

CLINICAL VALIDITY

Question 20. Are there methods to resolve clinical false positive results in a timely manner?

Clinical false positives are defined as women who carry a deleterious *BRCA1/2* mutation and neither have breast or ovarian cancer nor will develop one of these cancers during their lifetime. As with most presymptomatic DNA testing, there are no methods to resolve clinical false positives among women identified with a mutation conveying increased susceptibility. If a woman has a *BRCA1/2* mutation and has not developed breast and/or ovarian cancer by the time of testing, estimates of breast and ovarian cancer risks can be given based on age and family history. Preventive/risk-reducing measures can then be considered. However, there is currently no way of determining whether an individual woman will develop breast cancer later in life.

CLINICAL VALIDITY

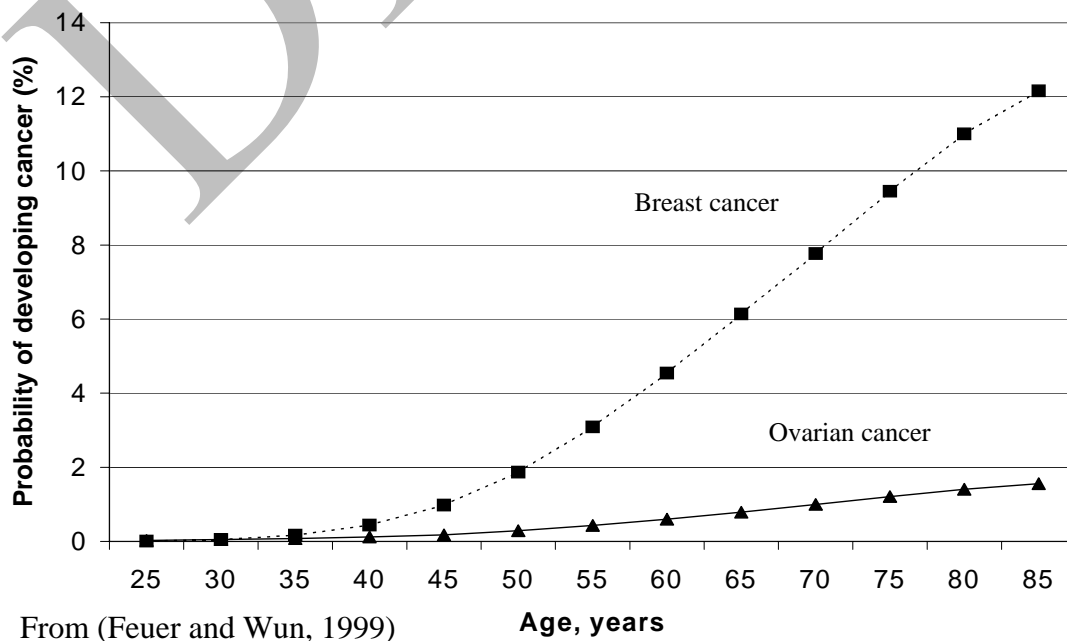
Question 21. What is the prevalence of breast/ovarian cancer in women with a positive family history?

Summary

- Risk associated with family history of ovarian/breast cancer varies according to number of affected relatives, age of relative(s) at diagnosis, and degree of relatedness (e.g. first-degree).
- The cumulative incidence of breast cancer by age 45 in women with at least one affected first-degree relative is estimated to be 386 per 10,000 women.
- The cumulative incidence of breast cancer by age 70 in women with at least one affected first-degree relative is estimated to be 1,995 per 10,000 women.
- The cumulative incidence of ovarian cancer by age 70 in women with at least one affected first-degree relative is estimated to be 304 per 10,000 women.

An appropriate study design to determine the probability of developing ovarian and breast cancer in women with a first-degree family history (cumulative incidence) would be to assemble a large cohort of such women and follow them to observe the number that develops one of these cancers. This type of prospective cohort study without intervention has not been reported in the literature. Alternatively, there are several indirect methods that can be used. One of these methods relies on age-specific probabilities for developing ovarian or early onset breast cancer based on the Surveillance, Epidemiology, and End Results (SEER) program (Figure 3-8). These can then be multiplied by a relative risk derived from case-control studies involving family history data.

Figure 3-8. The Probabilities of Developing Breast and Ovarian Cancer by Age, Regardless of Family History.



Relative risk for developing breast cancer

Risk associated with family history of breast cancer varies according to number of affected family members, age of family member(s) at diagnosis, and degree of relatedness (e.g. first-degree). Two reviews/meta-analyses have examined the association between family history and breast cancer risk using cohort studies, case-control studies with population controls, and case-control studies with hospital controls. (2001; Pharoah et al., 1997) The first systematic review and meta-analysis (Pharoah et al., 1997) involved pooling estimates of relative risk (RR) from 74 published studies (Table 3-17). Among women with a positive family history, these relative risks were further increased when the woman was under age 50 and also when the relative had been diagnosed before age 50. Fifty-two studies were analyzed in the second review (2001), also shown in Table 3-17. The risk ratios were greatest at young ages. For women of a given age, the risk ratios were greater the younger the relative was when diagnosed. The results did not differ substantially between women reporting an affected mother or sister. A woman having any family member with breast cancer has a relative risk of 1.9 (row 1 in Table 3-17). This indicates that her individual risk for developing breast cancer is 1.9 times higher than her age-associated risk (Figure 3-8). If this woman is less than 50 years of age and has a first-degree relative who had breast cancer before 50 years, her risk of developing breast cancer is 3.3 times higher than her age-associated risk (row 8 in Table 3-17). This relative risk will be used in future calculations.

Table 3-17. Relative Risk of Developing Breast Cancer at any Age, Depending on Family History of Breast Cancer

Affected Family Member(s)	Relative Risk	95% Confidence Interval
Reported by Pharoah et al., 1997		
Any	1.9	1.7-2.0
First degree	2.1	2.0-2.2
Mother	2.0	1.8-2.1
Sister	2.3	2.1-2.4
Daughter	1.8	1.6-2.0
Mother and sister	3.6	2.5-5.0
Second degree relative	1.5	1.4-1.6
Any first degree relative < 50 years*	3.3	2.8-3.9
Reported by Collaborative Group on Hormonal Factors in Breast Cancer (2001)		
One first degree	1.8	1.7-1.9
Two first degree	2.9	2.4-3.6
Three or more first degree	3.9	2.0-7.5
Any first degree relative < 40 years**	5.7	2.7-11.8
Any first degree relative 40-49 years**	2.9	1.9-4.4

* the woman whose risk is being estimated is < 50 years

** the woman whose risk is being estimated is < 40 years

Relative risk for developing ovarian cancer

A single systematic review and meta-analysis of family history and risk of ovarian cancer has been reported. (Stratton et al., 1998) The relative risks (RR) from fifteen studies (13 case-control and 2 cohort) were pooled to estimate the lifetime risk of developing ovarian cancer. The relative risks, based on 17,982 observations, are shown in Table 3-18.

Table 3-18. Relative Risk of Developing Ovarian Cancer at any Age, According to Family History of Ovarian Cancer

Affected Family Member(s)	Relative Risk	95% Confidence Interval
Reported by Stratton et al., 1998		
First degree	3.1	2.6-3.7
Sisters	3.8	2.9-5.1
Daughters	6.0	3.0-11.9
Mothers	1.1	0.8-1.6

Ovarian cancer risk, estimated from a population-based family registry for breast and ovarian cancer that included 1,567 women, was not significantly increased in first-degree relatives of breast cancer probands (mothers RR=1.5, 95 percent CI 0.9-2.4; sisters RR=1.8, 95 percent CI 1.0-3.0) and was statistically significant only for mothers of ovarian cancer probands (RR=4.6, 95 percent CI 2.1-8.7). (Ziogas et al., 2000) Because of the small sample size of this study, we have chosen to use the relative risk from Table 3-18, Row 1 for later calculations.

Cumulative incidence of breast cancer by age 45 in women with a first-degree family history

The probability of developing breast cancer by age 45 years is 1.17 percent. (2003) Thus, 117 out of 10,000 women will be expected to develop breast cancer by age 45. The relative risk estimate for developing breast cancer in women less than 50 years of age with an affected first-degree relative diagnosed before age 50 is 3.3. (Pharoah et al., 1997) Applying this risk (1.17 x 3.3) results in approximately 386 out of 10,000 women under 45 years of age in this category developing breast cancer.

Cumulative incidence of breast cancer by age 70 in women with a first-degree family history

The probability of developing breast cancer by age 70 years is 9.5 percent. (2003) Thus, 950 out of 10,000 women will be expected to develop breast cancer by age 70. The relative risk estimate for developing breast cancer in women of all ages with an affected first-degree relative is 2.1. (Pharoah et al., 1997) Applying this risk (9.5 x 2.1) results in approximately 1,995 out of 10,000 women in this category developing breast cancer.

Cumulative incidence of ovarian cancer by age 70 in women with a first-degree family history

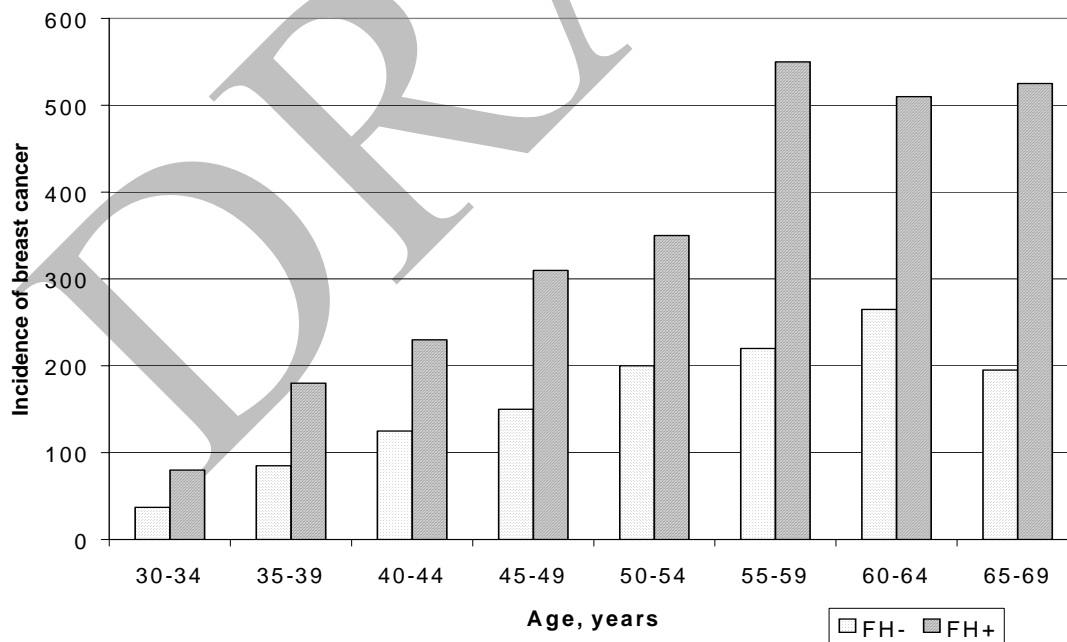
The probability of developing ovarian cancer by age 70 years is 0.98 percent. (2003) Thus, 98 out of 10,000 women will be expected to develop ovarian cancer by age 70. The relative risk estimate for developing ovarian cancer when a woman has an affected first-degree family

member is 3.1. (Stratton et al., 1998) Applying this risk (0.98×3.1) results in 304 out of 10,000 women with a first-degree family history developing ovarian cancer.

Incidence of breast cancer

Incidence of breast cancer increases with age among women, regardless of family history, but at any age, the incidence is higher among women with at least one affected first degree relative. Two large cohort studies have reported incidence rates of breast cancer in women with negative and positive family histories. (Colditz et al., 1996; Madigan et al., 1995) Incidence rates have also been estimated from population-based case-control studies but are not addressed here, due to relatively small numbers and/or generalizability of results. Population-based breast cancer incidence rates (age-adjusted) in women with a negative or positive family history (in a first-degree relative) were 175 and 470 per 100,000 person-years, respectively. (Madigan et al., 1995) In women without a family history of breast cancer, breast cancer incidence rates from the Nurses' Health Study increased from 37 per 100,000 in women 30 to 34 years of age to 265 per 100,000 in post-menopausal women. Among women with a positive family history of breast cancer, the rate increased from 80 per 100,000 to 550 per 100,000 (Figure 3-9). (Colditz et al., 1996) These incidences are consistent with the cumulative incidence estimates shown earlier (Figure 3-8), but are not specifically used in any further analyses.

Figure 3-9. Age Specific Incidence of Breast Cancer per 100,000 Women, According to Family History.



From (Colditz et al., 1996)

According to a report from the Surveillance, Epidemiology, and End Results (SEER) program, incidence rates for invasive breast cancer among women age 30-54 years in the United States are highest among whites, Hawaiians, Alaska natives, blacks, Filipinos, and Japanese. (Miller et al., 1996) The rates range from 115 to 136 per 100,000 in these populations. The lowest levels of

risk occur among the American Indians in New Mexico, Koreans, Vietnamese, Chinese, and Hispanics. Incidence rates per 100,000 in these populations range from 55 to 87.

Incidence of ovarian cancer

Similarly, the incidence of ovarian cancer increases with age among women both with and without a positive family history of breast/ovarian cancer and is higher among women with at least one affected first degree relative. Data similar to those shown for breast cancer are not found in the published literature. Age-adjusted incidence rates per 100,000 for ovarian cancer in the SEER areas are highest among American Indian women in New Mexico (17.5), followed by white (15.8), Vietnamese (13.8), Hawaiian (11.8), and Hispanic (11.4) women. The lowest rate of 7 per 100,000 is in Korean women. (Miller et al., 1996)

References

- 2001, Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease, *Lancet* **358**(9291):1389-99.
- 2003, DevCan: Probability of developing or dying of cancer software, Statistical Research and Application Branch, National Cancer Institute.
- Colditz, G. A., Rosner, B. A., and Speizer, F. E., 1996, Risk factors for breast cancer according to family history of breast cancer. For the Nurses' Health Study Research Group, *J Natl Cancer Inst* **88**(6):365-71.
- Feuer, E. J., and Wun, L. M., 1999, DEVCAN: Probability of developing or dying of cancer software, Bethesda, Maryland.
- Madigan, M. P., Ziegler, R. G., Benichou, J., Byrne, C., and Hoover, R. N., 1995, Proportion of breast cancer cases in the United States explained by well-established risk factors, *J Natl Cancer Inst* **87**(22):1681-5.
- Miller, B. A., Kolonel, L. N., Bernstein, L., Young, J. J. L., Swanson, G. M., West, D., Key, C. R., Liff, J. M., Glover, C. S., Alexander, G. A., et al., (eds) 1996, Racial/ethnic patterns of cancer in the United States 1988-1992, National Cancer Institute, NIH Pub. No. 96-4104. Bethesda, MD.
- Pharoah, P. D., Day, N. E., Duffy, S., Easton, D. F., and Ponder, B. A., 1997, Family history and the risk of breast cancer: a systematic review and meta-analysis, *Int J Cancer* **71**(5):800-9.
- Stratton, J. F., Pharoah, P., Smith, S. K., Easton, D., and Ponder, B. A., 1998, A systematic review and meta-analysis of family history and risk of ovarian cancer, *Br J Obstet Gynaecol* **105**(5):493-9.
- Ziogas, A., Gildea, M., Cohen, P., Bringman, D., Taylor, T. H., Seminara, D., Barker, D., Casey, G., Haile, R., Liao, S. Y., Thomas, D., Noble, B., Kurosaki, T., and Anton-Culver, H., 2000, Cancer risk estimates for family members of a population-based family registry for breast and ovarian cancer, *Cancer Epidemiol Biomarkers Prev* **9**(1):103-11.

CLINICAL VALIDITY

Question 22. Has the test been adequately validated in all populations to which it may be offered?

Summary

- The specific *BRCA1/2* mutations responsible for susceptibility to breast and ovarian cancer may vary by race/ethnicity. However, mutation testing via direct sequencing is believed to reliably identify all mutations that are detectable by this methodology, regardless of race/ethnicity.
- The majority of testing has been done in non-Hispanic Caucasian and Ashkenazi Jewish women.

BRCA1/2 mutation testing via direct sequencing is aimed at identifying mutations that are associated with susceptibility to breast and ovarian cancer. Direct sequencing is designed to identify mutations in these genes, regardless of the characteristics of the individual being tested (e.g., race or ethnicity). Although the specific mutations responsible for the disorder may vary by race/ethnicity, the test is believed to reliably identify all the mutations that are detectable using direct sequencing methodology. One limitation of the sequencing methodology is its inability to detect large genomic rearrangements. This type of mutation is found in certain ethnicities (e.g. founder mutations in the Dutch population are large rearrangements, not detected by direct sequencing).

The prevalence of three specific deleterious *BRCA1/2* mutations among Ashkenazi Jewish women has been well documented. (Fodor et al., 1998; Hartge et al., 1999; King et al., 2003; Moslehi et al., 2000; Oddoux et al., 1996; Roa et al., 1996; Satagopan et al., 2001; Struewing et al., 1995; Struewing et al., 1997; Warner et al., 1999) The prevalence of other *BRCA1/2* mutations in women of other specific ancestries is less well defined. Myriad Genetic Laboratories has published data on 10,000 individuals undergoing testing for *BRCA1/2* mutations. (Frank et al., 2002) The majority of these individuals have a personal and/or family history of breast and/or ovarian cancer. Among individuals undergoing mutation testing who specified a single ancestry, the prevalence of deleterious *BRCA1/2* mutations was: 712/4,379 (16 percent) among Europeans, 25/133 (19 percent) among Africans, 31/177 (18 percent) among Latin American/Caribbeans, 15/104 (14 percent) among Native Americans, 11/91 (12 percent) among Asians, and 6/69 (9 percent) among Near/Middle Easterners. There was no indication of frequently recurring founder mutations in any of these populations. The prevalence of mutations among individuals undergoing mutation testing did not differ significantly between any of the ancestries. Distinct variations in the *BRCA1/2* genes have been reported among African American women. (Gao et al., 2000; Olopade et al., 2003; Panguluri et al., 1999) Many of these variations are classified as genetic variants of uncertain clinical significance. Additional testing is needed before these variants can be classified as to whether or not they are deleterious. There are currently no published data on the types of variants or genomic rearrangements for Hispanics, Asians, or Native Americans.

References

- Fodor, F. H., Weston, A., Bleiweiss, I. J., McCurdy, L. D., Walsh, M. M., Tartter, P. I., Brower, S. T., and Eng, C. M. 1998. Frequency and carrier risk associated with common BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer patients. *Am J Hum Genet* **63**(1):45-51.
- Frank, T. S., Deffenbaugh, A. M., Reid, J. E., Hulick, M., Ward, B. E., Lingenfelter, B., Gumper, K. L., Scholl, T., Tavtigian, S. V., Pruss, D. R., and Critchfield, G. C., 2002, Clinical Characteristics of Individuals With Germline Mutations in BRCA1 and BRCA2: Analysis of 10,000 Individuals, *J Clin Oncol* **20**(6):1480-90.
- Gao, Q., Tomlinson, G., Das, S., Cummings, S., Sveen, L., Fackenthal, J., Schumm, P., and Olopade, O. I., 2000, Prevalence of BRCA1 and BRCA2 mutations among clinic-based African American families with breast cancer, *Hum Genet* **107**(2):186-91.
- Hartge, P., Struewing, J. P., Wacholder, S., Brody, L. C., and Tucker, M. A. 1999. The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews. *Am J Hum Genet* **64**(4):963-70.
- King, M. C., Marks, J. H., and Mandell, J. B. 2003. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science* **302**(5645):643-6.
- Moslehi, R., Chu, W., Karlan, B., Fishman, D., Risch, H., Fields, A., Smotkin, D., Ben-David, Y., Rosenblatt, J., Russo, D., Schwartz, P., Tung, N., Warner, E., Rosen, B., Friedman, J., Brunet, J. S., and Narod, S. A. 2000. BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. *Am J Hum Genet* **66**(4):1259-72.
- Oddoux, C., Struewing, J. P., Clayton, C. M., Neuhausen, S., Brody, L. C., Kaback, M., Haas, B., Norton, L., Borgen, P., Jhanwar, S., Goldgar, D., Ostrer, H., and Offit, K. 1996. The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%. *Nat Genet* **14**(2):188-90.
- Olopade, O. I., Fackenthal, J. D., Dunston, G., Tainsky, M. A., Collins, F., and Whitfield-Broome, C., 2003, Breast cancer genetics in African Americans, *Cancer* **97**(1 Suppl):236-45.
- Panguluri, R. C., Brody, L. C., Modali, R., Utley, K., Adams-Campbell, L., Day, A. A., Whitfield-Broome, C., and Dunston, G. M., 1999, BRCA1 mutations in African Americans, *Hum Genet* **105**(1-2):28-31.
- Roa, B. B., Boyd, A. A., Volcik, K., and Richards, C. S. 1996. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nat Genet* **14**(2):185-7.
- Satagopan, J. M., Offit, K., Foulkes, W., Robson, M. E., Wacholder, S., Eng, C. M., Karp, S. E., and Begg, C. B. 2001. The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Cancer Epidemiol Biomarkers Prev* **10**(5):467-73.
- Struewing, J. P., Abeliovich, D., Peretz, T., Avishai, N., Kaback, M. M., Collins, F. S., and Brody, L. C. 1995. The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. *Nat Genet* **11**(2):198-200.
- Struewing, J. P., Hartge, P., Wacholder, S., Baker, S. M., Berlin, M., McAdams, M., Timmerman, M. M., Brody, L. C., and Tucker, M. A. 1997. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* **336**(20):1401-8.
- Warner, E., Foulkes, W., Goodwin, P., Meschino, W., Blondal, J., Paterson, C., Ozelik, H., Goss, P., Allingham-Hawkins, D., Hamel, N., Di Prospero, L., Contiga, V., Serruya, C., Klein, M., Moslehi, R., Honeyford, J., Liede, A., Glendon, G., Brunet, J. S., and Narod, S. 1999. Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. *J Natl Cancer Inst* **91**(14):1241-7.

CLINICAL VALIDITY

Question 24. What are the genotype/phenotype relationships?

Summary

- While there has been much research in the area of genotype/phenotype relationships of *BRCA1/2* and breast/ovarian cancer, results have not had an impact on the clinical management of the mutation carriers' disease.

Questions that address the relationship between genotype (the specific mutation) and phenotype (the clinical appearance of disease) have been widely investigated. However, most studies have analyzed relatively few participants, and data are conflicting in some areas.

Genotype/phenotype relationships for the *BRCA1* gene

- Tumors in women with a *BRCA1* mutation may be associated with a more severe phenotype than tumors without a mutation, as defined by mitotic index indicative of highly proliferating tumors.
- These tumors are more aggressive, but may be more amenable to treatment.
- Tumors in women with a *BRCA1* mutation are more frequently estrogen receptor (ER) negative and of high nuclear and histologic grade. (1997b; Karp et al., 1997; Lakhani et al., 1998; Robson et al., 1998; Verhoog et al., 1998)
- Atypical medullary carcinoma is over-represented in *BRCA1* mutation carriers. (1997b; Armes et al., 1998)
- Very early onset cancer (occurring before 35 years of age) is more strongly associated with *BRCA1*. (Cortesi et al., 2000)
- The risk of ovarian cancer relative to breast cancer appears to be significantly higher when mutations occur in the central region of the gene. (Thompson and Easton, 2002) In addition, breast cancer risk associated with mutations in the central region is significantly lower than for other mutations, whereas ovarian cancer risk associated with mutations 3' to nucleotide 4191 is significantly reduced relative to the rest of the gene.

Genotype/phenotype relationships for the *BRCA2* gene

- Mutations in the central portion of *BRCA2* are associated with a significantly higher ratio of ovarian cancer to breast cancer (lower risk of breast cancer and higher risk of ovarian cancer). (Ford et al., 1998; Gayther et al., 1997; Neuhausen et al., 1998; Thompson and Easton, 2001)
- Tubular carcinoma is less common in *BRCA2* mutation carriers. (1997b)

These findings suggest that breast cancer due to *BRCA1* has a different natural history in comparison to *BRCA2* or to apparently sporadic disease. These findings do not have an impact on current clinical management.

References

- 1997, Pathology of familial breast cancer: differences between breast cancers in carriers of BRCA1 or BRCA2 mutations and sporadic cases. Breast Cancer Linkage Consortium, *Lancet* **349**(9064):1505-10.
- Armes, J. E., Egan, A. J., Southey, M. C., Dite, G. S., McCredie, M. R., Giles, G. G., Hopper, J. L., and Venter, D. J., 1998, The histologic phenotypes of breast carcinoma occurring before age 40 years in women with and without BRCA1 or BRCA2 germline mutations: a population-based study, *Cancer* **83**(11):2335-45.
- Cortesi, L., Turchetti, D., Bertoni, C., Bellei, R., Mangone, L., Vinceti, M., Federico, M., Silingardi, V., and Ferrari, S., 2000, Comparison between genotype and phenotype identifies a high-risk population carrying BRCA1 mutations, *Genes Chromosomes Cancer* **27**(2):130-5.
- Ford, D., Easton, D. F., Stratton, M., Narod, S., Goldgar, D., Devilee, P., Bishop, D. T., Weber, B., Lenoir, G., Chang-Claude, J., Sobol, H., Teare, M. D., Struewing, J., Arason, A., Scherneck, S., Peto, J., Rebbeck, T. R., Tonin, P., Neuhausen, S., Barkardottir, R., Eyfjord, J., Lynch, H., Ponder, B. A., Gayther, S. A., Zelada-Hedman, M., and et al., 1998, Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium, *Am J Hum Genet* **62**(3):676-89.
- Gayther, S. A., Mangion, J., Russell, P., Seal, S., Barfoot, R., Ponder, B. A., Stratton, M. R., and Easton, D., 1997, Variation of risks of breast and ovarian cancer associated with different germline mutations of the BRCA2 gene, *Nat Genet* **15**(1):103-5.
- Karp, S. E., Tonin, P. N., Begin, L. R., Martinez, J. J., Zhang, J. C., Pollak, M. N., and Foulkes, W. D., 1997, Influence of BRCA1 mutations on nuclear grade and estrogen receptor status of breast carcinoma in Ashkenazi Jewish women, *Cancer* **80**(3):435-41.
- Lakhani, S. R., Jacquemier, J., Sloane, J. P., Gusterson, B. A., Anderson, T. J., van de Vijver, M. J., Farid, L. M., Venter, D., Antoniou, A., Storer-Isser, A., Smyth, E., Steel, C. M., Haites, N., Scott, R. J., Goldgar, D., Neuhausen, S., Daly, P. A., Ormiston, W., McManus, R., Scherneck, S., Ponder, B. A., Ford, D., Peto, J., Stoppa-Lyonnet, D., Easton, D. F., and et al., 1998, Multifactorial analysis of differences between sporadic breast cancers and cancers involving BRCA1 and BRCA2 mutations, *J Natl Cancer Inst* **90**(15):1138-45.
- Neuhausen, S. L., Godwin, A. K., Gershoni-Baruch, R., Schubert, E., Garber, J., Stoppa-Lyonnet, D., Olah, E., Csokay, B., Serova, O., Laloo, F., Osorio, A., Stratton, M., Offit, K., Boyd, J., Caligo, M. A., Scott, R. J., Schofield, A., Teugels, E., Schwab, M., Cannon-Albright, L., Bishop, T., Easton, D., Benitez, J., King, M. C., Goldgar, D., and et al., 1998, Haplotype and phenotype analysis of nine recurrent BRCA2 mutations in 111 families: results of an international study, *Am J Hum Genet* **62**(6):1381-8.
- Robson, M., Gilewski, T., Haas, B., Levin, D., Borgen, P., Rajan, P., Hirschaut, Y., Pressman, P., Rosen, P. P., Lesser, M. L., Norton, L., and Offit, K., 1998, BRCA-associated breast cancer in young women, *J Clin Oncol* **16**(5):1642-9.
- Sobol, H., Stoppa-Lyonnet, D., Bressac-de-Paillerets, B., Peyrat, J. P., Kerangueven, F., Janin, N., Noguchi, T., Eisinger, F., Guinebretiere, J. M., Jacquemier, J., and Birnbaum, D., 1996, Truncation at conserved terminal regions of BRCA1 protein is associated with highly proliferating hereditary breast cancers, *Cancer Res* **56**(14):3216-9.

- Thompson, D., and Easton, D., 2001, Variation in cancer risks, by mutation position, in BRCA2 mutation carriers, *Am J Hum Genet* **68**(2):410-9.
- Thompson, D., and Easton, D., 2002, Variation in BRCA1 cancer risks by mutation position, *Cancer Epidemiol Biomarkers Prev* **11**(4):329-36.
- Verhoog, L. C., Brekelmans, C. T., Seynaeve, C., van den Bosch, L. M., Dahmen, G., van Geel, A. N., Tilanus-Linthorst, M. M., Bartels, C. C., Wagner, A., van den Ouweland, A., Devilee, P., Meijers-Heijboer, E. J., and Klijn, J. G., 1998, Survival and tumour characteristics of breast-cancer patients with germline mutations of BRCA1, *Lancet* **351**(9099):316-21.

DRAFT

CLINICAL VALIDITY

Question 25. What are the genetic, environmental or other modifiers?

Summary

- Multiple factors other than *BRCA1/2* genotype are likely to play a role in the natural history of breast and ovarian cancer. Many are not modifiable (e.g., age, gender, family history), while others are (e.g., obesity, alcohol consumption).

A number of factors consistently associated with increased risk of breast and ovarian cancer are not modifiable, while others are modifiable.

Non-modifiable risk factors for breast/ovarian cancer:

Genetic Predisposition – Table 3-21 shows the estimated frequency of *BRCA1/2* disease-causing mutations in the general population, along with the likelihood of breast and ovarian cancer occurring in women with one of these mutations and the proportion of all breast and ovarian cancers associated with these mutations. Even though inherited cancer from this cause accounts for a relatively small percent of the total, considerable attention has focused on *BRCA1/2* mutations for the following reasons: 1) they are the most common mutations discovered so far for which a causal link has been established, 2) identifying one of these mutations in a woman offers an opportunity to consider primary prevention options. These options might be considered either environmental modifiers (bilateral mastectomy and oophorectomy) or pharmacologic modifiers (tamoxifen). The first of these options, although extreme, appears justifiable on the basis of data in Table 3-21, even though risk is not completely eliminated by such “risk-reducing” surgery (Question 28).

Other, more rare, susceptibility alleles for breast cancer include *p53* (Li-Fraumeni Syndrome), *STK11/LKB1* (Peutz-Jeghers Syndrome), *PTEN* (Cowden Syndrome), *MSH2/MLH1* (Muir-Torre Syndrome), and *ATM* (Ataxia-telangiectasia). Ovarian cancer has been associated with basal cell nevus (Gorlin) syndrome, multiple endocrine neoplasia type 1 (*MEN1*), and hereditary nonpolyposis colon cancer (HNPCC).

Less well understood is the reason why, in the absence of any intervention, a fair proportion of the women who carry one of the disease-causing mutations does not develop either breast or ovarian cancer during their lifetime. Table 3-22 summarizes studies that have evaluated possible relationships between selected gene variants and risk for breast or ovarian cancer in the presence of a disease-causing *BRCA1/2* mutation. Collectively, these studies offer preliminary evidence toward understanding why some of the women do not develop cancer. Neither the strength of the evidence nor the strength of the effects, however, are sufficient to allow information about these genes to be factored into clinical decision-making.

Table 3-21. Estimated Lifetime Risks for Breast and Ovarian Cancer Among Women with Either a *BRCA1* or *BRCA2* Mutation and Proportion of Total Cases Attributable to this Cause

	Disease-Causing Mutation	
	<i>BRCA1</i>	<i>BRCA2</i>
Proportion of women in general population with one of these mutations ¹	0.051	0.068
Proportion of women with one of these mutations that develop breast cancer	35-87 ²	37-74 ³
Proportion of women with one of these mutations that develop ovarian cancer	11-66 ⁴	9-27 ⁵
Proportion of all breast cancer cases associated with these mutations	1-2 (Question 18)	
Proportion of all ovarian cancer cases associated with these mutations	4-9 (Question 18)	

¹ (Antoniou et al., 2002)

² (2000; Antoniou et al., 2000; Antoniou et al., 2002; Brose et al., 2002; Easton et al., 1995; Ford et al., 1994; Risch et al., 2001)

³ (2000; Antoniou et al., 2002; Schubert et al., 1997; Thorlacius et al., 1998)

⁴ (Antoniou et al., 2000; Antoniou et al., 2002; Brose et al., 2002; Easton et al., 1995; Ford et al., 1994; Risch et al., 2001)

⁵ (Antoniou et al., 2002; Ford et al., 1998)

Table 3-22. Genes Whose Variants Might Play a Role in Modifying Cancer Risk in Women with *BRCA1/2* Mutations

Name of Gene	Function	Variant of Interest	Effect on Cancer Risk
Androgen receptor (<i>AR</i>) ¹	Hormone metabolism	At least one long allele (29 CAG repeats)	Women with <i>BRCA1</i> mutations develop cancer earlier if variant is present
<i>AIB1</i> ^{2*}	Hormone metabolism	Alleles with at least 28 or 29 polyglutamine repeats	Risk of breast cancer is higher if variant is present
Progesterone receptor ³	Hormone metabolism	PROGINS allele(s)	Risk of ovarian cancer is higher among women with <i>BRCA1/2</i> mutations if variant is present

<i>Rad51</i> ⁴	DNA damage response	C>G substitution in 5' untranslated region	Risk of breast cancer is higher among women with <i>BRCA2</i> mutations if variant is present
<i>HRAS1</i> ⁵	Mitogenic signaling (a proto-oncogene)	A rare HRAS allele	Risk of ovarian cancer is higher among women with <i>BRCA1/2</i> mutations if this rare allele is present

¹ (Rebbeck et al., 1999)

² (Rebbeck et al., 2001)

³ (Runnebaum et al., 2001)

⁴ (Levy-Lahad et al., 2001; Scully et al., 1997; Wang et al., 2001)

⁵ (Phelan et al., 1996)

- *Gender* – While men can develop breast cancer, it is extremely rare (approximately 1 percent of all incident cases and deaths from breast cancer are male). Ovarian cancer affects only females.
- *Age* – After gender, age is a woman's single most important risk factor for developing breast or ovarian cancer. Cumulative risk of breast cancer increases with age, with most breast cancers occurring after age 50. Before 30 years of age, the risk of developing ovarian cancer is remote. Ovarian cancer incidence rises linearly between age 30 and 50 and continues to rise at a lesser rate after age 50. The highest incidence is in women 70-79 years of age.
- *Family History* – Women with a family history of breast/ovarian cancer, especially in a first-degree relative, have an increased risk of developing breast/ovarian cancer themselves (Question 21).
- *Use of Fertility Drugs/Infertility* – Some studies identify certain fertility drugs as increasing a woman's risk for ovarian cancer, while others contend that it is not the fertility treatments but the infertility itself that raises this risk. (Holschneider and Berek, 2000; La Vecchia, 2001; Runnebaum and Stickeler, 2001) More research is needed to determine the relationship between fertility drugs and ovarian cancer.
- *Radiation Exposure* – Observations in Hiroshima/Nagasaki survivors and in women who have received therapeutic radiation treatments to the chest and upper body document markedly increased breast cancer risk. (Bhatia et al., 1996; Land, 1995; Wolden et al., 1998)
- *History of Breast Disease* – Benign breast disease (BBD) is an independent risk factor for breast cancer. The risk among women with atypical hyperplasia is 2.5 to 5.3 times that among women with nonproliferative BBD. (Carter et al., 1988; Dupont and Page, 1985; London et al., 1992) Women who have proliferative disease without atypia are at a 1.6 to 1.9 times greater risk. Even among women with fibroadenomas who have no evidence of proliferative disease, breast cancer risk is increased 40-90 percent over an average of 22 years of follow-up. (Dupont et al., 1994)
- *Hormonal Factors (some are modifiable)* – A number of hormonal factors that might influence risk for hereditary breast/ovarian cancer have been examined and are summarized in Table 3-23. The use of hormone replacement therapy in postmenopausal women has been

shown to raise the risk of breast cancer by approximately 26 percent. (1997a; 2002; Chen et al., 2002; Hulley et al., 2002) However, its use has not been evaluated in women at high risk for hereditary breast cancer. Tamoxifen reduces risk of breast cancer and is discussed later (Questions 27, 29, and 34). Nulliparity, early age of menarche, and late menopause are associated with increased ovarian cancer risk. Conversely, pregnancy, lactation, and use of oral contraceptives have been associated with a protective effect. The risk of ovarian cancer is increased in postmenopausal women who use either estrogen or hormone replacement therapy. (Lacey et al., 2002; Riman et al., 2002) Increased ovarian cancer mortality is associated with postmenopausal estrogen use for 10 or more years. (Rodriguez et al., 2001)

Table 3-23. Hormonal Factors that Might Influence Risk for Breast Cancer in Women with BRCA1/2 Mutations or a Family History

Factor	Determinant Used for Assessment	Effect on Risk of Cancer
Menarche	Age < 12 years	None found ¹
Menopause	Age ≥ 55 years	None found ¹
Number of pregnancies	Nulliparity or fewer	None found ¹
Oral Contraceptive Use	<ul style="list-style-type: none"> • Before 1975 • Before age 30 • For > 5 years 	Increased risk of early onset breast cancer ²
Hormone Replacement Therapy	Postmenopausal use (natural or induced)	Not evaluated in this population
Tamoxifen	Questions 27, 29, 34	

¹ (Colditz et al., 1996)

² (Narod et al., 2002)

Modifiable risk factors for breast/ovarian cancer:

- *Alcohol Consumption* – A meta-analysis of more than 50 epidemiologic investigations suggested that the equivalent of 2 drinks per day may increase breast cancer by 25 percent. This increased risk is dose-dependent. (Schatzkin and Longnecker, 1994) A pooled analysis of cohort studies also concluded that alcohol consumption is associated with a linear increase in breast cancer incidence. (Smith-Warner et al., 1998)
- *Physical Activity* – Fourteen published cohort studies and 22 case-control studies have investigated the association between physical activity and risk of breast cancer. Of these 36 studies, 26 found clear evidence of a reduced risk for breast cancer in women who were the most active compared with sedentary women. (McTiernan, 2000) Estimates of protection ranged from 10 percent to 70 percent. Large variations in method of activity assessment exists among studies (e.g. some looked at college sports participation, some looked at occupational physical activity only, several examined recreational activity only, some utilized a single question, while others involved detailed questioning, and some looked at physical activity at a single point in time while others assessed physical activity over the woman’s lifetime).
- *Dietary Fat/Caloric Intake/Obesity* – Adult weight gain uniformly and independently has been found to increase risk for breast cancer in postmenopausal women. (Greenwald et al., 1997) Other evidence exists for an association between dietary fat and increased breast and

ovarian cancer risk. As with the assessment of physical activity, variations in methods of dietary assessment, the complexity of nutrient intake/interaction, and effects of different types of fat complicate this research. (Hunter and Willett, 1993)

- *Dietary Antioxidants* – There are conflicting data on the effects of micro-nutrient antioxidants on risk of breast and ovarian cancer. (Hunter and Willett, 1993; Sato et al., 2002) Results have ranged from antioxidants being unrelated to risk to being strongly protective. Methods of ascertainment range from a variety of food questionnaires to serum measurements.
- *Tubal Ligation/Hysterectomy* – These surgical interventions reduce the risk of developing ovarian cancer by 30-80 percent. (Runnebaum and Stickeler, 2001)
- *Risk Reducing Surgeries (mastectomy and oophorectomy)* – These interventions are discussed in Questions 27, 29, and 34.
- *Talcum Powder* – Epidemiologic studies of ovarian cancer have found an increased risk for women exposed to perineal talc (relative risk 1.0-3.3). (Whysner and Mohan, 2000)

In summary, the role of non-genetic modifiers in women with *BRCA1/2* mutations is largely unknown. Exogenous hormone use appears to increase risk of breast and decrease the risk of ovarian cancer. However, this evidence is modest, at best, and conflicting, at worst. Primary prevention modifiers (e.g. risk-reducing surgery and tamoxifen) are discussed in a later section (Questions 27, 29, and 34).

References

- 1997a. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet* **350**(9084):1047-59.
- 1997b. Pathology of familial breast cancer: differences between breast cancers in carriers of BRCA1 or BRCA2 mutations and sporadic cases. Breast Cancer Linkage Consortium. *Lancet* **349**(9064):1505-10.
2000. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. *Br J Cancer* **83**(10):1301-8.
2001. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet* **358**(9291):1389-99.
2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* **288**(3):321-33.
2003. DevCan: Probability of developing or dying of cancer software, Statistical Research and Application Branch, National Cancer Institute.
- Antoniou, A. C., Gayther, S. A., Stratton, J. F., Ponder, B. A., and Easton, D. F. 2000. Risk models for familial ovarian and breast cancer. *Genet Epidemiol* **18**(2):173-90.
- Antoniou, A. C., Pharoah, P. D., McMullan, G., Day, N. E., Stratton, M. R., Peto, J., Ponder, B. J., and Easton, D. F. 2002. A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. *Br J Cancer* **86**(1):76-83.
- Armes, J. E., Egan, A. J., Southey, M. C., Dite, G. S., McCredie, M. R., Giles, G. G., Hopper, J. L., and Venter, D. J. 1998. The histologic phenotypes of breast carcinoma occurring before age 40 years in women with and without BRCA1 or BRCA2 germline mutations: a population-based study. *Cancer* **83**(11):2335-45.
- Bhatia, S., Robison, L. L., Oberlin, O., Greenberg, M., Bunin, G., Fossati-Bellani, F., and Meadows, A. T. 1996. Breast cancer and other second neoplasms after childhood Hodgkin's disease. *N Engl J Med* **334**(12):745-51.
- Brose, M. S., Rebbeck, T. R., Calzone, K. A., Stopfer, J. E., Nathanson, K. L., and Weber, B. L. 2002. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. *J Natl Cancer Inst* **94**(18):1365-72.
- Carter, C. L., Corle, D. K., Micozzi, M. S., Schatzkin, A., and Taylor, P. R. 1988. A prospective study of the development of breast cancer in 16,692 women with benign breast disease. *Am J Epidemiol* **128**(3):467-77.
- Chen, W. Y., Colditz, G. A., Rosner, B., Hankinson, S. E., Hunter, D. J., Manson, J. E., Stampfer, M. J., Willett, W. C., and Speizer, F. E. 2002. Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. *Ann Intern Med* **137**(10):798-804.
- Colditz, G. A., Rosner, B. A., and Speizer, F. E. 1996. Risk factors for breast cancer according to family history of breast cancer. For the Nurses' Health Study Research Group. *J Natl Cancer Inst* **88**(6):365-71.
- Cortesi, L., Turchetti, D., Bertoni, C., Bellei, R., Mangone, L., Vinceti, M., Federico, M., Silingardi, V., and Ferrari, S. 2000. Comparison between genotype and phenotype identifies a high-risk population carrying BRCA1 mutations. *Genes Chromosomes Cancer* **27**(2):130-5.

- Dupont, W. D., and Page, D. L. 1985. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* **312**(3):146-51.
- Dupont, W. D., Page, D. L., Parl, F. F., Vnencak-Jones, C. L., Plummer, W. D., Jr., Rados, M. S., and Schuyler, P. A. 1994. Long-term risk of breast cancer in women with fibroadenoma. *N Engl J Med* **331**(1):10-5.
- Easton, D. F., Ford, D., and Bishop, D. T. 1995. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Am J Hum Genet* **56**(1):265-71.
- Feuer, E. J., and Wun, L. M., 1999, DEVCAN: Probability of developing or dying of cancer software, Bethesda, Maryland.
- Fodor, F. H., Weston, A., Bleiweiss, I. J., McCurdy, L. D., Walsh, M. M., Tartter, P. I., Brower, S. T., and Eng, C. M. 1998. Frequency and carrier risk associated with common BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer patients. *Am J Hum Genet* **63**(1):45-51.
- Ford, D., Easton, D. F., Bishop, D. T., Narod, S. A., and Goldgar, D. E. 1994. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Lancet* **343**(8899):692-5.
- Ford, D., Easton, D. F., Stratton, M., Narod, S., Goldgar, D., Devilee, P., Bishop, D. T., Weber, B., Lenoir, G., Chang-Claude, J., Sobol, H., Teare, M. D., Struewing, J., Arason, A., Scherneck, S., Peto, J., Rebbeck, T. R., Tonin, P., Neuhausen, S., Barkardottir, R., Eyfjord, J., Lynch, H., Ponder, B. A., Gayther, S. A., Zelada-Hedman, M., and et al. 1998. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet* **62**(3):676-89.
- Frank, T. S., Deffenbaugh, A. M., Reid, J. E., Hulick, M., Ward, B. E., Lingenfelter, B., Gumpfer, K. L., Scholl, T., Tavtigian, S. V., Pruss, D. R., and Critchfield, G. C. 2002. Clinical Characteristics of Individuals With Germline Mutations in BRCA1 and BRCA2: Analysis of 10,000 Individuals. *J Clin Oncol* **20**(6):1480-90.
- Gao, Q., Tomlinson, G., Das, S., Cummings, S., Sveen, L., Fackenthal, J., Schumm, P., and Olopade, O. I. 2000. Prevalence of BRCA1 and BRCA2 mutations among clinic-based African American families with breast cancer. *Hum Genet* **107**(2):186-91.
- Gayther, S. A., Mangion, J., Russell, P., Seal, S., Barfoot, R., Ponder, B. A., Stratton, M. R., and Easton, D. 1997. Variation of risks of breast and ovarian cancer associated with different germline mutations of the BRCA2 gene. *Nat Genet* **15**(1):103-5.
- Greenwald, P., Sherwood, K., and McDonald, S. S. 1997. Fat, caloric intake, and obesity: lifestyle risk factors for breast cancer. *J Am Diet Assoc* **97**(7 Suppl):S24-30.
- Hartge, P., Struewing, J. P., Wacholder, S., Brody, L. C., and Tucker, M. A. 1999. The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews. *Am J Hum Genet* **64**(4):963-70.
- Holschneider, C. H., and Berek, J. S. 2000. Ovarian cancer: epidemiology, biology, and prognostic factors. *Semin Surg Oncol* **19**(1):3-10.
- Hulley, S., Furberg, C., Barrett-Connor, E., Cauley, J., Grady, D., Haskell, W., Knopp, R., Lowery, M., Satterfield, S., Schrott, H., Vittinghoff, E., and Hunninghake, D. 2002. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* **288**(1):58-66.
- Hunter, D. J., and Willett, W. C. 1993. Diet, body size, and breast cancer. *Epidemiol Rev* **15**(1):110-32.

- Karp, S. E., Tonin, P. N., Begin, L. R., Martinez, J. J., Zhang, J. C., Pollak, M. N., and Foulkes, W. D. 1997. Influence of BRCA1 mutations on nuclear grade and estrogen receptor status of breast carcinoma in Ashkenazi Jewish women. *Cancer* **80**(3):435-41.
- King, M. C., Marks, J. H., and Mandell, J. B. 2003. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science* **302**(5645):643-6.
- La Vecchia, C. 2001. Epidemiology of ovarian cancer: a summary review. *Eur J Cancer Prev* **10**(2):125-9.
- Lacey, J. V., Jr., Mink, P. J., Lubin, J. H., Sherman, M. E., Troisi, R., Hartge, P., Schatzkin, A., and Schairer, C. 2002. Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA* **288**(3):334-41.
- Lakhani, S. R., Jacquemier, J., Sloane, J. P., Gusterson, B. A., Anderson, T. J., van de Vijver, M. J., Farid, L. M., Venter, D., Antoniou, A., Storer-Isser, A., Smyth, E., Steel, C. M., Haites, N., Scott, R. J., Goldgar, D., Neuhausen, S., Daly, P. A., Ormiston, W., McManus, R., Scherneck, S., Ponder, B. A., Ford, D., Peto, J., Stoppa-Lyonnet, D., Easton, D. F., and et al. 1998. Multifactorial analysis of differences between sporadic breast cancers and cancers involving BRCA1 and BRCA2 mutations. *J Natl Cancer Inst* **90**(15):1138-45.
- Land, C. E. 1995. Studies of cancer and radiation dose among atomic bomb survivors. The example of breast cancer. *JAMA* **274**(5):402-7.
- Levy-Lahad, E., Lahad, A., Eisenberg, S., Dagan, E., Paperna, T., Kasinetz, L., Catane, R., Kaufman, B., Beller, U., Renbaum, P., and Gershoni-Baruch, R. 2001. A single nucleotide polymorphism in the RAD51 gene modifies cancer risk in BRCA2 but not BRCA1 carriers. *Proc Natl Acad Sci U S A* **98**(6):3232-6.
- London, S. J., Connolly, J. L., Schnitt, S. J., and Colditz, G. A. 1992. A prospective study of benign breast disease and the risk of breast cancer. *JAMA* **267**(7):941-4.
- Madigan, M. P., Ziegler, R. G., Benichou, J., Byrne, C., and Hoover, R. N. 1995. Proportion of breast cancer cases in the United States explained by well-established risk factors. *J Natl Cancer Inst* **87**(22):1681-5.
- McTiernan, A., 2000, Physical Activity and the Prevention of Breast Cancer.
- Miller, B. A., Kolonel, L. N., Bernstein, L., Young, J. J. L., Swanson, G. M., West, D., Key, C. R., Liff, J. M., Glover, C. S., Alexander, G. A., and al., e., 1996, Racial/ethnic patterns of cancer in the United States 1988-1992, National Cancer Institute, Bethesda, MD.
- Moslehi, R., Chu, W., Karlan, B., Fishman, D., Risch, H., Fields, A., Smotkin, D., Ben-David, Y., Rosenblatt, J., Russo, D., Schwartz, P., Tung, N., Warner, E., Rosen, B., Friedman, J., Brunet, J. S., and Narod, S. A. 2000. BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. *Am J Hum Genet* **66**(4):1259-72.
- Narod, S. A., Dube, M. P., Klijn, J., Lubinski, J., Lynch, H. T., Ghadirian, P., Provencher, D., Heimdal, K., Moller, P., Robson, M., Offit, K., Isaacs, C., Weber, B., Friedman, E., Gershoni-Baruch, R., Rennert, G., Pasini, B., Wagner, T., Daly, M., Garber, J. E., Neuhausen, S. L., Ainsworth, P., Olsson, H., Evans, G., Osborne, M., Couch, F., Foulkes, W. D., Warner, E., Kim-Sing, C., Olopade, O., Tung, N., Saal, H. M., Weitzel, J., Merajver, S., Gauthier-Villars, M., Jernstrom, H., Sun, P., and Brunet, J. S. 2002. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst* **94**(23):1773-9.
- Neuhausen, S. L., Godwin, A. K., Gershoni-Baruch, R., Schubert, E., Garber, J., Stoppa-Lyonnet, D., Olah, E., Csokay, B., Serova, O., Lalloo, F., Osorio, A., Stratton, M., Offit,

- K., Boyd, J., Caligo, M. A., Scott, R. J., Schofield, A., Teugels, E., Schwab, M., Cannon-Albright, L., Bishop, T., Easton, D., Benitez, J., King, M. C., Goldgar, D., and et al. 1998. Haplotype and phenotype analysis of nine recurrent BRCA2 mutations in 111 families: results of an international study. *Am J Hum Genet* **62**(6):1381-8.
- Oddoux, C., Struwing, J. P., Clayton, C. M., Neuhausen, S., Brody, L. C., Kaback, M., Haas, B., Norton, L., Borgen, P., Jhanwar, S., Goldgar, D., Ostrer, H., and Offit, K. 1996. The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%. *Nat Genet* **14**(2):188-90.
- Olopade, O. I., Fackenthal, J. D., Dunston, G., Tainsky, M. A., Collins, F., and Whitfield-Broome, C. 2003. Breast cancer genetics in African Americans. *Cancer* **97**(1 Suppl):236-45.
- Panguluri, R. C., Brody, L. C., Modali, R., Utley, K., Adams-Campbell, L., Day, A. A., Whitfield-Broome, C., and Dunston, G. M. 1999. BRCA1 mutations in African Americans. *Hum Genet* **105**(1-2):28-31.
- Pharoah, P. D., Day, N. E., Duffy, S., Easton, D. F., and Ponder, B. A. 1997. Family history and the risk of breast cancer: a systematic review and meta-analysis. *Int J Cancer* **71**(5):800-9.
- Phelan, C. M., Rebbeck, T. R., Weber, B. L., Devilee, P., Rutledge, M. H., Lynch, H. T., Lenoir, G. M., Stratton, M. R., Easton, D. F., Ponder, B. A., Cannon-Albright, L., Larsson, C., Goldgar, D. E., and Narod, S. A. 1996. Ovarian cancer risk in BRCA1 carriers is modified by the HRAS1 variable number of tandem repeat (VNTR) locus. *Nat Genet* **12**(3):309-11.
- Rebbeck, T. R., Kantoff, P. W., Krithivas, K., Neuhausen, S., Blackwood, M. A., Godwin, A. K., Daly, M. B., Narod, S. A., Garber, J. E., Lynch, H. T., Weber, B. L., and Brown, M. 1999. Modification of BRCA1-associated breast cancer risk by the polymorphic androgen-receptor CAG repeat. *Am J Hum Genet* **64**(5):1371-7.
- Rebbeck, T. R., Wang, Y., Kantoff, P. W., Krithivas, K., Neuhausen, S. L., Godwin, A. K., Daly, M. B., Narod, S. A., Brunet, J. S., Vesprini, D., Garber, J. E., Lynch, H. T., Weber, B. L., and Brown, M. 2001. Modification of BRCA1- and BRCA2-associated breast cancer risk by AIB1 genotype and reproductive history. *Cancer Res* **61**(14):5420-4.
- Riman, T., Dickman, P. W., Nilsson, S., Correia, N., Nordlinder, H., Magnusson, C. M., Weiderpass, E., and Persson, I. R. 2002. Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women. *J Natl Cancer Inst* **94**(7):497-504.
- Risch, H. A., McLaughlin, J. R., Cole, D. E., Rosen, B., Bradley, L., Kwan, E., Jack, E., Vesprini, D. J., Kuperstein, G., Abrahamson, J. L., Fan, I., Wong, B., and Narod, S. A. 2001. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. *Am J Hum Genet* **68**(3):700-10.
- Roa, B. B., Boyd, A. A., Volcik, K., and Richards, C. S. 1996. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nat Genet* **14**(2):185-7.
- Robson, M., Gilewski, T., Haas, B., Levin, D., Borgen, P., Rajan, P., Hirschaut, Y., Pressman, P., Rosen, P. P., Lesser, M. L., Norton, L., and Offit, K. 1998. BRCA-associated breast cancer in young women. *J Clin Oncol* **16**(5):1642-9.
- Rodriguez, C., Patel, A. V., Calle, E. E., Jacob, E. J., and Thun, M. J. 2001. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA* **285**(11):1460-5.

- Runnebaum, I. B., and Stickeler, E. 2001. Epidemiological and molecular aspects of ovarian cancer risk. *J Cancer Res Clin Oncol* **127**(2):73-9.
- Runnebaum, I. B., Wang-Gohrke, S., Vesprini, D., Kreienberg, R., Lynch, H., Moslehi, R., Ghadirian, P., Weber, B., Godwin, A. K., Risch, H., Garber, J., Lerman, C., Olopade, O. I., Foulkes, W. D., Karlan, B., Warner, E., Rosen, B., Rebbeck, T., Tonin, P., Dube, M. P., Kieback, D. G., and Narod, S. A. 2001. Progesterone receptor variant increases ovarian cancer risk in BRCA1 and BRCA2 mutation carriers who were never exposed to oral contraceptives. *Pharmacogenetics* **11**(7):635-8.
- Satagopan, J. M., Offit, K., Foulkes, W., Robson, M. E., Wacholder, S., Eng, C. M., Karp, S. E., and Begg, C. B. 2001. The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Cancer Epidemiol Biomarkers Prev* **10**(5):467-73.
- Sato, R., Helzlsouer, K. J., Alberg, A. J., Hoffman, S. C., Norkus, E. P., and Comstock, G. W. 2002. Prospective study of carotenoids, tocopherols, and retinoid concentrations and the risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* **11**(5):451-7.
- Schatzkin, A., and Longnecker, M. P. 1994. Alcohol and breast cancer. Where are we now and where do we go from here? *Cancer* **74**(3 Suppl):1101-10.
- Schubert, E. L., Lee, M. K., Mefford, H. C., Argonza, R. H., Morrow, J. E., Hull, J., Dann, J. L., and King, M. C. 1997. BRCA2 in American families with four or more cases of breast or ovarian cancer: recurrent and novel mutations, variable expression, penetrance, and the possibility of families whose cancer is not attributable to BRCA1 or BRCA2. *Am J Hum Genet* **60**(5):1031-40.
- Scully, R., Chen, J., Plug, A., Xiao, Y., Weaver, D., Feunteun, J., Ashley, T., and Livingston, D. M. 1997. Association of BRCA1 with Rad51 in mitotic and meiotic cells. *Cell* **88**(2):265-75.
- Smith-Warner, S. A., Spiegelman, D., Yaun, S. S., van den Brandt, P. A., Folsom, A. R., Goldbohm, R. A., Graham, S., Holmberg, L., Howe, G. R., Marshall, J. R., Miller, A. B., Potter, J. D., Speizer, F. E., Willett, W. C., Wolk, A., and Hunter, D. J. 1998. Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA* **279**(7):535-40.
- Stratton, J. F., Pharoah, P., Smith, S. K., Easton, D., and Ponder, B. A. 1998. A systematic review and meta-analysis of family history and risk of ovarian cancer. *Br J Obstet Gynaecol* **105**(5):493-9.
- Struewing, J. P., Abeliovich, D., Peretz, T., Avishai, N., Kaback, M. M., Collins, F. S., and Brody, L. C. 1995. The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. *Nat Genet* **11**(2):198-200.
- Struewing, J. P., Hartge, P., Wacholder, S., Baker, S. M., Berlin, M., McAdams, M., Timmerman, M. M., Brody, L. C., and Tucker, M. A. 1997. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* **336**(20):1401-8.
- Thompson, D., and Easton, D. 2001. Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. *Am J Hum Genet* **68**(2):410-9.
- Thompson, D., and Easton, D. 2002. Variation in BRCA1 cancer risks by mutation position. *Cancer Epidemiol Biomarkers Prev* **11**(4):329-36.
- Thorlacius, S., Struewing, J. P., Hartge, P., Olafsdottir, G. H., Sigvaldason, H., Tryggvadottir, L., Wacholder, S., Tulinius, H., and Eyfjord, J. E. 1998. Population-based study of risk of breast cancer in carriers of BRCA2 mutation. *Lancet* **352**(9137):1337-9.

- Verhoog, L. C., Brekelmans, C. T., Seynaeve, C., van den Bosch, L. M., Dahmen, G., van Geel, A. N., Tilanus-Linthorst, M. M., Bartels, C. C., Wagner, A., van den Ouweland, A., Devilee, P., Meijers-Heijboer, E. J., and Klijn, J. G. 1998. Survival and tumour characteristics of breast-cancer patients with germline mutations of BRCA1. *Lancet* **351**(9099):316-21.
- Wang, W. W., Spurdle, A. B., Kolachana, P., Bove, B., Modan, B., Ebbers, S. M., Suthers, G., Tucker, M. A., Kaufman, D. J., Doody, M. M., Tarone, R. E., Daly, M., Levavi, H., Pierce, H., Chetrit, A., Yechezkel, G. H., Chenevix-Trench, G., Offit, K., Godwin, A. K., and Struwing, J. P. 2001. A single nucleotide polymorphism in the 5' untranslated region of RAD51 and risk of cancer among BRCA1/2 mutation carriers. *Cancer Epidemiol Biomarkers Prev* **10**(9):955-60.
- Warner, E., Foulkes, W., Goodwin, P., Meschino, W., Blondal, J., Paterson, C., Ozelik, H., Goss, P., Allingham-Hawkins, D., Hamel, N., Di Prospero, L., Contiga, V., Serruya, C., Klein, M., Moslehi, R., Honeyford, J., Liede, A., Glendon, G., Brunet, J. S., and Narod, S. 1999. Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. *J Natl Cancer Inst* **91**(14):1241-7.
- Whysner, J., and Mohan, M. 2000. Perineal application of talc and cornstarch powders: evaluation of ovarian cancer risk. *Am J Obstet Gynecol* **182**(3):720-4.
- Wolden, S. L., Lamborn, K. R., Cleary, S. F., Tate, D. J., and Donaldson, S. S. 1998. Second cancers following pediatric Hodgkin's disease. *J Clin Oncol* **16**(2):536-44.
- Ziogas, A., Gildea, M., Cohen, P., Bringman, D., Taylor, T. H., Seminara, D., Barker, D., Casey, G., Haile, R., Liao, S. Y., Thomas, D., Noble, B., Kurosaki, T., and Anton-Culver, H. 2000. Cancer risk estimates for family members of a population-based family registry for breast and ovarian cancer. *Cancer Epidemiol Biomarkers Prev* **9**(1):103-11.