and international committees on various aspects of epidemiology and preventive medicine. He received the PHS Commendation Medal in 1976, the Meritorious Service Medal in 1984, and the Distinguished Service Medal in 1990. Dr. Hoover received the Gorgas Medal for distinguished work in preventive medicine from the Association of Military Surgeons of the United States in 1996. He is also the recipient of the John Snow Award from the American Public Health Association, the Distinguished Achievement Award from the American Society of Preventive Oncology, the 2001 U.S. Public Health Service Commissioned Corps Physician Researcher of the Year Award, the Distinguished Service Award by DES ACTION USA, the NCI/NIH Technology Transfer Award, and the DCEG Award for Exemplary Service.*

Epidemiology and Biostatistics Program
Cancer Epidemiology

Research: A variety of studies are being conducted in collaboration with investigators throughout the Program and Division. The studies span the spectrum of epidemiologic methods, and many have biochemical or molecular components integrated into their research designs. A wide range of exposures is being assessed in relation to cancer risk, and outcomes include a large breadth of tumors.

Exogenous Hormonal Exposure and Breast Cancer Risk
Emphasis is being given to studies of hormonally related tumors, especially of the breast and endometrium. With respect to exogenous hormonal exposures, breast cancer risk associated with menopausal hormone replacement therapy, particularly the recent shift to the combined estrogen and progestin regimen, is perhaps the most important question with both etiologic and public health implications. In a study of 2,000 breast cancer cases occurring in 46,000 women followed for over 12 years, risk was elevated for recent users of both estrogen alone and estrogen-progestin, but it was higher among users of the combination therapy. For the combined regimen, the relative risk increased by 0.08 for each year of use.

Early Life Exposure to Diethylstilbestrol and Cancer Risk
Several lines of evidence suggest that hormonal exposures early in life, including in utero, may influence risk of breast and other hormonally related tumors in adults. To assess this hypothesis, we worked closely with five collaborating centers to reassemble and combine the U.S.-based cohorts of diethylstilbestrol (DES)-exposed daughters, sons, and mothers that were studied in the 1970s and 1980s. Two followup efforts (1994 and 1998) have been conducted, covering approximately 3,600 exposed and 3,500 unexposed

mothers, 4,500 exposed and 1,500 unexposed daughters, and 1,800 exposed and 1,600 unexposed sons.

Compared with the unexposed group, exposed mothers had a 10 percent overall excess risk of incident cancers of all sites combined, based on 600 cases (RR=1.10, 0.99–1.23). The excess was essentially all due to a 30 percent increase in breast cancer risk (RR=1.27, 1.07–1.52) and appeared within the first 10 years following exposure, similar to that observed for oral contraceptive and menopausal hormone use. However, unlike these other hormonal effects, the DES effect persists for at least 40 years following cessation of the exposure. While the risk is relatively small, it is noteworthy that the same estimate was obtained from the followup of a randomized trial of DES treatment (RR=1.23) as from the followup of observational studies (RR=1.29). There were no significant differences between exposed and unexposed mothers for any other cancer sites.

Overall, the frequency of all cancers combined among women exposed in utero to DES was similar to those not exposed and to expected rates based on general population experience. The three cases of vaginal or cervical clear-cell adenocarcinoma among DES-exposed women were 40 times greater than expected and led to the first direct estimate of this tumor's attack rate (1.5/1,500) for women through age 30. The overall relative risk of breast cancer was 1.18 (0.56–2.49), with a nonsignificant excess for women after age 40 (RR=3.17, 0.73–13.83) that appears to derive more from a deficit of unexposed cases than an excess among the exposed when compared to the general population experience.

The most controversial issue concerning DES and cancer involves squamous dysplasia of the cervix and vagina among daughters exposed in utero. Special efforts were made to address this issue through extensive record collection, independent pathology review, and multiple attempts to control for differences in screening practices. Based on our analysis, in utero DES exposure was associated with an excess risk of squamous dysplasia of the cervix and vagina (RR=2.12, 1.19–3.77). There was also evidence of an inverse relationship of relative risk with timing of exposure during pregnancy, ranging from 2.82 when exposure began before the 8th week of pregnancy to 1.35 when it occurred after the 15th week.

Because of the small population available for study, we were constrained in addressing cancer risks among men exposed in utero. Overall, no excess risk was observed for all sites combined (RR=1.0 based on 27 cases). The relative risk for testicular cancer, the only site under a priori suspicion appropriate for analysis, was 2.04 (0.8–4.2) compared with the general population and 3.05 (0.65–21.96) compared with the unexposed group.

Keywords

breast cancer, cervical adenocarcinoma, diethylstilbestrol (DES), exogenous hormones, in utero, vaginal clear-cell adenocarcinoma

Recent Publications

Hoover RN, Troisi, RJ. Understanding mechanisms of breast cancer prevention. *J Natl Cancer Inst* 2001;93:1119–20.

Hoover RN. Sex hormones and human carcinogenesis: Epidemiology. In *Principles and Practice of Endocrinology and Metabolism* 3rd ed. Becker KL, Bilezikian JP, Bremner WJ, et al., editors. Philadelphia: Lippincott Williams & Wilkins, 2001.

Brinton L, et al. Cancer risk at sites other than the breast following augmentation mammoplasty. *Ann Epidemiol* 2001;11:248–56.

Kaufman RH, et al. Continued follow-up of pregnancy outcomes in diethylstilbestrol-exposed offspring. *Obstet Gynecol* 2000;96:483–89.

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Biography: *Dr. Hartge received a B.A. from Radcliffe College, an M.A. in economics from Yale University, and an Sc.D. in epidemiology from the Harvard School of Public Health. Since 1977, she has conducted research at the NCI, carrying out studies on the etiology of lymphoma, melanoma, and cancers of the bladder, ovary, and breast. In 1996, Dr. Hartge was appointed Deputy Director of the DCEG Epidemiology and Biostatistics Program. From 1988 to 1992, she served as the Assistant Editor of the* American Journal of Public Health *and currently serves on the editorial board of* Epidemiology. *Dr. Hartge is an Adjunct Professor at George Washington University and a member of the Board of Directors of the American College of Epidemiology.*

Epidemiology and Biostatistics Program
Novel Methods for Assessing Environmental and Genetic Cancer Risk in Populations

Research: The ongoing revolution in biology calls for the development of new approaches to epidemiologic design and analysis of population risks and for rigorous application of established approaches. Similarly, the detection of cancer-related chemicals at low levels in the general environment requires new approaches to exposure assessment and integrated analysis. We collaborate with other DCEG investigators to conduct studies that offer the

possibility of developing new epidemiologic methods of immediate scientific value and wider capability utility. Current work centers on non-Hodgkin's lymphoma and cancers of the ovary and breast.

Non-Hodgkin's Lymphoma
Non-Hodgkin's lymphoma (NHL) incidence rates have risen 3 percent per year in the United States for four decades; mortality from NHL has risen 1.6 percent, compared with 0.2 percent for all cancers combined. An analysis of trends in both sexes and around the world suggests that an etiologic agent has become increasingly prevalent in the general environment. Farmers exposed to pesticides have increased risk, so environmental pesticide exposures also warrant examination. In a multidisciplinary case-control study of non-Hodgkin's lymphoma in the United States, we are measuring pesticide residues in household dusts, serum samples, and tap water, and collecting questionnaire data on history of residential pesticide use. We are also examining the role of viruses such as HTLV-I, HHV-6, KSHV, and EBV promoters, and are assessing immune-related medical conditions and treatments, sunlight exposures, diet, hair dye use, and other hypothesized risk factors. We are developing analytic approaches to synthesizing data collected from biospecimens, environmental samples, and computer-assisted questionnaires.

Genes and Environment in Breast and Ovarian Cancer
Assessing genetic risks in populations requires new epidemiologic approaches. For example, alterations in *BRCA1* and *BRCA2* genes predispose to breast and ovarian cancers and probably prostate cancer, but the risks cannot be estimated accurately using data from the high-risk families who are studied to locate and sequence the genes. We developed a statistical technique to infer carrier risks from family history, a technique we term "kin-cohort." With this approach, we estimated the risk of developing breast cancer or ovarian cancer by age 70 as 56 percent and 16 percent, respectively, in carriers of three specific alterations found in Ashkenazi Jews. We extended the approach to examine the effect of *BRCA1/2* on survival following breast cancer. Carriers and noncarriers showed similar survival time. Our ongoing research aims to measure whether childbearing patterns and oral contraceptive use modulate risks of breast and ovarian cancer in carriers of the altered genes, whether common genetic polymorphisms influence gene expression, and whether ovarian cancer screening is effective for alteration carriers. In addition, we are measuring pesticide levels in household dust and tap water collections given possible hormonal effects of residential pesticide use.

Keywords

BRCA1, BRCA2, non-Hodgkin's lymphoma, ovarian cancer

Recent Publications

Modan B, et al. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a *BRCA1* or *BRCA2* mutation. *N Engl J Med* 2001;345:235–40.

Titus-Ernstoff L, et al. Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. *Br J Cancer* 2001;84:126–33.

Recent Publications (continued)

Hartge P, et al. Complex ovarian cysts in postmenopausal women are not associated with ovarian cancer risk factors: Preliminary data from the prostate, lung, colon, and ovarian cancer screening trial. *Am J Obstet Gynecol* 2000;183:1232–37.

Jemal A, et al. Cancer surveillance series: Changing patterns of cutaneous malignant melanoma mortality rates among whites in the United States. *J Natl Cancer Inst* 2000;92:811–18.

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Biography: *Dr. Ziegler is currently a Senior Investigator in the Office of the Director of the Epidemiology and Biostatistics Program of the National Cancer Institute. Her research on diet, nutrition, and cancer has emphasized both etiology and public health implications, and has integrated biochemical and molecular techniques. Dr. Ziegler received a B.A. in chemistry and English from Swarthmore College, a Ph.D. in biochemistry from the University of California at Berkeley, and an M.P.H. in epidemiology and public policy from the Harvard School of Public Health. She has developed and taught courses on public health nutrition, international nutrition, and global food resources at Yale, Harvard, and Tufts universities. Dr. Ziegler helped establish the Nutritional Epidemiology Research Interest Section of the American Society of Nutritional Sciences and currently serves on the editorial boards of the* Journal of the National Cancer Institute*, the* American Journal of Clinical Nutrition*, and the* Nutrition Action Healthletter*. In 1996, she was awarded the NIH Merit Award for her research on the role of vegetables, fruits, and micronutrients in the etiology of cancer.*

Epidemiology and Biostatistics Program
Multidisciplinary Studies of Diet, Nutrition, and Cancer

Research:

Vegetables, Fruits, and Carotenoids

Previously, we demonstrated that diets high in vegetables, fruits, and carotenoids were strongly associated with reduced risk of lung and upper aerodigestive tract cancers. To explore the individual contributions of the major carotenoids, we conducted nested case-control studies in the Honolulu Heart Program cohort. High serum levels of several carotenoids were associated with decreased risk of lung, oral-pharyngeal, esophageal, and laryngeal cancer, with α-carotene the most predictive. Recently, in the Nurses and Health Professionals cohorts, using repeated dietary measures, we found that high vegetable and fruit intake was associated with only a modestly reduced risk of lung cancer in women and no risk reduction in men. Our analyses suggested that the strength of this widely accepted relationship might have been exaggerated because confounding by smoking has not always been adequately controlled. Since other recent publications have questioned whether vegetable intake can reduce the risk of colorectal cancer, we are exploring opportunities to continue to evaluate the importance of vegetables and fruits in cancer etiology, with emphasis on prospective studies, range and variety in intake, and accurate assessment of exposure. Initially, we will explore vegetable and fruit intake, circulating levels of individual carotenoids, and risk of colorectal polyps at various stages in the speculated progression to cancer, using data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) cohort.

Lycopene, a carotenoid concentrated in tomato products, has been linked to reduced risk of prostate cancer in several studies. In a case-control study conducted among U.S. blacks and whites, we found that high circulating lycopene was protective in both races. In addition, circulating levels were lower in the blacks, which suggested that low lycopene might contribute to

the substantially higher rates of prostate cancer among U.S. blacks. The protective influence of lycopene-rich diets has been most consistently seen in U.S. studies, so we are now exploring the influence of high circulating lycopene in a cohort of Finnish men with distinct dietary patterns.

One-Carbon Metabolism

Disruption of one-carbon metabolism can interfere with DNA synthesis, repair, and methylation and thus promote carcinogenesis. Efficient one-carbon metabolism requires not only folate but also vitamins B_2, B_6, and B_{12} and optimal activity of multiple enzymes, such as methylene tetrahydrofolate reductase and methionine synthase. In a community-based case-control study of invasive cervical cancer in five areas in the United States, we found that low serum and red blood cell folate were only modestly predictive of increased risk. However, elevated serum homocysteine was strongly and significantly predictive (RRs~2–3), which suggested that pervasive problems in one-carbon metabolism might be involved. We are now assessing the contribution of B-vitamin inadequacies and common polymorphisms in key one-carbon metabolism genes. In addition, we will be evaluating the importance of one-carbon metabolism in the etiology of brain and colorectal cancer. Dietary and vitamin supplement information are being analyzed in a multicenter case-control study of brain cancer and will be complemented by assays for genetic polymorphisms. In the PLCO cohort, 2,400 men and women were diagnosed with colorectal adenomatous polyps at baseline. The dietary information, serum, and DNA collected in this study will allow us to relate the role of one-carbon metabolism to the speculated progression of colorectal cancer. Since folic acid fortification has already been shown to decrease homocysteine levels in populations with a variety of nutritional and genetic impairments, our results may indicate how targeted supplementation and/or fortification schemes may contribute to cancer prevention.

Breast Cancer

International variation in breast cancer incidence and migrant studies indicate that modifiable factors play a major role in breast cancer etiology, although the specific lifestyles and environmental exposures remain elusive. We designed a large, population-based case-control study of breast cancer in Asian-American women to take advantage of their diversity in diet and breast cancer risk. Childhood, adolescent, and adult exposures were assessed by interviewing both study participants and their mothers. To complement the extensive interview information, body size and shape were measured, and blood and urine samples were collected. Endogenous hormones, phytoestrogens, growth factors, micronutrients, and fatty acids have been or will be measured in selected specimens. We found a six-fold gradient in breast cancer risk by migration history within our study population, comparable to the international differences in breast cancer incidence rates. Exposures during adult life substantially influenced risk. Furthermore, there was no evidence of an especially susceptible period during menarche or early reproductive life. Increased adiposity and weight gain in the decade preceding diagnosis were critical determinants of risk. Thus, excess weight may function as a late stage promoter in breast carcinogenesis, and weight maintenance or reduction as an adult may have a significant and rapid impact on breast cancer risk. We are currently exploring which endogenous hormones, hormone metabolites, growth factors, and dietary patterns are

most correlated with migration history, and thus likely determinants of the six-fold gradient in breast cancer incidence. Circulating estrogens were only weakly associated with Westernization, while circulating androgens were inversely associated in both pre- and postmenopausal women. Decreased intake of soy was associated with a doubling of breast cancer risk. We now want to examine the broader dietary patterns associated with soy intake: in particular, its relationship to vegetable, fruit, and grain consumption; the relative contributions of childhood and adult soy intake; and what specific isoflavones and lignans seem important. Since height was a strong and consistent predictor of risk in these Asian-American women, we are seeking biologic explanations, with emphasis initially on insulin-like growth factors.

Keywords

α-carotene, β-carotene, β-cryptoxanthin, brain cancer, breast cancer, carotenoids, cervical cancer, colorectal cancer, diet, dietary supplements, fat, folate, fruits, growth factors, height, laryngeal cancer, lung cancer, lycopene, methyl metabolism, migrants, nutrition, oral cancer, pharyngeal cancer, phytochemicals, phytoestrogens, prostate cancer, vegetables, vitamin supplements, weight

Recent Publications

Feskanich D, et al. Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. *J Natl Cancer Inst* 2000;92:1812–23.

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Vogt TM, et al. Serum lycopene, other serum carotenoids, and risk of prostate cancer in U.S. blacks and whites. *Am J Epidemiol* 2002;155:1023–32.

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Epidemiology and Biostatistics Program
Biostatistics Branch

The Biostatistics Branch develops statistical methods and data resources to strengthen observational studies, intervention trials, and laboratory investigations of cancer. The Branch also provides information on cancer rates for generating etiologic leads and developing appropriate study designs, and it plans and conducts independent and collaborative descriptive and analytic studies of cancer etiology. Members of the Branch consult and collaborate with scientists throughout the NCI and NIH, and with investigators and public health officials at other government agencies and academic and research institutions in this country and abroad.

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The Branch consists of the Office of the Chief and three research sections. The Epidemiologic Methods Section conducts cancer studies in human populations. The Statistical Research and Applications Section supports population-based field studies and laboratory investigations. The Descriptive Studies Section analyzes and interprets data on trends and patterns in cancer incidence and mortality.

Collaborative Studies

Branch investigators are key participants in large, complex interdisciplinary studies of cancer etiology and risk assessment. In a recent example, they were major collaborators in a case-control study of children with acute lymphoblastic leukemia, which found that risk was not associated with exposure to electromagnetic fields (EMF). Statistical elements of the study included assessing the validity of exposure measurements, designing and analyzing reliability studies, and evaluating dose-response relationships. In an ongoing collaboration, Branch investigators are leading analyses of hormone assays to determine their reliability for studies aimed at understanding the etiology of hormone-related cancers.

Descriptive Studies of Cancer

The Branch studies geographic patterns and temporal trends in cancer incidence and mortality rates to generate etiologic hypotheses, evaluate consistency with other hypotheses, and identify cancer sites warranting special study. Etiologic leads may also be suggested from studies of temporal trends in cancer subsites and histologic subtypes. Branch members develop statistical methods to interpret geographic variation, which they apply in collaborative studies to explain variations in breast cancer rates due to differences in the prevalence of known risk factors. Recently, the Branch published a U.S. atlas of cancer mortality data spanning the years 1950 to 1994, which identified

geographic areas with high rates of specific cancers and spatial and temporal patterns that may suggest particular carcinogenic exposures. The atlas is available in printed and electronic formats (**http://www.nci.nih.gov/atlas**). Branch scientists also develop statistical methods to analyze associations of age, calendar time, and year of birth with cancer rates. These age-period-cohort analyses found a decrease in risk of breast cancer among black and white women born since 1948, despite later age of childbearing than in earlier cohorts.

Cancer Risk Assessment
A major research thrust within the Branch is quantifying risk of developing cancer from exposure to known carcinogens. Studies of underground miners yielded risk estimates of lung cancer from exposure to radon, and data from a combined analysis of 11 such studies worldwide indicated that 10–12 percent of all U.S. lung cancer deaths each year may be attributable to indoor radon exposure. A recent analysis of data from eight case-control studies of exposure to radon in the home yielded risk estimates consistent with those from studies of underground miners. Branch scientists also developed a model for predicting the risk of breast cancer over a defined time interval for a woman with specific risk factors, such as a strong family history. This model has been used to assist in counseling women and to define eligibility criteria for intervention studies, such as the NCI Breast Cancer Prevention Trial. The model has also be used to help assess risks and benefits of tamoxifen for preventing breast cancer in high-risk women.

Methodologic Research
Branch scientists develop methods for increasing efficiency and improving analysis of case-control and cohort designs. High priority is being given to methodologic issues in genetic epidemiology. Recently, Branch members developed methods for estimating risk associated with an identified autosomal dominant gene from family studies in which one member volunteers to be genotyped and to provide disease histories of first-degree relatives (kin-cohort design). Other research focuses on various methods for characterizing exposure history and overcoming problems associated with measurement error and missing information.

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Biography: *Dr. Gail received an M.D. from Harvard Medical School in 1968 and a Ph.D. in statistics from George Washington University in 1977. He joined the NCI in 1969 and became Chief of the Biostatistics Branch in 1994. Dr. Gail is a Fellow and former President of the American Statistical Association, a Fellow of the American Association for the Advancement of Science, an elected member of the American Society for Clinical Investigation, and an elected member of the Institute of Medicine of the National Academy of Sciences. He has received the Spiegelman Gold Medal for Health Statistics, the Snedecor Award for Applied Statistical Research, the Howard Temin Award for AIDS Research, the NIH Director's Award, and the PHS Distinguished Service Medal.*

Epidemiology and Biostatistics Program, Biostatistics Branch
Statistical Methodology Applications to Breast and Gastric Cancer

Research: Our research is directed at providing statistical consultation and active collaboration on studies of cancer etiology and risk assessment, conducting selected studies, developing new statistical methods, adapting available methods to meet study objectives, and developing data resources.

Breast Cancer Risk

We developed a model to predict the risk of developing breast cancer for a woman with specific risk factors, such as a positive family history. This model has been used to assist in counseling women and defining eligibility criteria for entry into the NCI Breast Cancer Prevention Trial. This trial demonstrated that tamoxifen reduced the risk of breast cancer over a five-year period. We adapted the risk model to aid in counseling women on the risks and benefits of tamoxifen. Although we validated the model using independent datasets, we are now exploring the feasibility of improving it by incorporating information on mammographic density and by using genetic information. In related work, we proposed the use of such a model for making individualized recommendations for mammographic screening of women in their forties. We are also using the model and extensions of it to determine whether geographic variation in breast cancer rates can be explained by regional differences in the prevalence of known risk factors.

Gastric Cancer Etiology and Prevention

We conducted a series of observational and experimental studies whose results suggest that three interventions, alone or in combination, have the potential to retard the progression of precancerous gastric lesions, including chronic atrophic gastritis, intestinal metaplasia, and dysplasia. The interventions are antibiotic treatment of *Helicobactor pylori* infection, dietary supplementation with an extract of garlic, and supplementation with selenium and vitamins E and C. A study using a factorial design to investigate

the effectiveness of these interventions is under way. Related investigations will determine whether somatic mutations or certain inherited polymorphisms are associated with rates of transition among precancerous gastric lesions.

Methods for Descriptive Cancer Epidemiology
We developed methods to estimate cancer prevalence from registry data on cancer incidence and on survival following cancer diagnosis. We also developed methods to identify cancer types that exhibit large geographic heterogeneity in mortality rates. Such cancers are considered in determining whether they warrant special studies to evaluate the causes of geographic variation in mortality rates.

Population-Based Estimates of Risk from Identified Genes
Genes that predispose to cancer are often identified from studies in highly affected families. We studied the strengths and weaknesses of population-based designs to determine risks from such genes in the general population. We compared cohort and case-control designs with designs based on families ("kin-cohort" designs). These comparisons raise challenging methodological issues, such as how to estimate gene-specific survival functions from kin-cohort designs and how to account for familial aggregation unrelated to the target genes ("residual familial correlation"). We developed techniques to estimate such survival curves from kin-cohort data by the method of maximum likelihood and by alternative methods that are easier to compute. In addition, we developed statistical procedures to detect residual familial correlation with kin-cohort data.

Other Methodologic Work and Data Resource Development
We conducted research on methods for validating exposure measurements, assessing the reliability of such measurements, and adjusting analyses to account for effects of measurement error. We are applying such methods to study the reliability of hormone assays used in investigations of breast and endometrial cancers. We also developed new techniques for assessing agreement between two types of exposure measurements, such as dietary intake through use of a retrospective food frequency questionnaire and a prospective daily record of food intake. Other methods were developed for analyzing case-control data in which controls are obtained by cluster sampling, as in the Waksberg telephone survey method. In addition, we developed randomization-based methods for analyzing community intervention trials, such as the NCI Community Intervention Trial for Smoking Cessation. These methods allow for loss to follow-up and covariate adjustment and offer guidance on the efficiency of matched designs. Beside this methodologic work, we helped develop record-linkage systems for determining whether particular cancers are associated with previous medical conditions. These systems are being used to study risk factors associated with Hodgkin's disease, non-Hodgkin's lymphoma, and cancers associated with connective tissue disorders.

Keywords

breast cancer, gastric cancer, genetics, record-linkage study

Recent Publications

Gail MH, et al. Weighing the risks and benefits of tamoxifen for preventing breast cancer. *J Natl Cancer Inst* 1999;91:1829–46.

Gail MH, et al. Designing studies to estimate the penetrance of an identified autosomal dominant mutation: Cohort, case-control and genotyped proband design. *Genet Epidemiol* 1999;16:15–39.

Gail MH, et al. On meta-analytic assessment of surrogate outcomes. *Biostatistics* 2000;1:231–46.

Gail MH, et al. Effects of violations of assumptions on likelihood methods for estimating the penetrance of an autosomal dominant mutation from kin-cohort studies. *J Stat Planning and Inference* 2001;96:167–77.

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Epidemiology and Biostatistics Program, Biostatistics Branch
Biostatistical Methodology for Studying Genetic and Environmental Causes of Cancer

Research: Novel epidemiological data often give rise to challenging theoretical and methodological problems in statistics, and lead to the identification of several important areas of research.

Survival Analysis Methods in Genetic Epidemiology
We have developed survival analysis methods to analyze age-at-onset-of-disease data for a number of scientific problems in genetic epidemiology. New statistical methods were developed for analyzing kin-cohort data from the Washington Ashkenazi Study, and a previously proposed method for estimating penetrance from family history data of genotyped study participants was refined by developing a nonparametric survival analysis approach that guarantees the estimates of the cumulative risk functions to be nondecreasing functions of age. We have shown that compared to alternative likelihood approaches, this method is more robust to the presence of other sources of familial aggregation of the disease that cannot be explained by the genes under investigation.

By making use of models for multivariate survival distributions, we have developed a method to quantify and estimate the residual familial aggregation of the disease from these data. Application of this method revealed that family history is an important predictor of the risk of breast cancer among noncarriers of *BRCA1* and *BRCA2* mutations. Other projects include investigations of the effect of *BRCA1/BRCA2* mutations on the risk of second cancers after primary breast and ovarian cancer; the interaction between reproductive risk factors and *BRCA1/BRCA2;* and the interaction between these mutations and other breast cancer susceptibility genes. We are also estimating the effect of these gene mutations on overall mortality due to causes other than breast and ovarian cancers in females and prostate cancer in males.

Cure modeling is a technique for survival analysis when a certain fraction of individuals under study are never expected to develop the endpoint of interest however long they may be followed. For studying time to recurrence of a disease after treatment, for example, it is conceivable that a certain proportion of the individuals will be cured by the treatment and will never experience recurrence. We have developed an extension of this model to the bivariate setting that can be used to analyze familial correlation in time-to-event data when cure or insusceptibility or immunity is a possibility. We have also collaborated on developing methods for analyzing case-control family studies that collect age-at-onset and covariate data for both the subjects in the case-control sample and their relatives.

Two-Phase Designs
Epidemiological cohort or case-control studies requiring biological and questionnaire data collection on a large number of subjects may be prohibitive due to cost and other practical considerations. Two-phase designs provide an efficient cost-effective alternative. In this class of designs, investigators collect crude or inexpensive covariate information for a relatively large number of subjects at phase I and then ascertain the detailed, expensive covariate information only for a small, efficiently selected subsample of phase II subjects. We have developed a new statistical method for analyzing data from these designs that is novel in several aspects. First, unlike alternative methods, it does not require that the probability of being selected at phase II is positive for all units. This property enables the application of the new method to an important class of restricted two-phase designs, where due to efficiency or/and practical considerations one restricts sampling at the second phase to only certain strata based on the response of the phase I subjects. Second, even when alternative methods are applicable, the new method is computationally simple yet achieves almost the same efficiency as more complex but fully efficient methods. Work is in progress for application of these designs for gene-environment interaction studies.

Methods for Analyzing Epidemiologic Studies with Disease Subgroups
The ongoing Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) clinical trial is investigating the effect of various baseline covariates such as diet and smoking on the risk of prevalent colorectal adenoma among men and women who underwent sigmoidoscopy. Data are available to classify the adenomas by size (large versus small), morphology (villous versus nonvillous), and multiplicity (single versus multiple). We have developed a regression analysis approach for such epidemiological data when various disease subtypes can be defined using multiple characteristics. Our approach uses a multilevel polytomous logistic regression model that can be used to look at the effect of exposure variables on the different characteristics of the disease both individually and jointly. Methods for inference under this model and related theories are developed for both small and large numbers of disease subgroups.

Keywords

genetic epidemiology, statistical methods, survival analysis, two-phase designs

Recent Publications

Chatterjee N, et al. A marginal likelihood approach for estimating penetrance from kin-cohort designs. *Biometrics* 2001;57:245–52.

Moore DF, et al. Pseudo-likelihood estimates of the cumulative risk of an autosomal dominant disease from a kin-cohort study. *Genet Epidemiol* 2001;20:210–27.

Chatterjee N, et al. Association and aggregation analysis using kin-cohort designs with applications to genotype and family history data from the Washington Ashkenazi Study. *Genet Epidemiol* 2001;21:123–38.

Chatterjee N, et al. A bivariate cure-mixture approach for modeling familial association in diseases. *Biometrics* 2001;57:779–86.

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Epidemiology and Biostatistics Program, Biostatistics Branch
Descriptive Studies of Cancer

Research: We plan and conduct descriptive studies of cancer incidence and mortality in the United States and other countries, including analyses of trends in cancer rates and variations by age, sex, race, and other demographic factors. Databases on deaths are used to produce maps of cancer mortality. The maps and associated descriptive and correlational studies are utilized by researchers at the NCI and elsewhere to generate etiologic leads and test hypotheses through targeted studies into causes of cancer.

Geographic Variation in Cancer Rates

Evaluation of geographic variation in cancer rates may suggest clues to the roles of environmental or cultural influences as risk factors. Identification of regions at notably high or low risk may indicate areas where more intensive studies could be particularly fruitful. We published a new U.S. atlas of cancer mortality covering the years 1950 through 1994. The atlas is based on data files for cancer deaths of more than 9.5 million whites and 1.1 million blacks who died during the years 1970 to 1994, and for 4.8 million whites who died during the years 1950 to 1969. Corresponding estimates of person-years at risk were used to calculate observed and expected counts, age-adjusted rates, and confidence limits for more than 40 forms of cancer by race, sex, time period, and geographic area. Using special graphics software designed for a personal computer running Microsoft Windows, more than 250 maps at the county or State Economic Area level were generated for the atlas, along with summary tables and figures. The maps show that the patterns previously observed for several cancers persist, such as the broad stretches of high rates for cancers of the breast, colon, and rectum in the Northeast. Still, the regional variation has diminished somewhat as rates have risen in many areas of the South. For some tumors, the geographic clustering of areas with elevated rates has become more pronounced in the recent time period, as seen for cancers of the corpus uteri, prostate, bladder, and biliary tract. For lung cancer, there have been remarkable changes in the geographic maps, which correspond to regional/temporal variations in cigarette smoking trends by sex and race. These maps show the recent emergence of high mortality rates among white men across the South, among white women in the far western states, and among blacks in northern urban areas. The updated geographic maps of cancer mortality are helpful in formulating etiologic and other hypotheses, and in targeting high-risk populations for further epidemiologic research and cancer control efforts.

The text, maps, rates, and the data used to generate the cancer mortality atlas are accessible on the Internet at **http://www.nci.nih.gov/atlasplus/**. In addition, a component on the Internet site allows the user to customize maps based on parameters selected from a menu.

We collaborated with investigators at the International Agency for Research on Cancer in assessing the international burden of and the time trends in cancer incidence and mortality. We estimated that, worldwide, there would be over 10 million new cases, 6.2 million deaths, and 22.4 million persons living with cancer in the year 2000. Lung cancer is the main cancer in the world today, whether considered in terms of numbers of cases (1.2 million) or deaths (1.1 million), because of the high case fatality (ratio of mortality:incidence = 0.9). Breast cancer, although it is the second most common cancer overall (over 1 million new cases), ranks much lower (fifth) as a cause of death because of the relatively favorable prognosis (ratio of mortality:incidence = 0.4). Colorectal cancer is third in importance in terms of number of cases (945,000 cases, 492,000 deaths), and stomach cancer (876,000 cases, 647,000 deaths) fourth. We considered the eight most common cancers today (the above four, plus liver, prostate, cervix uteri, and esophagus) in terms of their overall frequency and geographical distribution, their recent trends in incidence and mortality, and the more important causes (risk factors) that explain these observations. A brief summary of the most promising strategy

for prevention, in the current state of knowledge, was also included. Of particular note is the presentation of temporal trends in incidence and mortality in 14 areas of the world using comparable scaling not only within each figure but also across figures for all eight cancers, allowing comparison of the magnitude of the rates and trend slopes.

Generating New Hypotheses Based on Cancer Trends and Demographic Factors

We conduct a variety of descriptive epidemiologic studies to quantify the incidence of and mortality from cancer, investigate variations in cancer rates by demographic factors, examine temporal trends and geographic patterns, and identify leads for further analytic research. Using national and international incidence and mortality data, we analyzed the descriptive epidemiology for cancers of the esophagus, stomach, liver, lung, breast, cervix, prostate, bladder and kidney, multiple myeloma, the leukemias, and cancers among children, the elderly, and women.

In contrast to mortality data, which are limited to specifying the form of cancer, records on incidence data include information on histologic type and often the subsite of origin. We used incidence data from the NCI Surveillance, Epidemiology, and End Results (SEER) program to investigate further the demographic patterns of tumor subgroups that may be of etiologic significance. Since clinical investigations have shown prognostic heterogeneity among non-Hodgkin's lymphoma (NHL), we assessed demographic patterns and trends in population-based rates of different histologic subgroups of NHL. Overall, the broad categories of small lymphocytic, follicular, diffuse, high-grade and peripheral T cell NHL emerged as distinct entities with specific age, sex, racial, temporal, and geographic variations in rates.

Using population-based data from the Shanghai Cancer Registry, we updated incidence trends for the years 1972 through 1994. Over the 23-year period, the rate for all cancers combined, excluding nonmelanoma skin cancer, decreased from 248 to 215 per 100,000 person-years among men and from 174 to 154 per 100,000 person-years among women. However, trends for individual forms of cancer varied considerably. Rates doubled for cancers of the colon and biliary tract in both sexes, and increased substantially for cancers of the brain and nervous system, kidney, pancreas, prostate, corpus uteri, female breast and ovary, and for NHL. There was little change in rates for cancers of the lung and rectum. Incidence rates declined by at least one-half for cancers of the esophagus and cervix, with notable decreases also for cancers of the stomach and liver. Although some of these trends may reflect variations in diagnostic or screening practices, changes in lifestyle and other environmental exposures are likely to play important roles.

Using Descriptive Data to Assess Consistency with Hypotheses

Cancer incidence and mortality rates may be used to assess consistency with etiologic hypotheses suggested by other studies. Ovarian cancer incidence and mortality rates have declined among U.S. women age 35 to 59 years during the period 1970 through 1995. Epidemiologic studies have shown that ovarian cancer risk decreases with increasing parity and increasing duration of oral contraceptive use. During this time period, parity declined while oral

contraceptive use increased. We compared temporal trends in observed ovarian cancer incidence rates with rates predicted by changes in parity and duration of oral contraceptive use. Predicted rates agreed well with observed rates in young women (age 30 to 49), but were substantially lower than observed rates in older women (age 50 to 64). In another analysis, we studied the relation between retinoblastoma incidence and ultraviolet (UV-B) radiation levels in the United States using weighted regression, as well as in international data after adjusting for race, economic development, and climate. Our findings suggest that environmental factors other than UV-B may be responsible for the geographic patterns of retinoblastoma.

Keywords

cancer incidence, cancer mortality, cancer trends, descriptive studies, geographic variation, hypothesis testing

Recent Publications

Devesa SS, et al. *Atlas of cancer mortality in the United States, 1950–94.* Washington, DC: U.S. Govt Print Off 1999, NIH Publ No. (NIH)99-4564.

Groves FD, et al. Cancer surveillance series: Non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. *J Natl Cancer Inst* 2000;92:1240–51.

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Epidemiology and Biostatistics Program, Biostatistics Branch
Biostatistical Consulting and Research

Research: As part of an ongoing collaboration with epidemiologists in the DCEG and elsewhere, quantitative methods are introduced into study designs and analyses to help investigators achieve more efficiently their research objectives. Issues in design and analysis frequently arise which motivate new methodologic research.

Followup of Childhood Cancer Survivors

The DCEG participated in two studies of the long-term impact of treatment for childhood cancer. In the Five Center Study, cancer registries identified children who were diagnosed with cancer between 1945 and 1974 and interviewed all adult survivors and their siblings between 1980 and 1983. This open historical cohort provided opportunities to study outcomes such as early menopause, reproductive problems and birth defects, marriage and divorce, and death from noncancer causes. Since the Five Center Study, survival has dramatically improved for children diagnosed with acute

lymphoblastic leukemia. To study long-term effects of cancer treatment among this group, we identified children participating in clinical trials sponsored by the NCI-funded Children's Cancer Group and interviewed long-term survivors and their siblings. The unusual study design allowed entry into the study at different times and required development of special computer programs for data analysis. In this large cohort, younger female patients who received 1,800 cGy cranial radiation and those who received 2,400 cGy below the diaphragm experienced early or delayed menarche. Patients treated with 2,400 cGy cranial radiation experienced educational difficulties. Other long-term effects studied in this cohort include loss of fertility, birth defects, psychosocial outcomes, and general health problems.

Carcinogenic Effects of Sunlight Exposure
Nonmelanoma skin cancer is the most common malignancy in Caucasians. Although it is generally accepted that ultraviolet radiation from the sun is the dominant risk factor, epidemiologic study of these cancers has been limited because most patients are not hospitalized. In 1977–1980, we conducted nonmelanoma skin cancer incidence surveys and interview studies at 10 U.S. locations where it was feasible to estimate the dose-response relation between ultraviolet radiation exposure and skin cancer incidence. Interview studies conducted at each location, employing complex samples of cases and controls, served as the basis for methodologic research. We have prepared review articles, one on the epidemiology of nonmelanoma skin cancer and the second on solar radiation as a carcinogen.

Some reports have suggested that non-Hodgkin's lymphoma (NHL) may be related to sunlight exposures. In a study of geographic patterns of mortality rates, however, we found that ultraviolet radiation does not have the same clear relation to NHL that is evident for melanoma and nonmelanoma skin cancer. The etiology of melanoma remains unclear, although an association with sunlight exposure has been found, particularly when it occurs intermittently at young ages and in relation to sunburns. We also studied the role of melanocytic and dysplastic nevi in the development of familial and sporadic melanoma. We are now investigating a measure of exposure to solar radiation, based on residential history, in an effort to better understand the relation between solar ultraviolet radiation and risk of melanoma.

Asian-American Breast Cancer Study
Plasma and urine samples were collected as part of a case-control study of breast cancer among Asian-American women. We plan to evaluate the association between the risk of breast cancer and hormone levels in these biologic samples. To assure the reliability and validity of hormone assays, we studied their reproducibility in several laboratories. Our findings suggest that estrogen assays performed over several months are sufficiently reliable for epidemiologic studies. An evaluation is under way of the results for androgen assays. A careful examination of laboratory procedures on biologic specimens is under way, including the effects of repeated freezing and thawing, use of borate as a preservative, and length of time in storage. An example of the fallibility of the Wald statistic was observed in these data.

Methodology

At each location in the nonmelanoma skin cancer studies, interviews with control subjects were obtained using a population-based, two-stage cluster sampling procedure known as random digit dialing. A pseudo-likelihood approach for analyzing these data was developed to allow the effects of ultraviolet radiation exposure to be evaluated while adjusting for other risk factors. The methods yield estimates of absolute risk, as well as relative risk with standard errors.

Keywords

childhood cancers, hormone assay reliability, melanoma, nonmelanoma skin cancer, ultraviolet radiation

Recent Publications

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Fears TR, et al. Reproducibility studies and interlaboratory concordance for androgen assays in female plasma. *Cancer Epidemiol Biomark Prev* 2000;9(4):403–12.

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Jemal A, et al. Cancer surveillance series: Changing patterns of cutaneous malignant melanoma mortality rates among whites in the United States. *J Natl Cancer Inst* 2000;92:811–18.

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Epidemiology and Biostatistics Program, Biostatistics Branch
Survey Methods and Biostatistical Research

Research: National health survey data are used for many purposes by the NCI, including cancer surveillance as well as descriptive and analytical epidemiology studies. Surveys provide national and subgroup estimates of the prevalence of cancer risk factors, and subjects surveyed can be followed as nationally representative cohorts for estimating associations between risk factors and cancer incidence. When data is analyzed from national surveys, attention needs to be given to the data's complex sample designs. These designs often use multiple stages of cluster sampling to obtain survey subjects and require sample weighting to make the survey data representative of the target population. Our collaborations with biomedical researchers have led us to develop statistical methods for using national health survey data in addressing issues in cancer etiology and surveillance.

Survey Methods Research
We developed methods for efficiently testing regression parameters for data from surveys with highly inefficient sample designs. These designs can have widely variable sample weights resulting in much larger standard errors than one would obtain from a simple random sample of the same number of sampled subjects. In addition, many national surveys have limited degrees of freedom for estimating standard errors, because of small numbers of first stage sampled clusters. Our methods involve augmenting the regression model with independent variables that determine the sample weights. This approach models the effect of the sample weighting without explicitly weighting the regression analysis. To address the limited degrees of freedom, we base the variance estimation on the more numerous clusters at higher stages of sampling, which results in more degrees of freedom.

We also conducted research into other statistical methods for analyzing survey data, including: (1) graphing survey data with local linear kernel density smoothing adapted for weighted data and developing jackknife methods for estimating the pointwise standard errors for mean smoothed curves, (2) generalized direct standardized estimation for linear and nonlinear regression models in which adjusted treatment effects are standardized to a distribution of the covariates and estimated design-based standard errors,

(3) Wald tests for goodness-of-fit for logistic regression models that use the F-distribution and a Monte Carlo simulated distribution, and (4) estimating variances for superpopulation parameters.

Dr. Graubard and Dr. Edward Korn of the NCI's Division of Cancer Treatment and Diagnosis have written a graduate-level textbook entitled *Analysis of Health Surveys* which provides a compilation of practical statistical techniques for use in analyzing health survey data.

Biostatistical Methodology
Correlated observations from cluster samples occur in meta-analyses where each study or experiment is a cluster, and in nonrandomized community studies where the community is the cluster. We developed statistical methods to address this correlation in meta-analyses and community studies. For a meta-analysis of animal experiments that tested for the effect of dietary fat and total caloric intake on mammary tumorigenesis, we developed sandwich estimates of variance for conditional logistic regression which were robust to model misspecification. We are developing statistical methods for analyzing changes in the prevalence of smoking between states (where the state is the cluster) that did or did not receive resources to promote smoking cessation in the nonrandomized American Stop Smoking Intervention Study (ASSIST). These methods include variance estimation for nonparametric smoothing of tobacco sales data that use the bootstrap techniques and regression methods involving random effects models with time-dependent covariates to estimate the effectiveness of ASSIST in reducing tobacco consumption and prevalence.

Epidemiologic Collaboration
We collaborate on the design and analyses of a wide range of epidemiologic studies. We are working with NCI investigators on these issues in a study to evaluate the accuracy of reporting of cancer in first and second degree relatives. The sensitivity and specificity of the reporting will be estimated using the Connecticut cancer registry, records from the Health Care Financing Administration, and personal medical records to validate reports about family members from a population random sample of individuals living in Connecticut. Analyses from the NHANES I Epidemiologic Followup Study cohort are being conducted to examine associations between physical activity and the incidence of breast cancer, the intake of aspirin and total mortality, and cancer mortality and cardiovascular mortality. Analyses of data from participants in the Breast Cancer Detection and Demonstration Project found that women in the upper 25 percent of diet quality had about a 30 percent reduction in mortality.

Keywords

complex survey data, nutrition, statistical methods, tobacco

Recent Publications

Korn EL, Graubard BI. Scatter polts with survey data. *Am Stat* 1998;52:58–69.

Korn EL, Graubard BI. Variance estimation for superpopulation parameters. *Statistica Sinica* 1998;8:1131–51.

Recent Publications (continued)

Graubard BI, Korn EL. Predictive margins with survey data. *Biometrics* 1999;55:652–59.

Graubard BI, Korn EL. Analyzing health surveys for cancer-related objectives. *J Natl Cancer Inst* 1999;91:1005–16.

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Epidemiology and Biostatistics Program, Biostatistics Branch
Biostatistical Methodology and the Epidemiology of Lung and Other Cancers

Research: Lung cancer is the leading cause of cancer mortality in the United States. After cigarette smoking, the inhalation of radioactive radon and its decay products in homes may be the most important risk factor for lung cancer. Epidemiologic studies of the carcinogenic effects of radon in mines and in homes are under way to characterize the exposure-response

relationship and to evaluate other relevant factors. These studies are being linked to cellular and molecular approaches to aid in estimating the effects of low-level exposure to indoor radon. Other areas of research include studies to evaluate cancer risk associated with the use of commercial and noncommercial pesticides, exposure to chlorination byproducts and arsenic in drinking water and occupational exposures to arsenic, as well as an assessment of the long-term health effects of augmentation mammoplasty. The focus of methodologic areas of research is on design limitations that impede indoor radon studies, including exposure uncertainties, low total exposures with small expected relative risks and means for effectively evaluating gene-environment interactions. In addition, methodologic research is addressing the impact of uncertainties in radiation dosimetry in assessing the effects of head and neck irradiation on risk for cancers of the thyroid.

Studies of Underground Miners

Previous studies of radon-exposed underground miners showed that exposure to radon decay products causes lung cancer. However, these studies were limited in size and were unable to assess risks for children or for long durations of exposure. Our study in Chinese tin miners, nearly one-third of whom were first exposed under age 13, revealed that radon was a lung carcinogen but that children did not incur any extra risk as adults due to early-life exposures. We also found an inverse exposure-rate effect that showed for equal total exposure, long duration of exposure at a low exposure rate was more harmful than a short duration exposure at a high exposure rate. Collaborating with principal investigators of all the studies of radon-exposed underground miners, including 11 cohort studies, we pooled original data on 65,000 miners and over 2,700 lung cancer deaths. The exposure-response relationship was consistently linear in cumulative exposure, suggesting that radon progeny exposure at lower levels, such as in homes, would carry some risk. The effects of radon exposure diminished with time since last exposure, but there was no consistent relationship between risk and age at first exposure. The exposure-response trend for never-smokers was three-fold greater than for smokers. Among the miners, radon progeny exposure was responsible for an estimated 40 percent of all lung cancer deaths, 70 percent of lung cancer deaths in never-smokers, and 40 percent of lung cancer deaths in smokers. Biophysical models predict that at low total exposure, as occurs in homes, the inverse exposure-rate effect should not occur, since at low total exposure a target cell is unlikely to experience more than one radiation dose, and thus cannot "know" a reduction in exposure rate. Analysis of the pooled miner data demonstrated this diminution of the inverse exposure-rate effect. Aside from lung cancer, a detailed analysis of the underground miners found no other anatomic site at an increased risk of cancer from exposure to inhaled radon.

Studies of Residential Radon Exposure

There are major uncertainties in estimates of radon effects in the general population due to differences between working in mines and living in houses. To reduce these uncertainties, case-control studies of lung cancer in women were undertaken in Shenyang, China, and in Missouri. Results were consistent with extrapolations from miners, but showed no clear-cut effect from radon. A third case-control study is ongoing in Gansu Province, China, where 40 percent of the houses have indoor radon concentrations above

levels at which the U.S. Environmental Protection Agency (EPA) recommends remedial action. We also conducted a meta-analysis of eight published studies, which included a total of 4,263 lung cancer cases, and estimated a relative risk at the EPA action level of 1.14 with 95 percent confidence interval (1.0,1.3). The combined trend in the relative risk was significantly different from zero (p=0.03). This estimate was similar to extrapolations from miner studies and to the relative risk computed directly from miners with low exposures comparable to those in homes. We concluded that the true risk from exposure to indoor radon for the general population is unlikely to be markedly greater than predicted from miners, and that the indoor radon studies provide general validity for using a miner-based model for risk estimation.

In other research, a detailed analysis was undertaken of a cohort 8,014 arsenic-exposed, copper smelter workers, with over 50 years of followup. For 428 deaths from respiratory cancer, there was a linear increase in the excess relative risk of respiratory cancer with increasing arsenic exposure. Since inhaled airborne arsenic increases systemic levels of arsenic, as measured by arsenic in urine, there is concern that inhaled arsenic may also increase risk of cancers of the skin, bladder, kidney, and liver, which have been linked to drinking arsenic-contaminated water. Among the smelter workers, there were no consistent excess risks observed for these sites or for circulatory diseases or diabetes mellitus.

Design and Analysis of Epidemiologic Studies
Methodologic studies have shown that errors in exposure assessment, missing exposure history data, and the mobility of the population can dramatically influence the power of indoor radon studies to detect an excess risk. This finding suggests that studies must be much larger than previously thought, or that data from them should be pooled to increase sample size. Also, our research showed that the type of model assumed for gene-environment interaction markedly influences the size of the study needed for evaluating this effect, while error in exposure assessment (or error in genotyping) reduces the power to detect interactions.

Keywords

arsenic, gene-environment interaction, lung cancer, radon, thyroid cancer

Recent Publications

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Wang LD, et al. Lung cancer and environmental tobacco smoke in a nonindustrial area of China. *Int J Cancer* 2000;88:139–45.

Lubin JH, et al. Respiratory cancer in a cohort of copper smelter workers: Results from over 50 years of follow-up. *Am J Epidemiol* 2000;151:554–65.

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Epidemiology and Biostatistics Program, Biostatistics Branch
Gastric and Esophageal Cancers and Their Precursors

Research: Geographic regions with high rates of a specific cancer offer unique opportunities for investigating the etiology and prevention of that cancer. In collaboration with scientists in China, we conducted studies in Linxian, China, an area with epidemic rates of squamous esophageal and adenomatous gastric cardia cancer. The research provided the opportunity

to characterize the natural history of precursor lesions of these cancers, implement therapeutic intervention trials of nutritional supplements, and conduct epidemiologic studies on associations between specific exposures and risk.

Intervention Trials and Prospective Epidemiologic Studies of Vitamin/Mineral Supplements

From 1985 to 1991, we conducted two intervention trials in which nutritional supplements or placebo were given to over 30,000 individuals in Linxian. We found that people taking supplemental β-carotene, vitamin E, and selenium had significantly reduced total mortality (9 percent), total cancer mortality (13 percent), and gastric cancer mortality (21 percent). Individuals who took a multivitamin supplement had a significantly greater (23 percent) reversion of dysplastic cancer precursor lesions to normal cytology. Preliminary results from our followup study indicate that the protective benefits of selenium, vitamin E, and β-carotene persisted for five years after stopping supplementation. The benefit from the multivitamin use has increased during this period. We are performing more detailed analyses to ascertain more precisely the time course of the effects of these supplements.

To further understand the results of the intervention trial and to expand our knowledge of other potential nutritional risk factors, we examined the relation between presupplementation serum levels of minerals and vitamin and the subsequent risk of cancer. A recently completed study of 1,100 incident cancer cases found that the higher the presupplementation selenium level, the lower the risk of esophageal and gastric cardia cancer. Individuals in the highest quartile of selenium had half the risk of those in the lowest quartile. Overall, we estimate that the cancer epidemic in Linxian could be reduced by 26 percent by eliminating the selenium deficiency in the population. Similar analyses are under way for the B vitamins, vitamin E, and β-carotene.

Prospective Epidemiologic Studies of Infectious Diseases

We are investigating the role of infectious diseases and fungal contaminants of grain on the risk of esophageal and stomach cancers. In a study of *Helicobacter pylori* infection and risk of gastric cardia and noncardia cancers, we found *H. pylori* seropositivity associated with a two-fold increased risk for both cancer types. This finding is in contrast to reports from Western countries suggesting that *H. pylori* infection protects against gastric cardia cancer. In a similar study of human papillomavirus, serotypes 16 and 73 were associated with increased rates of squamous esophageal cancer and gastric cardia cancer. No association was found between infection with Epstein-Barr virus and gastric cancer risk. Ecologic studies have reported a positive association between increased risk of esophageal cancer and consumption of corn contaminated with *Fusarium verticillioides,* a mold that produces the toxin fumonisin. We recently completed a prospective study to assess the relationship between sphingolipids, a biomarker of fumonisin exposure, and cancer incidence. No significant association was found between the biomarker and risk of squamous esophageal carcinoma.

Genetic Polymorphisms, Nutrient Deficiencies, and Cancer Risk
Numerous genetic polymorphisms may be of potential importance in the risk of esophageal and gastric cancers. We are studying whether polymorphisms of B vitamin metabolism, phase I and II detoxifying enzymes, and DNA repair enzymes are related to risk of these cancers.

Standard analysis of the results from serum nutrient studies only estimate the relative risk that low levels of nutrients have on cancer incidence. We developed methods to assess the absolute increase in risk that a nutrient deficiency conveys for an individual, and to quantify the public heath impact that would ensue from correcting the deficiency.

Keywords

antioxidants, biomarkers, esophageal cancer, *Fusarium verticillioides,* gastric cancer, *Helicobacter pylori,* human papillomavirus, multistage carcinogenesis, precancerous lesions, vitamins

Recent Publications

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Mark SD, Katki H. Influence function based variance estimation and missing data issues in case-cohort studies. *Lifetime Data Anal* 2001;7:331–44.

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Epidemiology and Biostatistics Program, Biostatistics Branch
Biostatistical Consulting and Research

Research: Several ongoing collaborations and consultations with scientists in the DCEG have led to adapting available statistical methods and new methodologic research.

Statistical Methods for Family Data Accounting for Ascertainment
We developed a model to estimate the effects of measured exposures on individual risk probabilities, given familial and unmeasured genetic effects. The two level mixed-effects model allowed us to incorporate a genetic component accounting for the different genetic correlations among family members and to adjust for ascertainment by conditioning on the number of cases in the family. Conditional maximum likelihood analysis based on this model was performed. When genetic effects are negligible, this conditional likelihood reduces to standard conditional logistic regression. We showed that the simpler conditional logistic regression typically yields biased estimates of exposure effects. Conditions under which the conditional logistic approach remains applicable were given. The sensitivity of the model with regard to violations of underlying assumptions was assessed in a simulation study, and the model was applied to family data from a linkage study on nasopharyngeal carcinoma.

Pooling Methods for Estimation of Joint Mutation Prevalences
We adapted group-testing methods to estimate the joint prevalence of two or more mutations. The estimates from pooled data can then be used in population studies to estimate the linkage disequilibrium coefficient, an important parameter in determining disease-marker associations. In case-control data, joint prevalence estimates of two or more genetic variants are used to estimate the relative risk from joint exposure. By incorporating the error rates of the tests, our method extends existing work that considers the problem of estimating the proportions of individuals with multiple traits. We have shown that pooling drastically reduces the number of assays that have to be evaluated with a modest loss of precision, especially if the variants are rare.

Mixture Models and Applications
We developed a two component mixture model to analyze serologic data on *Helicobacter pylori* infection from the Shandong Intervention Trial. The mixing proportions corresponded to the probability that a latent variable, i.e., the true unknown infection status of a person, is either 0 (uninfected) or 1 (infected). By using a logistic model for these probabilities, we were able to incorporate covariate information. The distribution of the true infection status given the antibody value and a set of covariates was calculated using the antibody distribution function. An optimal cutoff point was found by minimizing the probability of misclassification for the Shandong data. We contrasted results from the mixture model with results from standard logistic regression based on fixed cut-points. Applying the mixture model to the data indicated that a slightly lower cutoff value than the predefined cut-point can reduce misclassification rates.

The same method was used to find the optimal cutoff point for a newly developed assay for SEN viruses (SEN-V), a family of eight blood borne DNA viruses, designated A-H. The cutoff points were used to estimate the prevalence of SEN-V in a sample of street-recruited injection drug users in the San Francisco area and a sample of U.S. blood donors.

Keywords

association studies, family studies, genetics

Recent Publications

Gail MH, et al. On meta-analytic assessment of surrogate outcomes. *Biostatistics* 2000;1:231–46.

Pfeiffer R, et al. A mixture model for the distribution of IgG antibodies to *Helicobacter pylori:* Application to studying factors that affect prevalence. *J Epidemiol Biostat* 2000;5:267–75.

Pfeiffer R, et al. Inference for covariates that accounts for ascertainment and random genetic effects in family studies. *Biometrika* 2001;88:933–48.

Pfeiffer R, et al. Efficiency of DNA pooling to estimate joint allele frequencies and measure linkage disequilibrium. *Genet Epidemiol* 2002;22:94–102.

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Epidemiology and Biostatistics Program, Biostatistics Branch
Tracking the AIDS Epidemic in the United States

Research: AIDS is the leading cause of death in the United States among young adults aged 25 to 44 years, yet there are limited direct data to track trends in the incidence of HIV infection. We developed statistical methods to monitor trends in the HIV epidemic which work backwards from the numbers of persons diagnosed with AIDS on the basis of its natural history. The models have been refined and validated over time and are used to determine incidence trends according to gender, race/ethnicity, mode of HIV transmission, and age. In parallel with these efforts, we conducted detailed studies of the natural history of HIV infection in prospectively followed cohorts of HIV-positive individuals. We are now applying these disease models for surveillance and natural history to studies of cancer.

Refining the Statistical Methods

We are developing models to estimate HIV incidence from AIDS case data using the mathematical principle of deconvolution. These "back-calculations" require knowledge of the distribution of the incubation period between HIV infection and AIDS diagnosis, called the incubation distribution, obtained from natural history cohort studies. Back-calculation was initially used to assess aggregate trends in HIV incidence with respect to the single time scale of calendar time. While useful, these models did not reflect that HIV infection occurs primarily among young people. We extended the methodology to accommodate the dual time scales of calendar time and age. Using this two-dimensional back-calculation approach, we are able to estimate time trends in HIV incidence according to age.

Assessing the National Epidemic
We applied two-dimensional back-calculation methods to surveillance data from the national database of AIDS cases compiled by the CDC. We showed that fewer persons overall were infected than previously thought, but that HIV prevalence was higher than previously recognized among persons in their late twenties and thirties and among racial and ethnic minorities. These estimates were shown to be consistent with available HIV seroprevalence data and were used to derive the most recent official Public Health Service estimates of HIV prevalence in the United States. Considering trends by risk group, we found that HIV prevalence was increasing fastest among persons at risk through heterosexual contact.

Characterizing HIV Natural History
The validity of back-calculation depends on the reliability of the incubation distribution that is used. We incorporated the most recent followup data from natural history cohort studies and also used these data to identify cofactors of disease progression. In collaborative work, we showed that younger age at seroconversion is associated with slower progression to AIDS. In addition, we found that hemophiliacs progress to AIDS more slowly than homosexual men of the same age at seroconversion and that the level of HIV viremia during early chronic infection is a strong and age-independent predictor of AIDS risk. We are currently conducting an international meta-analysis of genetic effects on HIV disease progression, including the those of polymorphisms of specific chemokine receptors (CCR2 and CCR5) and their ligands (SDF-1) on risk of AIDS and death.

Identifying Incidence Trends Among the Young
AIDS case data for the period 1993 to 1995 have been difficult to interpret following the broadening of the definition of AIDS in 1993. However, using the CDC's new method to adjust for the impact of the revised case definition, we are now able to analyze AIDS data from this time period. We found that among young persons, HIV incidence in homosexual men and injection drug users was slowing by 1993, though this favorable trend was offset by the increasing heterosexual transmission of HIV, especially in young minorities.

Keywords

acquired immunodeficiency syndrome (AIDS), back-calculation, chemokine receptors, human immunodeficiency virus (HIV), statistical models

Recent Publications

Rosenberg PS, Biggar RJ. Trends in HIV incidence among young adults in the United States. *JAMA* 1998;279:1894–99.

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Rosenberg PS. HIV in the late 1990s: What we don't know may hurt us. *Am J Public Health* 2001;91:1016–17.

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Biography: *Dr. Tarone received a Ph.D. in mathematics from the University of California at Davis in 1974. He joined the NCI in 1974 and was named Chief of the Statistical Research and Applications Section in 1993. Dr. Tarone was elected a Fellow of the American Statistical Association in 1983. He received the NIH Director's Award in 1992 for sustained excellence in developing statistical methodology and providing consulting services, and the DCEG Exemplary Service Award in 1999 for sustained research accomplishments and outstanding service to the DCEG and the NCI.*

Epidemiology and Biostatistics Program, Biostatistics Branch
Statistical Methods in Biomedical Research

Research: The mission of the Statistical Research and Applications Section is to develop new or improved statistical methods for solving problems in biomedical research. Our goal is to accelerate the use of quantitative methodology in all aspects of cancer research through innovative statistical research and active collaboration with scientists in a wide variety of investigations.

Statistical Methods
Methodologic research is aimed at solving problems that arise in diverse research settings. We developed statistical methods for conducting epidemiologic analyses of complex surveys, such as methods for estimating standardized means and rates from regression models. We also developed formulas for determining the sample size needed to meet a specified power requirement in stratified analyses of vaccine trials, and developed improved methods for computing confidence intervals for the kappa measure of agreement. In addition, we developed novel nonparametric methods for analyzing secular trends in population disease rates, with the goal of detecting changes in the trends of risk in succeeding generations (i.e., changes in birth cohort trends in age-period-cohort models). We assisted in devising mapping methods to show changes in the magnitude of cancer rates over time in cancer atlases.

In the laboratory setting, we developed methods for analyzing mutational spectra in specified genes, such as the *p53* tumor suppressor gene. Examining *p53* mutations in cancer cells from different patients, we formulated procedures to identify characteristic mutational hot spots for specific cancers, different populations, and particular environmental exposures. We also derived methods to examine other specific mutational patterns, such as determining if mutations occur more often than expected at adjacent bases in a specified gene. Computer programs have been developed to implement the derived methods.

Epidemiologic Collaboration
Statistical consultation and collaboration are provided in many epidemiologic studies. Among the ones we support in depth are a large U.S. case-control study of brain cancer, which has an emphasis on occupational exposures; the Agricultural Health Study, which is a prospective investigation of farmers and their families; a collaborative case-control study of childhood leukemia in relation to magnetic fields; the ALTS/LSIL Triage Study, which is a randomized trial of alternative treatment protocols for women with abnormal PAP smears; and a record-linkage study of mortality in Navy veterans exposed to microwave radar. We provide statistical direction or assistance for numerous other investigations, including a prospective study of radiologic technologists, a followup study of survivors of retinoblastoma, studies of chromosome aberrations in cohorts of people exposed occupationally or medically to high doses of radiation, studies of immunological markers in people infected with human T lymphotrophic virus type 1, and studies of serological tests for human papillomavirus infection.

Laboratory Collaborations
We consult and collaborate on a wide range of laboratory research. Several collaborations involve studies of the capacity of cultured cells from people with cancer-prone or neurodegenerative diseases, including xeroderma pigmentosum, retinoblastoma, and Alzheimer's disease, to repair DNA damage induced by radiation or chemical exposure. Some studies of cultured cells involve indirect assays that measure the ability of cells to form colonies or the susceptibility of cells to form mutations or chromosome aberrations. Direct assays measure the ability of cells to remove particular types of DNA damage from their own DNA, or from damaged DNA introduced into cells by transfection. Other laboratory collaborations include studies of carcinogenic processes in animals and humans, such as using knock-out mice to investigate the role of different genes in the *p53* pathway in UV-induced apoptosis; studies of human mutational spectra to investigate the mechanism of hypermutation in immunoglobulin variable genes; a study of the distribution of mutations in the *p53* gene in second cancers after treatment for Hodgkin's disease; and studies to examine DNA-repair capacity in melanoma patients.

Keywords

age-period-cohort models, DNA repair, mutational spectra, statistical methods, study design

Recent Publications

Tarone RE, et al. Age-period-cohort analyses of breast-, ovarian-, endometrial- and cervical-cancer mortality rates for Caucasian women in the USA. *J Epidemiol Biostat* 2000;5:221–31.

Tarone RE, et al. Nonparametric evaluation of birth cohort trends in disease rates. *J Epidemiol Biostat* 2000;5:177–91.

Grauman DJ, et al. Alternate ranging methods for cancer mortality maps. *J Natl Cancer Inst* 2000;92:534–43.

Tarone RE, et al. Implications of stage-specific survival rates in assessing recent declines in prostate cancer mortality rates. *Epidemiology* 2000;11:167–70.

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Epidemiology and Biostatistics Program, Biostatistics Branch
Statistical Methods in Epidemiologic Studies

Research: Our research agenda is driven by study design and interpretation issues facing scientists in the DCEG and elsewhere who are trying to understand the causes of cancer and means for its prevention. In addition, much of our independent and collaborative work involves molecular epidemiology, which has become a major research thrust within the DCEG. In both substantive and methodological work, research questions being addressed include:

- What is the best study design to apply to a particular class of scientific issues?
- How can elapsed time, cost, and number of subjects in a study be reduced?
- How serious are biases affecting epidemiologic studies?
- What should we try to estimate from studies?

Design of Epidemiologic Studies

- **Case-control studies.** Based on a longstanding interest in the principles and practice of control selection for case-control studies, we are addressing new challenges posed by molecular epidemiology. With DCEG colleagues, we recently estimated the bias from population stratification in evaluating the effect on cancer of a common polymorphism from cohort and case-control studies with unrelated controls. We found that the bias is likely to be small in ethnically mixed populations of non-Hispanic Europeans in the United States. Another research interest involves two-phase designs in which only a fraction of individuals in a study are selected for an expensive, onerous, or time-consuming aspect of exposure assessment. Properly planned and implemented, these designs are very efficient and yield unbiased estimates of the target effects. Other interests include assessing the impact of selection bias, measuring and reporting error and confounding in epidemiologic studies, studying gene-environment interactions, and studying pathologic changes.
- **Cohort studies.** Cohort studies allow the evaluation of many outcomes, thereby compensating for their initial high costs. Exposure data collected prospectively avoids problems in retrospective studies from differential

reporting and disease influences on biochemical measurements. The cost associated with cohort studies can be reduced by efficient sampling designs, such as nested case-control and case-cohort studies, and the use of special sampling schemes. We continue to work on the theoretical and practical aspects of these approaches.

- **Kin-cohort design.** Together with colleagues in the DCEG and the National Human Genome Research Institute, we developed the kin-cohort design to estimate penetrance (risk of developing disease) of a rare mutation from a study of volunteers. This design is useful when a quick and relatively cheap estimate of penetrance is desired for individuals in families with fewer affected individuals than those normally used for linkage studies. A case series can be used instead of volunteers. Extensions of this approach allow estimating survival after diagnosis in carriers and noncarriers.

Collaboration in Epidemiologic Studies

Considerable time is spent in collaborating on a variety of DCEG studies, including decisions about whether a study should be initiated, its basic design, selection of study participants, and assessment of exposure and disease. Other important collaborative matters involve quality control and other field work issues, the analytic plan and specific analyses, interpretation of results, and preparation of publications.

We are currently involved in collaborative studies of occupational (benzene and diesel) and viral (human papillomavirus) exposures, rare mutations, and metabolizing polymorphisms. Other collaborative work includes studies of leukemia and cancers of the cervix, lung, ovary, and breast. These studies provide a practical perspective to methodologic research, since they face some of the issues of case and control selection, efficient design, interpretation of joint effects of genetic and environmental factors, and exposure measurement error.

Keywords

case-control studies, epidemiologic methods, gene-environment interaction, genetic epidemiology, molecular epidemiology, statistical methods, study design

Recent Publications

Wacholder S, et al. The kin-cohort study for estimating penetrance. *Am J Epidemiol* 1998;148:623–30.

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Wacholder S, et al. Population stratification in epidemiologic studies of common genetic variants and cancer: Quantification of bias. *J Natl Cancer Inst* 2000;92:1151–58.

Modan B, et al. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a *BRCA1* or *BRCA2* mutation. *New Engl J Med* 2001;345:235–40.

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The Environmental Epidemiology Branch conducts research to identify groups at high risk of cancer, clarify the natural history of various cancers, understand the interactive effects of genetic and environmental factors on cancer risk, and elucidate biologic mechanisms of carcinogenesis. To identify risk factors for hormonally related tumors, we assess reproductive and family history, endogenous hormones, exogenous hormones (oral contraceptives and menopausal hormones), hormonal correlates of risk, and conditions related to marked hormonal perturbations, such as infertility and endometriosis. Another major area of research is focusing on the role of the human papillomaviruses in the etiology of genital tumors. Emphasis is also being given to defining risk factors for several rare malignancies, including cancers of the nasopharynx and biliary tract. Investigations are often preceded by methodologic studies to determine the best approaches to specific study-related issues.

Breast Cancer

We are investigating the proportion of breast cancer attributable to specific risk factors. Studies are also assessing the extent to which geographic differences in breast cancer rates are influenced by established and speculative risk factors. Among the environmental exposures being evaluated are organochlorine products, which are known endocrine disruptors. Several studies are focusing on this chemical class in uniquely exposed populations, including one in India where the use of DDT is still prevalent. Since physical activity has been shown to influence endogenous hormone levels, we are attempting to improve methods for measuring this variable in studies exploring its effects on breast cancer risk. The impact of silicone breast implants on breast cancer risk is also of interest, especially since they can interfere with mammographic visualization of breast lesions.

Several major research efforts are focusing on assessing gene-environment interactions in two large case-control studies, one in two areas of Poland and the other in three U.S. centers. Biologic samples from these studies (buccal washes, blood samples) will be used to measure common polymorphisms in a variety of genes. Of interest will be genes involved in carcinogen and hormone metabolism as well as those involved with DNA repair mechanisms. It is hoped that by subdividing study subjects according to their ability to metabolize agents, it may be possible to clarify the role of a number of speculative environmental risk factors for breast cancer, including exogenous hormone use, alcohol consumption, and cigarette smoking. The Poland study also involves collection of urine samples (which will be used to measure environmental

chemicals) and breast tissue (for which microarray techniques will be used to assess a variety of biologic markers that may provide insights into mechanisms of carcinogenesis).

The effects of endogenous hormones have been investigated by studying cancer risks associated with a number of conditions related to hormonal perturbations, such as endometriosis and other gynecologic disorders, and by directly measuring hormone levels in analytic studies. Following a number of methodologic studies, several investigations are examining the relationship of a variety of hormones, including estrogen and androgen metabolites, to breast cancer risk. In addition, studies are investigating growth factors that influence hormone levels, such as insulin growth factors. Data from several of these studies are also being used to better understand how cancer risk factors relate to endogenous hormone levels.

Other Hormonally Related Tumors: Endometrium, Ovary, and Prostate
A number of studies are attempting to identify risk factors for other malignancies affected by hormonal mechanisms. For endometrial and ovarian cancers, we are focusing on risk factors hypothesized to operate through hormonal mechanisms, such as physical activity and organochlorines, and on those for specific pathologic subgroups. We are also assessing the effects of ovulation-stimulating drugs on ovarian and other cancers. For prostate cancer, genetic and environmental determinants are being assessed in a population with rising rates. The role of endogenous hormones in prostate cancer risk is also being examined, and includes efforts to relate serologic hormone measurements with levels in prostate tissue. In addition, dietary influences on endogenous hormone levels are being evaluated using data from cross-sectional studies and clinical trials.

Human Papillomaviruses
A major objective of our interdisciplinary research activities is to clarify how human papillomaviruses (HPV) and host and environmental factors interrelate to influence the progression of cervical lesions to cancer. The major focus of this research are two large cohort studies, one in a low-risk setting (Portland, Oregon) and the other in a high-risk region (Guanacaste, Costa Rica). These studies provide the framework for gaining a better understanding of the natural history of cervical lesions with respect to HPV, especially the influence of immunologic and hormonal factors. Clarifying the pathogenesis of this disease is being approached on four levels: (1) the molecular pathogenesis of progression to carcinoma in situ and on to invasive cancer, (2) microscopic pathogenesis using new computer-assisted cytologic techniques, (3) visual pathogenesis using new optical-galvanic examination techniques, and (4) immunologic assessment using serology and cell-mediated immune assays. The influence of HPV on cancer risk at other sites is also of research interest, especially for rare female reproductive tumors such as cancers of the vulva and vagina, as well as cancers of the penis, esophagus, and oral cavity.

Rare Malignancies
Case-control studies are being conducted to advance our knowledge about the etiology of rare, poorly understood cancers. The studies are often conducted in foreign settings, where the cancers are more common or there are unusual relevant risk factors. Recent studies include investigations of nasopharyngeal cancer in Taiwan and biliary tract cancer in China. Attempts are made to clarify the interplay of genetic and environmental influences through analyses of risk factor information and genetic polymorphisms, endogenous hormones, specific metabolites, and tumor markers.

Methodologic Studies
Many of our studies require methodologic work to determine the appropriate epidemiologic approach or biochemical adjuncts for large-scale efforts. This work includes attempts to reduce errors in exposure and disease classification, as well as to improve statistical approaches to study designs. In some research areas, such as with HPV, methods work evolved into limited diagnostic research. In the area of endogenous hormones, measurement assays have been assessed to determine their reliability and validity for use in analytic epidemiologic studies.

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Epidemiology and Biostatistics Program
Environmental Epidemiology Branch
Cancers of the Breast and Female Reproductive System

Research: Despite extensive epidemiologic studies, the causes of a large proportion of cancers of the female breast and reproductive system are unknown. A number of etiologic leads have recently emerged, which we are pursuing in a variety of studies. Many of these efforts include biochemical components that will contribute to an increased understanding of the biologic mechanisms underlying observed relationships with risk factors.

Breast Cancer

In a major approach to understand the role of environmental factors on risk of breast cancer, we are examining their effects among subgroups defined by genetic markers. These markers include breast cancer susceptibility genes that are known to affect hormone or carcinogen metabolism. Two collaborative studies are under way, one at three U.S. centers and the other in Poland. Each study has a sample size large enough to achieve statistical power for evaluating gene-environment interactions. The Polish study is also assessing the relation between breast cancer risk and occupational exposures, as a large proportion of Polish women work outside their homes, often in industrialized settings. In addition, the study is examining risk associated with physical activity, as measured by accelerometers worn by the women during recreational, occupational, and household activities.

Bone density is recognized as a predictor of breast cancer risk, but the mechanism underlying this relationship is unknown. We are collaborating on a followup study of women previously screened for bone density to evaluate their risk of breast and other hormonally related cancers. Sera collected earlier from these women, together with DNA that will be obtained from buccal cell swabs, offer the opportunity for assessing interrelationships among bone density, endogenous hormones, and genetic polymorphisms.

Gynecologic Cancers
We are pursuing research opportunities for expanding our knowledge about etiologic factors for endometrial and ovarian cancers. Since a large number of women are treated for these malignancies within the Gynecologic Oncology Group, we are developing mechanisms for integrating epidemiologic components into several ongoing clinical trials. The identification of molecular markers for early-stage ovarian cancer and endometrial cancer of varying histologies is of particular interest.

Exposures Unique to Women
Clues about hormonal mechanisms of carcinogenesis may be derived from studies of cancer risk in populations with known hormonal alterations. A collaborative record-linkage study in Denmark and Sweden found that patients with endometriosis had significant excesses of non-Hodgkin's lymphoma and cancers of the ovary and breast. We are pursuing additional research to gain further insights into the pathology of the ovarian tumors. Plans are under way to study several other conditions linked to hormonal alterations, including some that are androgen related.

To address the long-term effects of silicone breast implants, we conducted a retrospective cohort study among women with augmentation mammoplasties, using a comparison group of women with other types of plastic surgery. Despite clinical evidence that implants interfere with the visualization of breast lesions, we found no evidence that implants were associated with altered breast cancer risk. Patients with breast implants, however, presented with somewhat later stages of breast cancer at diagnosis than other patients. Data from the study are also being analyzed to evaluate the incidence of other cancers and connective tissue disorders, as well as cause-specific mortality, among implant patients. In a study conducted in collaboration with Swedish investigators, we sought to determine reasons for a reduced risk of breast cancer observed among women who had breast reduction operations. Our study found that the reduction in risk appeared to be inversely related to the amount of breast tissue removed.

Although reports indicate that ovulation-stimulating drugs may predispose to ovarian cancer, the studies are limited by small numbers and imprecise information on causes of infertility and medication use. To clarify this relationship, an ongoing large retrospective cohort study is reviewing detailed medical data on women who were evaluated and treated for infertility as long ago as the 1960s. Questionnaires are being administered to collect additional data on subsequent health events and other risk factors. In a separate study, we are evaluating cancer risk among children conceived following their mother's use of ovulation-stimulating drugs.

Keywords

breast cancer, breast implants, endometrial cancer, genetic polymorphisms, genetics, genital cancers, gynecological conditions, hormones, ovulation-stimulating drugs

Recent Publications

Lacey JV Jr, et al. Oral contraceptives as risk factors for cervical adenocarcinomas and squamous cell carcinomas. *Cancer Epidemiol Biomark Prev* 1999;8:1079–87.

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Epidemiology and Biostatistics Program
Environmental Epidemiology Branch

Molecular Epidemiology Studies of Hormonal and Environmental Causes of Cancer

Research: The goal of our research is to identify factors that influence susceptibility to known or suspected hormonal and environmental carcinogens.

Molecular Epidemiology Studies of Breast, Ovarian, and Endometrial Cancers

Genetic variation in synthesizing and metabolizing sex steroids may influence the endogenous levels of these hormones and affect susceptibility to hormone-related cancers. The influence of genetic polymorphisms on endogenous levels of sex steroids in serum is being investigated using data from two cross-sectional studies of premenopausal women. Specifically, levels of estradiol, estrone, androstenedione, testosterone, and DHEA are being examined in relation to polymorphisms in the *CYP11a, CYP19, CYP17, CYP1B1,* and *COMT* genes.

In collaboration with the University of Wisconsin, Harvard School of Public Health, and Dartmouth-Hitchcock Medical Center, we have collected buccal cell DNA samples from about 4,000 breast cancer cases and a similar number of controls that completed a telephone interview in a population-based case-control study in three states (Wisconsin, Massachusetts, and New Hampshire). This study is examining the role of genetic polymorphisms in sporadic breast cancer susceptibility. In another effort, we are conducting a large population-based case-control study of breast, ovarian, and endometrial cancer in Poland (Institute of Oncology in Warsaw and the Nofer Institute of Occupational Medicine in Lodz). This study involves the collection of detailed exposure information in a personal interview (risk factor questionnaire, physical activity monitors, and anthropometric measurements), and the collection of biological specimens (cryopreserved whole blood, plasma, buffy coat, red blood cells, serum, blood clots, buccal cells, 12-hour overnight urine, and paraffin-embedded and snap-frozen tissue samples). The focus of the study will be to identify environmental and genetic risk factors for breast,

ovarian, and endometrial cancer using information from personal interviews as well as biomarkers of exposure, early biologic effect, and susceptibility. In addition, tumors and unaffected breast tissue samples from cases will be characterized using molecular markers at the DNA, RNA, and protein level.

Molecular Epidemiology Study of Bladder Cancer
In collaboration with the Municipal Institute of Medical Research (IMIM) in Barcelona, Spain, we conducted a hospital-based study of 1,204 bladder cancer cases and 1,240 controls. This study combines state-of-the-art exposure assessment using a computer-assisted interview and the collection of biological specimens. The main focus of the study is to evaluate genetic susceptibility factors for bladder cancer risk and their interaction with environmental and occupational exposures.

Evaluation of Gene-Environment Interactions
Under general conditions, both differential and nondifferential misclassifications of exposure tend to bias multiplicative interaction effects towards the null value. As a result, sample size requirements to evaluate interactions increase in the presence of misclassification. We conducted a methodological study to evaluate sample size needs to study gene-environment interactions and the impact of exposure and genotype misclassification. We found that even small errors in measuring environmental or genetic factors could have a strong impact on sample size requirements. High quality exposure and genotype assessments are therefore crucial in obtaining unbiased estimates of interaction effects and in assessing interactions with a manageable study size. We also developed statistical software to perform power and sample size calculations for studies of gene-environment interactions, as well as to evaluate the impact of misclassification in a particular study.

Methodologic Considerations for the Collection of Buccal Cell Samples
Buccal cells are a promising source of DNA in large epidemiologic studies, since they can be obtained using self-administered, noninvasive, and relatively inexpensive techniques. We conducted a study to assess DNA yields and quality collected by two protocols (cytobrush and mouthwash) designed to obtain buccal cells by mail. A single mouthwash sample was found to provide substantially larger amounts of high molecular weight DNA than two cytobrush samples. Given the relatively small DNA yields recovered from buccal samples (median of about 20 ug/mouthwash sample and 1 ug/two cytobrush samples), we are evaluating variations in the collection protocols that might increase yield. In addition, we are exploring whole genome amplification techniques to increase the amount of DNA available for genetic assays. Finally, we are also exploring the use of saliva recovered in mouthwash samples to estimate levels of internal dose for chemicals of interest.

Keywords

bladder cancer, breast cancer, DNA collection, endometrial cancer, gene-environment interaction, genetic susceptibility, molecular epidemiology, ovarian cancer

Recent Publications

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Epidemiology and Biostatistics Program
Environmental Epidemiology Branch

Host and Exogenous Factors in the Pathogenesis of DNA Virus-Related Tumors

Research: We are conducting large-scale studies to investigate exogenous and host factors involved in the pathogenesis of DNA virus-related tumors. Two groups of tumors are under investigation: female gynecological cancers linked to HPV and nasopharyngeal cancer linked to EBV. Nonviral factors involved in the pathogenesis of HPV- and EBV-related cancers are also being examined, since infection alone is rarely sufficient for the development of cancer.

Cervical Cancer
Our previous studies suggested that in addition to HPV infection, important determinants of cervical disease progression may include host immune response to HPV; exogenous and behavioral factors, such as parity and oral contraceptive use; and infection with sexually transmitted agents other than HPV. To further define the factors related to the progression of low-grade squamous intraepithelial lesions (LSIL), large cohort studies are being conducted in Costa Rica and in the United States. The Costa Rica cohort is a population-based study of 10,000 women, which is in its seventh and final year of followup. As part of this study, women with evidence of HPV infection, with or without LSIL, and a sample of the remaining cohort are being followed every six months to one year with repeat cytological screening, biological specimen collection, and assessment of risk factor profiles. Specific factors being evaluated include mucosal immune response, HLA alleles, chromosomal alterations, contraceptive and reproductive practices, diet, cigarette smoking, and infection with sexually transmitted agents other than HPV.

The U.S.-based study, in which women are being seen at four clinical centers, is aimed at investigating specific immune responses to viral infection and risk of subsequent persistence and/or progression of lesions. In this study, close to 1,000 women diagnosed with LSIL are being followed with repeat Pap smears, specimen collection, and risk factor assessment every six months for

a period of two years. Biological samples are being tested for cellular and humoral responses to HPV to assess various immunological markers that may correlate with disease status over time.

We have recently begun to determine the efficacy of two prophylactic HPV vaccines. Phase I and II safety and immunogenicity trials were conducted in the United States, and a large efficacy phase III trial is now under way in Costa Rica.

Nasopharyngeal Cancer

Nasopharyngeal cancer has a very distinct geographic and ethnic distribution, occurring at high rates among ethnic Chinese from southeastern China and at much lower rates among Caucasians. While infection with EBV is believed to be necessary for development of the cancer, both genetic and exogenous factors are also thought to be important. To investigate the role of genetic, dietary, occupational, and behavioral factors in the etiology of nasopharyngeal cancer, a case-control study was conducted in Taiwan. Analyses thus far suggest an association between risk and specific variants of the enzyme CYP2E1, HLA type, smoking, and dietary micronutrients. Other dietary and occupational factors are being evaluated, including consumption of nitrates, nitrites, and nitrosamines; and occupational exposure to formaldehyde, solvents, wood dusts, and nitrosamines. A large-scale linkage study is under way in Taiwan to assess systematically the genetic and environmental determinants of nasopharyngeal cancer.

Keywords

cervical cancer, DNA tumor viruses, genetic susceptibility, human papillomavirus (HIV), immune response, nasopharyngeal cancer, vaccines

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Epidemiology and Biostatistics Program
Environmental Epidemiology Branch
Hormone-Related Cancers

Research: We are carrying out population-based interdisciplinary studies to investigate the determinants of hormone-related cancers, particularly of the prostate and biliary tract. Risk of these cancers is being evaluated in relation to endogenous and exogenous hormones, lifestyle factors, and genetic susceptibility and their interactive effects. Methodologic studies are examining hormone levels in serum and tissues, polymorphisms in targeted genes and cellular proliferation, and lifestyle factors in an effort to increase our understanding of hormonal carcinogenesis. We are also assessing these variables in relation to differences in cancer rates among racial groups.

Prostate Cancer
Little is known about the etiology of prostate cancer, although it is the most commonly diagnosed cancer among men in the United States. Despite a similar prevalence of latent prostate tumors around the world, incidence rates for clinical prostate cancer in Western men are 30 to 50 times higher than those for Asian men. This finding and data from migrant studies suggest a role for environmental factors in promoting late-stage disease. To improve our understanding of prostate cancer etiology and to identify preventive measures, we conducted a population-based case-control study of prostate cancer in Shanghai, China, where the reported incidence for clinical prostate cancer is the lowest in the world, but is rising rapidly.

Results thus far have provided important etiologic leads concerning the substantial racial differences in prostate cancer risk. Analyses of the interview data suggest that increased risk is associated with higher levels of education, a larger waist or smaller hips, a higher waist-to-hip ratio, and a higher intake of total calories, red meat, and animal fat and protein, while a reduced risk is associated with higher consumption of allium vegetables, peppers, and mushrooms. Risk was not associated with smoking, alcohol use, tea drinking,

family history of prostate cancer, sexual behavior, physical activity, body mass index, weight history, or obesity in adolescence. Among the factors examined, a high waist-to-hip ratio (an indicator of central obesity) is associated with the strongest risk. Assuming that central obesity is a causal factor, a waist-to-hip ratio higher than the first quartile (>0.87) can explain 43 percent (95 percent CI 22 percent to 64 percent) of the cases in Shanghai, and 23 percent of the 50- to 60-fold difference in incidence rates between the United States and China. Special efforts are being made to evaluate further the roles of energy, fat type, and individual fatty acids. In addition, we are assessing the potential protective effect of tea polyphenols and isoflavones, chemicals with weak antiestrogenic activity found in soy foods.

Most of the risk factors for prostate cancer, such as central obesity, a Western diet, and physical activity, may have a hormonal basis. We are investigating this hypothesis in biochemical and molecular studies that may define more clearly relevant exposures and biologic mechanisms. Results thus far show that higher serum levels of insulin and insulin-like growth factor I (IGF-I) and lower serum levels of IGF binding proteins (IGFBP-1 and IGFBP-3) are associated with a significantly increased risk. Analyses are correlating serum levels of hormones, IGFs, insulin, and leptin with anthropometric factors and physical activity, which may shed light on hormonal and other mechanisms of prostate carcinogenesis.

Environmental factors alone are unlikely to explain all of the racial difference in prostate cancer risk. We are therefore assessing the role of several genetic markers involved in the regulation of androgens, including the androgen receptor *(AR)* and the steroid 5 alpha-reductase type 2 *(SRD5A2)* genes. An increased risk was associated with a shorter CAG repeat length in the *AR* gene, while no association was found with polymorphic markers in the *SRD5A2* gene, including A49T, V89L, R227Q, and TA repeats. We are planning to evaluate other genes involved in the androgen metabolic pathways, including *CYP17, CYP19, CYP3A4,* HSD3, HSD3, and HSD17. We are also investigating whether somatic mutations of the *SRD5A2* gene are associated with tumor aggressiveness and prostate cancer prognosis.

Analyses will be initiated to evaluate whether 5 alpha-reductase activity, as measured indirectly by serum levels of androstenediol glucuronide and polymorphisms of the *SRD5A2* gene, is determined largely by genetics or modulated through lifestyle factors. In addition, circulating hormone levels will be correlated with genetic polymorphisms and lifestyle factors to evaluate how phenotypic and genotypic factors interact to modulate risk.

It is unclear whether serum levels of hormones reflect intraprostatic androgenicity. To address this issue, we are carrying out a methodologic study to assess the correlation among hormones measured directly in the prostate, serum hormone levels, and polymorphisms of hormone-related genes. The study is taking into account factors such as age, smoking, and body size that might alter serum-tissue correlations. To better estimate total intraprostatic androgenicity, prostate tissue will be measured directly for levels of androgen receptor and its associated protein, such as ARA 75 and 55. Because this study is investigating androgenicity in prostate tissue directly, it will help guide future epidemiologic studies of prostate cancer.

We are also conducting a prostate cancer survey in Accra, Ghana, to assess the burden of prostate cancer among West African men who share genetic ancestry but have vastly different lifestyle factors compared to African Americans, a group that has one of the highest prostate cancer risks in the world. Through medical records review, one study component aims to enumerate and characterize clinical prostate cancer cases to estimate clinical prostate cancer incidence in Accra. In the second component of the study, 1,000 healthy men aged 50 to 74 randomly selected from the population will undergo interview, blood collection, and prostate cancer screening with digital rectal examination and prostatic specific antigen blood test in order to estimate the extent of prostate cancer burden in this unscreened population.

Biliary Tract Cancers

Cancers of the biliary tract include tumors arising from the gallbladder, extrahepatic bile duct, and ampulla of Vater. These malignancies are relatively uncommon and little is known about their etiology. Previous analytic studies have been limited by small numbers, proxy interviews, and inability to evaluate risk separately by anatomic subsite.

During the last 25 years, biliary tract cancer incidence has increased more rapidly than any other malignancy in Shanghai, suggesting a change in prevalence of risk factors. To identify these factors, we are conducting a large-scale, population-based case-control study to evaluate risks associated with gallstones, bacterial infections of the biliary tract, dietary factors, obesity, use of tobacco and alcohol, reproductive factors, and exogenous hormones. With 900 cancer cases and 1,000 population controls, the study should provide sufficient statistical power to investigate separately the etiology of each subsite.

Since gallstone disease tends to cluster in families, we will attempt to evaluate whether genetic predisposition plays a role in biliary tract cancer. Analyses will examine family history, polymorphisms of susceptibility genes, and genetic interactions with lifestyle factors.

Keywords

5-alpha reductase, androgen receptor, androgens, biliary tract cancers, diet, genetic polymorphism, hormones, insulin, insulin-like growth factors, methodologic studies, obesity, prostate cancer, racial/ethnic variation

Recent Publications

Hsing AW, et al. Polymorphic CAG and GGN repeat lengths in the androgen receptor gene and prostate cancer risk: A population-based case-control study in China. *Cancer Res* 2000;60:5111–16.

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Hsing AW. Hormones and prostate cancer: What's next? *Epidemiol Rev* 2001;23:42–58.

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Epidemiology and Biostatistics Program
Environmental Epidemiology Branch
Cancers of the Breast and Female Reproductive System

Research: Reproductive hormones play an undisputed but incompletely understood role in cancers of the breast, endometrium, ovary, and cervix. Traditional risk factors, such as parity, oral contraceptives, and menopausal hormone replacement therapy (HRT), represent crucial determinants of cancer risk. As methodologies to measure hormones evolve and improve, epidemiologic studies seek to integrate multidisciplinary approaches to better understand the role of hormones in reproductive cancers.

Ovarian Cancer and Endometrial Cancer

Substantial evidence indicates that hormone replacement therapy (HRT) increases the risks of breast cancer and endometrial cancer, but those increased risks vary according to whether HRT includes unopposed estrogen or estrogen combined with progestin. We consider identification of cancer risk associated with HRT a priority and continue to investigate the complex relationships between HRT and cancer risk. We are pursuing the unresolved associations between HRT and ovarian cancer in the 60,000-woman Breast Cancer Detection Demonstration Project (BCDDP) Follow-Up Study, a prospective cohort study that includes former participants in a nationwide breast cancer screening program from the 1970s. Follow-up data from 1980 through 1998 are now available. Although other studies suggested that HRT was not associated with ovarian cancer, initial data from the BCDDP Follow-Up Study suggest that long-term use of unopposed estrogen significantly increases risk. In contrast, combination estrogen-progestin regimens appear to be unrelated to ovarian cancer risk. Analyses of these data continue and will be expanded to include risks of endometrial cancer associated with HRT, as

well as risks of ovarian cancer and endometrial cancer associated with anthropometry, reproductive factors, and other medical conditions.

Bone Mineral Density

One challenge facing investigations of hormonal risk factors for cancers of the breast and female reproductive system is the numerous sources of endogenous and exogenous hormones. Exogenous risk factor data obtained by questionnaire or interview, endogenous hormone data measured in biologic specimens, and genetic predictors of hormone metabolism each represent components of a woman's hormonal milieu; to date, no single measure of total estrogen exposure has been identified. Bone mineral density, however, may serve as a biologic marker of lifetime estrogen exposure. Previous studies suggest that a history of fractures—which presumably represents low bone mineral density, and therefore is a marker for lower estrogen levels—reduces the risks of breast cancer and endometrial cancer. We have embarked on a collaborative study to assess cancer risk associated with measured bone mineral density. This large retrospective cohort study offers the opportunity to integrate questionnaire-based data, measured bone mineral density, stored sera collected 10 years ago, and genetic data from buccal cell specimens. Our multidisciplinary approach will focus on breast cancer, endometrial cancer, and colorectal cancer, but opportunities to investigate other cancers, such as lung cancer, may also arise.

Hormonal Cofactors in Cervical Carcinoma

Infection with human papillomaviruses (HPV) is a necessary, but not sufficient, cause of all cervical carcinomas, and the Environmental Epidemiology Branch conducts numerous studies to explore potential cofactors for cervical carcinogenesis. Although squamous cell carcinomas represent almost 85 percent of all cervical carcinomas, the relative and absolute incidence of the rare cervical adenocarcinomas has recently risen. Hormonal factors are hypothesized to be key cofactors for the development of cervical adenocarcinomas, and a recent multicenter case-control study assessed cofactors for cervical adenocarcinomas. To identify cofactors that may operate differently for the two histologic types, we included cervical adenocarcinoma cases, squamous cell carcinoma cases, and healthy controls for comparison. Utilizing an accurate DNA-based HPV detection method, we observed positive associations between oral contraceptives and adenocarcinoma in situ but no associations with invasive adenocarcinomas or squamous cell tumors. These data suggest that residual confounding by HPV infection or Pap smear screening might account for the consistently reported associations with invasive adenocarcinomas and squamous cell carcinomas, but oral contraceptives may indeed increase risk for adenocarcinoma in situ.

In other analyses, we noted that estrogen-only HRT was suggestively associated with adenocarcinomas but not squamous cell carcinomas. Another analysis revealed that smoking, which has been proposed as a causal risk factor for cervical carcinoma, also apparently operates differently for squamous cell carcinomas and adenocarcinomas. After controlling for confounding by HPV, smoking was positively associated with squamous cell tumors but significantly inversely associated with adenocarcinomas. These three analyses clearly suggest that cofactors for adenocarcinoma and squamous cell carcinoma differ. The associations between adenocarcinoma,

HRT, and smoking support the hypothesis that cofactors for cervical adenocarcinomas resemble risk factors for endometrial adenocarcinoma, which points to similar hormonal mechanisms for these two cancers. Additional analyses of other risk factors, such as sexual behaviors and anthropometry, are under way to better understand the potential similarities between endometrial cancer and cervical adenocarcinoma. These results also raise questions about the potential mechanisms for cofactors in cervical cancer. For example, if smoking is a true cofactor, how might it increase the risk of squamous cell carcinoma yet decrease the risk of adenocarcinoma? Other opportunities to investigate hormonal influences on cervical cancer include a study of endogenous hormones as cofactors in the natural history of HPV infection and cervical carcinoma in young women.

Keywords

bone mineral density, breast cancer, cervical adenocarcinoma, endometrial cancer, estrogens, hormone replacement therapy, hormones, ovarian cancer, progestins

Recent Publications

Lacey JV Jr, et al. Oral contraceptives as risk factors for cervical adenocarcinomas and squamous cell carcinomas. *Cancer Epidemiol Biomark Prev* 1999;8:1079–87.

Lacey JV Jr, et al. Use of hormone replacement therapy and adenocarcinomas and squamous cell carcinomas of the uterine cervix. *Gynecol Oncol* 2000;77:149–54.

Lacey JV Jr, et al. Tubal sterilization and risk of cancer of the endometrium. *Gynecol Oncol* 2000;79:482–84.

Lacey JV Jr, et al. Associations between smoking and adenocarcinomas and squamous cell carcinomas of the uterine cervix (United States). *Cancer Causes Control* 2001;12:153–61.

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Epidemiology and Biostatistics Program
Environmental Epidemiology Branch

Molecular Epidemiology of Testicular and Liver Cancers

Research: The incidence of testicular cancer and primary liver cancer are increasing in many populations, although there is wide geographic and ethnic variability in their rates. The reasons for the increases are unclear. We are using a variety a study designs to investigate risk factors that may contribute to the increasing rates, including the role of genetic susceptibility.

Testicular Cancer
Testicular cancer is the most common malignancy among U.S. men in the 25- to 45-year-old age group. Its etiology, however, is poorly understood. The only well described risk factors are cryptorchism and a personal or family history of testicular cancer. We are initiating a large case-control study of testicular cancer to examine a wide variety of endogenous and exogenous risk factors. Of particular interest are organochlorine exposures, endogenous hormone levels, viral exposures, prenatal milieu, and genetic susceptibility.

Although it has been argued that organochlorine exposures may be related to the development of testicular cancer, the hypothesis has never been tested. A new case-control study conducted among members of the U.S. Armed Forces for whom prediagnostic sera are available will permit us to examine the effect of organochlorines and to determine whether genetic susceptibility influences the development of testicular cancer in organochlorine-exposed individuals. The effect of hormones on testicular cancer risk has been difficult to investigate because of the retrospective nature of most studies. In general, however, case-control studies reported that men with testicular cancer have higher follicle stimulating hormone levels and somewhat lower testosterone levels than controls. These observations suggest that testicular cancer arises in a state of "gonadotropin overdrive" in which the gonads have lost the ability to respond to gonadotropins. Our study will test this hypothesis by examining gonadotropin levels in prediagnostic sera to determine whether higher levels are also seen prior to cancer diagnosis.

An infectious etiology of testicular cancer has been suggested based on epidemiologic similarities with Hodgkin's disease. While a number of studies have examined viral antibody titres in affected men, few have had adequate power to test an association with testicular cancer. The most promising candidate viruses, Epstein-Barr virus (EBV) and cytomegalovirus (CMV), are members of the herpes family and are known to cause *p53* overexpression, a common finding in testicular cancer. In addition, both viruses have oncogenic potential, and CMV infection during pregnancy has been associated with cryptorchism in the newborn. Recently, the DNA of parvovirus B19, a member of the parvoviridae family, was found in testicular germ cell tumors. Antibody titres of CMV, EBV, and parvovirus B19 will be assessed among the case-control study participants. If any virus appears to be related to case status, the viral sequences in the tumor tissue will be examined.

The suggestion that testicular cancer may be associated with both hormonal aberrations and environmental endocrine modulators indicates that risk may be affected by genetic variability in loci related to hormonal and organochlorine metabolism. Given the early-onset age of testicular cancer and its association with congenital anomalies, our study will examine risk factors related to the perinatal milieu. Information will be collected from mothers and sons on a variety of factors, including congenital anomalies such as hypospadias, inguinal hernia, hydrocele, and testicular atrophy; prematurity; birth weight; birth order; sibship size; neonatal jaundice; singleton/twin status; and chromosomal aberrations. Maternal factors that will be evaluated include childbirth age, bleeding during pregnancy, degree of nausea during pregnancy, hormonal use (including DES) during pregnancy, body weight, and socioeconomic status.

Primary Liver Cancer

In most high-risk areas of the world, such as east Asia and sub-Saharan Africa, chronic infection with hepatitis B virus (HBV) and consumption of foods contaminated with aflatoxin B1 (AFB1) are established risk factors for hepatocellular carcinoma (HCC). In lower risk areas, infection with hepatitis C virus (HCV) and alcohol consumption carry a greater attributable risk. It is unknown whether risk of HCC is affected by other factors, including genetic predisposition. To examine this issue, we are conducting cohort studies in locales with high rates of HBV infection, AFB1 exposure, and HCC.

In a preliminary analysis, we reported that risk of aflatoxin B1-related HCC is mediated by genetic variants at the aflatoxin metabolic loci, epoxide hydrolase 1 (EPHX1) and glutathione-S-transferase M1 (GSTM1). In addition, a hot spot mutation in codon 249 of the *p53* tumor suppressor gene appeared to be related to the same genetic variation. In an expanded dataset, we again found that the EPHX1 2 allele is significantly overrepresented among HCC cases. The GSTM1 locus was also associated with increased HCC risk, although the null genotype was underrepresented in the cases, contrary to previously findings. The GSTM1 results may indicate that the locus serves only as a marker of risk rather than a determinant. Overall, our results suggest that individual variability in AFB1 metabolism plays a significant role in AFB1-related HCC.

Lipotrope (methionine, choline, folate, and vitamin B12) insufficiency enhances the effects of AFB1 on HCC risk in experimental animals. To determine whether this phenomenon exists in humans and whether genetic variability at lipotrope-associated loci affects risk, we are studying the relationships among lipotrope status, genotypes, viral status and HCC-associated outcomes.

Both experimental and ecologic studies indicate an inverse relation between selenium status and HCC, and that total body iron stores appear to increase the risk of HCC. We are examining both hypotheses by measuring iron and selenium levels in nails and sera. Preliminary evidence suggests that selenium levels may be related to the development of HCC. We are also evaluating prospectively selenium and iron levels and correlating them with polymorphisms in relevant loci. In vitro experiments found that 1,25-dihydroxyvitamin D3, the active metabolite of vitamin D3, inhibits the proliferation of human HCC cell lines if vitamin D receptors are expressed. It is unknown whether increased in vivo levels of vitamin D are associated with a decreased risk of HCC. To examine this question and to study whether polymorphisms in the vitamin D receptor (VDR) are related to HCC, pre-diagnostic serum levels of vitamin D metabolites and VDR genotypes will be examined in a high-risk population. Experimental studies have also consistently found an increased occurrence of primary liver cancer among animals exposed to organochlorines. It is unknown, however, whether exposure to this chemical class affects risk of liver cancer in humans. We will examine this question by measuring organochlorines in prediagnosis sera to determine if levels differ between individuals with and without primary liver cancer.

Keywords

folate, genetic susceptibility, hepatitis B virus (HBV), hormones, liver cancer, organochlorines, testicular cancer, vitamin D

Recent Publications

Tseng M, et al. Serum ferritin concentration and recurrence of colorectal adenoma. *Cancer Epidemiol Biomark Prev* 2000;9:625–30.

McGlynn KA. Environmental and host factors in testicular germ cell tumors. *Cancer Invest* 2001;19:840–51.

McGlynn KA, et al. International trends and patterns in primary liver cancer. *Int J Cancer* 2001;94:290–96.

Peters U, et al. Vitamin D, calcium, and vitamin D receptor polymorphisms in colorectal adenomas. *Cancer Epidemiol Biomark Prev* 2001;10:1267–74.

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Epidemiology and Biostatistics Program
Environmental Epidemiology Branch
Molecular Epidemiology of Genital Cancers

Research: The Interdisciplinary Studies Section conducts molecular epidemiologic research on multistage carcinogenesis. A major objective is to clarify the natural history of human papillomavirus (HPV) infection in relation to risk of cervical cancer. Studies also focus on other DNA tumor viruses and nonviral molecular epidemiologic topics of scientific interest. Junior investigators participate in all aspects of the research under the mentorship of more senior members.

Human Papillomavirus Infection and Cervical Cancer: Natural History Studies

After molecular biologists suggested in the early 1980s that human papillomavirus (HPV) is a cause of cervical cancer, our group began studying methods for detecting the virus. We are continuing methodologic research aimed at optimizing the measurement of HPV infection and host response by viral DNA, serologic, and cellular immune assays. Using increasingly

accurate HPV testing strategies, we initiated several large natural history studies of HPV infection and cervical cancer. The first, a ten-year study of 24,000 women enrolled in the Kaiser Permanente health plan in Portland, Oregon, is focusing on the epidemiologic determinants of HPV infection and on the transition from infection to precancer/cancer. The data thus far have shown a strong prospective association between HPV infection and cervical precancer/cancer, sexual transmission of HPV, and a decreasing prevalence of infection with age. The trend with age, which is related to viral disappearance, sheds light on why the virus only rarely causes cancer.

In a second effort, we are conducting a more intensive, population-based, cohort study of HPV and cervical neoplasia among 10,000 women in Guanacaste, Costa Rica, where the rates of cervical cancer are perennially high. State-of-the-art visual, microscopic, and molecular screening tests are being used to examine the origins of cervical precancer/cancer and to explore which factors make a geographic region "high risk." The sensitivity of previous screening and treatment efforts appear to be most important, as opposed to more complicated biological answers. The Guanacaste study, which is in the seventh and final year of followup, involves a variety of subprojects. We are examining several potentially important etiologic cofactors, such as chronic inflammation and endogenous hormone levels, that may contribute to cervical cancer risk. Most ambitiously, over 20,000 DNA and 20,000 plasma specimens are being tested for HPV DNA and antibodies, respectively, to determine whether type-specific HPV antibodies are protective against subsequent reinfection by the same variant. Based on results thus far, we have published in the scientific literature our findings supporting or questioning prominent hypotheses in the etiology of cervical cancer.

In a new, U.S.-based study, we are now beginning a search for biomarkers of risk of progression of HPV infection. The focus will be on microdissection and RNA expression.

HPV Infection and Cervical Cancer: Immunology Studies
It is now accepted that HPV infections usually clear spontaneously. Our attempts to understand the phenomena underlying HPV immunology are linked to ongoing vaccine efforts. We are conducting studies to examine the serologic and cellular immune responses accompanying HPV disappearance and persistence, and progression to high-grade lesions as part of a U.S. multicenter, randomized, clinical trial (ALTS) designed to evaluate three alternative methods of managing low-grade (LSIL) and equivocal (ASCUS) cervical cytologic diagnoses. In the Costa Rica cohort, women have been tested repeatedly by HPV VLP (virus-like particles) serology to examine whether seropositivity signals subsequent immunity to reinfection. A phase III trial of two prophylactic HPV vaccines, which were developed by the NCI and have undergone phase I/II testing in the United States, is currently under way in Costa Rica.

HPV Infection and Cervical Cancer: Prevention Studies
Results from HPV natural history studies suggest several strategies that could be applied in cervical cancer prevention. For example, HPV testing could be used to clarify equivocal Pap smears, a diagnosis affecting about three million

U.S. women yearly. In collaboration with the NCI's Division of Cancer Prevention, ALTS is evaluating HPV DNA testing along with two visual and two automated cytology techniques in determining the optimum strategy for managing low-grade cervical abnormalities. Over 5,000 women are enrolled and have been followed for about two years. The results of this effort will guide cervical screening and management practice in this country and elsewhere. In Costa Rica, we are examining HPV DNA testing, thin-layer cytology, and cervicography for cervical cancer screening in the general population. Vaccination is the ultimate goal in preventing HPV-associated cervical disease.

Keywords

cervical cancer, human papillomaviruses (HPV), molecular epidemiology, multistage carcinogenesis, prevention, vaccines

Recent Publications

Schiffman M, et al. HPV DNA testing in cervical cancer screening: Results from women in a high-risk province of Costa Rica. *JAMA* 2000;283:87–93.

Herrero R, et al. Population-based study of human papillomavirus infection and cervical neoplasia in rural Costa Rica. *J Natl Cancer Inst* 2000;92:464–74.

Solomon D, et al. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: Baseline results from a randomized trial. *J Natl Cancer Inst* 2001;93:293–99.

Stoler M, et al. Interobserver reproducibility of cervical cytologic and histologic interpretations: Realistic estimates from the ASCUS-LSIL triage study. *JAMA* 2001;285:1500–1505.

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Epidemiology and Biostatistics Program
Environmental Epidemiology Branch

Genetic Susceptibility and Molecular Markers of Cancer Pathogenesis

Research: We are conducting molecular epidemiology studies to identify genetic markers of susceptibility in the exposure-to-disease continuum as well as biomarkers of cancer development and progression in two tumor systems, cervical neoplasia and non-Hodgkin's lymphoma. For both tumors, ongoing studies include investigations of markers of susceptibility with particular emphasis on immune and immune-related genes. In addition, identifying molecular markers of disease pathogenesis are under way utilizing novel biological methods, including cytogenetic techniques, gene expression via microarray technologies, and restriction landmark genome scanning.

Genetics of Cervical Neoplasia: Susceptibility Genes for HPV Infection and Cervical Cancer

While infection by human papillomavirus (HPV) is accepted as the central risk factor for cervical cancer, it is unlikely to be sufficient for developing cancer. Only a subset of HPV-infected individuals develop persistent infection, and of those, a subset develop low-grade lesions and fewer develop high-grade lesions and subsequent cancer. These findings indicate that factors in addition to HPV infection are likely to be important determinants in cervical cancer carcinogenesis. Ongoing research includes investigating the role of specific genetic factors in determining HPV persistence and subsequent progression to disease. Since genetic factors may modify HPV infection, our research includes efforts aimed at assessing genes that influence immune function. In three NCI-sponsored studies, including a population-based cohort of 10,000 women in Costa Rica, a population-based cohort of 24,000

women in Portland, Oregon, and a case-control study in the Eastern United States, we are examining the association between various polymorphic genes important to immune function, such as human leukocyte antigen (HLA) class I and II alleles, with various stages of cervical disease (low-grade lesions, high-grade lesions, and cancer). For the upcoming HPV vaccine efficacy trial in Costa Rica, we are planning studies to assess the role of genetic factors in the heterogeneity of vaccine responses and in rapid onset disease.

Biomarkers of Risk for Progressive Cervical Neoplasia
To increase our understanding of the mechanisms involved in cervical carcinogenesis and to develop a new set of biomarkers that can distinguish those at highest risk of cervical cancer from those with benign infection, we are implementing a new study that comprehensively assesses biomarkers of risk for progressive cervical neoplasia. Employing an epidemiologic study design, we plan to identify, validate, and quantify the risk relationships of candidate biomarkers in cervical carcinogenesis. We are developing a comprehensive list of potential risk biomarkers via gene expression and microarray technology. By measuring gene expression profiles, we will gain a comprehensive in vivo picture of cervical neoplasia carcinogenesis. Candidate biomarkers will subsequently be validated for key outcomes related to progression or nonprogression.

Using resources from ongoing studies, we are also evaluating the validity of candidate markers such as the newly proposed biomarker for progressive low-grade cervix disease, $p16^{INK4a}$. We are also conducting smaller studies to identify candidate biomarkers of disease via restriction landmark genome scanning (RLGS), which may identify methylated promoters of tumor suppressor genes.

Genetics of Non-Hodgkin's Lymphoma: Susceptibility Genes for Non-Hodgkin's Lymphoma
We are currently evaluating the role of genetic polymorphisms in non-Hodgkin's lymphoma (NHL) susceptibility in the NCI-sponsored NHL multicenter case-control study in the United States. While the major risk factors for NHL are not yet known, studies have consistently shown a strong relationship between factors that alter the immune system and NHL. We are therefore investigating candidate genes that are relevant to immune pathways hypothesized to play a role in NHL etiology. These include: (1) inflammatory and regulatory cytokines, (2) Th1/Th2 cytokines, (3) genes involved in innate immunity, and (4) chemokines. In addition, the role of polymorphisms in genes that metabolize or have a role in NHL-relevant environmental exposures are also being evaluated, including organophosphates, solvents and chemicals, organochlorines, and DNA repair capacity from chemical exposures.

Cytogenetic Biomarkers of Risk for Non-Hodgkin's Lymphoma
Traditionally, cytogenetic markers have been used as markers of early biologic effect in assessing carcinogenic exposures. However, recent cohort studies suggest that cytogenetic markers, i.e., chromosomal aberrations in peripheral lymphocytes, may be predictive of subsequent risk of cancer. If validated, the implications of cytogenetic markers serving as predictive markers of cancer could be substantial, especially if shown to be independent

of exposure. We are therefore investigating the hypothesis that cytogenetic markers are indicative of cancer risk in the current ongoing NCI-sponsored case-control study of NHL using classic cytogenetic techniques and fluorescent in situ hybridization (FISH) methods.

Keywords

cervical cancer, genetic susceptibility, human papillomavirus (HPV), molecular epidemiology, non-Hodgkin's lymphoma, somatic mutations

Recent Publications

Wang SS, et al. Elevated HPRT mutation frequencies in aflatoxin-exposed residents of Daxin, Qidong County, People's Republic of China. *Carcinogenesis* 1999;20:2181–84.

Wang SS, et al. Is the G985A allelic variant of medium-chain acyl-CoA dehydrogenase a risk factor for sudden infant death syndrome? A pooled analysis. *Pediatrics* 2000;105:1175–76.

Wang SS, et al. Early diagnosis of cystic fibrosis in the newborn period and risk of *Pseudomonas aeruginosa* acquisition in the first ten years of life: A registry-based longitudinal study. *Pediatrics* 2001;107:274–79.

Wang SS, et al. HLA class I/II alleles and cervical neoplasia in a population-based cohort in Guanacaste, Costa Rica. *J Infect Dis* 2001;184:1310–14.

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Epidemiology and Biostatistics Program
Nutritional Epidemiology Branch

The Nutritional Epidemiology Branch carries out a wide range of interdisciplinary studies to clarify the role of diet and nutrition in the etiology of human cancer. Observational, experimental (clinical trials), and metabolic studies are undertaken and, whenever feasible, biospecimens are collected to explore the physiologic, cellular, and molecular processes linking nutrition and cancer risk. The Branch emphasizes the exposure side of nutrition and cancer research, with studies of dietary patterns, intake biomarkers, food composition databases, and dietary measurement error. Nutrition is conceived broadly, comprising dietary factors, body size and composition, physical activity, and energy balance. Our etiologic research aims to strengthen the scientific foundation of public health measures that reduce the occurrence of cancer.

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The Branch's research encompasses investigations of individual nutrient and nonnutritive food constituents as well as more integrative studies of multifactorial nutritional exposures, such as glycemic load. Nutritional factors may operate as primary modulators of carcinogenesis or serve as cofactors for other key exposures. We are increasingly incorporating potential genetic modifiers of risk into studies, such as our investigations of diet-gene interactions involving the metabolism of calcium/vitamin D, folate/homocysteine, and cruciferous vegetable intake.

A major focus of our activities is defining the "exposure" side of the nutrition and cancer question. This research entails developing studies that encompass a wide intake range for major foods and nutrients. We also give considerable attention to improving dietary/nutritional assessments and quantifying dietary measurement error. This methodologic work includes developing statistical approaches to energy adjustment; statistical and biospecimen-based research on dietary measurement error, particularly with respect to relative risk attenuation; new relevant databases; and dietary pattern definitions. The work also includes research for additional biomarkers of nutrient intake.

Much of the Branch's research is interdisciplinary in nature and includes nutrition, epidemiology, clinical medicine, biochemistry, and biostatistics. Collaboration is an essential part of our interdisciplinary approach and involves investigators in other components of the DCEG and the NCI as well as at other NIH Institutes and research centers in this country and abroad. These collaborators bring additional disciplines to our work, including molecular biology, genetics, anthropometry, and immunology. Branch investigators are collaborating on a variety of projects, including major prospective cohort and intervention studies of diet and cancer.

The Branch offers training opportunities for postdoctoral researchers, visiting investigators from around the world, and students working on doctoral theses and other relevant projects. Scientists in the training program can participate in a variety of study-related activities, including data analysis from studies on which field work is completed, and take part in ongoing projects and in planning new initiatives. We welcome inquiries about the Branch's collaborative and training opportunities.

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Epidemiology and Biostatistics Program
Nutritional Epidemiology Branch

Intervention, Cohort, and Methodologic Studies of Nutrition and Cancer

Research: We are focusing on three areas of research to clarify the relation between nutrition and cancer: error in dietary assessment, dietary homogeneity within study populations, and uncontrolled or unmeasured confounding in observational studies. Intervention studies complement observational investigations by minimizing the potential for confounding and guaranteeing wide intake differences across randomization groups. Intensive biomarker studies, in conjunction with new mathematical modeling techniques, aid in quantifying dietary measurement error in a new generation of large prospective epidemiologic studies of diet and cancer.

Diet and Colorectal Neoplasia
The Polyp Prevention Trial was a multicenter intervention study of the effect of a low-fat (20 percent calories from fat), high-fiber (18 g dietary fiber/1,000 kcal), high-fruit and -vegetable (5–8 daily servings) eating plan on the recurrence of colorectal adenomatous polyps, precursor lesions for most large bowel cancers. Results after four years of followup showed no difference in recurrence of any or advanced adenomas between the intervention and control groups. Trial participants will be followed for an additional five years. Several observational epidemiologic studies are near completion, including those of NSAIDs use, blood carotenoids, and hormone replacement therapy in relation to subsequent adenoma recurrence. Additional observational studies of adenoma recurrence in this population are feasible.

The trial incorporated several interdisciplinary, biospecimen-based substudies. Serum lipids and carotenoids were used to monitor the intervention progress and provide a biochemical complement to self-reported dietary assessments. Integration of bromodeoxyuridine and proliferating cell nuclear antigen assays of rectal mucosal biopsy specimens into the main trial enables us to evaluate the effect of dietary change on cell proliferation as well as the extent to which proliferation indices predict neoplasia. An initial report

documents considerable "noise" in proliferation markers, emphasizing the need for gathering information on sources of biomarker variability, and suggesting that some of these markers may have limited utility in population studies. In the first of two molecular genetic studies, we are examining *ras* and *p53* mutations in resected adenomas to determine whether dietary change alters somatic mutations. In the second study, using DNA extracted from white blood cells, we are investigating interactions of dietary factors and allelic variants of polymorphic genes encoding metabolizing enzymes, such as *MTHFR* and the *NAT* and *GST* gene families, in relation to adenoma formation.

NCI-AARP Diet and Health Study

The NCI-American Association of Retired Persons Diet and Health Study, comprising over 560,000 men and women in the United States, was designed to overcome specific methodologic limitations of previous epidemiologic studies of diet and cancer. The large cohort exhibits substantial dietary heterogeneity for major nutrients and foods, thereby circumventing the narrow intake range in many previous study populations. The prospective study design avoids the dietary recall bias that limits case-control studies. Also, its large size offsets, at least partially, the attenuation in relative risk resulting from dietary measurement error. The study uses a new food frequency questionnaire based on cognitive psychologic principles and extensive focus-group testing. In order to characterize qualitatively and quantitatively the error structure of the new dietary assessment instrument, we incorporated a calibration study of approximately 2,000 participants who completed multiple food records along with repeated food frequency questionnaires. The large study size also facilitates the evaluation of interactions among dietary factors and environmental exposures or host characteristics. The study is expected to yield nearly 4,000 incident breast, over 4,000 incident colorectal, over 10,000 incident prostate, approximately 900 pancreatic, and over 400 ovarian cancers by 2003.

Additional Prospective Studies

The Breast Cancer Detection Demonstration Project Follow-up Study is a prospective cohort study of approximately 50,000 older women established from a large NCI-sponsored breast cancer screening program. A decade ago, we integrated a food frequency questionnaire into the study along with queries on supplement use, body size, and physical activity. Over 1,000 breast cancer cases and over 450 colorectal cancer cases subsequently developed in about 40,000 women who completed the questionnaire satisfactorily. One analysis showed a direct association between adult body mass index and increased risk of breast cancer, especially among older women. Other investigations have shown no overall association between dietary fat and breast cancer, an analysis that considered multiple methods of energy adjustment; an inverse relation between physical activity and breast cancer; and little association between fruit and vegetable intake and large bowel cancer. Ongoing studies include dietary patterns in relation to breast and colorectal cancers, dietary fiber vis-à-vis colorectal cancer, folate and one-carbon metabolism in colorectal cancer, and meat consumption and large bowel cancer.

We collaborated with investigators at the National Heart, Lung, and Blood Institute and Boston University to generate the cancer outcomes component of the original Framingham Heart Study cohort and the Framingham Offspring Study cohort. Using these prospective studies, we examined the relation between alcohol and breast cancer (no association); physical activity and colorectal cancer (protective in men); physical activity and breast cancer (no association); central to peripheral body fat ratio and breast cancer (direct association); and bone mineral density, a possible proxy for cumulative exposure to exogenous estrogens, and breast cancer (direct association).

We established an interagency agreement with the Department of Veterans Affairs to create a biologic specimen bank within a unique Veterans Affairs study of adenoma prevalence and recurrence among asymptomatic persons undergoing full colonoscopy. In addition to analyzing blood micronutrients in relation to prevalent and recurrent adenomas, we are using DNA extracted from banked white cells to explore diet-gene interactions in the study population.

In a study similar to the VA study, we have established an interagency agreement to study adenoma prevalence among asymptomatic women undergoing full colonoscopy at regional Naval hospitals in the United States (the CONCeRN study). We will be able to analyze blood and colonic tissue micronutrients, in conjunction with information on dietary and genetic polymorphisms, in relation to prevalent adenomas.

Methodologic Research

In a large collaborative study with investigators from the NCI's Division of Cancer Control and Population Sciences, we are assessing energy expenditure (using the doubly labeled water technique) and protein intake (via urinary nitrogen excretion) to estimate the error (generally underreporting) in a food frequency questionnaire and multiple 24-hour recalls. Previous studies, even those "adjusting" for measurement error, took into account biases in the food frequency questionnaire but did not fully considered biases associated with the "reference" instrument (24-hour recall), especially the potential correlation of biases in the two instruments. The information on measurement error from this study can be used in interpreting and adjusting data from the NCI-American Association of Retired Persons Diet Study and other epidemiologic investigations.

In conjunction with NCI biostatisticians, we investigated the utility of intermediate and surrogate endpoint markers in cancer research. We showed that a priori validity for a potential cancer surrogate requires a marker to be virtually a necessary component in the carcinogenesis pathway. A marker in one but not another causal pathway to cancer—thereby being nonnecessary and having an attributable fraction less than one—may give misleading answers about the effect of an intervention on cancer. Moreover, a marker may be a reasonable cancer surrogate for one intervention (or exposure) but not for another. Even reasonably valid surrogates, like colorectal adenomas, cannot be considered definitive in themselves and must be evaluated in conjunction with observational and experimental epidemiologic findings as well as other types of evidence.

Keywords

adenoma, alcohol, anthropometry, biomarkers, breast cancer, clinical trials, colonoscopy, colorectal cancer, diet-gene interactions, dietary intervention studies, dietary measurement error, epithelial cell proliferation, prostate cancer, somatic mutations

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Kipnis V, et al. Empirical evidence of correlated biases in dietary assessment instruments and its implications. *Am J Epidemiol* 2001;153:394–403.

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Epidemiology and Biostatistics Program
Nutritional Epidemiology Branch

Nutrition and Nutrition-Related Factors in Cancer Etiology

Research: Dietary and nutritional exposures have long been thought related to population and individual differences in cancer rates and risk, yet much remains unknown regarding specific cause and effect relationships and biological mechanisms. We are conducting a population-based, epidemiologic research program of observational studies and controlled trials to investigate the etiologic role of nutritional, biochemical/molecular, and other factors in prostate, lung, colorectal and other cancers. Of particular interest are the effects of micronutrients—for example, carotenoids, tocopherols (vitamin E), selenium, and folate—and energy-related exposures such as caloric intake, anthropometry, and physical activity, with the overall objective of identifying preventive interventions and strategies for cancer.

Effects of β-Carotene and α-Tocopherol Supplementation

We studied the effectiveness of long-term supplementation with β-carotene and α-tocopherol (vitamin E) for preventing lung, prostate, and other cancers in the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study of 29,133 50- to 69-year-old male smokers. This landmark trial was the first to show that supplemental β-carotene might not prevent cancer and that it could adversely affect lung carcinogenesis in smokers. Within this cohort, we are testing hypotheses relevant to how β-carotene supplementation may have promoted cancer, including effects on peripheral and/or tumor cytochrome-p450 activity, oxidation products, PAH adducts, RAR/RXR expression, DNA methylation, and cell proliferation/apoptosis. Ongoing surveillance of the ATBC cohort is examining postintervention cancer incidence trends for the β-carotene, α-tocopherol, and placebo groups in order to delineate the long-term effects of supplementation. A substantial prostate cancer inhibitory effect for vitamin E supplementation was also shown in our trial, with 32 and 41 percent reductions in incidence and mortality, respectively, over a 5–8 year period. Significant progress has been made in systematically testing the

mechanisms through which vitamin E acted to prevent clinical prostate cancer, such as modulation of hormones and growth factors, including testosterone and IGF-I. Preliminary data show that circulating androgens were reduced by vitamin E, for example. Given the magnitude and public health implications of the main finding, we are collaborating with the Southwest Oncology Group on a confirmatory study of these hypotheses through a large, multicenter, phase III trial (SELECT) of supplementation with vitamin E (400 IU/day) and selenium (200 µg/day) in prostate cancer prevention.

Micronutrients and Genetic Polymorphisms

The role of various micronutrients, and their interactions with several relevant genetic polymorphisms, have been investigated based on prospectively collected serum, genomic DNA, tumor tissue, and high-quality epidemiologic data including dietary intake. Analyses of vitamins A, B6 and B12, C, D, and E, carotenoids, folate, selenium and other trace elements, androgens, and insulin-like growth factors and binding proteins have focused on lung, prostate, and large bowel cancers in particular, with some attention also on cancers of the pancreas, stomach, and bladder. Studies of genetic polymorphisms relevant to the metabolism and function of nutrients, growth factors, and hormones (e.g., MTHFR, IGF-I, SRD52) and to carcinogen activation/elimination (e.g., GSTM1 and CYP1A1) are testing both their direct associations with cancer as well as their interactions with the trial interventions and other important exposures relevant to cancer. For example, under study is the role of several genetic polymorphisms potentially relevant to prostate carcinogenesis and to the α-tocopherol preventive effect, including those relevant to sex hormone metabolism and function such as SRD52, HSD32, CYP17, and AR. Gene functionality is being evaluated through analysis of serum steroid hormones vis-à-vis the gene variants. Our discovery of an α-tocopherol effect on serum testosterone and androstenedione makes investigation of this area particularly timely in order to determine whether vitamin E directly affects androgen synthesis, release or clearance, or inhibits cell proliferation and induces apoptosis in the prostate. These studies are based on large numbers of cumulatively diagnosed cancers in the cohort; for example, approximately 1,800 lung, 800 prostate, 350 colorectal, 350 bladder, 200–250 each for stomach, pancreas, and kidney cancers.

Based on experimental data identifying a strong cancer preventive effect of energy restriction and/or increased energy expenditure, and epidemiologic studies of cancer risk associated with diet, anthropometry, and physical activity, we also continue to investigate the relationship between body size and physical activity and several cancers, including breast cancer.

Keywords

androgens, anthropometry, carotenoids, cohort studies, colorectal cancer, diet-gene interactions, folate, genetic polymorphisms, insulin-like growth factors, intervention studies, lung cancer, molecular epidemiology, pancreatic cancer, physical activity, prostate cancer, selenium, tocopherols, vitamin E

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Epidemiology and Biostatistics Program
Nutritional Epidemiology Branch
Diet, Body Size, Physical Activity, and Cancer

Research: In the past, nutritional epidemiology has been plagued with methodologic issues, including measurement error, recall bias, and other types of biases, which can threaten the validity of findings relating dietary factors to chronic diseases. In the Nutritional Epidemiology Branch, we are striving to minimize recall and selection biases by increasingly focusing our research efforts on data from large prospective studies. We plan to explore associations between diet, obesity, and physical activity and cancers of the bladder and pancreas in several large cohort studies to enhance our understanding of these serious malignancies.

In 1995–1996, the NCI initiated the NCI-AARP Diet and Health Study, a cohort study of 540,000 men and women. Both important lifestyle characteristics and dietary data were obtained on all participants at baseline. Given the exceptional size of this cohort study, case numbers are expected to be large within a few additional years of followup. The Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study of 29,133 male smokers aged 50–69 years will also provide an important resource to examine dietary hypotheses. Individual serum and dietary assessments were collected at baseline in this study. We also plan to collect tumor blocks for certain cancers in this cohort. In addition to the AARP and ATBC studies, we are currently collaborating with colleagues at the Harvard School of Public Health on two large cohort studies, the Health Professionals Follow-up Study (51,529 men) and the Nurses' Health Study (121,700 women). Given the breadth and quality of the dietary and other exposure data, these studies should greatly enhance our understanding of cancers.

Bladder Cancer
Associations between a number of dietary factors and the risk of bladder cancer have been largely inconsistent. In the Health Professionals Follow-up Study (HPFS) cohort at Harvard, for example, we recently reported a decrease in risk among individuals with high compared to low fluid consumption. However, other studies have observed opposite trends with fluid consumption. We plan to examine fluid intake in other cohorts, including the AARP and ATBC studies. Other exciting findings on cruciferous vegetables and vitamin E intakes in the HPFS cohort suggest that diet may play a critical role in the etiology of bladder cancer. Our future research will focus on: (1) dietary factors, such as intake of fruit and vegetables, among women and other groups such as smokers; (2) markers of progression in tissue blocks of bladder tumors; and (3) specific gene-diet interactions. This research will enhance our understanding of the pathogenesis of bladder cancer and facilitate efforts to prevent this malignancy.

Pancreatic Cancer
Pancreatic cancer is understudied in relation to its high fatality rates, and few risk factors are well established. Data from several studies suggest that hyperinsulinemia and insulin resistance may play a role in pancreatic carcinogenesis. Recent findings from the HPFS and the Nurses' Health Study provide support for this mechanism as obesity and physical inactivity were associated with pancreatic cancer incidence. In the ATBC study, an elevated risk was observed among those men who were sedentary at home and had low activity levels at work. We plan to investigate dietary factors that may predict glucose response and serum insulin, such as glycemic index and glycemic load, in relation to incidence of pancreatic cancer.

Keywords

bladder cancer, cohort studies, food frequency questionnaires, nutrition, pancreatic cancer

Recent Publications

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Michaud DS, et al. Prospective study of dietary supplements, macronutrients, micronutrients, and risk of bladder cancer in U.S. men. *Am J Epidemiol* 2000;152:1145–53.

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Michaud DS, et al. Coffee and alcohol consumption and the risk of pancreatic cancer in two prospective United States cohorts. *Cancer Epidemiol Biomark Prev* 2001;10:429–37.

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Epidemiology and Biostatistics Program
Nutritional Epidemiology Branch
Diet, Nutrition, and Genetic Susceptibility

Research: Only a small number of dietary components has been linked causally to cancer, even though diet is thought to be important in the etiology of certain human cancers. Our research focuses on interdisciplinary studies aimed at improving dietary exposure assessment using questionnaires and biochemical measures, as well as elucidating dietary exposures and biological mechanisms associated with cancer risk, including the role of genetic susceptibility. We are particularly interested in examining potential carcinogens formed in meats during the cooking process.

Cooking-Related Carcinogens

Cooking meats at high temperatures produces heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs), known mutagens and animal carcinogens. Epidemiologic studies examining the influence of meat doneness and cooking methods, however, have not consistently shown a relationship with cancer risk. To clarify the effects of cooking-related carcinogens, we developed a three-part research program: (1) to improve methods of diet assessment for cooked meat, HCAs, and PAHs, (2) to evaluate the role of genetic susceptibility factors in the metabolism of HCAs and PAHs, and (3) to test the hypothesis that HCAs and PAHs are etiologic factors in the risk of certain human cancers.

• **Exposure assessment.** A database and dietary food frequency questionnaire (FFQ) was developed to improve estimates of exposure. For the database, different types of meats were cooked by assorted methods to varying degrees of doneness. Measurements were made for 5 HCAs and 12 PAHs. Integrated into the database is a module on meat cooking practices in an FFQ format. The module collects information on usual intake of meat type, portion size, cooking method, internal doneness, and external browning. Photographs are used to standardize responses. The FFQ module has been validated among 150 people by 12-day dietary records and one 24-hour recall. To identify biological markers of internal exposure, we conducted a metabolic study to collect data on the metabolism and excretion of HCAs and their metabolites.

• **Genetic susceptibility assessment.** Carcinogenic HCAs are formed through enzyme-mediated activation. In humans, the major HCAs, 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQX) and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), are metabolized by cytochrome P4501A2 *(CYP1A2)* and N-acetyltransferase *(NAT2).* The results from our metabolism study on the interaction of these HCAs and polymorphic genes suggest that interindividual variation in *CYP1A2* activity is relevant to HCA-associated carcinogenesis. We are now investigating the genetic basis of the difference.

• **Epidemiologic studies.** Using methodologic tools that we developed, the role of meat intake and exposure to HCAs is being examined in the etiology of colorectal adenomas and cancers of the lung, breast, and prostate. In addition, using refined questionnaires and other information collection methods, high temperature cooking techniques and doneness levels of red meat are being evaluated in relation to colorectal, stomach, lung, and breast cancers. In the colorectal study, we found an elevated risk of 10 percent per 10g for red meat consumption. The increased risk was mainly associated with well-done/very well-done red meat, with an excess risk of 29 percent per 10g versus 10 percent per 10g for rare/medium red meat. We also found increased risks associated with high temperature cooking methods of 27 percent per 10g for grilled red meat and 15 percent per 10g for pan-fried red meat.

Using the HCA database with the refined questionnaire, we estimated intake of PhIP, MeIQx, and DiMeIQx. We found increased risk of colorectal adenomas associated with all three HCAs. However, increased risk was observed only for MeIQx after adjusting each HCA for the other. Our analysis suggests that intake of MeIQx could explain the risk associated with well-done and fried red meat, but not with grilled red meat. It is possible that this risk may be associated with intake of PAHs. For lung cancer, we found similar results for red meat doneness, fried meat, and estimated MeIQx intake. These exposure assessment approaches are being used in large prospective studies worldwide and should help to clarify the role of doneness, cooking practices, and pyrolysis products in the etiology of human cancer.

Keywords

cooking method, DiMeIQx, genetic susceptibility, heterocyclic amines, meat, MeIQx, PhIP, polycyclic aromatic hydrocarbons (PAHs)

Recent Publications

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The Occupational Epidemiology Branch conducts studies in the United States and abroad to identify and evaluate environmental and workplace exposures that may be associated with cancer risk. Workers often have heavier and more prolonged exposures to hazardous chemicals that also occur in the general environment, but at lower levels. When excess risks are detected from workplace studies, they may provide important leads as to the etiology of cancer in other settings. Occupational studies have identified many chemicals that cause cancer in humans, and they have provided direction for initiatives aimed at reducing or eliminating these carcinogens in the workplace and elsewhere.

The mission of Occupational Epidemiology Branch includes interdisciplinary research, resource development, and training. Research projects are designed to identify occupational, environmental, and other factors affecting cancer risk; to characterize exposure-response relationships; to elucidate biological mechanisms of action; to identify susceptible populations and gene-environment interactions; and to improve research methods for occupational investigations. Projects typically involve sophisticated exposure assessments, biological components for mechanistic evaluations, and intensive collaboration among epidemiologists, industrial hygienists, and molecular biologists. In addition to the major research areas summarized below, emphasis is placed on developing new and innovative approaches for assessing carcinogenic risks from occupational and environmental exposures.

Pesticides and Other Agricultural Exposures
Projects on pesticides and other agricultural exposures include: (1) a prospective study of nearly 90,000 farmers and their spouses in Iowa and North Carolina, which is being carried out in collaboration with the National Institute of Environmental Health Sciences and the Environmental Protection Agency; (2) case-control studies of stomach and brain cancer in Nebraska; (3) a biomarker investigation of intermediate outcomes and precursor states among herbicide applicators; (4) studies among migrant agricultural workers; and (5) a study of non-Hodgkin's lymphoma risk associated with exposure to pesticides and nitrates.

Industrial Chemicals
Major investigations under way on industrial chemicals include: (1) a study of cancer risk and mechanisms of susceptibility in a cohort of 75,000 benzene-exposed workers in China; (2) a cohort mortality study of 25,000 workers with exposure to acrylonitrile; (3) a case-control study of renal cancer in Eastern

Europe; (4) a case-control study of bladder cancer in Spain; and (5) a case-control study of lung cancer in a heavily industrialized region around St. Petersburg, Russia.

Occupational and Environmental Cancer Among Women
Studies aimed at occupational and environmental causes of cancer among women include: (1) a prospective cohort study of 75,000 women in Shanghai, which includes the collection of biologic specimens for evaluating gene-environment interactions; (2) investigations in Alaska, Michigan, and Alabama to evaluate breast cancer risk in relation to serum levels of DDT, PCB, PBB, and other organohalide chemicals; (3) a case-control study of breast cancer in Poland to evaluate risks associated with chemical exposures and gene-environment interactions; and (4) large cohort studies of farmers, dry cleaners, formaldehyde workers, benzene workers, and acrylonitrile workers that include a substantial number of women.

General Environmental Exposures
A number of projects are evaluating cancer risks associated with general environmental exposures, including: (1) studies of non-Hodgkin's lymphoma and cancers of the brain, bladder, colon, and stomach in relation to levels of nitrate, arsenic, and chlorination byproducts in drinking water in Iowa, Minnesota, and Nebraska; (2) a study of non-Hodgkin's lymphoma and pesticide exposure associated with domestic use or residential proximity to agricultural land; (3) a study of bladder cancer in relation to arsenic levels in drinking water and other risk factors in high-rate areas of the northeastern United States; and (4) a study of non-Hodgkin's lymphoma and multiple myeloma and cancers of the prostate, brain, ovary, and uterus among Norwegians in relation to serum levels of organochlorine chemicals.

Other Risk Factors
The examination of dietary, hormonal, and lifestyle factors on cancer risk is included in case-control studies of non-Hodgkin's lymphoma, multiple myeloma, and cancers of the oropharynx, esophagus, stomach, colon, rectum, pancreas, brain, bladder, kidney, and prostate. Special attention is also being given to dietary and lifestyle factors in three long-term prospective studies: (1) the Agricultural Health Study; (2) the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial; and (3) the Shanghai Women's Cohort. A major new study of renal cell cancer is investigating promising etiologic leads associated with this rapidly increasing tumor.

Methodologic Projects
Methodologic projects are carried out to develop and improve techniques and procedures in occupational epidemiology. Specialized job modules were constructed to obtain information on occupational exposures in case-control studies of non-Hodgkin's lymphoma and cancers of the brain and bladder. A computerized exposure assessment program, originally developed for an acrylonitrile-exposed cohort, was modified to make it usable for other cohort investigations. An occupational coding system (CodeSearch), which was developed for the personal computer, has lessened the burden of classifying jobs in epidemiologic investigations. In collaboration with the National Institute for Occupational Safety and Health (NIOSH), a Computerized Occupational Referent Population System, which aggregates completed cohort mortality studies conducted by NIOSH and ourselves, was constructed to provide data for referent populations in occupational cohort studies. The utility of remote sensing and geographic information systems in environmental epidemiologic research is being evaluated in studies in Nebraska. These research resources are available to the scientific community.

Collaboration and Training
The breadth of our occupational, environmental, and other risk factor research offers many possibilities for collaboration with investigators at other agencies and institutions, as well as training opportunities for young scientists. Extensive collaborations are under way in epidemiology, exposure assessment, biologic monitoring, and biomarker studies. Training opportunities for junior investigators include planning new projects, participating in ongoing investigations, and analyzing data from studies whose field work is completed. Predoctoral and postdoctoral fellows are mentored by senior investigators in the Branch.

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Biography: *Dr. Blair received a Ph.D. in genetics from North Carolina State University and an M.P.H. in epidemiology from the University of North Carolina. He joined the NCI as a Staff Fellow in 1976, and was appointed to head the Occupational Studies Section in 1978. Dr. Blair was appointed Chief of the group when it became a Branch in 1996. He received the NIH Director's Award, the PHS Special Recognition Award, the DHHS Quality of Work Life Award, and the University of North Carolina H.A. Tyroler Distinguished Alumni Award. Dr. Blair has authored more than 200 publications on occupational and environmental causes of cancer.*

Epidemiology and Biostatistics Program
Occupational Epidemiology Branch
Occupational Exposures and Cancer

Research: Our research focuses on evaluating cancer risks associated with exposure to pesticides and other chemicals in the workplace and the general environment, methodologic issues in occupational epidemiology, and studies of under-investigated groups at risk.

Pesticides

A number of pesticides are carcinogenic in laboratory animals. The widespread use of these agents raises questions about their carcinogenicity in humans. Several epidemiology studies include farmers, since they have heavier exposures than the general population and are able to identify their pesticide usage. Despite an overall lower mortality than the general population, farmers have excess cancers of the lip, stomach, brain, prostate, skin, and the lymphatic and hematopoietic system, as well as nonmalignant chronic diseases. Ongoing studies are designed to identify risk factors that account for these excesses.

Recent studies found evidence for a possible link between pesticides and pancreatic cancer in a case-control study in China, and certain carbamate and organophosphate insecticides and risk of non-Hodgkin's lymphoma. Although previous studies associated non-Hodgkin's lymphoma with potential exposure to the herbicide 2,4-D, possible mechanisms of action are unclear. In a biomarker study among herbicide applicators, we found an association between urinary levels of 2,4-D and increased lymphocyte replication, the level after exposure being greater than before. Another study found higher exposure levels among farmers who did not follow careful work practices while applying insecticides to animals. A major prospective investigation of farmers and their families (the Agricultural Health Study) in Iowa and North Carolina is gathering detailed information on pesticide use and collecting biologic specimens to evaluate gene-environment interactions of pesticides and other agricultural exposures. Use of fungicides among orchardists in the cohort was associated with retinal degeneration. Because investigators are often dependent upon information from interviews to assess

pesticide exposures among farmers, a methodologic study that obtained interview information from the same farmers a year apart found that they could reliably provide considerable detail on pesticide use.

Several ongoing investigations are evaluating possible relationships between serum levels of organohalide chemicals and cancer risk. In Alabama, a study is examining cancer and other health outcomes among mostly minority women who received heavy environmental exposure to DDT. In Michigan, breast disease is being investigated among women who were exposed to PBBs through accidental contamination of cattle feed. In Norway, a study is evaluating the relationship between serum levels of several persistent organohalide chemicals and risk of non-Hodgkin's lymphoma, leukemia, multiple myeloma, and cancers of the prostate, pancreas, brain, and skin.

Other Occupational Exposures

In a large case-control study in Iowa and Minnesota, leukemia was associated with employment in agriculture, nursing and health care, and several occupations with possible exposure to solvents. The mortality experience of dry cleaners exposed to solvents and industrial workers exposed to formaldehyde is being evaluated in the extended followup of established cohorts.

Keywords

agricultural exposures, breast cancer, environmental exposures, industrial exposures, leukemia, multiple myeloma, non-Hodgkin's lymphoma, pesticides, solvents

Recent Publications

Blair A, et al. Occupational cancer among women: Research status and methodologic considerations. *Am J Ind Med* 1999;36:6–17.

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Waddell BL, et al. Agricultural use of organophosphate pesticides and the risk of non-Hodkgin's lymphoma among male farmers (United States). *Cancer Causes Control* 2001;12:509–17.

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Biography: *Dr. Alavanja received a Dr.P.H. from the School of Public Health of Columbia University. Prior to joining the NCI, he served as an Assistant Professor of environmental health and epidemiology at Hunter College School of Health Sciences and as an epidemiologist and Section Chief at the National Institute for Occupational Safety and Health. In 1983, Dr. Alavanja joined the NCI as a Special Assistant for Epidemiology in the Office of the Associate Director for the Epidemiology and Biostatistics Program. In 1996, he transferred to the Occupational Epidemiology Branch of the DCEG. Dr. Alavanja received the PHS Meritorious Service Medal for initiating the Agricultural Health Study, the Outstanding Service Medal for work in quantitative risk assessment of environmental carcinogens, and two commendation medals, one for research on environmental causes of cancer and the other for studies of lung cancer etiology. He was a member of the NCI Intramural Advisory Board and is a Fellow of the American College of Epidemiology, serving on its membership committee.*

Epidemiology and Biostatistics Program
Occupational Epidemiology Branch
Lung Cancer Etiology

Research: Our research focuses on interdisciplinary studies to investigate cancer risks associated with environmental and occupational exposures. Both host and environmental risk factors are examined, including possible gene-environment interactions. Studies also include testing and application of innovative methods of exposure assessment.

Lung Cancer
A series of population-based case-control studies of lung cancer among smoking and nonsmoking women identified a number of new etiologic associations. Using an innovative technique to estimate radon exposure retrospectively, we detected a significant dose-response between lung cancer risk and residential radon at levels commonly found in North American and European homes. Environmental tobacco smoke was also found to be a significant risk factor, particularly among half the population with a GSTM1 (null) genotype. In addition, risk of lung cancer was associated with dietary intake of red meat, especially when cooked well done.

The heterocyclic aromatic amine, 2-Amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQX), formed in meat cooked at high temperature, was identified as a risk factor. A protective effect was related to regular consumption of fruits and vegetables. Women with preexisting nonmalignant chronic lung disease were at a 40 percent excess risk of lung cancer. Risks were also significantly elevated among women with a family history of lung cancer. In our Missouri study, we are continuing to examine *p53* and other markers of genetic susceptibility to evaluate potential gene-environment interactions. We are working with investigators at Lawrence Livermore Laboratories to study the health effects of heterocyclic aromatic amine exposure from consumption of meats cooked at high temperature.

Carcinogen Exposures in the Agricultural Environment
Studies around the world have observed that farmers and other agricultural workers are at elevated risk of several specific cancers, despite lower overall mortality and, in particular, cancer mortality. In this occupational group, excess risks are observed for Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, multiple myeloma, and cancers of the brain, skin, lip, stomach, and prostate. Work-related exposures suspected of contributing to the excesses include pesticides, sunlight, viruses, mycotoxins, well-water contaminants, and a variety of other agents encountered in the agricultural environment.

In collaboration with the National Institute of Environmental Health Sciences, the National Institute for Occupational Safety and Health, and the Environmental Protection Agency, we are conducting the Agricultural Health Study to evaluate exposures that may be responsible for the cancer excesses. This prospective cohort study of about 90,000 participants includes licensed private pesticide applicators, their spouses, and commercial pesticide applicators. Cohort members are being followed to collect data on cancer incidence and mortality. An evaluation will also be undertaken on disease risks among spouses and children of farmers. The study includes detailed exposure analyses and assessments of noncancer health outcomes. Epithelial cheek cells are being obtained from cohort members as a source of genomic DNA. Markers of genetic susceptibility will be assessed in a series of nested case-control studies. We are collaborating with investigators at the University of Iowa to evaluate pesticide exposures using fluorescent dyes and to study the epidemiology of injury among cohort members.

Keywords

diet, exposure assessment, lung cancer, pesticides, radon

Recent Publications

Alavanja MC, et al. Residential radon exposure and risk of lung cancer in Missouri. *Am J Public Health* 1999;89:1042–48.

Bennett W, et al. Environmental tobacco smoke, genetic susceptibility, and risk of lung cancer in never-smoking women. *J Natl Cancer Inst* 1999;91:2009–14.

Alavanja MC, et al. Characteristics of persons who self-reported a high pesticide exposure event in the Agricultural Health Study. *Environ Res* 1999;80:180–86.

Mage D, et al. A model for predicting the frequency of high pesticide exposure events in the Agricultural Health Study. *Environ Res* 2000;83:67–71.

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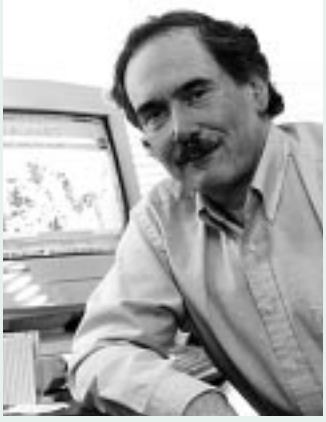

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Biography: *Dr. Cantor received a Ph.D. in biophysics from the University of California at Berkeley and an M.P.H. from the Harvard School of Public Health. He began work with the NCI epidemiology group on detail from the Environmental Protection Agency in 1976, and joined the NCI staff in 1981. Dr. Cantor received the NIH Merit Award for his contributions to the study of drinking water contaminants. He has advised several national and international panels on drinking water and health issues.*

Epidemiology and Biostatistics Program
Occupational Epidemiology Branch
Water Contaminants and Cancer Risk

Research: Our research focuses on general areas of environmental and occupational epidemiology. In the environmental realm, we are investigating the relation between human cancer and exposure to a variety of drinking water contaminants, including chlorination byproducts, nitrate, and arsenic. Other research interests include cancer risks associated with selected occupational exposures, such as pesticides and electromagnetic radiation.

Chlorination Byproducts
Several drinking water contaminants have been identified as potential carcinogens. Prominent among these are byproducts of chlorine disinfection, nitrate, and arsenic. Unintended chemical byproducts resulting from chlorination of drinking water were first discovered in 1974. We have conducted a number of epidemiologic studies to evaluate the carcinogenic risks posed by these byproducts. The first studies were ecologic in design, and pointed to cancers of the bladder, colon, rectum, and certain other sites as candidates for more detailed investigation.

Analyses of data from the National Bladder Cancer Study found an increased risk among persons who had consumed chlorinated surface water (elevated in byproduct levels) for more than 40 years, and who ingested above-median amounts of drinking water. Following up on these results, we conducted a case-control study of six cancer sites (bladder, colon, rectum, brain, pancreas, and kidney) in Iowa. A dose-response relation between duration of chlorinated surface water use and risk of rectal cancer was observed in both men and women, while elevated risks of bladder cancer and brain cancer were noted among men. An excess risk was not detected for cancer of the pancreas or kidney. This research is continuing on several fronts, including developing more precise measures of exposure for participants in the Iowa case-control study, initiating biochemical studies to evaluate the biologic plausibility of our observations, and following up on our initial findings, especially for brain and bladder cancers.

Nitrates
The endogenous formation of carcinogenic N-nitroso compounds can occur following ingestion of nitrate from drinking water. Nitrate is first reduced in the saliva to nitrite, which can react in the stomach with secondary amines and amides. The epidemiologic data are still quite limited on this issue.
An NCI study found a dose-response relation between risk of non-Hodgkin's lymphoma and exposure to elevated nitrate in drinking water. We are implementing additional studies to evaluate further the importance of drinking water nitrate in the etiology of lymphoma and other cancers.

Arsenic
Arsenic is recognized as a carcinogen in humans. It causes lung cancer after exposure to airborne dust, and skin cancer following ingestion of inorganic arsenic in food or water. Studies from Taiwan, Argentina, and Chile reveal that arsenic in drinking water also causes cancers of the lung and bladder, and possibly kidney and other cancers. Exposures in these studies are in the several hundred microgram/liter range. Additional epidemiologic investigation of arsenic carcinogenesis is a high priority, especially since no acceptable animal model exists. We collaborated on a small case-control study that suggested an elevated bladder cancer risk associated with arsenic exposure at relatively low levels in drinking water. We are now pursuing this finding using information from a more recent and larger case-control study of bladder cancer in the same region.

Keywords

arsenic, bladder cancer, chlorination byproducts, colon cancer, drinking water contaminants, nitrate, pesticides, rectal cancer

Recent Publications

Cantor KP, Lynch C, Hildesheim M, Dosemeci M, Lubin J, Alavanja M. Drinking water source and chlorination byproducts in Iowa: I. Risk of bladder cancer. *Epidemiology* 1998;9:21–28.

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Biography: *Dr. Chow received a Ph.D. in epidemiology from the University of Washington School of Public Health. She was on the faculty at Emory University before joining the NCI in 1991. Dr. Chow currently serves on the editorial boards of the* American Journal of Epidemiology *and* Cancer Epidemiology, Biomarkers and Prevention. *Dr. Chow's research focuses on environmental and lifestyle risk factors associated with kidney and gastrointestinal cancers. She is an elected member of the American Epidemiological Society.*

Epidemiology and Biostatistics Program
Occupational Epidemiology Branch

Environmental Risk Factors for Esophageal, Gastric, and Renal Cancers

Research: Variations in cancer incidence rates over time usually are related to changes in the prevalence of environmental risk factors in the population. Similarly, variations in incidence rates across geographic regions may reflect differences in exposure patterns. It is important to study cancers that are rapidly increasing in incidence or that have diverse incidence patterns in various populations for etiologic clues and preventive strategies. Opportunities to pursue these research objectives are particularly feasible when a broad range of exposures can be evaluated to enhance assessment of risk and dose-response relations.

Gastric and Esophageal Adenocarcinomas
Stomach cancer is the second most common malignancy worldwide, even with declines in incidence over the past few decades. Incidence rates vary substantially among populations, with generally high rates in East Asia, tropical South America, and Eastern Europe, and low rates in Western countries. Since Poland has among the highest gastric cancer incidence in Europe, we conducted a case-control study in Warsaw to identify risk factors and prevention measures. Our initial analyses revealed that risks are elevated among smokers and those reporting a family history of stomach cancer in first degree relatives. We also found that proinflammatory genotypes of the cytokine interleukin-1 loci increased both the risk of chronic hypochlorhydric response to *Helicobacter pylori* infection and the risk of gastric cancer. Ongoing analyses are examining risk in relation to other environmental and genetic factors.

Adenocarcinoma of the esophagus is among the fastest rising malignancies in the United States and Western Europe. Rates are also increasing substantially for adenocarcinoma of the gastric cardia. To pursue earlier leads and clarify risk factors for these tumors, we conducted a collaborative population-based case-control study with investigators at Columbia University, Fred Hutchinson Cancer Research Center, and Yale University. Analyses thus far

have confirmed our earlier observation that individuals with longstanding gastroesophageal reflux disease are at increased risk of esophageal adenocarcinoma, whether or not the symptoms are treated with H2 blockers or antacids. While use of medications that relax the lower esophageal sphincter was not related to risk in general, our data suggest that long-term use of certain asthma drugs may increase risk of esophageal adenocarcinoma. We are continuing to evaluate other exposures (e.g., occupational and dietary), family cancer history, genetic polymorphisms, and effect variation by tumor mutation type. Other analyses are examining environmental and host factors that may predict patient prognosis.

Renal Cell Carcinoma

Recent clinical surveys revealed that incidental detection of renal cell carcinoma is rising, partly because of increased use of imaging procedures such as ultrasonography, computed tomography, and magnetic resonance imaging. To clarify the pattern of rising trends of renal cell cancer, we examined data from the NCI Surveillance, Epidemiology, and End Results program. Between 1975 and 1995, rates increased two to three percent among whites and four or more percent among African Americans. Increases were greatest for localized tumors but were also seen for more advanced and unstaged tumors. In contrast, incidence rates for renal pelvis cancer have declined or remained stable. These results suggest that the increasing detection of presymptomatic tumors by imaging procedures does not fully explain the upward incidence trends of renal cell cancer. Ongoing analyses are examining the international incidence patterns of kidney cancer, as well as age-period-cohort patterns in incidence and mortality rates among Caucasian and African Americans in this country.

We previously observed that obesity and hypertension increase the risk of renal cell cancer. The increasing prevalence of these conditions in the United States may be contributing to the rising incidence of this tumor. To quantify the risk and evaluate the effects of changes in weight and blood pressure, we analyzed data from a cohort study of Swedish male construction workers who underwent physical examinations from 1971 to 1992. We found that even small excesses in weight or blood pressure may independently increase the long-term risk of renal cell cancer, while reduction in blood pressure may lower the risk. We are planning further epidemiologic studies to examine other potential genetic and environmental risk factors, including dietary and occupational exposures, and to identify reasons for the higher and more rapid increases in incidence among African Americans than Caucasians in the United States.

Cancer in Women: Occupational and Environmental Risk Factors

Little is known about occupational cancer risks among women. A limited number of studies suggest that women are susceptible to the same carcinogens as men, but their risks may vary due to hormonal, metabolic, genetic, or other gender differences. We are evaluating this issue in a collaborative study with investigators at Vanderbilt University and the Shanghai Cancer Institute. The study is assessing a number of cancer risk factors, with special attention to occupational and environmental exposures, in a cohort of 75,000 women in Shanghai, China. Environmental exposures and biomarkers of genetic susceptibility will be examined in blood, urine,

and buccal cell specimens. The study will become over time an invaluable data resource for identifying carcinogenic exposures and gene-environment interactions in women.

Keywords

esophageal cancer, gastroesophageal reflux disease, *Helicobacter pylori,* hypertension, interleukin-1, obesity, occupation, renal cell carcinoma, stomach cancer, women

Recent Publications

Chow WH, et al. Risk of stomach cancer in relation to consumption of cigarettes, alcohol, tea and coffee in Warsaw, Poland. *Int J Cancer* 1999;81:871–76.

Chow WH, et al. Rising incidence of renal cell cancer in the United States. *JAMA* 1999;281:1628–31.

El-Omar EM, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 2000;404:398–402.

Chow WH, et al. Obesity, hypertension, and the risk of kidney cancer in men. *New Engl J Med* 2000;343:1305–11.

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Epidemiology and Biostatistics Program
Occupational Epidemiology Branch
Exposure Assessment

Research: Our research and development activities include: (1) assessing occupational exposures in cancer epidemiology, (2) evaluating dose-response relationships between occupational exposures and cancer risk in interdisciplinary studies, (3) investigating methodologic issues related to exposure assessment and the effects of exposure misclassification on risk estimates, (4) developing new approaches for assessing the biologically effective dose of occupational exposures, and (5) designing user-friendly programs for mortality analyses and occupational and industrial coding.

Exposure Assessment
Our major research efforts include: (1) developing quantitative exposure estimates on more than 50 pesticides for about 90,000 applicators and their spouses in the Agricultural Health Study; (2) assessing exposures to benzene

and toluene for about 600 benzene-exposed workers in an interdisciplinary biomarker study in China; (3) estimating retrospective occupational exposure to electromagnetic fields (EMF) for about 1,500 participants in a multicenter case-control study of brain cancer; and (4) assigning levels of exposures to diesel, PAH, aromatic amines, and chlorinated hydrocarbons among 3,000 subjects in the interdisciplinary core-control study of bladder cancer in Spain. In addition, individually based exposure estimates are being developed for a number of other projects, including a hospital-based multisite case-control study in Turkey, and a case-control study of nasopharyngeal cancer in Taiwan.

NCI-based job exposure matrices are also being used to develop exposure estimates on about 40 agents for 5,500 participants in a pooled analysis of six U.S. case-control studies of pancreatic cancer; for 7.2 million decedents from a 24-state mortality data resource; for 75,000 women in a prospective cohort study in China; for 10 million people in the Swedish Cancer Environment Registry; and for 600 participants in case-control studies of childhood and adult leukemia in China. In addition, a new approach for estimating a biologically effective dose is being used to assess internal doses of smoking exposure in a case-control study of breast cancer in Buffalo.

Interdisciplinary Studies
A number of ongoing interdisciplinary studies involve complex exposure assessments. In Spain, we are conducting a collaborative case-control study of bladder cancer (1,250 cases and 1,250 controls). Blood is being collected to evaluate genetic susceptibility markers, such as *CYP1A1, NAT1, NAT2, GSTM1*, DNA repair capacity, and mutagen sensitivity; toenail clippings will be assayed for arsenic and selenium exposure. A computer-aided personal interview system is being used to assemble detailed information on cigarette smoking (black versus blond tobacco), occupational and environmental exposures, medical history and drug use, family history, and diet. In 17 regions around St. Petersburg, Russia, an autopsy-based case-control study of lung cancer (500 cases and 500 controls) will evaluate risk factors after obtaining lifetime work and residential histories, assessing exposures to 285 occupational agents and 48 air and water pollutants, and collecting normal and tumor tissues for markers of genetic susceptibility.

Evaluation of Dose-Response Relationships
In a hospital-based multisite case-control study in Turkey (8,000 cancer cases) and a death certificate-based study using occupational mortality data (7.2 million deaths) from 24 states, dose-response relationships are being evaluated between selected cancers and various occupational exposures, such as chlorinated hydrocarbons, metals, organic and inorganic dust, pesticides, acid mists, diesel exhaust, formaldehyde, acrylonitrile, nitrosamines, and electromagnetic fields. Other evaluations of dose-response relationships include: (1) combined effects of silica dust and other mineral exposures and lung cancer risk, (2) occupational exposure to electromagnetic fields and brain cancer risk, and (3) exposure to chlorinated hydrocarbons and gender differences in renal cell carcinoma risk.

Methodologic Activities
Ongoing methodologic activities include developing an exposure assessment procedure to estimate biological effective dose; using genetic susceptibility markers as potential modifying factors; selecting "optimum" exposure

indices, such as intensity, duration, probability, or cumulative exposure, in studies of dose-response relationships; investigating effects of exposure misclassification and confounders on risk estimates; and evaluating the reliability of self-reported occupational exposures in studies of benzene, silica, and pesticides.

Resource Development
Major resource development activities include constructing a user-friendly program for analyzing occupational risks from the study of 24-state mortality data, designing a code-search program for assigning occupational and industrial codes in occupational epidemiology studies, and preparing job-exposure matrices for a number of chemicals. These resources are available to intramural and extramural investigators in the United States and abroad.

Keywords

agricultural exposures, benzene, bladder cancer, case-control studies, chlorinated hydrocarbons, diesel, electromagnetic fields, epidemiologic methods, exposure assessment, formaldehyde, industrial exposures, interdisciplinary studies, job exposure matrices, leukemia, lung cancer, misclassification, occupation, pesticides, prostate cancer, renal cell carcinoma, silica, tobacco

Recent Publications

Dosemeci M, et al. An alternative test for trend in exposure-response analysis. *J Expo Anal Environ Epidemiol* 1998;8:10–16.

Dosemeci M, et al. Gender differences in risk of renal cell carcinoma and occupational exposures to chlorinated aliphatic hydrocarbons. *Am J Ind Med* 1999;36:54–59.

Dosemeci M. Retrospective exposure assessment in large occupational cohort studies in China: Advantages and concerns. *Ann Occup Hyg* 1999;43:377–79.

Elci OC, et al. Occupations and the risk of laryngeal cancer in Turkey. *Scand J Work Environ Health* 2001;27:233–39.

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Epidemiology and Biostatistics Program
Occupational Epidemiology Branch
Genetic and Environmental Determinants of Cancer

Research: Our research involves large-scale, population-based studies into the genetic and environmental determinants of cancer. Investigations of occupational cohorts provide unique opportunities to study cancer risks associated with high-level exposure to chemicals that are also found in the general environment, but at substantially lower levels. Cohort and case-control studies in the general population are undertaken to investigate factors influencing cancer risks, including gene-environment interactions.

Chemical Carcinogens in the Workplace

The spectrum of disease and level of risk associated with benzene exposure are not well understood, although the chemical is an important environmental and occupational exposure. Results from our epidemiologic investigations of benzene-exposed workers in China suggest that benzene is associated with a variety of hematologic neoplasms besides leukemia, and that excess risks occur at lower exposure levels than previously established. Myelodysplastic syndromes were also linked to benzene exposure. Furthermore, biochemical studies in this population identified benzene-related cytogenetic effects and genetic susceptibility factors. The studies also showed that the proportion of benzene metabolized to toxic compounds decreases as exposure increases. Work is continuing to evaluate risk of nonhematologic neoplasms and to characterize dose-response patterns at relatively low levels of exposure.

1,3-butadiene is used in the production of synthetic rubber and found in automobile exhaust and cigarette smoke. The chemical is genotoxic and carcinogenic in experimental animals, but there is only limited evidence of its carcinogenicity in humans. To elucidate further the effects of 1,3-butadiene in humans, we conducted a study that found increased lymphocyte and platelet counts and higher levels of a butadiene-associated hemoglobin adducts in exposed workers. However, no differences were found in cytogenetic

abnormalities (measured by fluorescence in situ hybridization) and somatic mutations (measured by glycophorin A and hprt assays). We are continuing to develop biologic markers of exposure to 1,3-butadiene and to evaluate its cytogenetic effects.

Formaldehyde exposure occurs among pathologists, anatomists, and workers in the funeral industry. It is also a ubiquitous environmental chemical, which has been found to cause nasal carcinomas in laboratory rats. We showed that workers in the funeral industry have excess malignancies of the lymphatic and hematopoietic systems, including myeloid leukemia and multiple myeloma. Our studies of embalming identified work practices associated with high exposure to formaldehyde, which increased risks of nasal epithelial and lymphocyte micronuclei and decreased lymphocyte O^6-alkylguanine DNA alkyltransferase activity. An ongoing case-control study of leukemia and related disorders is assessing risk in relation to work practices in the funeral industry and formaldehyde exposure.

Genes and the Environment

We are examining risk factors for prostate cancer in a large case-control study among African-American and white men in three regions of the United States. The study has thus far shown that risk increases among men whose brothers and fathers have a history of prostate cancer. Also, heavy alcohol use appears to be a risk factor. We recently showed a relationship between increased risk of prostate cancer and sexual behavior and sexually transmitted diseases, suggesting that a subset of this cancer may be due to a sexually transmissible agent.

In a case-control study in Puerto Rico, we found that risk of alcohol-related oral cancer was magnified among persons who had the *ADH31-1* genotype, a trait associated with efficient metabolism of alcohol to the toxic metabolite acetaldehyde. A substudy showed that smokers are at an increased risk of salivary gland tumors. We are investigating other genetic factors associated with the metabolism of alcohol and tobacco-related compounds in relation to risk of oral cancer.

A large cohort study of cancer etiology is being carried out within the NCI Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. The screening arm is examining the 74,000 participants over a 6-year period, and following them for cancer occurrence for 13 years through annual followup mailings. Thus far, more than 65,000 participants have had an initial screen. Biologic samples are collected at each screening exam. By the study's conclusion, we expect to observe more than 1,500 cases of prostate, lung, and colorectal cancers in the screened arm. Because of the prospective design, screening exams, and sequential prediagnostic blood sample collections, we will be able to evaluate temporal changes in biomarkers to the subsequent development of cancer. Our initial analyses are focusing on genetic and environmental determinants of adenomatous polyps and colorectal cancer, with additional studies being planned for other cancers.

Keywords

adenomatous polyps, African Americans, alcohol, benzene, butadiene, colorectal cancer, formaldehyde, gene-environment interactions, genetic susceptibility, industrial exposures, oral cancer, prostate cancer

Recent Publications

Hayes RB, et al. Tobacco and alcohol use and oral cancer in Puerto Rico. *Cancer Causes Control* 1999;10:27–33.

Hayes RB, et al. Sexual behaviour, STDs and risks for prostate cancer. *Br J Cancer* 2000;82:718–25.

Hayes RB, et al. Genotoxic markers among butadiene polymer workers in China. *Carcinogenesis* 2000;21:55–62.

Marcus PM, et al. Cigarette smoking, N-acetyltransferase 2 acetylation status, and bladder cancer risk: A case-series meta-analysis of a gene-environment interaction. *Cancer Epidemiol Biomark Prev* 2000;9:461–67.

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Epidemiology and Biostatistics Program
Occupational Epidemiology Branch
Molecular Markers and Cancer Risk

Research: We are investigating the role of various markers to measure the biological effects of carcinogens in human tissues. We use early biomarkers of effect such as the micronucleus assay and fluorescence in situ hybridization in human lymphocytes and exfoliated cells to look for exposure-dependent increases in genetic damage and aneuploidy in exposed individuals. We also use DNA to examine whether individuals carrying variant genotypes or polymorphisms of metabolism genes may be more susceptible to environmental carcinogens and thus more susceptible to cancer than those carrying wild-type copies of the same genes. More recently with the genomics revolution, this work has expanded to examine tumor tissues, DNA, and RNA using methods such as comparative genomic hybridization, immunohistochemistry, and arrays to determine how exposed tumors are different from unexposed tumors in the genetic changes they carry and the genes and proteins they express.

Molecular Epidemiology of Environmental Arsenic Exposure
Inorganic arsenic is considered one of the highest priority public health concerns, particularly because of its clear carcinogenic potential. The study of arsenic has worldwide and national importance since millions of people are currently exposed to low levels of naturally occurring arsenic in their drinking water. Arsenic is also considered the number one priority carcinogen by the Agency for Toxic Substance and Disease Registry, and currently the Environmental Protection Agency is considering a new maximum contaminant level for arsenic in drinking water. Although arsenic is an established human carcinogen that has been well studied in past years, the mechanism and dose at which it causes cancer are still unclear. Genetic studies comparing tumors from exposed and unexposed individuals can provide insight into the mechanism of chemically induced cancers. We conducted a case-case study comparing high and low arsenic-exposed tumors from Argentina and Chile. We used comparative genomic hybridization to define genetic aberrations throughout the genome, *p53* mutational spectrum analysis, and immunohistochemistry to determine if exposed and unexposed tumors were different. It was found that bladder tumors associated with higher levels of arsenic exposure showed increased chromosomal instability, and that most of the

specific chromosome changes associated with arsenic exposure were also associated with tumor stage and grade, suggesting that arsenic-exposed tumors may behave more aggressively, resulting in increased bladder cancer mortality. We also used *p53* mutational spectrum analysis to determine if the frequency, type, and location of *p53* mutations in exposed and unexposed tumors were different. Although the overall frequency of mutations was not different, we found that the type of mutations was different in exposed and unexposed tumors. While tumors associated with tobacco smoke contained more G to A transitions at CpG sites, arsenic-exposed tumors demonstrated an increase in the frequency of transversions at only nonCpG sites.

We are also examining variations in arsenic susceptibility using blood measurements of micronutrients, phenotypic markers of arsenic methylation and detoxification, and genetic markers of susceptibility in populations of India and South America. Evidence of a genetic contribution to methylation-mediated detoxification patterns was investigated in families using urinary methylation as a phenotypic marker of metabolism. There are plans to extend arsenic studies to include exposed regions in Inner Mongolia and New England.

Molecular Epidemiology of Renal Cell Carcinoma
Renal cell carcinoma has several known risk factors including obesity, hypertension, and cigarette smoking. TCE and other organic solvents are suspected carcinogens. Enzymes that biotransform carcinogens have high levels of activity in the kidney yet polymorphisms in genes that encode for these enzymes have received little study. Similarly, the relationship between genes involved in obesity, hypertension and renal cancer have not been examined. We are currently investigating whether the presence of polymorphisms in metabolism, hypertension, and obesity genes may increase renal cell cancer risk in patients enrolled in a multicenter Eastern European kidney cancer study. We are examining the von Hippel-Lindau (VHL) gene in tumor DNA from cases for exposure-specific inactivation via mutation and methylation. We also plan to conduct expression array analyses using RNA from a subset of cases to determine if environmental or host factors modify gene expression in renal tumors.

Keywords

arsenic, bladder cancer, genetic susceptibility, renal cell carcinoma, tumor markers

Recent Publications

Biggs RH, et al. Arsenic-laced water in Chile. *Science* 1998;281:785.

Steinmaus C, et al. Arsenic in drinking water and bladder cancer. *Cancer Invest* 2000;18:176–84.

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Moore LE, et al. Evaluation of buccal cell collection protocols for genetic susceptibility studies. *Biomarkers* 2001;6(6):448–54.

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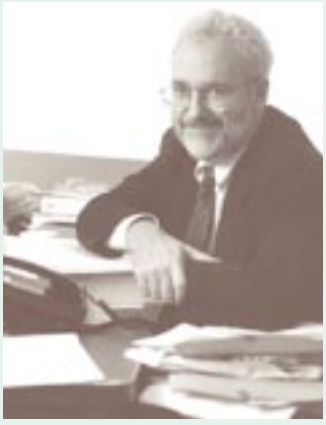

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Epidemiology and Biostatistics Program
Occupational Epidemiology Branch

Molecular Epidemiology Studies of Occupational and Environmental Causes of Cancer

Research: We are using biomarkers of exposure, early biologic effect, and genetic susceptibility to investigate the carcinogenic potential and mechanism of action of proven or suspected occupational and environmental compounds; to evaluate the influence of interindividual variation in metabolism on the formation of important early biologic markers, such as DNA adducts and cytogenetic aberrations; and to assess the risk of premalignant conditions and cancer associated with exposure to occupational and environmental agents.

Benzene

Benzene is an established human leukemogen, and it may also cause non-Hodgkin's lymphoma and other cancers. However, its mechanism of action is uncertain, and its ability to cause cancer at low levels of exposure is unknown. We carried out a study of healthy workers exposed to high levels

of benzene in China to identify mechanistically based biomarkers that reflect early biologic effects of benzene. We observed an increased frequency of cytogenetic and genetic alterations in peripheral white blood cells (e.g., t8;21, del(5q), del(7q), 5-,7-, AML-1/ETO fused transcript). These markers are relevant for leukemia and support the hypothesis that benzene's mechanism of action is mediated through chromosomal damage. An important unanswered question concerns the biologic effect of low exposure levels in the occupational setting and from environmental sources experienced by the general population. In a new investigation, we will be applying the most sensitive and specific biomarkers for benzene exposure to determine if the cytogenetic and molecular events observed in our previous study also occur among workers exposed to relatively low levels of benzene.

Aromatic Amines

We found that among workers in India exposed to the aromatic diamine benzidine, N-acetylated benzidine was the predominant DNA adduct in exfoliated urothelial cells. This finding documented that acetylation activates rather than detoxifies benzidine in humans, in contrast to the deactivation role of acetylation for aromatic monoamines, such as 4-aminobiphenyl. We also showed that urine pH, which is influenced primarily by the diet, had a profound influence on DNA adducts levels. This finding is consistent with previous in vitro results that acidic urine hydrolyzes glucuronidated aromatic amines, which enables free compounds to bind DNA. This research indicates that gene-environment interactions can be highly exposure-specific, and that nongenetic sources of susceptibility may interact with xenobiotic exposures and play an important role in determining an individual's cancer risk. We are pursuing these findings in a large case-control study of bladder cancer in Spain, which will for the first time combine state-of-the-art industrial hygiene exposure assessment techniques with biomarkers of genetic susceptibility. The effort will provide the opportunity to evaluate interactions between aromatic amine exposure from occupational and environmental sources, polymorphisms in relevant activating and detoxifying genes (e.g., *NAT1, NAT2, GSTM1*), and urine pH.

Organochlorines

The reasons for the steady increase in the incidence of non-Hodgkin's lymphoma since the late 1940s remain mostly unknown. To evaluate exposure to organochlorines, which are ubiquitous environmental contaminants and suspected human carcinogens, on the risk of non-Hodgkin's lymphoma, we conducted a nested case-control study within a cohort of 25,802 healthy subjects who provided blood samples in 1974. We found that serum PCB levels were strongly associated with subsequent risk of non-Hodgkin's lymphoma and that the effect was potentiated by seropositivity for the Epstein-Barr virus early antigen. We are following up these observations in similarly designed prospective studies.

Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) may play a role in the etiology of gastrointestinal tract cancers. These compounds may act directly as carcinogens or indirectly through the induction of enzymes that activate other potential carcinogens, such as heterocyclic aromatic amines. It has been difficult to assess PAH exposure using standard epidemiologic methods,

because humans are exposed from many different sources, including occupational, environmental, dietary, and tobacco. We demonstrated that various PAH metabolites and macromolecular adducts can be used to integrate major sources of recent exposure. We are applying these findings to a newly completed case-control study of colon adenomas to evaluate the relation between risk and PAH metabolites and adducts in urine and peripheral white blood cells. We will also use a database developed with the U.S. Department of Agriculture on dietary sources of PAH, as well as occupational and environmental exposure assessment methods, to estimate long-term PAH exposure and its influence on adenoma risk. We plan to apply these methods in case-control studies recently completed in Poland, the United States, and China to evaluate PAH exposure on risk of stomach and esophageal cancer, and to assess the interaction between PAH exposure and polymorphic genes (e.g., *CYP1A1, GSTM1,* and *NQO1*) that activate or detoxify these compounds.

Keywords

aromatic amines, benzene, benzidine, genetic susceptibility, molecular epidemiology, occupation, organochlorines, polycyclic aromatic hydrocarbons (PAHs), polymorphic genes

Recent Publications

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Rothman N, et al. The impact of misclassification in case-control studies of gene-environment interactions. *IARC Sci Publ* 1999;148:89–96.

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Rothman N, et al. The use of common polymorphisms to enhance the epidemiologic study of environmental carcinogens. *Biochim Biophys Acta* 2000;87:1–10.

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Biography: *Dr. Silverman received an Sc.D. in epidemiology from the Harvard School of Public Health and an Sc.M. in biostatistics from The Johns Hopkins Bloomberg School of Hygiene and Public Health. She joined the NCI as a biostatistician in 1972 and has served as a cancer epidemiologist since 1983. She was appointed an adjunct faculty member in the Department of Family Medicine at Georgetown University School of Medicine in 1984. Dr. Silverman received the PHS Special Recognition Award for research on environmental determinants of bladder and other cancers, the American Occupational Medical Association Merit in Authorship Award for her paper on a job/exposure linkage system, the NIH Merit Award, and the PHS Lucy Minnigerode Award for research on diesel exhaust markers. She was a finalist for the CDC Alice Hamilton Science Award for Occupational Safety and Health for her research on diesel exhaust exposure and lung cancer. Dr. Silverman is an elected member of the American Epidemiological Society and a Fellow of the American College of Epidemiology.*

Epidemiology and Biostatistics Program
Occupational Epidemiology Branch
Environmental and Host Determinants of Cancer

Research: Our research involves the design and conduct of epidemiologic investigations to evaluate environmental and host determinants of cancer. We closely monitor new findings from clinical observations, experimental studies, and descriptive and analytic epidemiology for leads as to causes of cancer. My research focuses particularly on the etiology of cancers of the bladder and pancreas and on the carcinogenic effects of diesel exhaust.

Pancreatic Cancer

We are conducting epidemiologic studies to identify risk factors that play a role in the etiology of pancreatic cancer and, in particular, contribute to the high rates experienced by African Americans. Because of the poor prognosis associated with this cancer, many previous case-control studies were based largely on interviews with proxy respondents, who often lacked detailed information on relevant environmental exposures. We addressed this shortcoming in a population-based case-control study in the United States in which more than 500 cases and 2,100 controls were interviewed directly. Our findings confirmed the causal link between cigarette smoking and risk of pancreatic cancer. Although consumption of alcohol at levels typically consumed within the general population did not appear to be associated with risk, heavy drinking may increase risk. Both African-American men and women had significantly higher risks associated with heavy alcohol drinking than whites. Obesity also increased risk of pancreatic cancer and appeared to contribute to the higher rates observed among African Americans, particularly among women. A role for energy balance in pancreatic carcinogenesis was suggested by a significant interaction between body mass index and total caloric intake, which was consistent by race and gender. Diabetes mellitus also increased pancreatic cancer risk, as well as being a possible complication of the tumor. These findings support the key role played by hyperinsulinemia in pancreatic carcinogenesis, particularly among nondiabetics with elevated

body mass index. An increased risk was also observed among first-degree relatives of affected individuals. A link to hereditary nonpolyposis colon cancer was suggested by elevated risks associated with a family history of cancers of the colon, endometrium, ovary, and breast. We are currently assembling pathologic samples from the histologically confirmed cases of pancreatic cancer, which we will examine for genetic and tumor-specific markers. The markers will also be evaluated for associations with data already collected on risk factors.

Bladder Cancer

Bladder cancer is recognized as an occupationally related tumor. During the past three decades, scores of bladder cancer studies have suggested more than 40 high-risk occupations, yet the specific exposures responsible for most of the excess risks remain largely unknown. Suspect occupational bladder carcinogens include diesel exhaust, oil mist, solvents, polycyclic aromatic hydrocarbons, aryl hydrocarbons, asbestos, and aromatic amines and their derivatives, such as methylene-bis-orthochloroaniline, dichlorobenzidine, orthotoluidine, magenta, auramine, and azo dyes. To clarify the role of these occupational agents, we are using newly developed techniques of exposure assessment in a case-control study of bladder cancer in heavily industrialized areas of Spain. The study will also evaluate several nonoccupational exposures, including cigarette smoking (black versus blond tobacco), phenacetin-containing analgesics, dietary factors, urinary tract infections, urination habits, urinary pH, fluid intake, and air and water pollution. Biologic specimens are being collected, which will be used to examine genetic susceptibility (e.g., *CYP1A1, CYP1A2, NAT1, NAT2, GSTM1,* DNA repair capacity, and mutagen sensitivity) and tumor markers (e.g., *H-ras* and *p53*) on risk of bladder cancer, and on their interaction with epidemiologic risk factors.

Carcinogenicity of Diesel Exhaust

Diesel exhaust is a general airborne contaminant that is classified by the International Agency for Research on Cancer as a probable human carcinogen. Exposure is ubiquitous in cities and among commuters who regularly use highways. Occupational exposures are common among transportation workers and operators of diesel-powered equipment. Some workers, such as miners who use diesel-powered equipment underground, may experience high levels of exposure. Although at least 30 studies have examined lung cancer risk and diesel exhaust, few used quantitative exposure measurements of diesel exhaust directly in their analyses. As a consequence, the risk of lung cancer associated with diesel exhaust is still not well defined. In collaboration with the National Institute for Occupational Safety and Health, we are conducting a retrospective cohort mortality study and nested case-control study of lung cancer among nonmetal miners to estimate lung cancer risk in relation to quantitative measures of exposure to diesel exhaust. Excess mortality from other causes of death will also be evaluated. An intrinsic part of this research effort is an extensive effort to characterize current and historical exposures to diesel exhaust and to develop estimates of personal exposures.

Keywords

alcohol, bladder cancer, diesel, energy intake, lung cancer, obesity, occupation, pancreatic cancer

Recent Publications

Silverman DT, et al. Dietary and nutritional factors and pancreatic cancer: A case-control study based on direct interviews. *J Natl Cancer Inst* 1998;90:1710–19.

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Boffetta P, Silverman DT. A meta-analysis of bladder cancer and diesel exhaust exposure. *Epidemiology* 2001;12:125–30.

Silverman DT. Risk factors for pancreatic cancer: A case-control study based on direct interviews. *Teratog Carcinog Mutagen* 2001;21:7–25.

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Biography: *Dr. Stewart received a Ph.D. in industrial hygiene from The Johns Hopkins School of Hygiene and Public Health and joined the NCI in 1982. Her research focuses on conducting exposure assessments for epidemiologic studies, improving assessment procedures, and evaluating the reliability and validity of assessment techniques. Dr. Stewart received the NIH Merit Awards for developing procedures for estimating exposures in occupational studies and for developing a computer system for assessing occupational exposures, a Federal Technology Transfer Act Award for designing questionnaires for occupational studies, and a DCEG Intramural Research Award for comparing exposure estimates from questionnaire responses with actual measurement data.*

Epidemiology and Biostatistics Program
Occupational Epidemiology Branch

Exposure Assessment for Occupational Epidemiologic Studies of Cancer

Research: Establishing exposure-response relationships is crucial in determining causal associations with human disease. Historically, duration of employment in a job or industry served as a surrogate for exposure in many occupational investigations. However, this crude method of exposure assessment can be grossly inaccurate and may fail entirely to detect exposure-response relationships because of misclassification. Current day assessment methods can more closely estimate actual exposures and reduce the likelihood of missing a relationship with disease risk. Our research focuses on conducting exposure assessments for cohort and case-control studies, improving exposure assessment procedures, and undertaking methodologic projects to determine the reliability and validity of assessment techniques.

Cohort Studies

We conducted extensive exposure assessments for several cohort studies, including ones of dry cleaners, aircraft maintenance workers, and industrial workers exposed to formaldehyde and acrylonitrile. An ongoing exposure assessment involving diesel fumes among underground miners at eight sites is being developed based on work histories, measurement data, and descriptive information. In another effort, we are exploring the feasibility of conducting a cohort study among migrant farm workers, which would involve an exposure assessment of pesticides and other agricultural agents.

Case-Control Studies

Exposure assessment in case-control studies is less sophisticated than in cohort investigations, since measurement data are not available on the study subjects. However, case-control designs offer the advantage of being able to ascertain information on potential confounding factors and to collect biologic tissues for studies of gene-environment interactions. To overcome the limitation on lack of measurement and descriptive data, detailed questionnaires

targeted toward occupation are administered to study subjects and their responses are reviewed by an industrial hygienist. We have completed or have ongoing exposure assessments for case-control studies of leukemia, non-Hodgkin's lymphoma, multiple myeloma, and cancers of the brain, larynx, breast, esophagus, prostate, stomach, bladder, kidney, nasopharynx, and pancreas.

We are developing ways to better assess information collected in questionnaires and other survey instruments with exposure data. We are also conducting research to document use patterns and exposure levels for chemical agents under assessment. In addition, criteria are being developed for describing how exposure levels are estimated in the absence of measurement data. Publication of chemical use patterns, exposure levels, and exposure estimation criteria should improve the accuracy and reliability of exposure assessment. We are currently examining these features for pesticides, polychlorinated biphenyls, solvents, wood dust, and diesel fumes.

Methodologic Studies

We are conducting methodologic studies to evaluate the quality of exposure assessment and improve assessment techniques. Ongoing projects are developing computerized exposure assessment programs to facilitate exposure assessments in epidemiologic studies with cohort or case-control designs. Both programs will be available to the research community. Using air and biologic measurements in Shanghai, China, another effort is evaluating how well occupational questionnaires compare to traditional approaches for assessing exposures.

Keywords

acrylonitrile, agricultural exposures, case-control studies, cohort studies, diesel, epidemiologic methods, exposure assessment, formaldehyde, industrial exposures, occupation, pesticides, polychlorinated biphenyls, solvents

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Vaughan TL, et al. Occupational exposure to formaldehyde and wood dust and nasopharyngeal carcinoma. *Occup Environ Med* 2000;57:376–484.

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Biography: *Dr. Ward received an M.S. in ecology from the University of Tennessee and a Ph.D. in epidemiology from The Johns Hopkins School of Hygiene and Public Health. Her research focuses on environmental and occupational causes of cancer, with special emphasis on pesticides and nitrates in relation to the etiology of non-Hodgkin's lymphoma, childhood leukemia, and gastric cancer. Dr. Ward is examining the etiologic role of nitrosamines and their precursors with respect to drinking water and dietary ingestion for cancers of the brain, bladder, colon, pancreas, stomach, esophagus, and nasopharynx. She is responsible for developmental work using geographic information systems for exposure assessment of environmental contaminants. For this effort, she received a DCEG Intramural Research Award in 1999 and an NIH Merit Award in 2000.*

Epidemiology and Biostatistics Program
Occupational Epidemiology Branch

Nitrates, Pesticides, and Cancer and Environmental Exposure Assessment

Research: We are using innovative methods such as geographic information systems (GIS) to display and analyze environmental exposure data. Using GIS and remote sensing data, we are participating in interdisciplinary collaborations to develop new methods of exposure assessment for epidemiologic studies of cancer risk in relation to drinking water contaminants and agricultural pesticides.

Nitrates
The endogenous formation of carcinogenic N-nitroso compounds can occur following ingestion of nitrate from drinking water. Certain foods are also sources of these agents. Only a limited number of analytic epidemiologic studies have evaluated this exposure issue with respect to diet and drinking water. We conducted a case-control study that found a dose-response relation between risk of non-Hodgkin's lymphoma and prior exposure to elevated nitrate in drinking water. Additional analytic studies are under way to evaluate further the importance of drinking water nitrate in the etiology of lymphoma, leukemia, and cancers of the brain, bladder, colon, kidney, pancreas, stomach, and esophagus.

An analysis of dietary intake of volatile N-nitroso compounds and risk of nasopharyngeal cancer (NPC) was the first study of NPC to estimate relative intake levels of these compounds from dietary sources. Higher intakes during early childhood were associated with elevated risk of NPC in adults. An analysis of individual food groups failed to show significant associations with risk, illustrating the importance of considering N-nitroso compound intake across all foods.

To further evaluate the possible role of drinking water nitrate exposure in the development of cancer, we are conducting an ecologic study of cancer

incidence in the Platte River Valley of Nebraska and Colorado, an area with some of the highest drinking water nitrate levels in the country. Population exposure via both community water supplies and private wells is being characterized at the block group level. Annual monitoring data is being used to characterize the population exposed to nitrate through community water systems. Through an interdisciplinary collaboration with colleagues in hydrology, engineering, and remote sensing, information about land use, fertilizer application rates, the location of livestock feeding operations, soil type, and other factors are being incorporated into a GIS to estimate levels of nitrate in drinking water for the population using private wells.

Pesticides

A feasibility study using remote sensing data and a GIS to estimate indirect exposure to pesticides demonstrated that using available data, accurate historical crop maps could be produced and that these could be linked to pesticide use data to estimate probabilities of indirect exposure to agricultural pesticides. A total of 24 percent of the study population in an agricultural area were determined to live within 500 meters of crop fields likely to have been treated with pesticides. This was the first study to estimate the prevalence of potential indirect exposure to agricultural pesticides in the general population. Further work in this area by our collaborators included the development of a method to automate crop mapping from satellite imagery. The method was found to be successful at classifying crops into two categories, corn and other crop types, over a 15 county area of Nebraska. We are continuing to refine the GIS-based approach to estimating agricultural pesticide exposure by incorporating information from a pesticide drift model. A validation study is under way in Iowa to compare agricultural pesticide levels in carpet dust samples with several GIS-based exposure metrics including one that incorporates information on wind direction and pesticide drift.

With collaborators in California, we are planning to evaluate agricultural pesticide use near residences as a risk factor for childhood leukemia in an ongoing study. Carpet dust samples will be analyzed for pesticides, and information about the current and historical location of crops near residences will be determined.

Chemicals

Using a GIS, residential proximity to specific industries, hazardous waste sites, and specific chemical releases as reported by the Environmental Protection Agency's Toxic Release Inventory are being evaluated in a recently completed study of non-Hodgkin's lymphoma at four centers. Plans are under way to do a similar type of an analysis in a new bladder cancer study in New England.

Keywords

agricultural exposures, bladder cancer, brain cancer, drinking water contaminants, exposure assessment, geographic information systems, nitrate, N-nitroso compounds, non-Hodgkin's lymphoma, stomach cancer

Recent Publications

Ward MH, Zahm SH, Blair A. Pesticides and cancer risk: Clues from epidemiology studies of farmers and the general population. *Pesticides People Nature* 1999;1:25–32.

Ward MH, et al. Dietary exposure to nitrite and nitrosamines and risk of nasopharyngeal carcinoma in Taiwan. *Int J Cancer* 2000;86:603–09.

Ward MH, et al. Identifying populations potentially exposed to agricultural pesticides using remote sensing and a geographic information system. *Environ Health Perspect* 2000;108:5–12.

Ward MH, Prince JR, Stewart PA, Zahm SH. Determining the probability of pesticide exposures among migrant farmworkers: Results from a feasibility study. *Am J Ind Med* 2001;40:538–53.

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The Radiation Epidemiology Branch carries out studies to identify and quantify the risk of cancer in populations exposed to radiation, alone or in combination with other agents, as well as to elucidate biological mechanisms of radiation carcinogenesis. Studies of radiogenic tumors contribute to an understanding of carcinogenesis in general, since models based on their findings often are relevant to other types of exposures.

The Branch conducts research in response to both scientific and public policy issues. These issues often arise jointly when there is widespread exposure to radiation, such as from the Chornobyl nuclear reactor accident, radioactive fallout from nuclear weapons production and testing, indoor radon, medical diagnostic and therapeutic procedures, and nonionizing radiation sources, such as power lines and cellular phones. Data from our studies are considered by national and international radiation protection agencies in quantifying risks and setting population and occupational exposure standards. Our findings are also used by organizations in preparing radiation-related reports, such as by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and the National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation (BEIR). Because our radiation epidemiology program is the largest and most diverse in the world, we often serve as advisors to national and international committees evaluating the health effects of radiation exposure.

We carry out investigations of radiation exposures wherever opportunities arise for advancing our knowledge of radiation carcinogenesis. Many opportunities occur outside of the United States, which has led to large and complex multicenter, international studies with collaborators at research institutions around the world. Major areas of research include cancer risks associated with exposures to ionizing radiation, such as medical, occupational, and environmental exposures; and to nonionizing radiation, such as magnetic fields and radio-frequency waves. Other research is aimed at examining the long-term health outcomes of various cancer therapies, evaluating the effects of radiation exposures among persons with genetic susceptibility to cancer, reconstructing radiation exposure histories, and developing methods and computer programs for radiation risk analyses. Study designs often include the collection of biologic specimens for evaluating markers of exposure, gene-environment interactions, and molecular "signatures" of radiation-associated tumors.

Medical Radiation Exposures
Studies of populations exposed to medical irradiation provide opportunities to quantify late radiation effects. Ongoing and past studies involve about 20 medically exposed populations. These studies include evaluations of cancer risk in patients given diagnostic I-131, patients with tuberculosis who received multiple chest fluoroscopies, patients treated with radiotherapy for benign head and neck conditions during childhood, patients who received frequent diagnostic X-rays for scoliosis, and patients with long-term exposure to radioactive Thorotrast.

We are currently estimating risk of cancer after exposure to Thorotrast among several large populations. Thorotrast, once used as an angiographic contrast agent, is not excreted from the body to any appreciable extent, and has been shown to induce high rates of liver angiosarcoma and leukemia. A recently completed 40-year mortality followup study of 693 Thorotrast-treated Swedish patients with neurological disorders found a significant dose-response relation for all causes of death combined, and for all malignant tumors combined.

We found that women who received multiple diagnostic X-rays during childhood and adolescence for scoliosis, an abnormal curvature of the spine, were at increased risk of dying of breast cancer. The 5,466 women in the study were younger than age 20 at diagnosis, which occurred between 1912 and 1965, and received an average of 25 X-rays. A 70 percent higher risk of breast cancer was detected among these women compared with women in the general population. The mean age of scoliosis diagnosis was 11 years, and the average length of followup was 40 years.

Occupational and Environmental Radiation Exposures
Quantitative information on chronic occupational or environmental exposure to radiation is necessary to establish public health and radiation standard setting. The best quantitative information for estimating health risks is derived from studies of populations that have experienced brief and high-dose exposures. Still, these estimates are subject to uncertainties associated with the shape of the dose-response functions and may not be directly applicable to situations where exposures are delivered over many years.

A number of studies are under way to evaluate cancer risks in populations that have been chronically exposed to radiation from occupational or environmental sources. These studies include thyroid cancer among people in Belarus and Ukraine who were exposed as children to fallout from the Chornobyl nuclear reactor accident; leukemia risk among Chornobyl clean-up workers; populations exposed to radioactive fallout from nuclear testing in the former Soviet Union; and cancer incidence and/or mortality among populations exposed to chronic radiation from the Mayak nuclear facility in Russia, radiologic technologists, and atomic bomb survivors.

Mayak nuclear facility workers comprise a unique cohort that was exposed to protracted, external radiation at high doses and to plutonium. Mortality analyses showed excess risks of bone and liver cancers, with higher risks among female workers than male workers, related to internal exposure to plutonium. In addition, initial analyses of external exposure to radiation revealed dose-response relationships for leukemia and all solid cancers.

X-ray technologists are potentially exposed to small doses of radiation over many years, with some technologists receiving cumulative doses of up to 0.2 Gy. A U.S. occupational cohort of over 100,000 certified radiation technologists, 73 percent of whom are female, offers the opportunity to study low-dose effects on the breast and thyroid, two radiation-sensitive organs. When the second health effects survey of technologists is completed, the cohort will be a valuable resource for studies of a variety of cancers. Efforts are under way to link individual work histories with dosimetry data and to collect biologic specimens for biomarker and genetic studies. The Life Span Study of 120,000 atomic bomb survivors in Japan is the primary source of quantifying radiation risks. In collaboration with the Radiation Effects Research Foundation, we are studying the effects of radiation on the incidence of tumors of the central nervous

system, thyroid, breast, ovary, and lymphoid tissue. Results thus far show variations in radiation effects by cell type, for example, a highly significant dose-response relationship for neurilemomas but not for gliomas. Among female atomic bomb survivors, a case-control study of breast cancer revealed that a high level of bioavailable estradiol is a risk factor.

We are also developing and improving dose reconstruction methods for use in epidemiologic studies. These efforts include enhancing dosimetry methods for radioactive fallout from nuclear testing and other radioactive releases, estimating individual doses for radiologic technologists, calculating radiation doses to specific parts of large body organs, and measuring electromagnetic fields. In addition, we are continuing to develop methods for analyzing epidemiologic data which takes into account uncertainty in dosimetry.

Nonionizing Radiation Exposures
Public and scientific interest in the long-term health effects from exposures to nonionizing radiation has increased substantially in recent years. Epidemiologic studies of cancer risk associated with magnetic field exposure have been inconsistent. To address this issue, we are conducting comprehensive investigations to improve our understanding of risks related to this exposure. We found that the recent use of hand-held cellular telephones did not increase the risk of brain tumors, and additional efforts are under way to evaluate other possible etiologic factors for brain tumors. Studies of residential magnetic field exposure metrics and risk of childhood leukemia found that most metrics were positively correlated with a time-weighted average metric, and that it was not associated with leukemia risk.

Health Effects of Cancer Radiotherapy and Chemotherapy
For many years, we have systematically evaluated the health effects related to cancer chemotherapeutic drugs, alone and in combination with radiotherapy. As more individuals become long-term cancer survivors, there is greater need to evaluate risk-benefit ratios for various treatment protocols. In one study, we showed that platinum-based chemotherapy for ovarian cancer was linked to a four-fold excess risk of leukemia. However, the substantial benefit of this treatment outweighs the relatively small increased leukemia risk. In another study, a three-fold elevated risk of leukemia was found among testicular cancer patients receiving radiotherapy, with risks rising with increasing radiation dose to active bone marrow. Radiotherapy was also associated with a small increase in the risk of second solid tumors among long-term survivors of prostate cancer.

We are currently conducting an international cohort study of 32,000 Hodgkin's disease patients to evaluate the risk of radiation and chemotherapy-induced second cancers. A substudy of 6,000 children and adolescents with Hodgkin's disease indicates a high risk for second cancers of the thyroid and respiratory tract for patients treated before age 10. At older ages, the highest risks were observed for cancers of the digestive tract and breast.

In collaboration with the International Bone Marrow Transplant Registry in Milwaukee and the Fred Hutchinson Cancer Research Center in Seattle, we have assembled a cohort of over 28,000 patients with allogenic bone marrow transplants at 235 centers. A recent finding revealed that long-term allogeneic bone marrow transplant survivors of childhood leukemia have an excess risk of solid tumors and lymphoproliferative diseases. This finding indicates that transplant recipients, especially those given radiation, should be monitored closely for second cancers. A cohort of 16,000 autologous transplantation patients is also being followed for second cancers, whose risk will be evaluated in relation to the intensive pretransplant antilymphoma therapy and possible carcinogenic exposures during the transplant procedure.

Training
The Branch offers fellowships in radiation epidemiology under the NCI Cancer Research Training Award Program and the NIH Visiting Scientist Program. Fellows receive training in radiation epidemiology, biostatistics, radiation biology, and risk assessment of radiation-related cancer. Fellowships provide unique

opportunities to conduct research on populations exposed to a variety of radiation sources. Academic courses are offered in collaboration with The Johns Hopkins University, which provides training in risk assessment. Fellows may spend up to two years at the Radiation Effects Research Foundation in Hiroshima, Japan, studying atomic bomb survivors. The goal of the training program is to increase the number of scientists with expertise in studies of radiation-associated cancer, thus enhancing prospects for improving public health and radiation protection.

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Epidemiology and Biostatistics Program
Radiation Epidemiology Branch
Ionizing Radiation and Cancer

Research: To address concerns about the health effects of radiation exposure, we are evaluating the risk of radiation-associated tumors in the medical, occupational, and environmental settings. In addition, we are examining biologic mechanisms related to radiation carcinogenesis. Our research focuses on quantifying the tumorigenic risk of external (X- and gamma ray) and internal (iodine-131) radiation, the carcinogenic effects of protracted or fractionated radiation exposure, and the etiology of thyroid disease.

Carcinogenic Effects of External Radiation
In collaboration with the Radiation Effects Research Foundation in Hiroshima, we are studying cancer incidence in approximately 90,000 Japanese atomic bomb survivors. We found that for some organs or tissues, radiation-related risk varies by histological type. An increased risk was observed for basal cell carcinoma of the skin, but not for squamous cell carcinoma. The dose-response relationship for basal cell carcinoma was strongest among persons who were exposed to the radiation in early childhood. No interaction was seen between exposure to ultraviolet radiation and radiation from the bombings. We also found a significant dose-response relationship for neurilemomas, all central nervous system (CNS) tumors combined, and pituitary tumors, but not for gliomas. Age at exposure was not a significant risk modifier for the CNS tumors.

In another study, we evaluated cancer incidence in a cohort of almost 1,000 Israeli women treated with radiotherapy for infertility. The majority of the women were irradiated to both the ovaries and pituitary gland. No significant excess or deficit occurred for any individual cancer type, although a nonsignificant 60 percent increase in colon cancer was observed.

Radioactive Iodines
Radioactive iodines are widely used in medicine and can pose a health threat when accidentally released into the environment by nuclear power plants. In an attempt to clarify the impact of radioiodines in carcinogenesis, we are studying several cohorts of patients exposed to diagnostic or therapeutic I-131. In an investigation of cancer mortality among almost 35,000 hyperthyroid patients, we found that over 50 percent were deceased by the end of followup. High-dose I-131 treatment was not linked to an overall increased risk of death from solid tumors or leukemia. Although mortality related to thyroid cancer was significantly elevated, the number of radiation-associated thyroid cancer deaths was small. We plan to conduct a pooled analysis of thyroid and other cancer risks after the ongoing medical I-131 studies are completed. In another project, we are investigating thyroid disease among persons potentially exposed to I-131 emissions from a nuclear facility in the Russian Federation. Preliminary data suggest that childhood exposure to I-131 emissions may pose a small increased risk of developing thyroid neoplasia.

Protracted Radiation Exposures
In a collaboration with investigators from the Russian Federation, the United States, and Japan, we are investigating the relationship between cancer mortality and protracted radiation exposure in occupational and environmental settings. The investigation includes nearly 20,000 workers at the Mayak nuclear facility in Ozyorsk, Russia, who were exposed to external and/or internal radiation, and about 30,000 persons living in villages near a river polluted by radioactive wastes from the facility. Preliminary results suggest dose-related increases in solid cancers and leukemia among long-term Mayak workers who experienced chronic exposures to external radiation.

Thyroid Disease
Radiation is the only well-defined cause of thyroid cancer. To elucidate other etiologic factors, we are collaborating in an international pooled analysis of 14 case-control studies of thyroid cancer. The analysis includes over 2,500 thyroid cancer cases and 4,000 controls. Results thus far indicate that risks associated with menstrual and reproductive factors are generally weak, but appear stronger among women diagnosed with thyroid cancer at younger ages. A moderately elevated risk in current oral contraceptive users was observed, but disappeared 10 or more years after usage stopped. The results also suggest that thyroid cancer incidence is related to height and weight at time of diagnosis. Consumption of fish was not significantly associated with thyroid cancer risk. In iodine-deficient areas, high fish intake may protect against risk of thyroid cancer.

Keywords

central nervous system tumors, radiation, skin cancer, thyroid cancer

Recent Publications

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Epidemiology and Biostatistics Program
Radiation Epidemiology Branch
Ionizing Radiation and Cancer

Research: Our research focuses on the health effects related to the 1986 accident at the Chornobyl nuclear facility in Ukraine. Collaborative studies are carried out with other Branch members, contractor personnel at Columbia University, and investigators in Belarus and Ukraine. The accident provides two notable opportunities for significant research on the carcinogenic effects of ionizing radiation: studies of children exposed to radioiodines, principally I-131, many of whom received thyroid doses greater than 1 Gy (100 rads), and studies of the hundreds of thousands of clean-up workers who were exposed mainly to whole-body gamma doses ranging from 0.01 to over 0.25 Gy (1 to 25 rads). In another area, research is continuing to investigate risk of liver cancer among survivors of the atomic bombings of Hiroshima and Nagasaki.

Thyroid Disease

We are conducting cohort studies of thyroid cancer among 39,000 participants in Belarus and 34,000 participants in Ukraine. At the time of the Chornobyl accident, the participants were children aged 0 to 18 years. Their thyroids were measured for radioactivity in 1986. The cohort members are being screened biennially by thyroid palpation, ultrasonography, and thyroid hormone assays. An intensive international dose-reconstruction effort is accompanying the clinical screening. Risk analyses will compare the carcinogenic effect of I-131 to that of external radiation (X- and gamma ray), for which good risk estimates exist. In other research, a case-control study using estimated individual doses found that the large increase in thyroid cancer incidence in Belarus following Chornobyl is attributable to radioiodine from the accident.

Leukemia

In Ukraine, a collaborative case-control study is investigating leukemia risk among 88,000 Chornobyl clean-up workers. An 18-month pilot study

determined the feasibility of this large ongoing study. The cohort is being created from the files of the Chornobyl Registry of the Ministry of Health. Case ascertainment is based on disease notification by diagnostic and treatment centers and use of a national cancer registry. Definitive diagnoses will be determined by hematologists directing the study and a review by international hematology experts. Because of the large-scale exposure at relatively low doses and low dose-rate, the study should help to reduce uncertainty about risk of leukemia from such exposures. The experience of the clean-up workers may also lead to better estimates of the time-response for leukemia, especially during the first five years following exposure when estimates from atomic bomb survivors are not available. In a related project, a major international effort is developing an approach for physical dose reconstruction.

Keywords

Chornobyl, leukemia, liver cancer, radiation, thyroid cancer

Recent Publications

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Epidemiology and Biostatistics Program
Radiation Epidemiology Branch
Ionizing Radiation and Cancer; Etiology of Primary Brain Tumors

Research: Our research focuses on cancer risks attributable to medical, environmental, and occupational exposures to ionizing radiation and the etiology of brain tumors in adults, including the possible effects of nonionizing radiation.

Medical Radiation Exposures

Studies of medically irradiated populations are important in elucidating risks related to specific medical procedures and in providing basic scientific information about radiation carcinogenesis. Detailed medical records of radiation exposure enable estimations of organ-specific doses, which often is essential in generalizing study-specific findings to other settings.

In a study carried out in Sweden, we evaluated risk of thyroid cancer associated with diagnostic X-rays. Exposure information was obtained from medical records. No evidence was found for an association between risk and history of diagnostic X-rays. In a methodologic study, we are comparing the exposure information from medical records to that obtained by interviewing

patients to evaluate the extent of any recall bias. We are also conducting studies of second cancers of the brain, thyroid, and breast following treatment for childhood cancer.

Environmental and Occupational Radiation Exposures
The Chornobyl nuclear reactor accident in 1986 resulted in a massive environmental release of radioactivity. Hundreds of thousands of men from throughout the former Soviet Union were sent to Chornobyl in the aftermath of the accident to assist in the clean-up effort. A study of workers from Estonia was conducted to assess risk of leukemia and thyroid disease. Using the Estonian Cancer Registry, no cases of leukemia were identified among nearly 4,850 clean-up workers followed from 1986 through 1995. Furthermore, thyroid screening of nearly 2,000 workers in 1995 did not find an excess of thyroid tumors or nodules.

Documented radiation doses for the Estonian clean-up workers averaged approximately 11 cGy. A mean dose of this magnitude or lower is suggested by studies of biological markers of exposure. Since doses may have been lower than initially presumed, it may be difficult to detect radiation-related health effects in epidemiologic studies. To increase the statistical power for detecting such effects, the Estonian cohort is being combined with ones from Latvia and Lithuania, giving a combined study population of more than 17,000 clean-up workers. Followup will be extended to accommodate latency periods for radiation-induced solid cancers.

Etiology of Brain Tumors in Adults
The etiology of brain tumors is poorly understood. Although brain cancer incidence rates have risen dramatically over the past several decades, it is unknown whether the rise is real, an artifact of improved diagnosis, or a combination of the two. Nonetheless, there is concern that it may be linked to one or more increasingly common environmental exposures, such as industrial chemicals, pesticides, food additives, or electromagnetic fields. To address this concern and investigate other possible causes, we are conducting a collaborative case-control study of malignant and benign brain tumors at three U.S. hospitals. Key features of the study include its large size; emphasis on rapid ascertainment of incident cases and interview of study participants rather than surrogates; use of detailed, job-specific questions to ascertain occupational exposures; and collection of blood samples to evaluate inherited susceptibility, biomarkers of exposure, and gene-environment and gene-gene interactions. Factors that are being analyzed in relation to risk include workplace exposures to chemical agents and electromagnetic fields, use of cellular telephones and home appliances, diet, reproductive history, hormonal exposures, family history of tumors, genetic determinants of susceptibility, viruses, and medical and dental exposure to ionizing radiation, along with other medical history.

Keywords
brain cancer, Chornobyl, leukemia, radiation, second cancers, thyroid cancer

Recent Publications

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Inskip PD, et al. Cellular-telephone use and brain tumors. *N Engl J Med* 2001;344:133–34.

Inskip PD. Thyroid cancer after radiotherapy for childhood cancer. *Med Pediatr Oncol* 2001;36:568–73.

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Epidemiology and Biostatistics Program
Radiation Epidemiology Branch
Ionizing Radiation Exposure and Cancer

Research: Our research focuses on epidemiologic studies to clarify the relation between cancer risk and exposure to ionizing radiation. Compared with most other known human carcinogens, a relatively large and well-quantified base of knowledge exists on radiation-related cancer risks. This knowledge base offers opportunities to explore more complex issues, such as biomarkers of radiation-related cancer and risk modifiers, including lifestyle variables, other carcinogenic exposures, and host factors like age, sex, and genetic predisposition to certain cancers.

Japanese Atomic Bomb Survivors
Using a variety of approaches, a cohort of 94,000 survivors of the Hiroshima and Nagasaki atomic bombings and 26,000 nonexposed subjects is being studied in collaboration with the Radiation Effects Research Foundation.

- **Site-specific studies of cancer incidence.** Cohort studies are used to quantify radiation dose-response and its relation to histological subtype of tumor, age at exposure, time following exposure, age at observation, and gender. Data analysis is under way for studies of tumors of the breast, central nervous system, and ovary. For breast cancer, the excess relative risk per unit dose decreases with increasing age at exposure in a three-step, descending staircase pattern, with steps at ages 20 and 40. Case ascertainment is nearly complete for lung cancer and continues for lymphoid cancers

- **Case-control studies.** A study of hormones in stored serum from women who later developed breast cancer found a significantly increased risk associated with level of unbound estradiol. The finding was observed both among women who were premenopausal and postmenopausal at the time of the blood draw. In another case-control study, an analysis of interview data suggest that increased risk of thyroid cancer is associated with a cancer history in sisters, history of goiter, tonsillectomy, ovariectomy, breast disease, and high body-mass index.

• **Case-case approaches.** A previous report of extremely high, dose-specific relative risks for early-onset breast cancer (before age 35) suggests increased sensitivity to radiation among a genetically predisposed population subgroup. We are addressing this hypothesis through compilation of family cancer pedigrees for early-onset and later-onset cases, and exploring the potential for molecular assays of stored lymphocytes and archival tumor tissue for biomarkers of susceptibility.

Heritable Retinoblastoma and Susceptibility to Radiation-Induced Bone Sarcoma

We are comparing bone sarcoma incidence data from patients treated by X-ray during early childhood for bilateral retinoblastoma with patients treated by injection of 224Ra for tuberculosis and other benign diseases. Preliminary analyses suggest that heritable retinoblastoma patients, whose baseline risk of bone sarcoma is already high, are unusually susceptible to radiation-related bone sarcoma.

Cancer Risk Associated with Environmental Radiation

Increased risk of thyroid disease, including cancer, is a well-established correlate of exposure to gamma and X-ray radiation from external sources, but risk from exposure to radioactive iodine is less well defined. In a collaborative study involving thyroid screening of 3,000 village residents living near the Semipalatinsk nuclear test site in Kazakstan, we investigated the prevalence of thyroid nodules and tumors, dietary patterns, and thyroid stimulating hormone levels in relation to radioiodine exposure. The prevalence of thyroid nodules and cancer was higher among those exposed than among nonexposed residents. For dose-response analyses, we are exploring differences and similarities between U.S. and Russian methods of dose reconstruction of fallout from nuclear testing in Nevada and Kazakstan. We are also biodosimetric methods, based on assays of chromosome translocation frequencies in cultured lymphocytes and electron paramagnetic resonance assays of archival tooth samples, to validate reconstructed dose estimates.

Algorithms for Expression of Risk

The 1985 report of the NIH Ad Hoc Working Group to Develop Radioepidemiological Tables, which was mandated by the U.S. Congress, provides a scientific basis for adjudicating claims of radiation-related injury and is used for that purpose by the Department of Veterans Affairs and other government agencies. We have recently updated this report, incorporating new scientific information and a more sophisticated treatment of the statistical and subjective uncertainties. In addition, the original tabular format is replaced by an interactive computer program.

Medically Exposed Populations

Cancer incidence and mortality following nasopharyngeal radium treatment for childhood eustachian tube dysfunction is being investigated among patients in The Netherlands. In another project, increased breast cancer mortality among women who were treated as children for scoliosis was related to reconstructed radiation dose to breast tissue.

Keywords

bone sarcoma, breast cancer, fallout exposure, genetic susceptibility, lung cancer, radiation, retinoblastoma

Recent Publications

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Ronckers CM, et al. Cancer mortality after nasopharyngeal radium irradiation in the Netherlands: A cohort study. *J Natl Cancer Inst* 2001;93:1021-1027.

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Epidemiology and Biostatistics Program
Radiation Epidemiology Branch
Hematopoietic, Lymphoproliferative, and Primary Brain Cancers

Research: Our research focuses on the etiology of hematopoietic, lymphoproliferative, and primary brain neoplasms in children and adults, the risk factors for which are poorly understood. We are conducting case-control and cohort studies to quantitatively assess risk, characterize exposure-response relationships, evaluate alternative methods of estimating exposure, and examine biologic mechanisms of action.

Nonionizing Radiation, Extremely Low Frequency

Because of the limitations of previous studies, public health concerns continued to exist regarding risk of childhood leukemia from exposures to extremely low frequency magnetic fields (50- or 60-Hertz). To address these concerns, we conducted a large case-control study with the Children's Cancer Group (an NCI-funded clinical trials cooperative group) to evaluate the role of these exposures from power lines and electrical appliances in relation to risk of childhood leukemia. We found that neither high, directly measured residential magnetic field levels nor high wire-code levels (a proxy measure for close distance of residence to power lines) was associated with significantly increased risks of childhood acute lymphoblastic leukemia. Exploratory analyses evaluating various alternative magnetic field exposure metrics, including measures of central tendency (e.g., 30th to 70th percentiles), peak values, threshold levels, and rate-of-change metrics, did not alter our conclusions, which were based on time-weighted average direct and proxy measures. Wire code categories were highly reproducible among wire coding technicians and were well-correlated with measured magnetic field levels.

In further analyses based on interview data, we found that acute lymphoblastic leukemia risks were significantly elevated in offspring whose mothers

reported use of an electric blanket during pregnancy, but reduced in offspring whose mothers used sewing machines prenatally. Risk was also increased among children whose mothers reported postnatal use of electric blankets, hair dryers, video machines in arcades, and video games connected to televisions, but patterns for duration or frequency of use of these appliances were inconsistent. While risks rose with increasing number of hours per day children spent watching television, risks were similar regardless of usual viewing distance from the television. A recent study showed that magnetic field exposures were equivalent to background levels at distances at which children typically sit while watching television.

Nonionizing Radiation, Radio Frequency

Public health concerns were raised by news reports of brain cancer among heavy users of cellular telephones. To investigate this issue, we conducted a hospital-based case-control study to evaluate brain tumor risk in relation to use of cellular telephones and other wireless communication devices. Study participants comprised about 800 cases and a similar number of matched controls from three U.S. cities. Using a computer-administered interview, participants answered questions about a broad array of past exposures, occupation, diet, tobacco use, hair dye use, and family history of brain and other neoplastic and nonmalignant diseases. We also collected blood samples for genetic susceptibility studies, such as the influence on risk of polymorphisms within the glutathione transferase family of genes. A comprehensive familial and genetic study of the glioma cases was initiated in 1999.

Benzene-Related Hematopoietic Disorders

A cohort study of cancer and mortality risks was carried out among 75,000 benzene-exposed and 35,000 nonexposed workers employed between 1949 and 1987 in 12 cities in China. We found a three-fold excess risk for non-Hodgkin's lymphoma, with risks rising with increasing duration of benzene exposure. In addition, risk was associated with distant past exposure to benzene. In contrast, a three-fold excess of acute myeloid leukemia was linked with recent exposures and risk did not vary according to exposure duration. Significantly elevated risks were also seen for myelodysplastic syndromes and aplastic anemia, but the number of cases was too small for analysis of duration or other metrics of exposure. There were nonsignificant excesses of acute lymphoid leukemia and chronic myeloid leukemia.

In a feasibility study done in 1998 to 1999, we showed that more than 90 percent of the benzene cohort members could be traced to assess mortality from all causes and incidence of hematopoietic disorders. An effort is now under way to follow the original cohort members for an additional 11 years to determine vital status and incidence of hematopoietic disorders. We are particularly interested in whether excess risks continue to be observed for non-Hodgkin's lymphoma, acute nonlymphocytic leukemia, myelodysplastic syndrome, aplastic anemia, chronic myelocytic leukemia, and acute lymphocytic leukemia. In addition, we will assess whether: (1) excess risks of these hematopoietic disorders occur among workers who have been exposed only to low levels of benzene, (2) increased mortality from lung cancer (seen in the original study) persists, and (3) elevations in mortality occur for other solid tumors. After the cohort followup is completed, we plan to conduct a nested case-control study of hematopoietic disorders, lung cancer, and benzene

hematotoxicity; a measurement validation project; and molecular investigations to evaluate associations of genetic and susceptibility traits, such as glutathione transferase theta 1 and NQO1 polymorphisms, with risk of benzene-induced hematopoietic disorders.

Keywords

benzene, brain cancer, childhood cancers, leukemia, lymphoma, radiation

Recent Publications

Linet MS, et al. Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. *J Natl Cancer Inst* 1999;91:1051–58.

Shu XO, et al. Breast-feeding and risk of childhood acute leukemia. *J Natl Cancer Inst* 1999;91:1765–72.

Neglia JP, et al. Patterns of infection and day care utilization as risk factors for childhood acute lymphoblastic leukemia. *Br J Cancer* 2000;82:234–40.

Inskip PD, et al. Cellular telephones and brain tumors. *N Engl J Med* 2001;344:79–86.

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Epidemiology and Biostatistics Program
Radiation Epidemiology Branch
Ionizing Radiation, Genetic Susceptibility, and Cancer

Research: Inherent susceptibility factors that may disproportionately increase cancer risk among individuals exposed to ionizing radiation are poorly understood. Leading candidates for radiation-related investigation are genes involved in the repair of DNA single- and double-strand breaks, since these events are likely the most important genetic effect of radiation by causing cell lethality, chromosomal aberrations, and mutations. We are particularly interested in evaluating single nucleotide polymorphisms (SNPs) that may confer subtle deficiencies in base excision repair, nucleotide excision repair, mismatch repair, homologous recombination, and nonhomologous end joining, as well as genes that regulate cell cycle progression and apoptosis.

Radiation Exposure and DNA Repair Genes
Ionizing radiation exposure produces heterogeneous responses to cancer susceptibility and acute tissue damage in humans and experimental animals. Individual response differences may be due to variations in DNA repair genes. These genes are polymorphic, with some allelic variants having amino acid substitutions that are not conserved and that may confer decreased function. Carriers of specific SNPs, or a collection of them, may be susceptible when exposed to carcinogens such as radiation. Although single SNPs can increase cancer risk, their contribution may not be significant given the amount of overlap and redundancy in DNA repair pathways. However, multiple polymorphic sites acting in concert could be sufficient to produce an increased risk. Given these possibilities, we are exploring the role of SNPs in nested case-control studies of thyroid and breast cancers among radiologic technologists using two approaches: (1) a quick, first-pass screening of large numbers of SNPs for crude allele frequencies, and (2) a more considered approach in which multiprotein complexes are examined as "clustered" within individuals.

Neutron Exposures
The health consequences of neutron exposure on humans is unknown, since there are few populations in which it can be studied directly. Compared to X-rays or gamma rays, the relative biological effectiveness of neutrons is

expected to be large, based on animal and cellular studies. This issue is important for workers occupationally exposed to neutrons from cosmic radiation, such as astronauts, pilots, and flight attendants.

We are analyzing data from a cohort of cancer patients who were treated with neutrons in the 1970s and 1980s at two large U.S. referral centers. Besides atomic bomb survivors (for whom the neutron dosimetry estimates may be revised), these patients represent a rare and potentially informative group for studying the carcinogenic effects, particularly leukemia, of neutron exposure in humans.

In collaboration with the National Institute for Occupational Safety and Health, we are investigating breast cancer risk in a cohort of flight attendants who predominantly flew long-haul transcontinental routes. In addition, we are using fluorescence in situ hybridization to compare chromosomal aberrations in flight attendants and teachers.

Second Thyroid Cancers Among Childhood Cancer Survivors
Previous studies of radiation treatment and second thyroid cancer risk among childhood cancer survivors have been based on less than 25 thyroid cancer cases. The Childhood Cancer Survivor Study has ascertained nearly three times this number of pathologically confirmed thyroid cancer cases, and we are assessing second thyroid cancer risk using data on risk factors from questionnaires and treatment history information from medical records. Dose to the thyroid is estimated by a radiation physicist. With the large number of cases, we aim to better describe the shape and magnitude of the dose-response curve.

Keywords

breast cancer, DNA repair, molecular epidemiology, neutrons, radiation, thyroid cancer

Recent Publications

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El-Zein R, et al. Increased chromosomal instability in peripheral lymphocytes and risk of human gliomas. *Carcinogenesis* 1999;20:811–15.

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El-Zein R, et al. Risk assessment for developing gliomas: A comparison of two cytogenetic approaches. *Mutat Res* 2001;490:35–44.

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Epidemiology and Biostatistics Program
Radiation Epidemiology Branch
Multiple Primary Cancers

Research: We are conducting epidemiologic studies to evaluate risks of multiple primary cancers associated with radiation, chemotherapy, and other factors; patterns and determinants of cancer risk following bone marrow transplantation; and tumor risks after long-term exposure to radioactive Thorotrast. We are also quantifying excesses of hematopoietic malignancies and related disorders among benzene-exposed workers in China.

Multiple Primary Cancers
The study of multiple primary cancers, particularly risks following exposure to ionizing radiation and cytotoxic drugs, is a major research interest. As survival following a diagnosis of cancer improves, it becomes more crucial to identify late consequences of therapy, including the induction of a new malignancy. The characterization of these risks enables clinicians to make informed decisions about treatment options, balancing efficacy against acute and chronic sequelae. Furthermore, quantifying late effects of cancer therapy provides a singular opportunity for establishing dose-response relationships, since patients receive known amounts of potentially cancer-inducing agents.

A recent research initiative involves an eight-center international survey of 80,000 patients with cancer of the testis or ovary. Our findings showed that platinum-based chemotherapy for ovarian cancer was linked to a four-fold risk of leukemia, with evidence of dose response as risks reached seven- to

eight-fold at 1,000 mg or more platinum. Radiotherapy for testicular cancer was associated with a three-fold elevated risk of leukemia. Risk increased with increasing dose of radiation to active bone marrow, with patients receiving radiotherapy to the chest and abdominal/pelvic fields accounting for much of the excess risk at higher doses. Radiation dose to active bone marrow and cumulative dose of cisplatin (P for trend=.001) were predictive of excess leukemia risk in a model adjusted for all treatment variables. In a second international project that consists of a cohort of 32,000 Hodgkin's disease patients at seven centers, we are evaluating site-specific risks of subsequent cancers, particularly solid tumors. This effort includes analytic studies of second cancers of the lung and breast.

Cancer Risk Following Bone Marrow Transplantation
Bone marrow transplantation is becoming an increasingly common procedure. Our group is examining posttransplant cancer risks associated with immunosuppression, total body radiotherapy, chemotherapy, viral cofactors, graft-versus-host disease, and the interactions of these factors. Among 19,000 allogeneic or syngeneic bone marrow recipients, we found a 2.7-fold increased risk of solid tumors, with a trend toward increasing risk over time, and higher risks among younger patients. In another analysis, we showed that risk of early-onset posttransplant lymphoproliferative disorders is strongly associated with unrelated or human leukocyte antigen mismatched related donor (RR=4.1), T cell depletion of donor marrow (RR=12.7), and use of antithymocyte globulin (RR=6.4) or anti-CD3 monoclonal antibody (RR=43.2) for prophylaxis or treatment of acute graft-versus-host disease. In ongoing work, we are examining cancer risk after autologous bone marrow transplantation, with case-control studies of myelodysplastic syndromes and leukemias following transplantation for lymphoma.

Cancer Risk Following Exposure to Radioactive Thorotrast
Radioactive Thorotrast, once used as an angiographic contrast agent, is not excreted from the body to any appreciable extent and has been shown to induce high rates of liver angiosarcoma and leukemia. We are estimating the risk of cancer after exposure to Thorotrast (Thorium-232) in several large populations. The study may provide an opportunity to evaluate the effects of low-level radon exposure, since Thorium-232 decays into radon, which is exhaled for life. Indoor radon is the single most important source of radiation exposure in the general population, and its relation to lung cancer risk is poorly understood.

Hematopoietic Disorders Among Benzene-Exposed Workers
We recently described the clinicopathologic features of hematopoietic malignancies occurring among 80,000 benzene-exposed factory workers in China. We noted that the characteristics of the acute nonlymphocytic leukemias resembled those occurring after chemotherapy or radiotherapy. Earlier, we quantified the dose-related incidence of hematologic neoplasms among these workers and showed that benzene is associated with a spectrum of hematologic neoplasms, with a tendency for risk to rise with increasing levels of exposure.

Keywords

benzene, bone marrow transplantation, chemotherapy, Hodgkin's disease, immunosuppression, leukemia, multiple primary cancers, non-Hodgkin's lymphoma, ovarian cancer, radiation, testicular cancer, Thorotrast

Recent Publications

Travis LB, et al. Risk of leukemia after platinum-based chemotherapy for ovarian cancer. *N Engl J Med* 1999;340:351–57.

Travis LB, et al. Treatment-associated leukemia following testicular cancer. *J Natl Cancer Inst* 2000;92:1165–71.

Groves FD, et al. Cancer surveillance series: Non-Hodgkin's lymphoma incidence by histologic subtype in the United States, 1978–1995. *J Natl Cancer Inst* 2000;92:1240–51.

Travis LB, et al. Mortality after cerebral angiography with or without radioactive Thorotrast: An international cohort of 3,143 two-year survivors. *Radiat Res* 2001;156:136–50.

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The Viral Epidemiology Branch conducts multidisciplinary studies of domestic and foreign populations that offer special opportunities for clarifying the relation of infectious agents, especially viruses, to human cancer and other health-related outcomes. Viruses may increase the risk of malignancies through several mechanisms, including direct transformation of cells, expression of oncoproteins that interfere with mitosis checkpoints or DNA repair, expression of cytokines or other growth factors, and alteration of the immune system. Our studies encompass all aspects of these viruses, including their molecular biology, epidemiology, natural history, and relationship to other conditions as well as cancer outcomes. Our major areas of emphasis are on human retroviruses, particularly human immunodeficiency virus type 1 (HIV-1) and human T lymphotropic viruses types I and II (HTLV-I and HTLV-II); human herpesviruses, particularly the Kaposi's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 and Epstein-Barr virus; hepatitis viruses, particularly hepatitis C virus (HCV) and hepatitis B virus (HBV), and polyomaviruses, particularly simian virus 40 (SV40).

The Branch carries out studies using the principles of infectious and chronic disease epidemiology. Exploiting the exogenous nature of viruses, efforts are directed at identifying their biology, transmission routes, and natural history. Studies are supported by statistical modeling and laboratory investigations carried out by collaborative researchers and at the Branch's viral epidemiology laboratory at the Frederick Cancer Research and Development Center (FCRDC). We are using classic and novel study designs and laboratory techniques to investigate significant issues regarding the role of viruses and other biologic agents in the etiology of cancer, with the ultimate aim of cancer prevention or cure. In addition to supporting epidemiologic field studies, the Branch's laboratory is striving to discover new viruses. The Branch's major research efforts are highlighted below:

- **Prospective cohorts at high risk of AIDS.** We initiated prospective cohort studies of persons at high risk of AIDS in the early 1980s. These studies yielded many significant findings on the major modes of HIV-1 transmission, the role of HIV-1 in the etiology of AIDS, age-specific AIDS hazard rates, the predictive value of CD4+ lymphocyte counts and other biomarkers of AIDS, and consequences of immune deficiency on infection by human papillomavirus (HPV) and hepatitis B and C viruses. Using 20 years of accumulated data and specimens stored in the Division's repository, recent studies have evaluated novel quantitative molecular markers of thymic output and HIV-1 proviral replication, GB virus C, and SEN viruses.

• **AIDS-Cancer Match Registry.** In an effort to identify HIV-associated malignancies, we linked population-based AIDS and cancer registry systems in 15 U.S. cities or states. Initial analyses revealed that the spectrum of malignancies is dominated by non-Hodgkin's lymphoma and Kaposi's sarcoma, but also includes Hodgkin's disease and testicular seminoma. Cancers associated with HPV infection, such as cervical and penile cancer, are also increased. However, AIDS-related immune deficiency plays little, if any, role in their etiology, implying that the excess results from recurrent or persistent HPV infection through sexual activity. Similarly, lung cancer is increased among persons with AIDS, which may reflect high rates of cigarette smoking in this population.

• **Molecular studies of AIDS malignancies.** With the advances of genetic understanding and using the new tools such as microarrays and proteomics, we are initiating new studies of cancers related to viruses. We have a long history of pioneering work in this area. Examples include our studies that revealed Kaposi's sarcoma is a disseminated clonal malignancy rather than a polyclonal reactive process, and our investigations that showed translocations specific to certain tumors (e.g., 8:14 in Burkitt's lymphoma) can be detected in peripheral blood samples of persons who have not developed these tumors. With the new tools available, we foresee many applications to samples already in our repositories, and these studies will take on increasing importance in future work.

• **Mother-to-infant transmission and natural history of HIV-1.** Results from the Mothers and Infants Cohort Study, a collaborative effort with the National Institute of Child Health and Human Development and the International Registry of HIV-Exposed Twins, found that HIV-1 is transmitted primarily during labor or delivery. The Perinatal Intervention Project, a clinical trial to reduce pediatric HIV-1 infections in Malawi, found that while cleansing the birth canal of women in labor with chlorhexidine did not reduce HIV-1 infection, it substantially reduced maternal and neonatal morbidity and mortality due to bacterial infections. In a followup study in Malawi, we have further evaluated HIV-1 infection in twin births to infected mothers.

• **HTLV.** HTLV-I is endemic in the Caribbean, Japan, and parts of Africa, and is associated with adult T cell lymphoma and tropical spastic paraparesis, also known as HTLV-associated myelopathy, a neurodegenerative disease. In extensive collaborative studies with universities and other research institutions in Jamaica, Trinidad, and Panama, we determined that both HTLV-I and HTLV-II are transmitted by breast milk from mother to infant, sexual intercourse, and transfusion of cellular blood components. Ongoing studies are examining risk factors and the biology involved in progression to malignancy or to neurological disease, including the role of genetics. At our laboratory, we developed new assays to quantify HTLV-I and HTLV-II burden, which should lead to more reliable assessments of the natural history of infection and potential antiviral therapies.

• **Hepatitis viruses.** Hepatocellular carcinoma is associated with infection by hepatitis B and C viruses. We have major international collaborations on groups with high hepatitis virus infection, in which we can explore all aspects of these infections, up to and including cancer outcomes. Our 15-year prospective Multicenter Hemophilia Cohort Study (MHCS) of more than 2,000 persons with hemophilia demonstrated active HBV infection in 8 percent and HCV infection in 80 percent. HIV-1 coinfection was associated with high rates of HCV genotype switches and of decompensated end-stage liver disease. A second MHCS has been launched, focused on HCV natural history and its association with liver diseases and malignancies. Branch studies of injection drug users are evaluating interactions of HCV viral load, humoral and cellular immunity, and human genetics on susceptibility to HCV infection and disease. In The Gambia, we recently completed a case-control study of hepatocellular carcinoma to elucidate how interactions of HBV infection, aflatoxin exposure, and genetic polymorphisms contribute to cancer risk. These studies offer opportunities for examining the virus strain diversity, epidemiology, natural history, human genetics, and interactions with or without HIV-1 in different environments.

• **Herpesviruses.** The association of Kaposi's sarcoma to HIV/AIDS and its related immunosuppression has been well known for decades. In 1994, KSHV, a gammaherpesvirus, was discovered and subsequently shown to be the primary etiologic agent of KS. We have developed a major program of field and laboratory research to understand all aspects of this virus and its relationship to KS. The Branch laboratory is making a concerted effort to discover new gammaherpesviruses and to identify plant extracts that

induce KSHV replication. Two highly sensitive and specific KSHV enzyme immunoassays and a KSHV viral load assay have been developed to support epidemiologic research. The field studies are based on data and samples from the Branch's cohorts, such as homosexual men and hemophiliacs, from international surveys of diverse populations including South American Amerindians and many populations in Africa, and from newly initiated studies in Africa, Europe, and the United States. Environmental, genetic, and nutritional factors are being evaluated in a case-control study of classical (that is, non-AIDS) KS in Italy. EBV, the prototype gammaherpesvirus and thus a relative of KSHV, was the first virus linked to human cancer. Interactions between KSHV and EBV and their roles in non-Hodgkin's lymphoma and Hodgkin's disease (particularly in the setting of HIV-1 infection and immunodeficiency) are being actively investigated.

- **Polyomaviruses.** SV40, an infection of monkeys that causes malignancy in rodents, contaminated poliovirus vaccines between 1955 and 1963 and resulted in exposure of tens of millions of people in the United States. Over the ensuing decades, neither a cancer excess nor any other adverse health consequence of this exposure has been found. However, based on the animal models and on detection by some laboratories of SV40 DNA in human cancers, especially mesotheliomas and ependyomas, the Branch continues to evaluate whether SV40 is associated with these or other cancers. The approaches include molecular studies of whether SV40 or the two human polyomaviruses, BK virus and JC virus, can be detected in human tumors, as well as evaluating cancer risk in large populations in the United States and Europe that did or did not receive SV40-contaminated vaccines.

Collaboration and Training

The Branch uses various means to explore the critical epidemiologic and biological issues in viral carcinogenesis, taking advantage of new research opportunities as they arise. We believe that investigator initiatives, complemented by constructive internal review and extensive intramural and extramural collaborations, are critical to achieve important advances. The Branch welcomes new investigators, who range from summer research interns to fellows who have completed doctoral and medical specialty programs. These young investigators are mentored by senior scientists and are given projects commensurate with their abilities, which may include developing research initiatives relevant to the Branch's mission.

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Epidemiology and Biostatistics Program
Viral Epidemiology Branch
Human Immunodeficiency Virus, AIDS, and Cancer

Research: AIDS is a unique immunologic disorder that includes an unusual array of opportunistic infections and viral-associated malignancies, which are facilitated by perturbations of cellular and humoral immune functions. Several cancer-associated viruses, particularly hepatitis C virus (HCV) and Kaposi's sarcoma-associated herpesvirus (KSHV), have recently been discovered. Natural history studies of viruses, with or without HIV/AIDS involvement, provide insights on how these biologic agents, other exogenous exposures, and host genetics interact to influence the carcinogenesis.

Multicenter Hemophilia Cohort Study I and II
In collaboration with 16 hemophilia centers in the United States and Europe, more than 2,000 men with hemophilia and their steady female sexual partners were followed from the early 1980s to the late 1990s in MHCS-I. Resulting publications helped to establish HIV as the cause of AIDS and to define the natural history of HIV and cofactors and predictive markers for AIDS development. More recent analyses using reposited samples and data have focused on HCV and its relationship to end-stage liver disease (ESLD). MHCS-II was launched in 2001, and will be a collaboration with approximately 50 hemophilia centers on three continents. The primary emphases will be to define the natural history of HCV and risk factors for ESLD, non-Hodgkin's lymphoma, hepatocellular carcinoma, and later complications of HIV/AIDS.

AIDS-Cancer Match Registry
Population-based AIDS and cancer surveillance data were linked in 11 U.S. cities or states to clarify risk factors for cancer among 366,034 persons with AIDS. Expected excesses were observed for the AIDS-defining cancers (Kaposi's sarcoma and non-Hodgkin's lymphoma), but non-AIDS–defining cancers also occurred in statistically significant 2.7-fold excess. Of individual cancers, Hodgkin's disease, lung cancer, penile cancer, soft tissue malignancies, lip cancer, and testicular seminoma met all three criteria for potential

association with immunosuppression. Cancer experience for children with AIDS resembled that for adults, with the additional risk of leiomyosarcoma. Papillomavirus-associated anogenital cancers were elevated among adults with AIDS, but this appeared to be a consequence of shared risk factors rather than AIDS-associated immunosuppression. Our current research is focusing on cancers among the elderly with AIDS and with HCV or KSHV coinfection.

Classical Kaposi's Sarcoma
Kaposi's sarcoma (KS) occurs in four epidemiologic patterns—classical, endemic/African, iatrogenic/transplant, and endemic/AIDS. KSHV infection is the primary cause of all types of KS. Classical KS is a slowly progressive malignancy typically arising on the feet or hands of elderly patients of Mediterranean or Jewish heritage, among whom the KSHV prevalence ranges from 5 percent to 25 percent. A case-control study is in progress to identify cofactors for classical KS among people with KSHV infection in Italy.

Keywords

acquired immunodeficiency syndrome (AIDS), anal cancer, brain cancer, cervical cancer, end-stage liver disease (ESLD), hemophilia, hepatitis C virus (HCV), Hodgkin's disease, homosexual men, host genetics, human immunodeficiency virus (HIV-1), human leukocyte antigens, immune deficiency, Kaposi's sarcoma (KS), Kaposi's sarcoma-associated herpesvirus (KSHV), leiomyosarcoma, multiple myeloma, non-Hodgkin's lymphoma, pediatrics, registry studies, seminoma, testicular cancer, viruses

Recent Publications

Goedert JJ, et al. Increased liver decompensation risk with atypical hepatitis C virus antibody levels. *J Infect Dis* 2000;182:590–94.

Frisch M, et al. Association of cancer with AIDS-related immunosuppression in adults. *JAMA* 2001;285:1736–45.

Vitale F, et al. Kaposi's sarcoma herpes virus and Kaposi's sarcoma in the elderly populations of 3 Mediterranean islands. *Int J Cancer* 2001;91:588–91.

Goedert JJ, et al. Quantification of T cell receptor excision circles, HIV-1 viral load, and HIV-1 2-LTR episomal DNA to predict AIDS in patients not receiving highly effective therapy. *AIDS* 2001;15:2245–50.

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Epidemiology and Biostatistics Program
Viral Epidemiology Branch

Human Immunodeficiency Virus and Human T Cell Lymphotropic Virus

Research: Persons infected with human immunodeficiency virus (HIV) or human T cell lymphotropic virus (HTLV) are at significantly increased risk of cancer. Our research is focusing on the biology and epidemiology of these viruses, including their transmission routes, natural history, and population distribution.

Perinatal Transmission Studies
Principal routes for the spread of HIV are sexual contact and exchange of blood products. However, perinatal transmission is a major contributor to risk of infection in Africa and other areas of the world with high HIV prevalence among young women. In Africa, infants are infected in utero (25 percent), at delivery (50 percent), and postnatally through breastfeeding (25 percent). We developed methods to measure HIV levels in dried blood spots. Viral level is independent of route of infection, and early levels predict levels at one year after infection. We found that HIV levels in infected infants are very high, which probably influences their clinical course. Cesarean delivery appears to lower the risk of infection significantly. Other findings indicate that subclinical mastitis increases viral levels in breast milk and is associated with higher rates of transmission to the infant. Vitamin A supplementation did not reduce risk of transmission. Our studies of twins born to HIV-infected mothers are continuing in an effort to better understand the factors that influence viral transmission.

Cancer Risk in HIV-Infected Individuals
Risks for Kaposi's sarcoma and non-Hodgkin's lymphoma are markedly increased in HIV-infected persons, and Hodgkin's disease is also increased by as much as eight-fold. To determine which other malignancies are associated with HIV infection or its sequelae and to quantify risks, we linked population-based AIDS and cancer registry data in 15 locations in the United States. Registry data were matched for over 300,000 AIDS patients. Compared with adults, the data show a lower risk (2.5 percent versus 6 percent) of

cancer in children with AIDS, but non-Hodgkin's lymphoma still dominates the increased risk. While most of the non-Hodgkin's lymphoma are B cell types, there is also an increase in T cell lymphomas. We also found that human papillomavirus infections increase the risk of dysplasia but do not affect invasive cancer incidence. Kaposi's sarcoma and non-Hodgkin's incidence have both declined in the general population in recent years because of the decline in AIDS cases and improved therapies for those with AIDS. This AIDS-related decline is sufficient to impact on the overall lymphoma incidence, but, excluding the changes related to AIDS, lymphoma incidence is continuing to increase.

Kaposi's Sarcoma-Associated Herpesvirus Studies
In extensive studies, we evaluated testing methods for Kaposi's sarcoma-associated herpesvirus (KSHV), a recently described virus etiologically linked to Kaposi's sarcoma. In Brazilian Amerindians, we found a remarkably high prevalence of KSHV, suggesting that it is an ancient virus associated with man. Examination of trends in KSHV serologic patterns over time are ongoing, and we hope to develop tools to better understand the relationship between viral levels and disease outcome.

Keywords

human immunodeficiency virus (HIV), human papillomavirus, human T cell lymphotropic virus (HTLV), immune deficiency, Kaposi's sarcoma, Kaposi's sarcoma-associated herpesvirus (KSHV), non-Hodgkin's lymphoma, registry studies, retroviruses, twins

Recent Publications

Biggar RJ, et al. Risk of cancer in children with AIDS. *JAMA* 2000;284:205–09.

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Biggar RJ, et al. Viral levels in newborn African infants undergoing primary HIV-1 infection. *AIDS* 2001;15:1311–13.

Frisch M, et al. Association of cancer with AIDS-related immunosuppression in adults. *JAMA* 2001;285:1736–45.

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Epidemiology and Biostatistics Program
Viral Epidemiology Branch
Human Immunodeficiency Virus, Kaposi's Sarcoma-Associated Virus, and Cancer

Research: Our research is focusing on studies to better define the natural history of human immunodeficiency virus (HIV) and Kaposi's sarcoma-associated herpesvirus (KSHV) through the use of markers that reflect disease progression. Statistical methods are used to model projected outcomes.

HIV Viral Load

In chronic infection by HIV, ongoing viral replication leads to gradual destruction of the immune system and acquired immunodeficiency syndrome (AIDS). The amount of HIV circulating in serum or plasma (viral load) reflects HIV replication throughout the lymphoid system and is a strong predictor of disease progression. The Branch's cohort studies of HIV-infected hemophilia patients and homosexual men provide a valuable resource for investigating predictors of HIV disease progression. An area of active research is the use of statistical methods to model the complex relationship between markers, such as HIV viral load, and disease progression to better understand pathogenesis.

Within the Multicenter Hemophilia Cohort Study, we recently examined the relationship between HIV viral load and disease progression in 389 participants with CD4+ lymphocyte counts below 200 cells/mm^3. For these

individuals with late-stage HIV infection, HIV viral load was a strong predictor of AIDS risk (hazard ratio 2.37 per log10 increase in viral load). The effect was most pronounced immediately after the HIV viral load was measured, but attenuated over time. This finding implies that viral load reflects short-term risk and thus, implicitly, immune deficiency. Indeed, viral load remained predictive of short-term risk even after controlling for CD4+ count, an established measure of immune function. These findings have implications for the clinical management of HIV-infected patients, for whom decisions regarding prophylaxis, treatment, and diagnostic evaluation often involve assessment of immune status.

HIV viral load is extremely high during the first few months of infection, declining thereafter to a "setpoint" with the development of HIV-specific immune responses. We studied viral load trends over time among HIV-infected children with hemophilia. At two years after HIV infection, on average, the children have lower viral load "setpoints" than vertically infected children, suggesting that the age at infection (and the maturity of the immune system) may influence how well individuals control HIV replication. On average, viral load increased slowly over time. We found significant heterogeneity among children in the level of viral load and its rate of change over time. These differences may be due to genetic variability among children or to differences in HIV strains infecting them. We have developed statistical methods for characterizing this heterogeneity and modeling differences among subjects in longitudinal studies of marker data.

Cancer Among HIV-Infected Persons

We are using the AIDS Cancer Match Registry study, which links data in U.S. AIDS and cancer registries, to investigate cancer risk factors in HIV-infected persons. The study includes over 300,000 persons with AIDS.

Hepatitis C virus infection is common among certain groups of HIV-infected persons, such as intravenous drug users and hemophiliacs. We examined the relationship between hepatitis C virus and risk of hepatocellular carcinoma in various groups with HIV infection. Risk was greatest in groups with high hepatitis C virus prevalence. However, even in groups with low hepatitis C virus prevalence, hepatocellular carcinoma risk was higher than in the general population.

In another study, we compared cancer risk between persons with and without AIDS-associated Kaposi's sarcoma. The comparison revealed that persons with AIDS-associated Kaposi's sarcoma were at higher risk for certain types of non-Hodgkin's lymphoma. The relationship appears specific, since no associations were found between Kaposi's sarcoma and other hematologic or solid malignancies.

Studies of Kaposi's Sarcoma-Associated Herpesvirus

Advances in understanding the epidemiology of Kaposi's sarcoma-associated herpesvirus (KSHV), which is etiologically linked to Kaposi's sarcoma, depend on highly accurate serological tests. In a recent study, we evaluated five KSHV serological tests. Two tests (an enzyme immunoassay to the K8.1 glycoprotein and an immunofluorescence assay) appeared to be most accurate, especially in detecting low-titer antibodies. A classification tree

algorithm, incorporating results from the two tests, performed better than either test alone. We also used techniques of latent class analysis to characterize the accuracy of these tests in populations from the Mediterranean region and sub-Saharan Africa. Ongoing work includes further KSHV assay development and evaluation in epidemiological applications.

Keywords

acquired immunodeficiency syndrome (AIDS), hepatitis C virus (HCV), hepatocellular carcinoma, human immunodeficiency virus (HIV), Kaposi's sarcoma-associated herpesvirus (KSHV), statistical models

Recent Publications

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Engels EA, et al. Risk of transfusion-associated transmission of human herpes virus 8. *J Natl Cancer Inst* 1999;91:1773–75.

Engels EA, et al. Zoster incidence in human immunodeficiency virus-infected hemophiliacs and homosexual men, 1984–1997. *J Infect Dis* 1999;180:1784–89.

Engels EA, et al. Identifying human herpesvirus 8 infection: Performance characteristics of serologic assays. *J Acquir Immune Defic Syndr* 2000;23:346–54.

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Epidemiology and Biostatistics Program
Viral Epidemiology Branch
Host Factors and Natural History of Oncogenic Infections

Research: Since the discovery of the Epstein-Barr virus in the 1960s, a number of biologic agents have been linked to cancer in humans, including hepatitis viruses, retroviruses, papillomaviruses, and *Helicobacter pylori.* It is estimated that nearly 15 percent of newly diagnosed cancers worldwide are attributable to infectious agents. With the continuing discovery of new infectious pathogens and the aging trends of the world's population, infectious agents are increasingly important causes of malignancy. Primary goals of our research are to examine the natural history of these infections and to identify factors that determine cancer risks in humans.

Natural History of HTLV-I: Risk Factors for Transmission and Disease Pathogenesis

Human T cell lymphotropic virus type I (HTLV-I) infection is endemic in southern Japan, the Caribbean, parts of Africa, the Middle East, and South America, and is causally associated with adult T cell leukemia/lymphoma. However, only about five percent of HTLV-I carriers develop adult T cell leukemia/lymphoma in their lifetime. Infection early in life appears to be a risk factor for this malignancy. Although the risk of adult T cell leukemia/lymphoma is higher in males than in females among Japanese, this gender difference is not apparent in the Caribbean population. The average age of diagnosis among Japanese is much higher than among patients in the Caribbean. The explanation for these geographic differences is unclear.

Much of our HTLV-I research has been conducted in the Caribbean countries of Jamaica and Trinidad-Tobago. In a prospective cohort study that initially enrolled pregnant mothers and their newborns in Jamaica, we described risk factors for vertical HTLV-I transmission. Analyses of mother-to-infant transmission found increased risk associated with high proviral load, high HTLV-I antibody titer, and the presence of antibody to tax regulatory protein. During the 10-year followup of the children, we described an incident case of infective dermatitis in an HTLV-I-positive child. In ongoing research, we are

evaluating changes over time in HTLV-I viral markers among infected carriers with respect to host genetics, immune response, and HTLV-I-associated morbidity.

In an attempt to identify other host characteristics that modify susceptibility to HTLV-I infection and disease pathogenesis, we are investigating associations of various polymorphic genes, such as human leukocyte antigens, with a variety of viral markers. Such markers for future longitudinal analysis may include clonality of HTLV-I-infected cells, levels of cytokines, and cytotoxic T cell response. We are also planning an extension of earlier research on HTLV-I-associated diseases among children, a followup of family members of patients afflicted with HTLV-I-associated diseases, and a prospective followup of HTLV-I-infected and -uninfected blood donors. Our efforts to identify markers of cancer risks among HTLV-I carriers are aimed at developing targeted intervention strategies for high-risk individuals.

Natural History of *Helicobacter pylori* Infection

We recently completed genotyping the predominant *Helicobacter pylori* strain in Jamaica (cagA-positive, vacA s1b-m1, and iceA2) and validating serologic assays for this agent. A preliminary analysis revealed that 80 percent of pregnant mothers and 20 percent of their two-year-old children were seropositive for *H. pylori.* Seropositivity in mothers was a significant predictor of seropositivity in their offspring. We are investigating the incidence of *H. pylori* infection among children followed to five years of age. We are also collaborating with intramural and extramural researchers to identify new molecular markers for risk of *H. pylori* infection.

Coinfections of Multiple Oncogenic Infectious Agents

There is a growing interest in studies of concurrent oncogenic infections, which may provide new insights into the process of viral oncogenesis. We showed increased hepatitis C virus (HCV) viral load among hemophiliacs coinfected with HIV compared with those infected with HCV alone. Consequences of increased HCV viral load among coinfected persons may include more rapid progression of liver diseases. However, our analysis found only a small increased risk of sexual transmission of HCV between partners due to HIV coinfection. In a cohort of U.S. drug users, we are also investigating the effect of coinfection with HTLV and HIV and with HTLV and HCV in relation to viral loads and their association with various host characteristics as well as liver disease mortality.

Other Viruses and Hematologic Malignancies

We are also interested in the occurrence of virus-associated cancers as second malignancies and second cancers following viral-associated malignancies. Using the NCI Surveillance, Epidemiology, and End Results (SEER) database, we described cases of Kaposi's sarcoma that occurred subsequent to chronic lymphocytic leukemia. A comparable analysis on hairy cell leukemia is currently under way.

Keywords

adult T cell leukemia/lymphoma, biomarkers, cancer susceptibility, coinfection, *Helicobacter pylori*, hepatitis C virus (HCV), human immunodeficiency virus (HIV-1), human T cell lymphotropic virus I (HTLV-I), second cancers

Recent Publications

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Hisada M, et al. Characteristics of *Helicobacter pylori* infection in Jamaican adults with gastrointestinal symptoms. *J Clin Microbiol* 2001;39:212–16.

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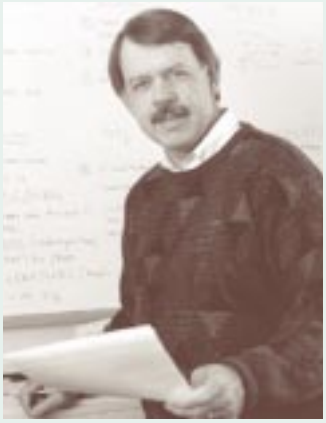

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Biography: *Dr. O'Brien received undergraduate and medical degrees from the University of Michigan and an M.P.H. from the Harvard School of Public Health. He was an Epidemic Intelligence Service Officer and Medical Epidemiologist with the Centers for Disease Control and Prevention from 1985 to 1992, when he joined the NCI Viral Epidemiology Branch. Dr. O'Brien's primary research interests involve studies on the transmission and natural history of oncogenic viruses, especially the human immunodeficiency viruses (HIV) and hepatitis C virus. He is the author of more than 85 scientific publications.*

Epidemiology and Biostatistics Program
Viral Epidemiology Branch
Oncogenic Viruses and Human Genetics

Research: By applying advances in molecular biology and genetics to population-based studies, epidemiologists are better able to understand the distribution and determinants of viral infections. Our research is focusing on HIV-1 RNA levels as markers of pathogenesis and prognosis, as well as on the role of genetic polymorphisms of chemokine receptors genes in HIV-1 natural history, transmission, and treatment.

Chemokine Receptor Gene Polymorphisms
Chemokine receptors play an essential role in immune cell trafficking, but also act as HIV-1 coreceptors. A 32-base pair deletion mutation in the gene for the CC-chemokine receptor 5 (CCR5), a major HIV-1 coreceptor, has a 10 percent allele frequency in Caucasians. Individuals who are homozygous for the CCR5 mutation are resistant to HIV-1 infection, while HIV-1-infected heterozygotes have delayed progression to AIDS. Blockade of CCR5 has been proposed as therapy for HIV-1.

Several large studies, totaling over 2,500 infected subjects, did not find any HIV-1-infected individuals who were homozygous for the CCR5 32-base pair deletion. However, we identified an HIV-1-infected hemophiliac who was homozygous for this allele, demonstrating that CCR5 is not required for infection. An intensive virological investigation revealed that the virus from this patient was restricted to the CXCR4 chemokine receptor, which acted as the HIV coreceptor.

To determine whether CCR5 32-base pair deletion homozygotes have phenotypic expressions other than those related to HIV-1, we investigated this genotype among men not infected with HIV-1. We found that they were generally similar to CCR5 wild-type subjects, except for a higher prevalence of hypertension, higher lymphocyte counts, and higher hepatic enzyme levels in those infected with hepatitis C virus.

Published data are inconsistent on the relationships between various genetic polymorphisms and AIDS risk. To better determine these relationships, we are conducting an international meta-analysis of chemokine receptor polymorphisms and risk of AIDS.

Both the natural history of HIV infection and the virus's response to antiretroviral therapy are heterogeneous. It is known that some of the variation in natural history may be explained by polymorphisms in chemokine receptor genes. We recently showed that polymorphisms may also explain some of the heterogeneity in sustaining viral suppression, which has been observed among patients receiving potent antiretroviral therapy.

Studies are under way to examine genetic factors that alter susceptibility to hepatitis B virus, hepatitis C virus, and other infectious agents.

HIV-1 RNA Levels

We demonstrated that a single HIV-1 RNA level, measured early in the course of infection, strongly predicts long-term risk of AIDS. The level reflects the rate of viral replication, which is the driving force of AIDS pathogenesis. HIV-1 RNA levels are now routinely measured in the clinical care of HIV-1-infected patients.

In a long-term cohort, we measured longitudinally HIV-1 RNA levels to determine whether HIV-1 remained in a steady state over time. For most subjects, HIV-1 RNA levels increased with time, with the rate of increase predicting the risk of AIDS. We also found that HIV-1 RNA values measured longitudinally were more predictive than the initial level alone. These findings were considered by a U.S. Public Health Service panel convened to make recommendations for optimal treatment of HIV-1-infected patients. More recently, we used the data from this research in a collaborative effort to demonstrate a mathematical relationship between HIV-1 RNA levels and survival time, such that a patient's cumulative exposure to viral replication predicts length of survival.

Our measurements of HIV-1 RNA levels in subjects having a wide range of ages shed new light on HIV-1 pathogenesis. We found that HIV-1 RNA levels measured early in the course of infection were higher in subjects older than 35 years compared with younger subjects. This finding suggests that immune senescence, leading to higher HIV-1 replication rates, may explain the previously established association between older age and shorter AIDS incubation time.

Kaposi's Sarcoma-Associated Herpesvirus Studies

Kaposi's sarcoma-associated herpesvirus (KSHV) DNA sequences have been found in Kaposi's sarcoma tumor specimens and other malignancies, suggesting an oncogenic role for the virus. In an interdisciplinary collaborative effort, we developed serologic and polymerase chain reaction assays for KSHV infection. Applying these assays, we determined that KSHV infection was relatively frequent in homosexual men in the early 1980s, consistent with an epidemic of KSHV that paralleled the HIV-1 epidemic in the United States.

Keywords

acquired immunodeficiency syndrome (AIDS), chemokine receptors, genetics, hepatitis B virus (HBV), hepatitis C virus (HCV), HIV-1 RNA levels, human immunodeficiency viruses (HIV), incubation period, Kaposi's sarcoma, Kaposi's sarcoma-associated herpesvirus (KSHV), viruses

Recent Publications

Michael NL, et al. Exclusive and persistent use of the entry coreceptor CXCR4 by human immunodeficiency virus type 1 from a subject homozygous for CCR5 delta32. *J Virol* 1998;72:6040–47.

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Ioannidis JP, et al. Effects of *CCR5-D32, CCR2-64I* and SDF-1 3¹A alleles on HIV-1 disease progression: An international meta-analysis of individual patient data. *Ann Intern Med* 2001;135:782–95.

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Epidemiology and Biostatistics Program
Viral Epidemiology Branch

Cancer Associated with Human Immunodeficiency Virus and Other Infections

Research: With improvement in the treatment and prevention of opportunistic infections, malignancy is emerging as an important cause of HIV-related morbidity and mortality. Our studies are focusing on molecular mechanisms of HIV-related Kaposi's sarcoma and non-Hodgkin's lymphoma, as well as on cancers associated with other chronic infections.

HIV-Associated Malignancies

Kaposi's sarcoma-associated herpesvirus (KSHV) infection is an important factor in the pathogenesis of Kaposi's sarcoma. However, the prevalence of this virus in nondiseased populations is controversial because of great variation in reported seropositivity rates. We previously conducted a blinded comparison of assay results from leading U.S. and European laboratories to examine the correspondence of the various serological tests for KSHV. While many of the tests distinguished high-risk (e.g., Kaposi's sarcoma patients) and low-risk (e.g., blood donors) sera on a group level, the individual concordance between tests was low. Our laboratory is continuing to investigate new serologic assays for improved diagnosis of this infection.

AIDS-associated non-Hodgkin's lymphoma frequently has the characteristic *c-myc* t(8;14) translocation of Burkitt's lymphoma. We detected this translocation in circulating lymphocytes from individuals without lymphoma in our prospective cohort study of HIV-infected homosexual men. In some instances, translocated clones were persistently detectable for many years without the development of frank lymphoma. The prevalence of recombined clones increased with duration of HIV infection in parallel with the increase in lymphoma risk. We did not observe any increase in the frequency of circulating cells with the characteristic *bcl-2* t(14;18) translocation of follicular lymphoma, which is consistent with the lack of an HIV association with this histologic subtype.

The Epstein-Barr virus (EBV) is an important cofactor in a fraction of AIDS-associated lymphomas. We are assessing EBV viral load in two cohort studies of HIV-infected adults and children to determine its relation with risk of lymphoma and other complicating conditions. In preliminary analyses, subjects with lymphoma had higher median and mean EBV levels than controls. The highest levels were seen in Hodgkin's disease rather than non-Hodgkin's lymphoma. Humoral and cell-mediated immunity to EBV is also being assessed to determine whether host response to EBV is an intermediate marker of these malignancies.

Gastrointestinal Malignancies

Helicobacter pylori is a common gastric infection that causes variable inflammation of the stomach mucosa. Gastritis confined to the antrum is associated with excessive acid secretion and high risk of duodenal ulcer disease, whereas widespread gastritis leads to gastric atrophy and hypochlorhydria, precursor conditions for gastric cancer. We are examining genetic factors that control the immune and inflammatory response to *H. pylori* as potential determinants of these dichotomous outcomes. We have shown that genetic polymorphisms in interleukin-1 beta and tumor necrosis factor alpha, which are important mediators of inflammation and potent inhibitors of gastric acid secretion, are strongly associated with increased risk of both hypochlorhydria and gastric cancer. We are currently examining variations in other proinflammatory and anti-inflammatory cytokines for associations with these diseases.

Hepatitis C virus (HCV) infection is associated with some cases of liver cancer, but the absolute risk related to infection is unknown. We obtained followup information on the 17 (0.2 percent) HCV seropositive individuals who were among 8,568 Korean War-era military recruits with sera collected and banked between 1948 and 1954. During the 45-year followup period, 2 (12 percent) of the 17 were diagnosed with liver disease, but none had liver cancer. These findings suggest that healthy HCV-positive persons may not be at significant risk for progressive liver disease. We are examining this issue further in a cohort study of injection drug users recruited in the 1970s.

Human papilloma virus (HPV) is frequently detectable in cancers of the cervix, vagina, and vulva, but its role in endometrial and ovarian cancers is less certain. We examined the association of HPV type 16 (HPV-16) antibodies with subsequent risk of cervical (n=83), endometrial (n=34), and ovarian cancers (n=35) in a prospective study enrolling over 15,000 pregnant women. HPV-16 seropositivity was significantly associated with cervical cancer (OR=2.0, 95 percent CI 1.0 3.4), with the association more prominent for cancers in the first decade after serum sampling. Seropositivity was also associated with endometrial and ovarian cancers within 20 years after serum sampling (OR=2.2 for both), but not for those occurring later. Our results confirm that HPV-16 infection precedes the development of cervical cancer, and predictability of HPV-16 seropositivity for risk of other female cancers warrants further investigation.

Keywords

Epstein Barr virus (EBV), gastric cancer, HIV/AIDS, *Helicobacter pylori,* hepatitis C virus (HCV), Kaposi's sarcoma, Kaposi's sarcoma-associated herpesvirus (KSHV), liver cancer, non-Hodgkin's lymphoma

Recent Publications

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El-Omar EM, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 2000;404:398–402.

Hisada M, et al. Prospective study of antibody to human papilloma virus type 16 and risk of cervical, endometrial, and ovarian cancers (United States). *Cancer Causes Control* 2001;12:335–41.

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Epidemiology and Biostatistics Program
Viral Epidemiology Branch

Kaposi's Sarcoma-Associated Herpesvirus and Other Oncogenic Viruses

Research: Studying the biology and epidemiology of oncogenic viruses such as Kaposi's sarcoma-associated herpesvirus (KSHV) will help us to understand the pathogenesis of cancers caused by viruses. Laboratory techniques in molecular biology and immunology are rapidly advancing, and the Viral Epidemiology Laboratory aims to find new ways to exploit such advances in an epidemiological setting.

Kaposi's Sarcoma-Associated Herpesvirus
Both serological and molecular methods for identifying Kaposi's sarcoma-associated herpesvirus (KSHV) infection in asymptomatic individuals are problematic. We have evaluated many assay combinations and are using the best currently available assays for epidemiological studies of KSHV infection and disease. Major questions in KSHV epidemiology include why are there such striking geographical differences in the prevalence of KSHV, what are the routes of transmission of this virus, and what are the risk factors for KSHV infection and disease.

We have developed an in vitro KSHV activation assay that uses real-time PCR to measure virus reactivation in the latently infected primary effusion lymphoma (PEL) cell line BCP-1. In collaboration with the NCI's Natural Products Branch, we are using this assay to screen a natural products library for potential environmental cofactors for KSHV shedding, transmission, and pathogenesis.

In collaboration with the Department for Epidemiology and Cancer Registry, Institut Catal d'Oncologia, Barcelona, Spain, we are participating in a multicentric case-control study of lymphoma in Europe coordinated by the International Agency for Research on Cancer. The EPILYMPH study will examine the etiology of hematological malignancies, and we will lead the studies on KSHV.

Other Viruses
Aspects of HTLV-I entry and tropism are being studied in collaboration with the NCI's Dr. Kathy Jones in order to gain a greater understanding of the

mechanisms of HTLV-I transmission and pathogenesis. Studies have been initiated to identify new oncogenic viruses using modern molecular techniques combined with insights from previous epidemiological studies.

Keywords

activation, Kaposi's sarcoma, Kaposi's sarcoma-associated herpesvirus (KSHV), lymphoma, transmission

Recent Publications

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Whitby D, et al. Detection of antibodies to human herpesvirus 8 in Italian children: Evidence for horizontal transmission. *Br J Cancer* 2000;82:702–04.

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The Human Genetics Program was established in 1996 to provide an expanded focus for interdisciplinary research into the genetic determinants of human cancer. Advances in molecular genetics and related biomedical sciences provide extraordinary opportunities both to explore and identify heritable factors that predispose to cancer as well as to elucidate gene-environment interactions. Program investigators conduct family-based and population-based studies that integrate clinical, epidemiologic, and laboratory approaches to investigate genetic susceptibility to cancer. The Program is organized into the Clinical Genetics Branch and the Genetic Epidemiology Branch.

The Clinical Genetics Branch became operational in the Fall of 1999 with the recruitment of Dr. Mark H. Greene as Branch Chief, along with scientific and support staff. The Branch focuses on the translation of advances in molecular genetics into evidence-based management strategies, such as screening, prevention, and assessment of behavioral consequences, for persons at increased genetic risk of cancer. In carrying out this research program, molecular and clinical observations in cancer genetics are integrated into interdisciplinary approaches that involve epidemiologic, clinical, genetic, behavioral, statistical, and laboratory methods to define the role of susceptibility genes in cancer etiology. Initial areas of scientific concentration include interdisciplinary studies of cancer-prone families, analyses of genetic polymorphisms as determinants of cancer treatment outcomes, and chemoprevention trials that target genetically at-risk populations.

The Genetic Epidemiology Branch, under the leadership of Dr. Margaret A. Tucker, continues a long record of hereditary cancer research, dating back to the early 1960s, at the NCI. Today, the Branch focuses on families at high risk of cancer, mapping and cloning of predisposing genes, investigating identified genes in the general population, developing new genetic epidemiologic methodologies, conducting pharmacogenetic studies, and identifying late effects of treatment in survivors of cancer. In the area of predisposing genes to environmentally induced cancer, a major effort is under way to understand the role of polymorphic metabolizing genes, such as the cytochrome P450 group, the N-acetyl transferases, and the glutathione-S-transferases. Recent accomplishments related to hereditary cancers include defining clinical features and mapping/cloning of genes responsible for retinoblastoma *(RB1),* Li-Fraumeni syndrome *(TP53),* neurofibromatosis *(NF1* and *NF2),* melanoma *(CDKN2* and *CDK4),* breast and ovarian cancers *(BRCA1* and *BRCA2),* and Cowden's disease with breast cancer *(PTEN).*

Human Genetics Program
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The Clinical Genetics Branch (CGB) integrates molecular and clinical observations in cancer genetics into interdisciplinary approaches involving epidemiologic, clinical, genetic, behavioral, statistical, and laboratory methods to define the role of susceptibility genes in cancer etiology. The primary goal of this research program is to translate the burgeoning advances in molecular genetics into evidence-based management strategies (including screening, prevention, and assessment of behavioral consequences) for persons at increased genetic risk of cancer due to the effects of rare, highly penetrant genes or common, less penetrant genes. The central research strategy for highly penetrant genes employs detailed and multidisciplinary assessment of the individual members of cancer-prone families, while for less penetrant genes it relies upon intensive studies of genetic polymorphisms in populations with exposures and outcomes of interest.

Established as part of the Human Genetics Program in 1996, the Branch became operational in the Fall of 1999. We have focused on recruiting new staff members and formulating a broad set of research program areas in which we will direct our initial scientific efforts. Our research activities will complement and enhance those being carried out by the other components of the Human Genetics Program. In addition, we have a special responsibility for establishing constructive collaborations with extramural scientists, as many of the critical clinical cancer genetic problems can only be effectively addressed by multiple investigators pooling patient resources and cooperating in the design and execution of the needed studies.

Our research approach mandates: (1) identifying and characterizing phenotypic manifestations of genetic and familial cancer syndromes; (2) assessing genetic risk and counseling individuals at high risk of cancer; (3) considering risks and benefits associated with clinical predictive genetic testing; (4) offering germline mutation testing, with disclosure of results for clinical decision-making; (5) implementing linkage analyses and genome-wide searches for new cancer susceptibility genes in familial cancer syndromes; (6) assessing the ethical, psychosocial, and family dynamics aspects of the cancer risk assessment process; (7) developing cancer site-specific recommendations for surveillance and risk-reduction strategies, including intervention trials of screening and prevention, so as to minimize risks and maximize benefits associated with this activity; (8) acquiring critical, well-characterized biological specimens from cancer-prone family members for study by laboratory collaborators; and (9) creating appropriate educational materials for cancer-prone family members and their health care providers so as to optimize health care decision-making.

We also employ research strategies aimed at assessing the role of genetic polymorphisms as determinants of important outcomes of cancer treatment, such as therapy-related second malignancies and protective effects. In addition, we pursue astute clinical observations of unusual cancer occurrences which might provide new clues to cancer etiology. Pursuing such observations represents a "return to our roots," as this approach was a cornerstone upon which early successes of the NCI cancer epidemiology program was built.

Ruthann Giusti, M.D.

BRCA1 and _BRCA2_ Mutations

Familial and hereditary cancers are an important research focus within the CGB. Dr. Ruthann Giusti is leading our research efforts in hereditary breast and ovarian cancers, including a "Pilot Study of Breast Imaging Modalities in Hereditary Breast and Ovarian Cancers," which compares mammography, MRI, and PET imaging techniques in detecting lesions among women from *BRCA1* and *BRCA2* mutation-bearing families, and the "Israeli Prostate Cancer Study," which is determining the prevalence of *BRCA1* and *BRCA2* founder mutations to assess whether prostate cancer is part of the syndrome.

IGF-I Signaling Pathway Polymorphisms

Elevated levels of insulin-like growth factor 1 (IGF-I), a cytokine with both mitogenic and antiapoptotic effects, have been associated with increased risk for a variety of cancers. In a collaborative study, genetic polymorphisms in genes in the IGF-I signaling pathway are being identified and evaluated as determinants of cancer risk among participants in the NCI Prostate, Lung, Colorectal, and Ovarian Cancer screening trial. Dr. Giusti is also leading this effort.

Blanche Alter, M.D., M.P.H.

Fanconi's Anemia

A number of hereditary pediatric disorders predispose to bone marrow failure, acute leukemia, and solid tumors in adult survivors. Fanconi's anemia, the prototype of these disorders, forms the basis of an inter-disciplinary project designed to shed light on mechanisms of carcinogenesis in humans. Dr. Blanche Alter, an internationally recognized expert in Fanconi's anemia, is leading this project.

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Human Genetics Program, Clinical Genetics Branch
Familial and Hereditary Cancers

Research: With the discovery of genes underlying the hereditary components of certain common adult malignancies, such as *BRCA1* and *BRCA2* in hereditary breast and ovarian cancers, mismatch repair genes in hereditary nonpolyposis colorectal cancer, and the *CDKN2A* gene in hereditary melanoma, the molecular biology of familial cancer has outstripped our ability to manage germline mutation carriers in an effective, evidence-based fashion. Clinicians and patients are struggling to take advantage of these molecular breakthroughs, but at present they raise more questions than answers. We are focusing resources on acquiring the data needed to address these questions for both persons at increased genetic risk of cancer due either to rare, highly penetrant genes or to common, less penetrant genes.

Hereditary Breast and Ovarian Cancers
Hereditary breast and ovarian cancers have been under active investigation by the NCI epidemiology program for over 30 years. In continuing this effort, we are clinically following a cohort of 26 *BRCA1* and *BRCA2* mutation-bearing families, which includes 232 individuals tested or inferred to be positive for *BRCA1* or *BRCA2* mutations and 2,046 family members tested or inferred to be mutation negative. We are also developing the next generation of research studies to address the many issues related to this genetically high-risk population. A number of projects are in development or are under way. These include clinical, behavioral, genetic, and laboratory studies of hereditary breast and ovarian cancer families that involve clinical genetic testing, assessing tamoxifen-related decision making, performing breast duct lavage for early diagnosis and molecular markers, and profiling endogenous hormones; a pilot study of breast imaging modalities in hereditary breast and ovarian cancers, which compares mammography, MRI, and PET imaging techniques in detecting lesions; the Israeli Prostate Cancer Study, which is determining the prevalence of *BRCA1* and *BRCA2* founder mutations to assess whether prostate cancer is part of the syndrome; the National Prospective Cohort Study of Prophylactic Oophorectomy, which is assessing

the incidence of breast and peritoneal cancers and quality of life after prophylactic oophorectomy among women at increased genetic risk; a population-based case-control study of ovarian cancer, which is determining the prevalence of *BRCA1* and *BRCA2* mutations and analyzing interactions between mutation status and oral contraceptive use in ovarian cancer risk; and a study of family history of cancer and Westernization as risk factors among Asian-American women with breast cancer, which is analyzing data from a large, population-based case-control study of Chinese, Japanese, and Filipino women with breast cancer.

Other Familial Cancer Syndromes

We are initiating a number of efforts to elucidate genetic risks and mechanisms of carcinogenesis through studies of various familial cancer syndromes that are described below.

- A number of hereditary pediatric disorders predispose to bone marrow failure, acute leukemia, and solid tumors in adult survivors. Fanconi's anemia, the prototype of these disorders, will form the basis of an interdisciplinary project designed to shed light on mechanisms of carcinogenesis in humans.
- The DCEG familial testicular cancer study has been reactivated, following the mapping of a familial testicular cancer susceptibility gene to the X chromosome and the initiation of a new testicular cancer case-control study, which will be a source of new families. By joining the International Testicular Cancer Linkage Consortium, we will contribute data from our families to the ongoing mapping and positional cloning effort. In addition, we are developing a protocol to bring selected testicular cancer families to the NIH Clinical Center for more detailed etiologic studies.
- The combination of breast cancer and colon cancer in different members of the same family seems to occur more often than can be accounted for by known hereditary cancer syndromes. A family and genetic study of women with primary cancers of the breast and colon is being planned in an effort to clarify this association.
- Future projects will also address less well-studied familial cancer syndromes, including the systematic investigation of familial hematopoietic and lymphoproliferative disorders, with special attention to families with multiple *different* cancers associated with the conditions. This research effort would build on prior DCEG investigations of familial Hodgkin's disease and acute leukemia and current studies of familial non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and Waldenstrom's macroglobulinemia.

Genetic Polymorphisms and Cancer Therapy Outcomes

The DCEG has a long history of investigating the relationship between cancer therapies and risk of developing second primary cancers. These investigations provide unique opportunities to explore outcomes of human exposure to cancer-causing chemotherapeutic drugs and ionizing radiation. We plan to study the relationship between common polymorphisms that affect chemical carcinogen bioavailability and various outcomes, such as second cancers, thrombotic events, acute myelosuppression, treatment response, and survival. Information on the influence of genetic polymorphisms could significantly impact clinical decision-making.

Elevated levels of insulin-like growth factor 1 (IGF-I), a cytokine with both mitogenic and antiapoptotic effects, have been associated with increased risk for a variety of cancers. In a collaborative study, genetic polymorphisms in genes in the IGF-I signaling pathway are being identified and evaluated as determinants of cancer risk among participants in the NCI Prostate, Lung, Colorectal, and Ovarian Cancer screening trial. In another effort, we are planning a study to examine risks of endometrial cancer and breast cancer in relation to genetic polymorphisms in genes associated with tamoxifen and estrogen bioavailability.

Chemoprevention Studies in Persons at Increased Genetic Risk of Cancer
While progress is being made in identifying major cancer susceptibility genes, little is known about ways to intervene at the molecular level to ameliorate risk associated with mutations in these genes. We are in urgent need of safe and effective strategies for reducing cancer risks among mutation carriers. Accordingly, strategic planning is under way to create scientifically sound strategies by which we can make more significant contributions to relevant intervention studies. Concurrent with this planning process, we are supporting the breast cancer and colon cancer chemoprevention trials, under way within the NCI's Center for Cancer Research, by urging members of our cancer-prone families to participate in these important efforts.

Keywords

behavioral studies, *BRCA1, BRCA2,* breast cancer, breast imaging, cancer screening, case-control studies, chemotherapy, clinical trials, cohort studies, colon cancer, colon polyps, early cancer detection, endometrial cancer, estrogens, familial cancer, family studies, Fanconi's anemia, gene-environment interactions, genetic counseling, genetic polymorphisms, genetic susceptibility, genetic testing, genetics, hereditary cancer, hereditary nonpolyposis colorectal cancer, hormones, insulin-like growth factors, intervention studies, molecular markers, multiple primary cancers, ovarian cancer, positional cloning, precancerous lesions, prophylactic oophorectomy, prostate cancer, psychosocial studies, second cancers, tamoxifen, testicular cancer, treatment-related cancers

Recent Publications

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Lindor NM, et al. Papillary renal cell carcinoma: Analysis of germline mutations in the MET proto-oncogene in a clinic-based population. *Genet Test* 2001;5:101–06.

Hisada M, et al. Solid tumors after chronic lymphocytic leukemia. *Blood* 2001;98:1979–81.

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Human Genetics Program, Clinical Genetics Branch
Studies of Tumors of Unusual Occurrence

Research: New clues to cancer etiology have come from peculiarities in unusual occurrences of tumors. Such peculiarities have sometimes been detected by astute bedside observations. Examples include the identification of the Li-Fraumeni family cancer syndrome, which led to its link to germline mutations in the *p53* gene, and delineation of the concurrence of Wilms' tumor of the kidney in childhood and congenital absence of the iris of the eye (aniridia). Observations such as these laid the foundation for the novel hypothesis, proposed first by Dr. Alfred Knudson, that various forms of childhood and adult cancers are related to inactivation of tumor suppressor genes. Our research focuses on clinical approaches, which often open new avenues of laboratory investigation, that may provide critical etiologic insights.

Werner's Syndrome

Werner's syndrome leads to premature aging. Gray hair, cataracts, and diabetes mellitus are early features of the syndrome, an autosomal recessive disorder, which has been studied since 1966 in an effort to gain new insights into the mechanisms of human aging. Multiple organ-systems are affected, including immunologic, hormonal, cardiovascular, and especially connective tissue. The syndrome is much more common in Japan than elsewhere, as that population's high rate of inbreeding raises the probability of pairing of recessive genes. Werner's syndrome is associated with mutations in a DNA helicase gene, located on chromosome 8p12. Although more than 20 specific gene mutations have been described worldwide, two of them account for 86 percent of cases in Japan, which are thought to represent founder mutations in that country's population.

At the 1994 U.S.-Japan Cooperative Cancer Research Program workshop on cancer clusters, Dr. Makoto Goto summarized 800 case reports of Werner's syndrome. He noted the excess occurrence of six types of rare cancers. Subsequently, in a collaboration between the NCI and Cancer Institute in Tokyo, the case reports were analyzed and substantial excesses were documented for soft-tissue sarcoma, osteosarcoma, myeloid leukemia and its precursors, thyroid carcinoma, benign meningiomas, and a rare form of melanoma. The melanoma excess was confined to the feet and nasal mucosa, unusual sites that normally occur with similar frequency among all races. The pathology and genotype of these peculiarities of occurrence are now under study.

Since the cloning of the gene for Werner's syndrome, rapid tests for the gene are being developed to screen unaffected individuals at high risk, including young members of Werner syndrome families, patients with incomplete forms of the disease, and students who do not have an adolescent growth spurt, the first clinical manifestation of the disorder. It is hoped that early detection will lead to treatments to ameliorate certain severe manifestations of the syndrome, such as hyperlipidemia as a factor in atherosclerotic heart disease, a leading cause of death (average age=47 years) among Werner's syndrome patients.

Two additional helicase genes were identified in Japan but were not altered in Werner's syndrome. In collaboration with the NCI and the Mayo Clinic, one of the two genes was linked to Rothmund-Thomson syndrome, which also has features of premature aging and a high rate of osteosarcoma.

Ewing's Sarcoma After Retinoblastoma

The excessive occurrence of two or more types of cancer in the same person or separately among close relatives is an indicator that the malignancies may share a common etiology. A classic example of this phenomenon is the occurrence of both retinoblastoma and osteosarcoma in persons with mutations in the RB-1 gene. In a literature review, we found 10 cases of Ewing's sarcoma of bone occurring after retinoblastoma. The fact that most of these patients had bilateral retinoblastoma strongly suggests that they carry a germline mutation in the RB-1 gene. Given the rarity of Ewing's sarcoma and retinoblastoma in the general population, virtually no cases with both cancer types were expected. Besides these cancers, four cancers of the olfactory nerve were identified among retinoblastoma patients. These cancers had been classified as Ewing's sarcoma because of the histologic similarity of the two neoplasms under the microscope. (Ewing's sarcoma and olfactory nerve tumors arise from neural crest tissue.) Three of the four retinoblastomas cases were bilateral, so it is likely that both cancers were associated with germline mutations in the *RB1* gene. Histochemical studies of the olfactory tumor tissue excluded the diagnosis of Ewing's sarcoma, suggesting that they were primary olfactory nerve neoplasms. These observations extend the spectrum of second cancers observed in patients with hereditary retinoblastoma.

Keywords

cancer genetics, congenital malformations, etiology, Ewing's sarcoma, helicase gene, melanoma, multiple primary cancers, osteosarcoma, *RB1* gene, Rothmund-Thomson syndrome, Werner syndrome

Recent Publications

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The Genetic Epidemiology Branch (GEB) designs and conducts interdisciplinary clinical, epidemiologic, genetic, and laboratory studies of persons, families, and populations at high risk of cancer. These studies are aimed at identifying genes and exposures that confer cancer predisposition and at exploring the combined effects of predisposition and specific exposures. As part of this effort, the Branch maintains a familial cancer registry and biospecimen repositories. Families participating in studies receive counseling about cancer risk and screening or intervention options. Cancer-related educational materials are developed for family members, health care providers, and the general public.

Recent advances in laboratory technologies often allow direct measurement of genetic variations as risk factors for specific cancer types. A broad range of methodologies are used in our interdisciplinary investigations, including family, case-control, cohort, and pharmacogenetic designs. Family studies are undertaken to map and identify genes predisposing to cancer, which can then be evaluated for nonfamilial cancer in specific populations. Family studies are often expanded to evaluate modifiers of genetic risk, such as environmental exposures or other genes. Pharmacogenetic studies typically examine variations in the metabolism of carcinogens, procarcinogens, medications, hormones, and dietary factors. Metabolic variation may determine the effective dose of an agent, and thus the biological consequences of exposure. Such studies are key to understanding gene-environment interactions, which may result in differences in cancer susceptibility among individuals. To advance research in this area, the Branch undertakes methodologic investigations to develop analytic tools for exploring gene-environment interactions.

The Branch is organized into the Family Studies Section, Pharmacogenetics Section, and Population and Statistical Genetics Section, all of which work closely in carrying out major research projects. Highlighted below are some of the studies being conducted by the Branch.

Family Studies

• Studies of melanoma-prone families over the last 20 years have led to the identification of germline mutations in the *CDKN2A* and *CDK4* genes in some of the families, and quantifying the risk of melanoma and pancreatic cancers according to *CDKN2A* genotype status. Most of the mutations in the *CDKN2A*

gene are founder mutations, and there are no phenotypic differences in families with *CDKN2A* and *CDK4* mutations except for risk of pancreatic cancer.

- Germline mutations were identified in the *PTCH* gene, which is associated with nevoid basal cell carcinoma syndrome families. In addition, sun exposure and ionizing radiation, and their synergistic effect, were found to be important risk factors for the syndrome. Studies are being carried out on genotype-phenotype correlations.
- Descriptions were reported of detailed genotype-phenotype analyses of neurofibromatosis 2, as well as of the clinical variance in phenotype and natural history of the disorder.
- Breast and ovarian cancer families are being genotyped for mutations in the *BRCA1* and *BRCA2* genes, and the family members are counseled on cancer risk. In addition, we are exploring risk of intra-abdominal carcinomatosis following prophylactic oophorectomy and searching for potential modifiers of *BRCA1* and *BRCA2* penetrance.
- Families with a history of chordoma are being clinically evaluated for possible gene mapping studies.
- Families prone to chronic lymphocytic leukemia are being clinically evaluated, and studies are being conducted to map candidate genes.
- Candidate genes for Hodgkin's disease are being evaluated with parametric and nonparametric linkage analyses.
- Families with von Hippel-Lindau disease are participating in a study to identify possible modifier genes or environmental exposures that alter disease expression. Other studies being carried out include families with Li-Fraumeni syndrome, Waldenstrom's macroglobulinemia, non-Hodgkin's lymphoma, testicular cancer, Beckwith-Wiedemann syndrome, and other heritable cancers.

Pharmacogenetic Studies

- Case-control studies of lung cancer are evaluating a wide variety of metabolic genotypes and phenotypes, along with germline and somatic mutations, in relation to risk. A new large case-control study of lung cancer will also evaluate some smoking-related genes.
- A cohort study of individuals in a smoking cessation program is examining genetic factors that may influence outcome.
- Cancer risk is being evaluated in a cohort of individuals from Seveso, Italy, who were accidentally exposed to high levels of dioxin.

Population and Statistical Genetics

- A case-control study of ovarian cancer in a Jewish population is being conducted in collaboration with Israeli investigators to evaluate risk associated with three common mutations in *BRCA1* and *BRCA2* genes.
- Data analysis is under way of a multicenter, case-control study of melanoma.
- Tumors from a cohort of clinically evaluated patients with medulloblastoma are being examined for mutations in candidate genes (including *PTCH*).
- A cohort of patients with neural tumors following radiation for tonsillar hypertrophy is being evaluated for somatic alterations in the neurofibromatosis 2 gene *(NF2).*
- Cancer risk is being assessed among family members of patients identified through a case-control study of brain tumors.
- A population-based registry study is evaluating cancer risk among heterozygotes with mutations in the ataxia-telangiectasia gene *(ATM).*

Collaboration and Training
The Branch offers many opportunities for interdisciplinary collaboration in studies of cancer genetics. In addition, the Cancer Genetics and Epidemiology Training Program provides unique postdoctoral training in clinical, epidemiologic, and laboratory approaches to cancer genetics.

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Biography: *Dr. Tucker received an M.D. from Harvard Medical School and completed training in internal medicine and medical oncology at Stanford University Medical Center. She spent three years at the NCI between her residency training and oncology fellowship, returning to the Institute as Clinical Investigator in 1983. Dr. Tucker has been responsible for the family studies research program since 1985. She was named Chief of the Genetic Epidemiology Branch in 1992. Dr. Tucker's major research interests are familial cancers, the etiology of melanoma, and multiple primary cancers.*

Human Genetics Program, Genetic Epidemiology Branch
Cancer Genetics

Research: We are focusing on investigations of families and individuals at high risk of cancer, since they may reveal new insights into carcinogenesis and provide etiologic clues relevant to the general population. Families with multiple members who have an unusual pattern or number of cancers are evaluated clinically and risk factor information is obtained for analysis. Population studies are undertaken when specific genetic alterations or host characteristics are identified that may predict risk. Studies of individuals at high risk of cancer may also yield important information about causation. Of particular interest are individuals whose medical exposures, such as radiation or chemotherapy, may produce an increased cancer risk. Most of these investigations integrate clinical, epidemiologic, and molecular components into their research designs.

Cutaneous Melanoma
Since the late 1970s, we have studied the etiology of cutaneous melanoma, evaluating clinically and following over 800 members of melanoma-prone families. The genetic findings from these studies are summarized by Dr. Alisa Goldstein in her research narrative. In addition to clinical evaluation of the families, we examined histologically all of the removed pigmented lesions. Ongoing work is analyzing sun exposure data obtained by questionnaire. As part of the family study, we identified and described dysplastic nevi, precursor lesions of melanoma, which we used to compile an atlas of the natural history, clinical, and histologic characteristics of these lesions.

Based on the findings from the high-risk families, we conducted a multicenter case-control study of melanoma to evaluate the number and type of nevi associated with risk. An increased number of ordinary small (less than 5mm) nevi was found to confer a 2-fold excess risk, while an increased number of small and large ordinary nevi conferred up to a 4-fold excess risk. In addition, one dysplastic nevus was associated with a 2-fold excess risk, while 10 or more dysplastic nevi conferred a 12-fold excess risk. The effects of sun exposure appeared additive in the presence of dysplastic nevi.

We developed a new methodology to estimate cumulative ultraviolet dose based on residential history, which will be used to estimate ultraviolet exposure in high-risk families. Another outgrowth of our interest in melanoma-prone families is a recently completed description of the histology and natural history of genital nevi.

Breast and Ovarian Cancers
To investigate potential modifiers of risk, we are collaborating with investigators in Israel on a population-based case-control study of ovarian cancer among Israeli Jews. We are exploring potential interactions of parity, exogenous hormone use, and other risk factors with the presence of variant alleles in the *BRCA1* (185delAG and 5382insC) and *BRCA2* (6174delT) genes.

It has been hypothesized that heterozygote carriers of mutations in *ATM*, the gene for ataxia telangiectasia, have increased risk of breast cancer. In a collaborative effort with the Radiation Epidemiology Branch and Nordic Cancer Registries, we are conducting a population-based study of individuals carrying an altered *ATM* gene to assess risk of breast cancer.

Multiple Primary Cancers
Studies have shown that lung cancer can develop as a second malignancy following Hodgkin's disease, breast cancer, and other primary lung cancers. The increased risk has been attributed to radiation, smoking, and possibly chemotherapy. We evaluated the risk of nonsmall-cell lung cancer following small-cell lung cancer. Among survivors of two or more years, the risk of a second lung cancer was highest in those who both continued to smoke and received radiation therapy. There also was a suggestion that treatment with alkylating agents contributed to an increased risk. These data add to a growing body of evidence that smoking contributes significantly to risk of second lung cancers, and may act synergistically with radiation and possibly alkylating agent chemotherapy.

Reports have been consistent in describing an increased risk of melanoma following retinoblastoma. To explore this association in more depth, we are clinically evaluating individuals with both retinoblastoma and melanoma and their family members, and plan to initiate molecular studies to further probe the relationship.

Keywords

breast cancer, dysplastic nevi, gene-environment interaction, genetics, hereditary cancer, lung cancer, melanoma, ovarian cancer, second cancers, treatment-related cancers

Recent Publications

Kleinerman RA, et al. Hereditary retinoblastoma patients are at increased risk of lung cancer. *J Natl Cancer Inst* 2000;92:2037–39.

Olsen JH, et al. Cancer in patients with ataxia-telangiectasia and in their relatives in the Nordic countries. *J Natl Cancer Inst* 2001;93:121–27.

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Human Genetics Program, Genetic Epidemiology Branch
Genetic Components of Major Cancers

Research: We are conducting molecular epidemiology studies on lung, prostate, and lymphoproliferative cancers. The studies are aimed primarily at identifying and better understanding genetic components of these major cancers. In designing these interdisciplinary studies, we emphasize the integration of epidemiologic, genetic, and laboratory approaches.

Lung Cancer

The Branch has long been a pioneer in epidemiologic studies aimed at identifying genetic components of common cancers. Our research has emphasized polymorphic genes, such as *CYP2D6, NAT2,* and *GSTM1,* that may influence the metabolism of carcinogens, thereby modifying cancer susceptibility associated with certain exposures. Lung cancer is a logical model for this research because of clear evidence for an environmental etiology (tobacco smoking) and a genetic component (only a minority of heavy smokers develop lung cancer). Furthermore, somatic gene mutations are well documented in lung cancer, and relatives of lung cancer cases are also at increased risk.

We have launched a variety of studies to better understand the postulated genetic component to smoking-related cancer. These efforts include case-control studies of lung cancer with extensive biospecimen collection; studies of lung cancer determinants in nonsmokers; studies of the lung cancer in

different geographic, occupational, and ethnic groups; and studies of consecutive surgical lung cancer cases with emphasis on tissue collection for characterization of somatic genes. We have also studied families prone to lung and other smoking-related cancers, although suitable large, multigeneration families are difficult to accrue because of the death toll for smoking-related diseases. We are participating in the NCI Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, a cohort study of 70,000 individuals, which is expected to yield a large number of lung cancer cases over the next few years. We have currently fielded a large multicenter case-control study of lung cancer in Milan, Italy, with sufficient power to detect gene-environment interactions.

In other research, we are examining the hypothesis of a genetic component to the behavioral element of smoking. In particular, we investigated genetic polymorphisms affecting dopamine regulation and receptor stimulation as candidates for influencing genetic susceptibility to cigarette smoking. Preliminary findings suggest that the dopamine transporter gene *(DAT1),* which governs the reuptake of dopamine from the neuronal synapse, and the D2 dopamine receptor gene *(DRD2),* which is a postsynaptic receptor, may interact to influence smoking behavior. This finding indicates that smoking may be influenced by an interplay among multiple genes affecting dopaminergic reuptake and receptor stimulation. Understanding mechanisms of dopaminergic genes in smoking may facilitate development of improved strategies to prevent smoking and help smokers quit the habit.

Family Studies
We are involved in family studies in lymphoproliferative diseases, primarily chronic lymphocytic leukemia. We have recently described the kindreds in the NCI Familial Registry and are planning a new edition of our newsletter to update the status of family members and inform them of a new plan to obtain biospecimens. We have conducted a preliminary linkage study in 18 multiplex families and investigated a candidate gene, *ATM.* We are collaborating with other intramural investigators to conduct cytogenetics on stored material from the familial cases. We have also investigated a putative precursor condition for CLL in our kindreds, B cell monoclonal lymphocytosis (BCML).

Special Exposures
Studies of unusual population exposures provide opportunities to examine the role of mechanistically plausible genes in cancer causation. Such an opportunity arose from the industrial accident that contaminated Seveso, Italy, with the highly toxic compound 2,3,7,8-tetrachloro-dibenzo(*p*)-dioxin (TCDD). Two decades after the accident, we carried out a population-based study to determine TCDD plasma levels in a random sample of healthy individuals from the contaminated zones and surrounding areas.

The study showed that TCDD levels were significantly higher in women than in men in both the contaminated and surrounding areas. The higher levels in women may be partially due to increased body fat resulting in more prolonged retention of the highly lipophilic compound. However, gender retained an independent association with TCDD levels even after accounting for environmental factors, including smoking, distance from the accident site,

and consumption of animals raised in the area at the time of the accident. We plan to examine the relation between dose to risk of dioxin-related chloracne or cancer as well as to expression of polymorphisms of candidate genes, including *CYP1A1* and Ah receptor.

Methodological Studies

We conducted extensive pharmacogenetics studies, emphasizing genotype-phenotype relationships, to better understand the utility of probe drug assays for identifying genetic polymorphisms. Studies included ones using caffeine for *CYP1A2* and *NAT-2* and debrisoquine/dextromethorphan for *CYP2D6*. In some cases, we compared specific phenotyping approaches, such as the caffeine breath test and simple consumption of caffeine and the urine assay. Ongoing studies are examining the disposition of nicotine in relation to the *CYP2D6* genotype. In addition, research is being conducted on population stratification and other methodologic issues involving biomarkers in epidemiologic studies, on practical and ethical aspects of biospecimen use in field studies, on optimum study design to detect gene-environment interaction, and on new DNA collection procedures for large field studies.

Keywords

2,3,7,8-tetrachloro-dibenzo(*p*)-dioxin (TCDD), alcohol, alcohol dehydrogenase (ADH3), chronic lymphocytic leukemia, *CYP2D6*, dioxin, dopamine receptor gene *(DRD2),* dopamine transporter gene *(DAT1),* gene-environment interactions, genetics, *GSTM1,* lung cancer, molecular epidemiology, nicotine, pharmacogenetics, tobacco

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Biography: *Dr. Goldin received a Ph.D. in genetics from the University of North Carolina at Chapel Hill in 1978. She was a member of the Clinical Neurogenetics Branch of the National Institute of Mental Health until she joined the NCI Genetic Epidemiology Branch in 1998. Dr. Goldin's major research interests are in developing and evaluating statistical methods and study design for detecting susceptibility genes for complex diseases.*

Human Genetics Program, Genetic Epidemiology Branch
Gene Detection in Complex Diseases

Research: Our research goals are aimed at developing and testing analytic methods for detecting susceptibility genes for complex diseases by linkage and association, and applying promising methods to identify genes for different cancers. Nonparametric linkage methods are of particular interest, since they are more robust to uncertainties about the mode of inheritance. We are also carrying out studies to determine sample size requirements for

detecting susceptibility loci, so as to optimize the number and structure of families collected and the number of markers genotyped. The sample size requirements are applied in designing studies using linkage and association approaches.

Linkage Detection Uusing "Regional" Inference
The choice of an appropriate critical value in testing for linkage in a genomic screen is controversial. A number of critical values have been proposed for single-locus and multilocus linkage analyses. We carried out a simulation study to evaluate criteria based on multiple single-locus analyses (regional test criteria) for three different map densities. Appropriate critical values were determined based on results from simulations under the null hypothesis of no linkage. The power of each "regional test" was compared to the power of a single-locus test. Results suggest that the best power is found when moving averages of p-values over an interval size of 9-15 cM were computed, and that this procedure is superior to testing each single locus separately. The increase in power ranged from 7 percent to 29 percent over the simulations. We have found that other methods of "smoothing" may be superior. Application of unequal weights to consecutive markers can further improve the power. Under some conditions, the moving average procedure is as powerful as standard multipoint linkage analysis.

Familial Chronic Lymphocytic Leukemia
In collaboration with the Laboratory of Population Genetics, we are carrying out a genome scan in our sample of multiplex families with chronic lymphocytic leukemia to detect underlying susceptibility genes. Markers have been typed at 10cM density, and linkage analyses are in progress. Areas of the genome showing positive results, as well as regions containing candidate genes, will be followed up with denser markers. Of particular interest is a region of 13q14, which is frequently deleted in CLL tumor cells. Some candidate genes in this region are being sequenced. Among our families with chronic lymphocytic leukemia, we showed that age of disease onset is consistent with anticipation, where onset tends to be at an earlier age in the offspring generation than in the parental generation.

Familial Aggregation of Lymphoproliferative Malignancies
Evidence from case-control studies indicates that lymphoproliferative malignancies, such as non-Hodgkin's lymphoma, Hodgkin's disease, chronic lymphocytic leukemia, and multiple myeloma, aggregate together in relatives. Evidence also exists for associations of autoimmune diseases and lymphoproliferative malignancies. We plan to test for familial aggregation of these malignancies and autoimmune disorders using population-based linked registries in Sweden and Denmark.

Keywords

anticipation, association studies, chronic lymphocytic leukemia, genome screening, linkage studies, lymphoproliferative cancers

Recent Publications

Badner JA, et al. Optimal ascertainment strategies to detect linkage to common disease alleles. *Am J Hum Genet* 1998;63:880–88.

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Goldin LR, et al. Anticipation in familial chronic lymphocytic leukemia. *Am J Hum Genet* 1999;65:265–69.

Xiaohong Y, et al. Use of weighted p-values in regional inference procedures. *Genet Epidemiol* 2001;21:S484–89.

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Human Genetics Program, Genetic Epidemiology Branch
Genetic and Environmental Determinants of Cancer

Research: We are carrying out family and genetic epidemiologic studies of several cancers, including cutaneous malignant melanoma and its associated dysplastic nevi, and nevoid basal cell carcinoma syndrome. The main purpose of our studies is to investigate genetic and environmental determinants of cancer. We are also developing and evaluating methods to examine

gene-environment interactions in complex diseases. In designing studies, emphasis is placed on integrating epidemiologic, clinical, and molecular approaches.

Familial Melanoma

The Branch has been studying familial melanoma since the mid 1970s. To date, two melanoma susceptibility genes *(p16/CDKN2A* and *CDK4)* have been identified. *CDKN2A* appears to account for about one-fourth of familial melanoma kindreds, while mutations in *CDK4* have been detected in only three kindreds. Although *CDKN2A* is a tumor suppressor gene and *CDK4* an oncogene, we found no differences in age at melanoma diagnosis, number of tumors, or numbers of nevi between patients from families with *CDKN2A* mutations and *CDK4* mutations. Also, we recently showed that 20 families with the most common *CDKN2A* mutation, *G101W*, derived from a single common ancestral haplotype. The *G101W* mutation was estimated to have arisen 97 generations ago (range 70–133). Our ongoing studies are directed toward identifying additional melanoma genes, assessing risks of different tumors, and examining gene-gene and gene-environment interactions.

Nevoid Basal Cell Carcinoma Syndrome

Nevoid basal cell carcinoma syndrome (NBCCS) is an autosomal dominant, multisystem disorder with variable expression. The syndrome is characterized by multiple basal cell carcinomas, jaw cysts, congenital skeletal anomalies, pits of the palms and soles, and ectopic calcification. It may also include other abnormalities, such as ovarian and cardiac fibromas, and medulloblastoma. The NBCCS gene, *PTCH*, which is the human homolog of the *Drosophila* "patched" gene, was identified in 1996 as the result of a large international collaborative effort. Earlier, we showed that sun exposure and skin pigmentation contribute to the expression of the NBCCS in gene carriers. Future work includes examining genotype-phenotype correlations, identifying genes and environmental factors that modify risk, and assessing interactions among sun exposure, x-irradiation, and skin type.

In other research, a study of patients with medulloblastoma was recently initiated in collaboration with investigators from the NIH and the Children's National Medical Center in Washington, DC. We are clinically evaluating medulloblastoma patients, assessing risks for cancer among family members, examining tumors for mutations in the *PTCH* and other candidate genes, and evaluating the relation among molecular genetic alterations, tumor characteristics, response to treatment, and survival. Two patients also have NBCCS, exhibiting jaw cysts, pits of the palms and soles, and ectopic calcification, as well as developing hundreds of basal cell carcinomas in the radiation treatment field.

Recently, we completed a retrospective review of cranial CT studies of 56 patients from the medulloblastoma cohort. We showed that only children carrying the diagnoses of medulloblastoma and NBCCS had falx calcification in the peridiagnostic period, illustrating the importance of considering NBCCS when falx calcification is present in young patients with medulloblastoma.

Gene-Environment Interactions
The identification of disease susceptibility genes often leads to questions about their association with environmental factors and other genes. Methodologic assessments of different analytic approaches are necessary in determining the types of epidemiologic studies that would be most informative in identifying environmental factors in complex diseases and examining gene-environment interactions.

Previous studies suggested that using relatives as a control group could be helpful in detecting an interaction between an environmental exposure and an underlying genetic factor when the factor is common. We recently completed a comprehensive review of studies that examined gene-environment interactions in situations in which a gene was either known or unknown. Traditional epidemiologic approaches appear to have sufficient power to detect interaction in studies of common genetic and/or environmental factors. However, studies of rare factors will likely require alternative study designs, such as multistage sampling, counter-matching, or other novel designs. We are currently evaluating which types of controls and analytic approaches would be most efficient for detecting gene-environment interactions.

Keywords

CDK4, CDKN2A, gene-environment interaction, genetics, hereditary cancer, melanoma, nevoid basal cell carcinoma syndrome, *p16, PTCH*

Recent Publications

Andrieu N, et al. Counter-matching in gene-environment interaction studies: Efficiency and feasibility. *Am J Epidemiol* 2001;153:265–74.

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Human Genetics Program, Genetic Epidemiology Branch
Genetic and Environmental Risk Factors in Cancer

Research: Both genetics and environmental exposures play an integral role in carcinogenesis. The goal of our research is to integrate epidemiologic and laboratory approaches to study the genetic effects of environmental exposures on human health.

Familial Chronic Lymphocytic Leukemia
Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Western countries, accounting for 30 percent of all leukemia cases. The clinical picture of CLL is extremely variable with some patients having very indolent disease with survival greater than 10 years, while others have rapidly progressive disease that is unresponsive to treatment. Although advanced age, Caucasian ancestry, and family history are recognized risk factors, the etiology of CLL is unknown.

For the past 30 years, families with two or more living cases of CLL have been enrolled within the NCI Familial Registry. Medical records and biological specimens have been collected in these subjects. Based on the collection of these data, we found that age of onset in familial cases is approximately 10 years earlier than in sporadic cases, and a higher percentage of second primary tumors was also noted.

Our families provide an ideal opportunity to conduct whole genome searches, to study candidate genes, and to evaluate other biomarkers in investigating the etiology of this disease. One goal of the study is to better elucidate the clinical heterogeneity observed in this disease in order to identify patients who will have an aggressive course. We are studying biomarkers, such as CD38 expression and telomere length, to evaluate their utility as markers of disease progression. We are also recruiting new families to aid in the search for a susceptibility gene.

von Hippel-Lindau Disease
von Hippel-Lindau (VHL) disease is an autosomal dominant, multiple tumor syndrome in which affected individuals are predisposed to the formation of tumors and cysts in specific target organs, including the kidneys, brain and

spinal cord, retina, adrenal glands, and pancreas. Reported penetrance of the *VHL* gene is greater than 90 percent; however, the age of onset and severity of expression of VHL disease are variable.

While correlations between specific *VHL* mutations and disease phenotypes are beginning to be made, there is little information about the influences of environmental exposures and possible modifying genes on this disease. Because of the heterogeneity observed among individuals in disease presentation and progression, we are conducting a family-based case-control study to relate the expression of VHL tumors to lifestyle factors, occupational exposures, reproductive and hormonal factors, medication use, diet, and putative susceptibility genes. Data collection is ongoing. This study will allow for the evaluation of potentially modifiable environmental risk factors as well as the influence of genetic variation in carcinogen metabolism in VHL disease expression.

Keywords

chronic lymphocytic leukemia, gene-environment interaction, pharmacogenetics, von Hippel-Lindau disease

Recent Publications

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Ishibe N, et al. Clinical characteristics of familial B-CLL in the National Cancer Institute Familial Registry. *Leuk Lymphoma* 2001;42:99–108.

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Human Genetics Program, Genetic Epidemiology Branch

Epidemiologic Studies of Genetic and Environmental Causes of Cancer

Research: Association and linkage approaches are being used in genetic epidemiology studies of cancer etiology, with special emphasis on melanoma and lung cancer. We are also investigating the effects of environmental exposures, such as UV radiation, dioxins, and smoking, in combination with genetic, behavioral, and other host characteristics. Whenever feasible, biomarkers of genetic susceptibility, internal exposure, and early pathologic effect are used to define risk and elucidate mechanisms of carcinogenesis. Alternative study designs and methodological aspects related to emerging molecular techniques are explored in achieving our research goals.

Cutaneous Malignant Melanoma

We are conducting case-control and family studies of melanoma in populations thought to be at a reduced risk because of medium to dark skin pigmentation. Mediterranean families have been analyzed for clinical characteristics, presence and frequency of nonmelanoma tumors, and mutations in candidate genes. Melanomas in these families generally have the same clinical features of melanomas as in fair skinned populations, with the exception of a higher number of nodular melanomas. In affected and unaffected family members, the number of common nevi is correlated with presence and number of dysplastic nevi, and melanoma cases have higher numbers of dysplastic nevi than their relatives. The great majority of the families have no coding mutations in candidate genes, such as *CDKN2A, CDKN2B, p19ARF,* and *CDK4*. We are planning further candidate gene analyses, genome-wide mapping, followup of existing families, and recruitment of new families. Additional work also includes defining skin color and skin type with standardized and computerized instruments and comparing the information with recent sun-exposure for normal skin samples, lifetime sun exposure, DNA repair activity, and melanocortin-receptor gene variants.

Lung Cancer
Although smoking in general and lung cancer in particular may be the greatest single public health problem facing the United States, tobacco-related disease remains a major understudied area, as noted in the 1998 NCI Tobacco Research Implementation Plan. In a comprehensive evaluation of lung cancer and smoking, we are designing a large case-control/sib-pair study that integrates genetic factors (by candidate gene approach and genome-wide linkage disequilibrium mapping), environmental and behavioral information (active and passive smoking exposures, lifestyle, occupations, social and educational status, alcohol consumption, medical and family history, hormones, medications, etc.), clinical data (tumor stage, tumor type, histologic characteristics, clinical symptoms, metastatic status, diagnostic procedure, age at diagnosis, etc.), psychological indexes (Fagerstrom index, nicotine and other substance dependence, depression, etc.), lung tissue markers, and functional enzyme activities in viable cells. In addition, the study will examine the existence of specific exposure-dependent patterns of somatic point mutations or chromosomal aberrations in lung tissue in relation to germline mutations; differences among "normal," metaplastic, malignant, and metastatic cross-sectional samples of tissue by cytogenetic, molecular, and biochemical markers; differences in genotype, gene expression, and molecular characteristics of lung tissue by histologic type and smoking exposure; and biochemical, molecular, and morphological differences in lung tissue from former, never, and current smokers. We plan to enter the field phase of the study during 2002.

Health Consequences of Dioxin Exposure
2,3,7,8-Tetrachloro-dibenzo(*p*)-dioxin (TCDD) is a persistent environmental contaminant that exerts manifold biological effects at very low concentrations across species. Since the human health consequences of TCDD are controversial, newer approaches involving biomarkers may be key to unraveling the effects of this xenobiotic. The 1976 industrial accident near Seveso, Italy, provides a unique opportunity to study a large nonoccupational population that experienced a broad range of environmental exposures to dioxin. An ongoing study based on approximately 300,000 individuals, consisting of both genders and a wide age distribution, has revealed an increase in cancer incidence and mortality in the years following the accident.

We designed a population-based study to evaluate the impact of TCDD exposure on mechanistically based biomarkers of dioxin response. The study was conducted approximately 20 years after the accident in a random sample of subjects from the highest exposed zones and from the surrounding noncontaminated area. In individuals from the exposed areas, elevated plasma TCDD levels were present after a time roughly equivalent to two biological half-lives, with significantly higher levels in women than men. The aryl hydrocarbon receptor (AHR) mediates the effects of TCDD through a pathway that regulates the expression of cytochrome P4501A1 and P4501B1, as well as other genes. Using peripheral blood lymphocytes, we measured the expression of genes involved in the AHR-pathway, specifically AHR, aryl hydrocarbon receptor nuclear receptor translocator (ARNT), cytochrome P4501A1 and P4501B1, and CYP1A1-associated 7-ethoxyresorufin O-de-ethylase (EROD) activity. Expression levels of AHR pathway components were highly correlated with each other, but we did not observe

a strong association between current plasma TCDD levels and the AHR pathway. We are continuing to study dioxin-exposed subjects who developed chloracne after exposure.

Methodological Studies
We are exploring alternative study designs and quality control measures for biomarkers derived from new molecular assays, such as microarrays and DNA chips, used in epidemiologic investigations.

Keywords

aryl hydrocarbon receptor, biomarkers, *CDK4*, *CDKN2A*, *CDKN2B*, cytochrome P450, dioxin, DNA repair, dysplastic nevi, family studies, lung cancer, melanoma

Recent Publications

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Human Genetics Program, Genetic Epidemiology Branch
Genetic Predisposition to Tumors

Research: Since the early 1960s, family studies have been the central component of our research into cancer etiology. These studies involve clinical, genetic, and laboratory evaluations of kindreds at high risk of specific tumors. Over the years, the methodologic approach to studying these families has become more rigorous with the development of molecular and genetic epidemiologic techniques. These investigations form a major focus of our activities and provide important insights into cancer causation.

Neurofibromatosis 2

Our studies of neurofibromatosis 2 began in 1987. This disorder is characterized by development of bilateral vestibular schwannomas (schwann cell tumors of the vestibular branch of the 8th cranial nerve), which cause hearing loss and vestibular symptoms in early adulthood. Meningiomas and other benign central and peripheral nervous system tumors are also common. Although neurofibromatosis 2 is relatively rare, unilateral vestibular schwannomas and meningiomas comprise 30 percent of all brain tumors in adults. Our study population has consisted of two major groups: members of multigeneration multiplex neurofibromatosis 2 families, and sporadic cases whose parents are unaffected clinically. Patients with neurofibromatosis 2 and their at-risk relatives undergo a detailed clinical evaluation, which includes gadolinium-enhanced MRI of the brain (and the spine in affected individuals), ophthalmologic and audiologic assessments, and a physical examination with cranial and spinal nerve function tests. Blood samples are also collected for molecular genetic studies.

DNA from our largest family (11 affected individuals in three generations) contributed to the fine mapping of the *NF2* gene to a small region of the long arm of chromosome 22. Subsequently, DNA from affected individuals in the family was found to have a 234-base pair deletion in a candidate gene cloned from this region. The deletion was not present in any unaffected family members. The identity of the *NF2* gene was confirmed by cosegregation of the deletion with disease.

Our clinical studies also demonstrated the presence of two different types of cataracts at an early age, a new feature of neurofibromatosis 2. In addition, the studies suggested the existence of two major subtypes of neurofibromatosis 2 families. Patients with severe disease usually develop symptoms before age 20, have many central nervous system tumors in addition to vestibular schwannomas, and rapid clinical progression. In contrast, patients with mild disease are often symptom-free until the third decade of life and have few tumors other than vestibular schwannomas. In general, affected family members have similar manifestations. To date, 20 different *NF2* germline mutations have been identified in 21 of our neurofibromatosis 2 families. By comparing the clinical and molecular data from these families, we showed that phenotypic manifestations correlate strongly with type of mutation. Mutations that shorten the C terminus of the NF2 protein usually result in severe neurofibromatosis 2, whereas mutations that replace one amino acid with another usually lead to mild disease. Moreover, mutations that alter intron splicing result in variable phenotypes, even within members of the same family. We are now collaborating with other investigators to refine our understanding of genotype-phenotype correlations, and to examine the natural history of neurofibromatosis 2, beginning with vestibular schwannomas and spinal tumors.

Chordoma

Chordoma is a rare, low-grade, malignant bone tumor derived from remnants of the notochord, a structure that gives rise to the embryonic axial skeleton and almost always disappears by birth. Common sites for chordoma are the sacrum (57 percent), skull base, usually the clivus (36 percent), and vertebrae (17 percent). The tumor is locally aggressive and may metastasize. A cure is most likely with radical resection followed by high-dose radiation therapy. Typically, chordoma is a sporadic tumor. Only four multiplex families, each with two to three affected relatives, have been reported since 1958.

One of the multiplex families was referred to us in 1996. In the family, four living individuals in two generations had been diagnosed with chordoma over a period of nine years. One of the four individuals had a sacral tumor, and tumors in the other three involved the clivus or adjacent nasopharynx. We evaluated these 4 cases plus 14 first and second-degree relatives with MRI scans of the skull base and spine, and obtained blood for gene mapping studies. The scans showed tumors of the clivus or nasopharynx in six additional relatives, including a parent of each of the four index cases. The histopathology of three of the tumors confirmed chordoma. The presence in the family of both affected males and females plus two father-son pairs is consistent with transmission of an autosomal dominant mutation.

We used a genomic screen in an effort to map the chordoma gene in this family. Preliminary results suggest possible linkage of the candidate gene to a region on chromosome 7. We are employing a variety of different strategies to identify more chordoma families that will enable us to confirm this linkage and fine map and clone the chordoma gene.

Brain Tumors

Brain cancer is among the most lethal of adult cancers but little is known about its etiology. In 1994, the DCEG Radiation Epidemiology Branch began a comprehensive case-control study of brain tumors in adults. At the end of this four-year study, about 800 cases and 800 controls had donated blood for molecular studies and completed interviews about a broad range of potential genetic, lifestyle, and environmental risk factors, with emphasis on occupational and solvent exposures. The interview elicited history of cancer and selected other diseases in first-degree relatives. We are now contacting the first-degree relatives of the 500 cases with glioma and inviting them to participate in a family-based case-control study. We plan to obtain medical and risk factor information from participants and collect buccal cells as a source of DNA. Analyses done in the original case-control study will be repeated using relatives as controls. Of special interest will be association studies of common polymorphisms in genes for enzymes that metabolize drugs and carcinogens, as well as mutations in other candidate genes. Use of related controls in these analyses will ameliorate concerns about potential biases resulting from a comparison of cases with controls that differ genetically for the disease and genetic variables of interest.

Once established, this case-control family study will be a unique resource for other types of analyses designed to elucidate the role of genetic and environmental factors in the etiology of gliomas. Complex segregation analyses can be used to model genetic and environmental influences, including effects from a single major gene, as well as effects from many genes, each having small effects (polygenes). If statistical analyses of verified cancers in first-degree relatives suggest an excess of any cancer or group of cancers, and segregation analysis indicates that the pattern of occurrence of the excess cancer(s) is consistent with transmission of a single gene, we will extend data collection to second- and third-degree relatives in families with the cancers of interest and obtain blood samples for gene mapping studies.

Keywords

brain cancer, chordoma, gene mapping, genetics, glioma, hereditary cancer, neurofibromatosis 2 (NF2)

Recent Publications

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Recent Publications (continued)

Baser ME, et al. Predictors of vestibular schwannoma growth in patients with neurofibromatosis 2. *J Neurosurg* 2002;96:217–22.

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Biography: *Dr. Toro received an M.D. with honors from the State University of New York School of Medicine at Buffalo. He completed an internship in internal medicine at Stanford University and dermatology training at the University of California–San Francisco and Southern Illinois University School of Medicine. Dr. Toro joined the NCI's Dermatology Branch during the third year of his residency, and became a tenure track Investigator in the Genetic Epidemiology Branch in 2001. His research focuses on the genetic basis of genodermatoses with an increased risk of internal neoplasia and skin cancer.*

Human Genetics Program, Genetic Epidemiology Branch
Genodermatosis Studies

Research: We are focusing on clinical, epidemiologic, genetic, and laboratory investigations of individuals affected with genodermatoses and skin cancer to elucidate the mechanisms that contribute to benign and malignant diseases. We recruit and examine individuals and collect samples from affected individuals and their relatives for cytogenetic, haplotype, sequencing, and other molecular methods. The genomic localization of single and complex gene traits that predispose to genodermatoses and skin cancer is determined using various analytic and statistical genetic methods.

Birt-Hogg-Dube Syndrome
We characterized the dermatologic manifestations of Birt-Hogg-Dube (BHD) syndrome and its association with kidney tumors and spontaneous pneumothorax in three extended families with BHD. This investigation allowed the identification of individuals at risk of developing kidney cancer for appropriate surveillance and early detection so that early treatment could be initiated. Thirty-three additional families with BHD were subsequently identified. Molecular methods were used to exclude various candidate genes *(VHL, MET, PTCH, PTEN)* from involvement in the disorder. Using linkage analysis, we mapped the BHD gene locus to chromosome 17p.21 and narrowed the region to <4-cM. Screening of candidate genes in the BHD region is in progress. We hope to identify a novel gene with a role in kidney, lung, and hair-follicle development whose alteration can lead to kidney neoplasia.

Cutaneous Lymphomas
Our research seeks to understand the biology and pathogenesis of primary cutaneous lymphomas by defining and characterizing clinicopathological entities based on clinical, microscopic, immunophenotypic and molecular methods. We also have been interested in identifying and characterizing unique types of T cell lymphomas such as cutaneous gamma delta T cell lymphoma (CGD-TCL). The literature on patients with this lymphoma is unclear, because of its rarity and the limited access to large numbers of patients. Our prior studies have shown that CGD-TCLs are EBV-negative, cytotoxic lymphomas with frequent necrosis and/or apoptosis, preferential involvement of the extremities with necrotic tumors and subcutaneous nodules, and poor clinical outcome. We designed a population-based study to evaluate the role of different prognostic tools in the diagnosis of CGD-TCLs. Currently, we are completing a 12-year followup study of a cohort of 104 individuals with primary cutaneous peripheral T cell lymphoma to identify the clinical and pathologic features of CGD-TCLs and their prognostic significance. In addition, the study will examine germline and somatic mutations or chromosomal aberrations associated with CGD-TCLs.

Hermansky-Pudlak Syndrome
Hermansky-Pudlak syndrome (HPS) is an inherited autosomal recessive disorder that consists of oculocutaneous albinism, a platelet storage pool defect, and lysosomal accumulation of ceroid lipofuscin. The multiorganellar involvement in HPS suggests that it is integrally involved in the trafficking of melanosomes, platelets, and lysosomes. HPS occurs with high frequency in northwest Puerto Rico, where 1 in every 21 individuals is a carrier. HPS patients from this region are homozygous for a 16-bp duplication in exon 15 of the *HPS1* gene; this mutation is associated with significant risk of pulmonary fibrosis. We provided a detailed characterization of the dermatologic manifestations of HPS in a large cohort of patients. The 16-bp duplication in the *HPS1* gene appears to be limited to northwest Puerto Rico. Furthermore, we identified a novel type of HPS in central Puerto Rico where these patients exhibit a distinctive phenotype and lack mutations in the *HPS1* gene.

HPS is expected to be a molecularly heterogeneous disease, consistent with the genetically distinct mouse models displaying both pigment dilution and platelet storage pool defects. The possible existence of a genetic isolate of the disease in central Puerto Rico was evaluated by examining six families from

this region. Thirteen affected individuals were ascertained based upon their medical histories and clinical findings. Using homozygosity mapping on the pooled DNA of six families from central Puerto Rico, we localized a new HPS susceptibility gene to a 1.6 cM interval on chromosome 3q24. *HPS3* has 17 exons, a 3,024-bp coding region, and putative 114.1 kDa product. The homozygous, disease-causing mutation is a 3,904-bp deletion involving exon 1 and > 2 kb of upstream sequence. The deletion provides the second example of a founder mutation causing HPS on the small island of Puerto Rico. We also developed an allele-specific assay for diagnosing individuals heterozygous or homozygous for this mutation. The identification of new HPS genes will help us to understand the pathophysiology of the disease and to develop new therapies for its complications.

Keywords

albinism, Birt-Hogg-Dube, DNA repair, family studies, HPS, loss of heterozygosity, lymphoma, skin cancer

Recent Publications

Toro JR, et al. Birt-Hogg-Dube syndrome: A novel marker of kidney neoplasia. *Arch Dermatol* 1999;135:1195–1202.

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Anikster Y, et al. Mutation of a novel gene causes a unique form of Hermansky-Pudlak syndrome in a genetic isolate of central Puerto Rico. *Nat Genet* 2001;28:376–80.

Schmidt LS, et al. Birt-Hogg-Dube syndrome locus maps to chromosome 17p11.2. *Am J Hum Genet* 2001;69:876–82.

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