April 1998

T405

REPORT OF THE
STRATEGIC PLANNING CONFERENCE
DECEMBER 8–9, 1997

NEW DIRECTIONS IN Ovarian Cancer Research

Sponsored by
National Cancer Institute
Society of Gynecologic Oncologists
Public Health Service Office of
Women's Health

Executive Summary

An estimated 26,800 women were diagnosed with ovarian cancer in 1997, and an estimated 14,200 women died from ovarian cancer in 1997. The disease will affect approximately 25,400 additional women, and approximately 14,500 women will die from ovarian cancer in 1998. In addition, millions of women remain fearful and concerned about being diagnosed with this too often fatal disease.

While early detection improves the chances that ovarian cancer can be treated successfully, early cancers of the ovaries rarely cause symptoms that women would notice, or the symptoms are mistaken for menopausal ailments or intestinal illnesses. As a result, almost 70 percent of women with ovarian cancer are not diagnosed until the disease is advanced in stage. The 5-year survival rate for these women is only 15 to 20 percent. More than ever, there is a need for a greater awareness and understanding of ovarian cancer.

An agenda for investigative efforts into the areas of basic science and translational research, genetic susceptibility and prevention, diagnostic imaging, screening and diagnosis, and therapy holds the most promise for future discoveries leading to improved prevention, detection, and treatment of ovarian cancer.

The United States Public Health Service's Office on Women's Health (PHS OWH), the Society of Gynecologic Oncologists (SGO), and the National Cancer Institute (NCI), in an effort to put ovarian cancer at the forefront of our nation's cancer research agenda, sponsored a Strategic Planning Conference on New Directions in Ovarian Cancer Research on December 8 and 9, 1997, in Washington, DC. The purpose of the conference was to outline the priorities for ovarian cancer research over the next 5 years.

The conference brought together a group of experts in gynecologic oncology, medical oncology, radiation oncology, diagnostic imaging, molecular biology, molecular endocrinology, and genetics, already armed with the knowledge of current procedures and techniques, to answer the following key questions for the strategic plan:

- What are the research priorities for ovarian cancer?
- What must be done to implement the research priorities?
- What are the challenges and barriers that must be overcome to implement the research priorities?
- What are the positive effects this research could eventually have on patient care?

Those participating in the conference spent 2 days working within multidisciplinary groups to develop the answers to these key questions. From among all of the research priorities identified in each of the working groups, they identified the following eight critical components as essential in the strategy to attain a greater understanding of the disease, and they made a commitment to pursue increased funding and investment in biomedical research. The eight components are *not* ranked in order of importance, as they are *all* critical elements of the strategy for ovarian cancer research over the next 5 years.

Critical Components:

Educational Efforts

The first critical component is to support greater educational efforts for both the physician and the patient communities. Early detection of ovarian cancer is difficult, and warning signs are often confused with symptoms of other types of abdominal ailments. It is essential that primary care physicians and gynecologists, as well as their patients, become aware of the early warning symptoms and signs, the risk factors involved, and the importance of a complete medical history of both the patient and her family to assist in determining the presence of ovarian cancer and the patient's genetic risks for it.

A greater awareness and understanding of ovarian cancer can have a tremendous impact upon the quality of life for ovarian cancer patients and their families, and will substantially increase the potential for gathering significant outcomes data and expanding our knowledge about ovarian cancer.

Infrastructure for the Study of Ovarian Cancer

The second critical component is support for the development of a solid infrastructure for the study of ovarian cancer. Increased funding for ovarian cancer research is essential not only for Requests for Application (RFA's) and the creation of at least one Specialized Program of Research Excellence (SPORE), but also for the recruitment and retention of young investigators as well as trained investigators from other fields. In addition, support for clinical studies in imaging, screening, and treatment, conducted through cancer centers and the clinical trials cooperative groups and other mechanisms, should be strengthened. Innovative measures to protect time for clinician scientists to conduct research are crucial in light of the managed care environment in which medical professionals must now practice.

Tissue Procurement and Banking

The third critical component is support for tissue procurement and banking, intrinsic parts of clinical trials. By standardizing tissue collection and storage, we can gather epidemiological and follow-up data on ovarian cancer and correlate these data with molecular biological studies on the banked tissues. A tissue bank is already active through the Gynecologic Oncology Group, but it needs more financial support for the acquisition of specific types of specimens.

Identification of Genetic Changes Related to All Stages of Ovarian Cancer

The fourth critical component is support for identification of all genes expressed in ovarian cancer tumors at all stages of the disease. This will facilitate the identification of molecular prognostic indicators and tools for early diagnosis, the elucidation of the etiology of ovarian cancer, and the molecular targets for gene therapy.

Documenting the Efficacy of Screening Strategies for Ovarian Cancer

The fifth critical component is support for the collection of data to evaluate the utility of current tumor markers such as CA125 and current diagnostic imaging modalities on mortality of ovarian cancer in a multinational, prospective, randomized control trial. Such collection will also allow the evaluation of additional markers to aid in early detection of this cancer. As new markers and imaging modalities are developed, they should be evaluated prospectively in adequately sized clinical trials.

Cohort Study of Women at a Genetically High Risk for Ovarian Cancer

The sixth critical component is support for the development of a cohort study of women at a genetically high risk for ovarian cancer. Such a study would provide a basis for an assessment of ovarian cancer risk in relation to specific mutations, an evaluation of the benefits and risks of chemopreventive interventions, and an infrastructure for gathering tissue from prophylactic surgery in a uniform way for use in molecular studies.

Evaluation of Conventional Therapy Approaches to Ovarian Cancer

The seventh critical component is support for an ongoing, multinational evaluation of conventional therapy approaches to ovarian cancer. This would provide for an assessment of the role of cytotoxic chemotherapy and the role of surgical debulking, as well as an evaluation of the optimal time for surgical intervention.

Development and Evaluation of Novel Investigational Approaches to Ovarian Cancer

The eighth critical component is support for the development and evaluation of novel investigational approaches to treating ovarian cancer. This includes research into antiangiogenic agents, cancer vaccines, apoptosis targets, novel molecular targets, and gene therapy.

This report presents the conference participants' views of the critical components required for ovarian cancer research over the course of the next 5 years. It represents the consensus of conference attendees who are dedicated to the discovery of the new knowledge needed to advance the health of women who are diagnosed with or at risk for developing ovarian cancer.

Introduction

Twenty-seven years ago, the United States declared war on cancer with passage of the National Cancer Act of 1971. Since that time, great progress has been made in fighting the disease, but we cannot yet declare victory.

Although scientific discovery has given us new insights into cancer prevention, detection, and treatment, we are still losing too many lives to cancer. Gynecologic cancers will strike approximately 80,400 women in 1998 in the United States. Ovarian cancer ranks second among gynecologic cancers in the number of new cases per year and causes more deaths than any other cancer of the female pelvic reproductive system.

What Is Ovarian Cancer?

Ovarian cancer is cancer that begins in the cells that constitute the ovaries, including surface epithelial cells, germ cells, and the sex cord-stromal cells. Cancer cells that metastasize from other organ sites to the ovary (most commonly breast or colon cancers) are not then considered ovarian cancer.

According to the American Cancer Society, ovarian cancer accounts for 4 percent of all cancers among women and ranks fifth as a cause of their deaths from cancer. In 1998, an estimated 25,400 new cases of ovarian cancer will be diagnosed, and an estimated 14,500 women will die from it. The death rate for this disease has not changed much in the last 50 years.

Unfortunately, almost 70 percent of women with the common epithelial ovarian cancer are not diagnosed until the disease is advanced in stage—i.e., has spread to the upper abdomen (stage III) or beyond (stage IV). The 5-year survival rate for these women is only 15 to 20 percent, whereas the 5-year survival rate for stage I disease patients approaches 90 percent and for stage II disease patients approaches 70 percent.

There are many types of tumors that can start in the ovaries. Some are benign, or noncancerous, and the patient can be cured by surgically removing one ovary or the part of the ovary containing the tumor. Some are malignant or cancerous. The treatment options and the outcome for the patient depend on the type of ovarian cancer and how far it has spread before it is diagnosed.

Ovarian tumors are named according to the type of cells the tumor started from and whether the tumor is benign or cancerous. The three main types of ovarian tumors are:

Epithelial Tumors

Epithelial ovarian tumors develop from the cells that cover the outer surface of the ovary. Most epithelial ovarian tumors are benign. There are several types of benign epithelial tumors, including serous adenomas, mucinous adenomas, and Brenner tumors. Cancerous epithelial tumors are carcinomas. These are the most common and most deadly of all types of ovarian cancers. There are some ovarian epithelial tumors whose appearance under the microscope does not clearly identify them as cancerous; these are called borderline tumors or tumors of

low malignant potential (LMP tumors). Epithelial ovarian carcinomas (EOC's) account for 85 to 90 percent of all cancers of the ovaries. It is this group of cancers we refer to as "ovarian cancer" throughout the remainder of this report. It is this group of cancers we must expand our knowledge about in order to conquer its ravages.

The cells that make up EOC have several forms that can be recognized under the microscope. They are known as serous, mucinous, endometrioid, and clear cell types. Undifferentiated EOC's lack distinguishing features of any of these four subtypes and tend to grow and spread more quickly.

In addition to their classification by cell type, EOC's are given a grade and stage. The grade is on a scale of 1, 2, or 3. Grade 1 EOC more closely resembles normal tissue and tends to have a better prognosis than Grade 3 EOC, which looks less like normal tissue and usually implies a worse outlook than Grade 1 EOC.

The stage of the tumor can be ascertained during surgery, when it can be determined how far the tumor has spread from where it started in the ovary. The following are the various stages of ovarian cancer:

Stage I—Growth of the cancer is limited to the ovary or ovaries.

Stage IA—Growth is limited to one ovary and the tumor is confined to the inside of the ovary. There is no cancer on the outer surface of the ovary. There are no ascites present containing malignant cells. The capsule is intact.

Stage IB—Growth is limited to both ovaries without any tumor on their outer surfaces. There are no ascites present containing malignant cells. The capsule is intact.

Stage IC—The tumor is classified as either Stage IA or IB and one or more of the following are present: (1) tumor is present on the outer surface of one or both ovaries; (2) the capsule has ruptured; and (3) there are ascites containing malignant cells or with positive peritoneal washings.

Stage II—Growth of the cancer involves one or both ovaries with pelvic extension.

Stage IIA—The cancer has extended to and/or involves the uterus or the fallopian tubes, or both.

Stage IIB—The cancer has extended to other pelvic organs.

Stage IIC—The tumor is classified as either Stage IIA or IIB and one or more of the following are present: (1) tumor is present on the outer surface of one or both ovaries; (2) the capsule has ruptured; and (3) there are ascites containing malignant cells or with positive peritoneal washings.

Stage III—Growth of the cancer involves one or both ovaries, and one or both of the following are present: (1) the cancer has spread beyond the pelvis to the lining of the abdomen; and (2) the cancer has spread to lymph nodes. The tumor is limited to the true pelvis but with histologically proven malignant extension to the small bowel or omentum.

Stage IIIA—During the staging operation, the practitioner can see cancer involving one or both of the ovaries, but no cancer is grossly visible in the abdomen and it has not spread to lymph nodes. However, when biopsies are checked under a microscope, very small deposits of cancer are found in the abdominal peritoneal surfaces.

Stage IIIB—The tumor is in one or both ovaries, and deposits of cancer are present in the abdomen that are large enough for the surgeon to see but not exceeding 2 cm in diameter. The cancer has not spread to the lymph nodes.

Stage IIIC—The tumor is in one or both ovaries, and one or both of the following is present: (1) the cancer has spread to lymph nodes; and/or (2) the deposits of cancer exceed 2 cm in diameter and are found in the abdomen.

Stage IV— This is the most advanced stage of ovarian cancer. Growth of the cancer involves one or both ovaries and distant metastases (spread of the cancer to organs located outside of the peritoneal cavity) have occurred. Finding ovarian cancer cells in pleural fluid (from the cavity which surrounds the lungs) is also evidence of stage IV disease.

Germ Cell Tumors

Ovarian germ cell tumors develop from the cells that produce the ova or eggs. Most germ cell tumors are benign, although some are cancerous and may be life threatening. The most common germ cell malignancies are maturing teratomas, dysgerminomas, and endodermal sinus tumors. Germ cell malignancies occur most often in teenagers and women in their twenties. Prior to the modern era of combination chemotherapy, the most aggressive of these tumors, the GNP abnormal sinus tumor, was associated with a 1-year disease-free survival of only 10 to 19 percent. This occurred despite the fact that 70 percent of these tumors were diagnosed as stage I disease. Today, 90 percent of patients with ovarian germ cell malignancies can be cured and fertility preserved. We hope, ultimately, to achieve similar results in our strategic research planning for epithelial ovarian cancer.

Stromal Tumors

Ovarian stromal tumors develop from connective tissue cells that hold the ovary together and those that produce the female hormones, estrogen and progesterone. The most common types among this rare class of ovarian tumors are granulosa-theca tumors and Sertoli-Leydig cell tumors. These tumors are quite rare and are usually considered low-grade cancers, with approximately 70 percent presenting as stage I disease.

These statistics, and the information regarding tumor stage and grade, demonstrate that there is a critical need to establish an agenda for more research into the areas of basic and translational research, genetic susceptibility and prevention, diagnostic imaging, screening and diagnosis, and therapy. These could hold the most promise for future discoveries that will lead to improved prevention, detection, and treatment of ovarian cancer, particularly the common epithelial cancers.

This report outlines the priorities for expanding our knowledge base in ovarian cancer research. The sponsoring organizations hope that this nation will accelerate its commitment to basic biomedical research so that we can reduce or even eliminate the burden of ovarian cancer.

Ovarian Cancer Research Priorities for the Next 5 Years

The following five sections provide the details of the crucial steps that must be taken to expand the research base in the areas of basic and translational research, genetic susceptibility and prevention, diagnostic imaging, screening and diagnosis, and therapy.

Basic and Translational Research

Due to the unique pathophysiology of ovarian cancer, data cannot be readily extrapolated and/or applied from the study of other cancers to the study of ovarian cancer. Therefore, basic and translational research is essential for determining the answers to the distinctive questions presented by ovarian cancer, such as those related to early diagnosis, chemoprevention, risk assessment, development of new therapeutic approaches, individualization of therapy, and optimal utilization of current treatment options.

Research Priorities in Basic and Translational Research

The research priorities for ovarian cancer in basic and translational areas must parallel the important clinical research questions specific to ovarian cancer. Successful execution of these research priorities requires the recognition of the qualities unique to ovarian cancer coupled with the development of a directed research infrastructure.

The Basic/Translational Working Group identified the following seven priorities for ovarian cancer research:

1. Identifying molecular prognostic indicators to:
   - direct, design and monitor therapy;
   - allow individualization of therapy;
   - facilitate molecular rationale for trial design;
   - identify therapeutic targets; and
   - provide for mechanisms to regulate drug sensitivity and resistance.

The introduction of molecular markers into the pathologic analysis of ovarian cancer will drive an individualization of therapy which, in turn, would lead to more appropriate use of drugs, reducing unnecessary morbidity and optimizing health care economics. Coupled with a better understanding of the genetic and epigenetic reasons for drug resistance or sensitivity, use of these translational objectives may provide the molecular rationale to guide the choice of therapy and the duration of treatment for individual patients.

Understanding the mechanisms underlying drug resistance and sensitivity will lead directly to creative approaches for new drug discovery and for new uses of existing chemotherapeutics. This critical objective will also provide insight to drive new clinical trials aimed at converting the high response rate associated with initial treatment of ovarian cancer to a similarly high cure rate.

2. Developing tools for early diagnosis including:
   - markers for the identification of genetic changes;
   - markers for secreted or released molecules such as carbohydrates, lipids, proteins, or antibodies;
   - markers to screen bodily fluids such as urine, blood, or peritoneal fluids; and
   - diagnostic imaging tools.

Discovery of new markers and their application to diagnosis, in concert with the identification of the optimal use of the present tumor markers such as CA125, are necessary. Coupling validation of markers with investigation into more sensitive imaging modalities will lead to identification of clinical questions for screening clinical trials. Incorporation of genetic markers and epidemiologic risk will allow identification of low- and high-risk individuals for developing ovarian cancer and may also lead to stratification for treatment decisions.

In addition, discovery and validation of biomarkers are needed to identify both patients with early stage ovarian cancer who do not require adjuvant chemotherapy and patients with more aggressive disease for whom current therapeutic standards are not adequate. Chemoprevention and early diagnosis are needed as well. Incorporation of these markers into standard practice will greatly alter the patterns and degree of morbidity and toxicity associated with ovarian cancer treatment and will allow identification of patient cohorts for whom early direction into investigational trials is warranted.

3. Increasing the knowledge base of ovarian cancer etiology including:
   - determining the biology of the normal lining (epithelium) of the ovary;
   - determining the genetic basis for the microscopic structure of tissue (histologic) subtypes;
   - answering the questions of whether there is an ordered progression from normal ovarian epithelium to borderline ovarian tumor, to early invasive disease, to late invasive disease; and
   - answering the question of whether there is a common etiology for epithelial ovarian cancer, primary peritoneal carcinomatosis, serous papillary carcinoma of the endometrium, and fallopian tube cancer.

Understanding the etiology, genetic, and epigenetic mechanisms underlying the development of ovarian cancer will lead to discovery of new targets for directed therapy and biomarkers for the better evaluation of existing therapeutic modalities.

4. Studying primary and secondary chemoprevention and adjuvant therapy including:
   - targets;
   - intermediate markers;
   - mechanisms;
   - risk stratification; and
   - local versus systemic treatment.

The mechanism through which oral contraceptives and retinoids may reduce the incidence or recurrence of ovarian cancer must be understood. These studies will lead to the discovery of genes whose gene products may be applied as intermediate markers for clinical use and to an improved understanding of the etiology of ovarian cancer.

5. Identifying the molecular epidemiology of ovarian cancer and the mechanism for it including:
   - looking at noninherited ovarian cancer to try to understand why ovulation is causative, why oral contraceptives are protective, and to go further into the biology of the retinoids; and
   - looking at inherited ovarian cancer with regard to low frequency and high penetrance genes, as well as high frequency and low penetrance genes.

The identification of women at high lifetime risk for development of ovarian cancer due to family history or genetic aberrations in known ovarian cancer risk genes such as *BRCA1* and *BRCA2* or newly discovered genes requires development of management standards for these individuals. Important related issues are the social, psychological, health care coverage, confidentiality, and family implications of identifying these patients.

6. Studying tumor-host interaction and whether or not it increases or decreases tumor progression including:
   - tumor immune interaction with regard to cytotoxic immune cells, antibodies, and cytokines; and
   - tumor stroma interaction with regard to angiogenesis, invasion, and growth factors.

Studies into tumor and stromal interactions have already led to a better understanding of invasion and angiogenesis, which has resulted in the development of new therapeutic agents and new putative markers of ovarian cancer progression. These studies are currently making great progress.

7. Evaluating the peritoneal cavity as an approach to accessing a tumor including the use of:
   - vaccines;
   - antibodies-immunoconjugates;
   - gene therapy; and
   - small molecules.

The critical issues for implementation of these research priorities are as follows:

1. Identification of all genes expressed in normal ovarian epithelium, peritoneal mesothelium, epithelial cysts and crypts, borderline tumors, and early and late invasive tumors. It is important to look at cancers independently by stage, grade, and histotype to recognize the differences among them. It is also important to look at the primary and metastatic tissues, as well as the identification of the tumor and stroma, to see how their interaction regulates gene expression.

2. Tissue procurement and banking to identify genes as well as biomarkers and therapeutic development. The key issues related to tissue procurement and banking are as follows:
   - obtaining the informed consent of patients given the confidentiality and social implications associated with such consent;
   - sample handling and storage, which is critical for quality tissue, because without quality tissue the RNA and DNA necessary to identify the biomarkers and to identify important genes cannot be obtained;
   - epidemiology and followup to identify genes that are expressed under different situations, such as drug resistance and drug response;

- developing targeted tissue banks, such as one directed only to a clinical trial or one directed to a specific hypothesis-driven point; and
- global accessibility of tissue banks that are associated with the appropriate hypothesis.

3. Models for studying ovarian cancer essential for making progress in understanding the disease. Improvement is needed in in vitro models in three dimensional models, epithelial stromal interactions, and organ culture. There is a need to move forward to ovarian epithelium-specific promoters for transgenic mice or conditional knockout mice. Finally, there is a need to move toward in vivo animal model systems for studying the etiology, biomarkers, chemoprevention, therapeutic modeling, and preclinical developments in ovarian cancer.

4. To help facilitate the development of these models, establishing core facilities that have shared intellectual and physical resources. The current status of technology is too expensive for individual investigators to be able to approach these questions in their own laboratories, or maybe even in their own institutions. It is extremely important to put together groups that can use DNA and RNA laboratories and then provide these resources to the ovarian cancer community, as well as to improve methods to analyze proteins and protein functions—such as the Tandem Mass Spectroscopy system.

One resource now available is the NCI Cancer Genome Anatomy Program (CGAP). The CGAP ovarian cancer project is ongoing and provides an interactive link between the intramural and extramural ovarian cancer research communities to provide immediate access to on-line information regarding ovarian cancer gene expression from cDNA libraries as they are sequenced.

5. Finally, to maintain and enlarge a critical mass of investigators in all of the global components of basic, translational, and clinical science, to generate a critical mass and infrastructure for the study of epithelial ovarian cancer. The following points were identified as crucial components of this effort:
   - continuing relationship-building activities with the National Cancer Institute. This includes:
     - —addressing the appropriateness of peers selected for peer review;
     - —developing innovative mechanisms to support multidisciplinary groups, such as establishing protected time for clinical scientists to conduct research and support mechanisms for young investigators;
     - —increasing the number of independent investigator grants (R01's), RFA's, and SPORE's that are directed to ovarian cancer;
     - —supporting the SGO/GCF Clinician Scientist Training Program;
     - —increasing funding for ovarian cancer research at the Federal, state, philanthropic, and industry levels. Increased funding is essential not only for increasing the grants funded for ovarian cancer research, but also for recruiting colleagues from other fields into this area and to encourage young investigators to come into this field and to stay within it; and
   - encouraging bidirectional interaction with advocacy groups.

The Challenges and Barriers to Basic and Translational Ovarian Cancer Research

Identification and characterization of the unique and undiscovered genotype and phenotypes of epithelial ovarian cancer have proved to be formidable challenges. However, implementation of the research priorities that have been identified will lead to the development of a crucial pool of knowledge from which clinical and scientific investigations can advance. Additional critical basic and translational challenges include:

- the lack of an appropriate animal model;
- the lack of ovarian epithelium-specific promoters;
- the lack of access to precursor lesions; and
- the low proportion of ovarian cancer patients entering clinical trials.

The scientific barriers can be overcome through collaboration and cooperation coupled with directed resources. Funding initiatives such as ovarian cancer-specific RFA and SPORE grants, constitution of a study section with expertise in ovarian cancer, and a cooperative information network will provide a greatly needed infrastructure. Scientific and clinical progress will be seen with the requirement for translational research questions to be included in all clinical research studies; for banking of normal, low malignant potential, and tumor specimens from all patients on clinical trials; shared molecular resources; and greater patient entry into clinical trials.

Genetic Susceptibility and Prevention

With no family history of ovarian cancer, a person's lifetime risk of ovarian cancer is 1 in 55. With one first-degree relative, the risk goes up to 1 in 25 to 30. During the past few years, efforts have been made to isolate specific genes responsible for various familial ovarian cancer syndromes. Recently, mutations of the *BRCA1* gene have been linked to 40 to 50 percent of early onset hereditary breast cancer families and 80 to 90 percent of breast-ovarian cancer families. Somatic *BRCA1* mutations have also been found in 10 percent of sporadic ovarian cancers. Initial estimates based on high-risk families placed the lifetime risks for developing cancer based on *BRCA1* mutations at 80 to 90 percent (breast) and 60 percent (ovary), as well as a three- to four-fold increased risk of colon and prostate cancer. More recent data based on population studies (versus high-risk families) have reduced these cancer risk estimates to approximately half of the initial risk predictions. The ovarian cancer risk due to *BRCA2* mutations is probably less than with *BRCA1* mutations but is still much greater than that of the general population. The strong predictive value of *BRCA1/2* mutations makes *BRCA1/2* testing a potentially useful adjunct in the evaluation of women at risk for ovarian cancer. Furthermore, the incomplete penetrance of the ovarian cancer phenotype provides the opportunity to study factors controlling gene expression and potential prevention strategies.

Therefore, research in the areas of genetic susceptibility and prevention is critical in that further developments in the molecular analysis of *BRCA1/2* mutations may offer even more precise information for counseling and managing affected women. In addition, since approximately 90 percent of ovarian cancer cases occur sporadically and are not associated with highly penetrant mutations in genes such as *BRCA1/2*, we need to identify common genetic polymorphisms associated with ovarian cancer.

Research Priorities in Genetic Susceptibility and Prevention

The research priorities for ovarian cancer in the genetic susceptibility and prevention areas must continue to build from the intense efforts that are underway to identify the molecular genetic basis of ovarian cancer. With progress in increased understanding of the disease at the molecular level, there will be opportunities for the study of specific genetic polymorphisms in relation to ovarian cancer risk.

The Genetic Susceptibility and Prevention Working Group identified the following four priorities for ovarian cancer research:

1. Identifying a cohort of subjects at genetically high risk for ovarian cancer. The first priority identified was the need to establish a national cohort of women who have germline mutations of *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, or other ovarian cancer susceptibility genes. These women may be either free of ovarian cancer or recently diagnosed with the disease, and may have had a prior cancer. This registry would contain baseline epidemiological data on established ovarian cancer risk factors, a blood sample, archived tissue from prophylactic oophorectomies, and, among affected women, archived tumor tissue. Registry participants would be followed annually for changes in risk factors and in their health status, for phlebotomy, and for document screening. The registry, either on its own or in collaboration with other similar registries in other countries, would provide a resource for meeting several needs in ovarian cancer prevention.

   Among women unaffected with ovarian cancer, the registry would provide a basis for:

   - assessing ovarian cancer risk in relation to specific mutations, particularly among ethnically diverse populations;
   - evaluating the benefits and risks of specific formulations of oral contraceptives to better understand how these drugs protect against ovarian cancer. Possible breast cancer risk associated with oral contraceptives needs to be evaluated in this population;
   - evaluating the benefits and risks of prophylactic oophorectomy, tubal ligation, and possibly other chemopreventive interventions. Oophorectomy may require hormone replacement therapy with concomitant risks for breast cancer, and the risk/benefit ratio needs evaluation. New selective estrogen receptor modulators, such as raloxifene, need to be evaluated in this population. There is also a need to assess the role of laparoscopic oophorectomy in the management of high-risk patients;
   - providing the infrastructure for gathering tissue from prophylactic surgery in a systematic and uniform way for use in molecular studies;
   - permitting studies of the natural history of ovarian cancer and possibly identifying intermediate markers for the disease for use in chemoprevention trials;
   - providing a source of high-risk patients for studies of screening efficacy;
   - providing the infrastructure for the establishment of support groups for genetic counseling and for educating women about screening; and
   - evaluating quality of life in carriers of high-risk mutations.

   Among women affected with a prior ovarian cancer, the registry would provide a basis for:

   - using pathology blocks to examine molecular markers of tumor progression;
   - evaluating quality of life of ovarian cancer survivors;
   - evaluating sensitivity to treatment and impact on survival; and

- evaluating methods for improving survival and for preventing second primary peritoneal cancers.

2. Establishing an educational initiative with regard to the potential value and risks of presymptomatic genetic testing for ovarian cancer. Such an initiative would inform both health care professionals and the general public about:

   - what this testing can tell us about a patient's risk;
   - what it leaves unanswered;
   - how this information may allow us to intervene in a substantive way to reduce cancer risk; and
   - what effect screening results may have on insurance.

3. Identifying common genetic polymorphisms associated with ovarian cancer using population-based studies. Identification of these genetic alterations/polymorphisms and their interaction with the less common highly penetrant gene mutations may help to identify genetic mechanisms leading to ovarian carcinogenesis. Environmental cofactors, novel epidemiologic risk factors, and other genetic modifiers of disease penetrance could be identified with potential implications for the larger population. There are still familial ovarian cancer cases that cannot be accounted for by the known highly penetrant mutations in genes that could potentially be revealed by this approach.

   With ongoing technologic advances and adequate financial support, these studies could be undertaken in a meaningful way. A "candidate gene approach" using a variety of genes with potential roles in ovarian cancer, such as *CYP17*, could be undertaken first. At the same time, research to identify new genes using approaches such as the CGAP data bank would yield new genetic sequences that could be examined in these sporadic ovarian cancer cases to determine their contribution to genetic susceptibility.

   In addition, there is a need for further molecular epidemiologic research to distinguish the etiologies of different types of ovarian cancer. For example, do risk factors differ among ovarian cancers that have a mutated *p53* gene versus those that do not?

4. Preventing disease recurrence in ovarian cancer patients who have completed primary therapy should be targeted with an eye toward the genetic determinants of recurrence and long-term survival. One question that needs to be answered is whether late recurrences represent new cancers or a recurrence of the patient's prior disease. Interventions that may be considered include fenretinide (4–HPR), intraperitoneal immunotherapy, or cancer vaccines stimulating a nonspecific immune response. Whether patients should be required to undergo laparoscopy at entry and at defined points during study would need to be worked out in the design of these clinical trials. Identification of genetic determinants of long-term survivors would allow mechanistic studies and approaches aimed at capitalizing on these genetic influences in the larger population of ovarian cancer patients to delay the onset of recurrent disease.

The Challenges and Barriers in Ovarian Cancer Research Related to Genetic Susceptibility and Prevention

- The confidentiality issues associated with a registry of mutation carriers dictate a need to protect the privacy of study participants while allowing investigators with scientifically approved projects access to them.
- The difficulty is in enrolling adequate numbers of participants in the registry to provide enough ovarian cancer events for adequate statistical power in evaluating preventive strategies. Crude calculations that assume a United States population of one hundred million women over age 30 and a mutation rate of 1 in 500 women implies a potential population of 200,000 carriers. If 10 percent of these women have been tested and are willing to participate in the registry, the registry would contain 20,000 women. Assuming a lifetime ovarian cancer risk of 20 percent in carriers or an annual risk of 1 percent, 5 years of followup would provide approximately 1,000 events. If the registry contained 10,000 women, there would be 500 events after 5 years.
- Annual followup of ten to twenty thousand women is a costly undertaking, and special resources will be needed to handle this.
- Close coordination of our scientific and educational efforts with HMO's and other health care providers will be vital to completing most studies on ovarian cancer genetic susceptibility. Forming partnerships with insurers in both education and clinical implementation is vital.
- Financial support for genetic testing and patient participation in peer-reviewed clinical trials will be needed.
- Financial support for expanding the CGAP and other gene identification projects to facilitate the discovery of novel genetic modifiers of disease penetrance will be needed.

Diagnostic Imaging

The rationale of screening for early detection of ovarian cancer is the close relationship between the stage of the cancer at the time of diagnosis and survival. The long-term objective for ovarian cancer screening and diagnostic imaging is to improve the treatment planning of patients with ovarian cancer by the judicious use of noninvasive imaging tests. The morphologic information provided by imaging will complement clinical evaluation in the prediction of tumor extent, treatment planning, and patient outcome.

Research Priorities in Diagnostic Imaging, Screening, and Diagnosis

The research priorities for ovarian cancer in imaging, screening, and diagnosis will benefit from advances both in basic and translational research and in genetic susceptibility and prevention research. Any advances that lead to a consensus on ovarian cancer treatment will facilitate both the assessment of the clinical relevance of diagnostic imaging and the development of diagnostic imaging guidelines.

The Diagnostic Imaging, Screening, and Diagnosis Working Group identified the following five priorities for ovarian cancer research:

1. Screening the general population to obtain mortality data on the impact of screening. There is potential that such screening studies could show a major decrease in mortality in that ovarian cancer could be detected earlier and treatment could be less morbid. Additionally,

such studies could increase the understanding of the biology and natural history of the disease.

The group identified the following as the keys to implementing this objective:

- basing the project on existing randomized controlled trials and involving ultrasound centers;
- funding serum, plasma, and tissue banks;
- trying to address issues of precursor lesions; and
- ensuring standardization and quality control.

2. Diagnostic assessment of tumor burden to optimize the use of imaging markers and molecular technology in guiding type and intensity of management. There is potential for such studies to lead to improvements in disease-free survival and overall survival, a greater understanding of the disease, and decreased morbidity and costs.

   The group identified the clinical challenges, criteria for assessment, techniques, and types of studies necessary to implement this objective:

   Clinical Challenges

   - pretreatment staging
   - response to assessment with respect to guiding chemotherapy and IDS
   - second look operations
   - monitoring for recurrence
   - prognostic prediction
   - address issue of standardization and quality control

   Criteria for Assessment

   - resectability
   - location
   - tumor burden (volume)

   Techniques

   - US
   - CT/MRI
   - PET
   - CA125
   - other markers
   - molecular markers (staging)

   Types of Studies

   - prospective studies/clinical trials
     —observational
     —interventional
     —randomized controlled trials

3. Screening the at-risk population to identify a sensitive, specific, and cost-effective screening strategy. Such studies could lead to alternatives to oophorectomies.

   The group identified the following as the keys to implementing this objective:

   Types of Studies

   • prospective multicenter clinical trials

   —including data related to risk such as reproductive factors, family history, fertility drugs, and BRCA mutations

   —including second-level tests such as CT, MRI, and PET

   —establishing serum/tissue/DNA/plasma banks

   —addressing the issue of primary peritoneal carcinomatosis

   —establishing a method for validating the optimal strategy

   —defining goals for screening performance

4. Exploring novel methods and refining analysis of existing methods for early detection, characterization, staging, and monitoring to improve upon the power of available diagnostic and imaging technology. Such studies could lead to a decrease in the morbidity of ovarian cancer.

   The group identified the following existing and novel methods as the keys to implementing this objective:

   Types of Studies

   • single institutional animal studies

   • prospective observational studies

   —single institution

   —multi-institution

   Existing Methods

   • ultrasound-Doppler/3D/contrast

   • neural networks

   • existing markers

   • PET

   • CT/MRI—contrast agents

   • image fusion

   Novel Methods

   • optical technology such as Raman, fluorescent spectroscopy, and elastic light scattering

   • optical imaging such as optical coherence tomography

   • new tumor markers

   • molecular staging

   • office laparoscopy/culdoscopy

- study design could include single institution animal studies and multicenter and single institution prospective observational studies

5. To study health, economic, and psychosocial issues to document the impact of diagnostic intervention in the context of acceptability, compliance, quality of life, and health economics. Such studies could lead to decreased costs and therefore more availability of various technologies.

   The group identified the following as the keys to implementing this objective:

   - prospective modeling
   - data collection from:
     —randomized controlled trials of screening the general population
     —high-risk population screening
     —diagnostic assessment of tumor burden studies
     —meta-analysis
   - cost, benefit, and minimization
   - education

The Challenges and Barriers in Ovarian Cancer Research Related to Diagnostic Imaging, Screening, and Diagnosis

- the size, scale, and cost of the studies required to demonstrate a reduction in mortality related to screening;
- the difficult issue of the differences in the treatment received by the control and by the study groups in the randomized controlled trials;
- lack of consensus on ovarian cancer treatment;
- lack of consensus on resectability;
- lack of uniformity in interpretation and terminology in radiology;
- issues of accrual, confidentiality, followup, and counseling associated with large randomized controlled trials;
- lack of good animal models for exploring novel methods and refining analysis of existing methods for early detection, characterization, staging, and monitoring to improve upon the power of available diagnostic and imaging technology; and
- lack of available databases for modeling and meta analysis to study health, economic, and psychosocial issues to document the impact of diagnostic intervention in the context of acceptability, compliance, quality of life, and health economics.

Therapy Subgroup A: Primary Therapy

The high ratio of deaths to incident cases in ovarian cancer is a reflection of the advanced stage of the disease at the time of presentation as well as limited durable long-term responses realized following standard postoperative adjuvant cytotoxic therapy. An example of the latter is the two and one-half-fold increase in median survivorships during the past 20 years, but only a minimal increase has been observed in the 5-year survival rates. Hence, it would appear appropriate to strategically reassess the current approaches to the management of ovarian cancer, directing more innovative investigative efforts based on our ever expanding knowledge of the mechanisms of oncogenesis toward prevention, screening, staging, and therapy.

As we approach the 21st century, empirically derived cytoablative surgery and chemotherapy should be replaced with specific molecular-based therapy. This is not to minimize the large number of unanswered questions still plaguing clinical investigators. However, if we accept the premise that the biology of the tumor determines early dissemination, early recurrence, and treatment resistance, and ultimately compromises survival, the concepts of molecular staging and molecular-based therapy will dominate our patient-oriented research efforts over the course of the next decade.

Research Priorities in Primary Therapy

To optimize the probability of substantially improving the long-term survival of patients with ovarian cancer, we must develop new management paradigms that will allow meaningful integration of tumor biology and innovative therapeutic approaches. During the next decade, we must endeavor to increase the number of translational studies; therefore, a more efficient mechanism to incorporate basic science observations in phase I, II, and III clinical trials will be required.

The Primary Therapy Working Group identified eight priorities for patient-oriented ovarian cancer research.

1. Establishing standard patterns of care which would include:
   - the development of practice guidelines;
   - the development of outcome surrogates;
   - the development of a method of cost analysis to identify potential savings measured in dollars per extra year of life gained; and
   - patient education with regard to both the primary and secondary treatment modalities that can be provided by gynecologic oncologists.

   Standardizing patterns of care can enhance the quality of surgery that should be offered women, minimize the age/comorbidity biases that currently exist—particularly for those patients who are treated off-protocol, and reduce morbidity for early-stage disease patients.

2. Facilitating initiatives for the development of molecular indicators which would include:
   - correlation of molecular arrays;
   - development of tissue banks; and
   - establishment of information systems.

Development of molecular indicators will allow for a more appropriate treatment selection and a decrease in morbidity associated with chemotherapy drugs.

3. Neoadjuvant chemotherapy with no pretreatment surgical or major surgical intervention which would include:
   - an international or multicenter phase III clinical trial;
   - a simple design, thereby allowing reproducible execution of trials; and
   - a cytologic or tissue diagnosis.

   Neoadjuvant chemotherapy has the potential to reduce morbidity and cost and increase the quality of life for ovarian cancer patients.

4. Trials of multiagent chemotherapy which would include:
   - international cooperation; and
   - assessment of multiarmed, multiagent regimens.

   Such trials may answer chemotherapy research questions more rapidly and increase the survival of patients with ovarian cancer.

5. Considering the natural history of the disease, the assessment of antiangiogenic agents in early disease would include:
   - identification of appropriate agents in phase I or II trials;
   - collection of molecular marker information via tissue procurement and banking;
   - integration of these agents with cytotoxic agents; and
   - use of the appropriate or applicable agents in phase III trials.

   Use of antiangiogenic agents in early disease may, from a toxicity standpoint, decrease morbidity and thus offer potential survival advantages.

6. Initiate clinical trials with tumor vaccines aimed at inducing antibody or T cell responses against ovarian cancer:
   - phase I and II clinical trials with vaccines against individual antigens;
   - phase I and II clinical trials with a polyvalent vaccine consisting of a combination of these single vaccines;
   - phase II and III clinical trials of the polyvalent vaccine; and
   - tissue procurement and banking.

7. Initiate clinical trials using molecular-based therapies that would include:
   - phase I, II, and III clinical trials with such possibilities as inhibitors of farnesyl transferase, tyrosine kinase, CDK's, bcl-2, etc.;
   - integration of these trials with cytotoxic agents; and
   - tissue procurement and banking.

   Molecular-based therapies have the potential to increase the survival of ovarian cancer patients.

8. Implementing new initiatives that may prevent, modify, or reverse drug resistance and would include:
   - tissue procurement and banking; and
   - phase I, II, and III clinical trials.

   Such initiatives may increase the knowledge base of drug resistance to allow physicians additional agents for the reversal or modification of drug resistance, which may lead to a decrease in morbidity and an increase in survival rates.

The Challenges and Barriers in Ovarian Cancer Research Related to Primary Therapy

- patient accrual to clinical trials;
- restrictive health care/managed care plans;
- surgery performed by nongynecologic oncologists or those without appropriate expertise;
- difficulty in designing a process to control physician biases;
- lack of a systematic strategy for cooperative efforts;
- difficulty with ongoing competing studies;

- difficulty in coordinating international efforts;
- adequate procurement of tissue/fluid/serum;
- lack of appropriate laboratory expertise and standardization methodologies;
- lack of economic resources;
- difficulty in assuring quality control;
- difficulty in designing a process to control physician biases;
- difficulty in coordinating international efforts;
- lack of a systematic strategy for cooperative efforts;
- lack of cancer drug resources;
- difficulties with ongoing competing studies;
- lack of long-term toxicity data;
- lack of knowledge about the ultimate endpoints that can be measured for antiangiogenic agents;
- lack of information about specific markers for molecular-based therapy;
- need for identification of appropriate agents; and
- collection of information is based on evolving mechanisms.

Therapy Subgroup B: Secondary Therapy

A majority of patients with ovarian carcinoma will require second line treatment. The current management of patients with ovarian carcinoma that has recurred after initial chemotherapy rests on a consideration of the results of the initial chemotherapy.

Research Priorities in Secondary Therapy

The research priorities for ovarian cancer in secondary therapy must address the issues that will help guide the selection of appropriate therapy for recurrent ovarian cancer.

The Secondary Therapy Working Group identified the following nine priorities for ovarian cancer research:

1. Increase research that translates laboratory observations into large-scale clinical trials.

   Support should be provided to phase I, II, and III trials that explore the translation of laboratory observations directly into clinical trials. The optimal approach to this would be to provide cooperative groups involved in ovarian carcinoma with sufficient discretionary funds dedicated to supporting such trials. Peer review of the effort would come through the

peer review mechanism of the cooperative group. The monies would be used to support the laboratory operation, quality control of the laboratory component, and the collection of specimens.

While this approach has been criticized as a way of circumventing the usual peer review mechanism, the fact is that this research is critical to obtaining valid answers to translational questions with sufficiently large sample sizes. The mechanism suggested herein is the best way to obtain valid answers; since the usual review procedures are not appropriate for cooperative studies that have unique problems, they are traditionally undervalued.

2. Continue and enhance the evaluation of new agents through phase I and II trials.

   There is an effective mechanism within cancer centers and cooperative groups for the study of new agents and approaches through phase I and II trials that should be continued. The flow of potentially useful new agents should be enhanced by removing regulatory barriers, by improving relationships with industry, by increasing the willingness of third-party payers (including Medicare and Medicaid) to support patient care in clinical trials, and by facilitating the availability of new drugs through the National Cancer Institute.

3. Develop molecular markers for the assessment of the effects of specific drugs.

   This proposal ties in with the need to increase the amount of translational research called for in item 1. The evaluation of new drugs can be facilitated by the development of specific molecular markers that reflect a biologic effect of a specific new agent. These markers would need to be identified for each agent and validated as correlating with such endpoints as response and survival.

4. Define mechanisms of drug resistance and evaluate their clinical modulation.

   This proposal suggests that studies be directed to reversing resistance to known drugs. The emphasis would extend beyond MDR to a number of other mechanisms of resistance such as DNA repair. Work would need to be done to identify mechanisms of resistance, establish their relevance to clinical resistance in the ovarian population, and develop procedures to modulate them.

5. Investigate better methods to select regimens for testing in phase III trials of initial therapy.

   There are an expanding number of options for study in phase III trials. Selection of the best options for incorporation into these trials is a major problem. The development of surrogate endpoints (both molecular, as noted above, and others, such as CA125) is desperately needed. Also needed are improved statistical methodologies and enhanced access to patients who are candidates for trial both through funds to support patient recruitment and through investigator time to devote to such issues.

6. Seek, without restricting phase I and II testing of prospective regimens and drugs for front-line trials, alternative approaches to conducting phase III trials of secondary therapies, including the assessment of quality of life and pharmacoeconomics.

   Funds are needed to support the conduct of such trials in the Community Clinical Oncology Programs (CCOP's) and in community hospitals. Patients accrued to such trials should not come from the pool of patients currently included in existing studies. The funds should be

adequate to provide not only recruitment of participants but also quality control of the data. Studies to be performed in this setting should be simple, with streamlined eligibility criteria. Funding should not come from current cooperative mechanisms that have their own critical role to play in the development of new regimens for front-line trials. In addition to the usual outcome parameters, these studies should focus on quality of life issues and pharmacoeconomics.

7. Evaluate the value of dose-intense therapy within the framework of secondary therapies.

Dose-intense approaches such as intraperitoneal therapy and stem-cell-supported high-dose chemotherapy are used in practice in the absence of proven value to the patient receiving the secondary therapy. Randomized trials of these approaches are needed to assess the merits of these toxic approaches. Encouragement in the form of major monetary incentives should be provided for conducting such trials. Quality of life and pharmacoeconomic questions should be addressed as part of these trials.

8. Investigate the role of surgical approaches within the framework of secondary therapies.

The role of surgical approaches after primary therapy is at best unclear. Studies should assess the value of second-look laparotomy, secondary surgical cytoreduction, and less invasive surgical techniques.

9. Investigate palliative care issues such as pain control.

These issues should be evaluated in randomized trials. They could be performed as second randomizations in ongoing randomized trials or as independent studies.

The Challenges and Barriers in Ovarian Cancer Research Related to Secondary Therapy

- lack of sufficient funds;
- lack of the availability of clinical investigators with adequate time to conduct such studies in the current competitive environment;
- regulatory barriers/IRB approval process/IND paperwork requirements, etc.;
- need for assistance in the development of drugs that appear to be of limited commercial value;
- unwillingness of third party payers to support such studies;
- physician bias;
- differences in the nature of the approaches to be randomized when evaluating the value of dose-intense therapy; and
- need for educational efforts with third party payers, physicians, and patients.

Conclusion

Greater investment in the study of ovarian cancer will help researchers begin to capitalize on the vast potential that stands before us. We must continue to expand on the progress that has been made over the past several decades and extend the efforts that have yielded benefits for ovarian cancer patients.

Now is the time to create exciting new opportunities for progress in the following eight critical areas for ovarian cancer research: (1) educational efforts; (2) infrastructure for the study of ovarian cancer; (3) tissue procurement and banking; (4) identification of genetic changes related to all stages of ovarian cancer; (5) tumor markers and diagnostic imaging modalities; (6) a cohort study of patients at a genetically high risk for ovarian cancer; (7) the evaluation of conventional therapy approaches to ovarian cancer; and (8) the development and evaluation of novel investigational approaches to ovarian cancer.

The sponsors of the conference, the U.S. Public Health Service's Office on Women's Health, the Society of Gynecologic Oncologists, and the National Cancer Institute look forward to working with public policy leaders in the years ahead on behalf of women and their reproductive health.

Conference Working Groups and Participants

Basic/Translational Research:

Name	*Institution*	*Area of Expertise*
Dr. Edison Liu	National Cancer Institute	Medical Oncologist/ Molecular Epidemiology
Dr. Andy Berchuck	Duke University Medical Center	Gynecologic Oncologist/ Growth Factors
Dr. Tom Hamilton	Fox Chase Cancer Center	Drug Resistance/ Carcinogenicist
Dr. Barry Kacinski	Yale University Medical Center	Growth Factors
Dr. Elise Kohn*	National Cancer Institute	Antiangiogenesis
Dr. Gordon Mills*	M.D. Anderson Medical Center	Signal Transduction
Dr. Yung Chi Cheng	Yale University Medical Center	Pharmacologist
Dr. Phil Livingston	Memorial Sloan-Kettering Cancer Center	Vaccines
Dr. Jeanne Becker	University of South Florida	Immunology/ Tumor Cell Biology

Genetic Susceptibility/Prevention:

Name	*Institution*	*Area of Expertise*
Dr. Beth Karlan*	Cedars Sinai Medical Center	Screening
Dr. Carolyn Runowicz	Albert Einstein College of Medicine and Montefiore Medical Center	Screening
Dr. Alice Whittemore*	Stanford University	Epidemiology
Dr. Bruce Ponder	CRC Human Cancer Genetics Group	Genetics
Dr. Jeff Boyd	Memorial Sloan-Kettering Cancer Center	Genetics
Dr. Savio Woo	Mount Sinai	Gene Therapy/ Molecular Medicine

Dr. Funmi Olopade	University of Chicago Medical Center	Genetics
Dr. Joellen Schildkraut	Duke University Medical Center	Epidemiology

Diagnostic Imaging/Screening/Diagnosis:

Name	*Institution*	*Area of Expertise*
Dr. Ian Jacobs*	St. Bartholomew Hospital	Screening
Dr. Bob Bast	M.D. Anderson Medical Center	Tumor Markers
Dr. Hedi Hricak*	University of California, San Francisco	Imaging
Dr. Susan Ascher	PHS Office on Women's Health	Imaging
Dr. Arthur Fleischer	Vanderbilt University	Ultrasound
Dr. Kenneth Taylor	Yale University Medical Center	Ultrasound
Dr. Alfred Kurtz	Thomas Jefferson University	Ultrasound
Dr. Cirrelda Cooper	Georgetown University	Radiology/ Oncologic Imaging
Dr. Elliot Fishman	Johns Hopkins University	Medical Oncology/ Radiology
Dr. Richard Wahl	University of Michigan	Nuclear Medicine/ General Imaging
Dr. Peter Choyke	National Institutes of Health	Uroradiology
Dr. Marcia Javitt	George Washington University Medical Center	Radiology

Therapy:

Subgroup A: Primary Therapy

Name	*Institution*	*Area of Expertise*
Dr. Edward Trimble	National Cancer Institute	Gynecologic Oncology/ Clinical Trials
Dr. Peter Schwartz	Yale University Medical Center	Gynecologic Oncology/ Clinical Trials

Dr. Gillian Thomas*	University of Toronto*	Radiation Oncology/ Clinical Trials
Dr. Karl Podratz*	Mayo Clinic*	Gynecologic Oncology/ Clinical Trials
Dr. David Gershenson	M.D. Anderson Medical Center	Gynecologic Oncology/ Clinical Trials
Dr. Bob Ozols	Fox Chase Cancer Center	Medical Oncology/ Clinical Trials
Dr. Larry Copeland	Ohio State University	Gynecologic Oncology/ Clinical Trials
Dr. Bill McGuire	Private Practice	Medical Oncology/ Clinical Trials
Dr. Robert Park	Walter Reed Army Medical Center	Gynecologic Oncology/ Clinical Trials
Dr. Jan Neijt	University Hospital Utrecht	Medical Oncology/ Clinical Trials
Dr. Eddie Reed	National Cancer Institute	Medical Oncology
Dr. James Collier	National Aeronautics and Space Administration (NASA)	Aerospace Medicine

Subgroup B: Secondary Therapy

Name	*Institution*	*Area of Expertise*
Dr. James Tate Thigpen*	University of Mississippi	Medical Oncology/ Clinical Trials
Dr. Steve Rubin	University of Pennsylvania	Gynecologic Oncology/ Clinical Trials
Dr. Stephen Williams*	Indiana University	Medical Oncology/ Clinical Trials
Dr. David Spriggs	Memorial Sloan-Kettering Cancer Center	Medical Oncology/ Drug Development
Dr. Ed Sausville	National Cancer Institute	Medical Oncology/ Drug Development
Dr. Jon Berek	UCLA School of Medicine	Gynecologic Oncology/ Clinical Trials

Dr. Maurie Markman	Cleveland Clinic Foundation	Medical Oncology/ Clinical Trials
Dr. Catherine Classen	Stanford University School of Medicine	Psychiatry and Behavioral Sciences
Dr. Alice Kornblith	Memorial Sloan-Kettering Cancer Center	Psychiatry and Behavioral Sciences

**Group Leaders*

Representatives from the Public Health Service's Office on Women's Health

Dr. Susan Wood	Acting Deputy Director and Assistant Director for Policy
Dr. Saralyn Mark	Senior Medical Advisor

Representatives from the National Cancer Institute

Dr. Claudette Varricchio	Program Director, Community Oncology and Rehabilitation Branch, Division of Cancer Prevention
Dr. Lori Minasian	Chief, Community Oncology and Rehabilitation Branch, Early Detection and Community Oncology Program, Division of Cancer Prevention
Dr. Dan Sullivan	Associate Director, Diagnostic Imaging Program, Division of Cancer Treatment and Diagnosis
Dr. Faye Austin	Director, Division of Cancer Biology
Dr. Gary Kelloff	Chief, Chemoprevention Branch, Cancer Prevention Research Program, Division of Clinical Sciences
Dr. Ruthann Giusti	Special Assistant, Division of Cancer Epidemiology and Genetics
Dr. Patricia Hartge	Deputy Director, Epidemiology and Biostatistics Program, Division of Cancer Epidemiology and Genetics
Dr. Rebecca Troisi	Epidemiology and Biostatistics Fellow, Epidemiology and Biostatistics Program, Division of Cancer Epidemiology and Genetics
Dr. Iris Obrams	Associate Director, Epidemiology and Genetics Program, Division of Cancer Control and Population Science
Dr. Joseph Kelaghan	Program Director, Community Oncology and Rehabilitation Branch, Division of Cancer Prevention

Dr. Ronald Lieberman	Program Director, Chemoprevention Branch, Division of Cancer Prevention
Dr. Cheryl Marks	Program Director, Cancer Genetics Branch, Division of Cancer Biology

Representatives from the Patient Advocacy Community

Edgar Astrove	The Adler Foundation
Susan Butler	Ovarian Cancer National Alliance/Ovarian Cancer Coalition of Greater Washington
Patricia Goldman	Ovarian Cancer National Alliance
Ann Kolker	Ovarian Cancer National Alliance
Carolyn Marks	Ovarian Cancer National Alliance/National Ovarian Cancer Coalition
Mary Scroggins	Ovarian Cancer Coalition of Greater Washington
Martha Volner	Ovarian Cancer National Alliance

Acknowledgements

This conference could not have happened without the commitment and hard work of many members of the PHS Office on Women's Health (OWH), the Society of Gynecologic Oncologists (SGO), and the National Cancer Institute (NCI) and their staffs. Among the groups who contributed to this effort, several members of the staff of the sponsoring organizations played key roles.

We are thankful for the inspired work of the conference Group Leaders: Dr. Elise Kohn, Dr. Gordon Mills, Dr. Beth Karlan, Dr. Alice Whittemore, Dr. Hedvig Hricak, Dr. Ian Jacobs, Dr. Gillian Thomas, Dr. Karl Podratz, Dr. James Tate Thigpen, and Dr. Steve Williams.

We are grateful for the contributions of the conference Guest Speakers: Dr. Susan Wood of the PHS Office on Women's Health, Dr. Edison Liu of the NCI, and Dr. Jeanne Becker of the University of South Florida.

We are indebted to the conference participants listed above for their contributions, extremely hard work, devotion, and enthusiasm for this event. And we are extremely appreciative of the NCI's support for printing this document.

Special thank you to the members of the Conference Planning Committee:

Dr. Susan Ascher	PHS Office on Women's Health
Dr. Peter E. Schwartz	Society of Gynecologic Oncologists
Dr. Saralyn Mark	PHS Office on Women's Health
Dr. Edward L. Trimble	National Cancer Institute
Dr. Faina Shtern	PHS Office on Women's Health
Susan Coren	Staff, Society of Gynecologic Oncologists
Dr. Susan Wood	PHS Office on Women's Health
Jill Rathbun	Staff, Society of Gynecologic Oncologists
Dr. David M. Gershenson	Society of Gynecologic Oncologists
Dr. William J. Hoskins	Society of Gynecologic Oncologists