

DISORDER/SETTING

- Question 1: What is the specific clinical disorder to be studied?
- Question 2: What are the clinical findings defining this disorder?
- Question 3: What is the clinical setting in which the test is to be performed?
- Question 4: What DNA test(s) are associated with this disorder?
- Question 5: Are preliminary screening questions employed?
- Question 6: Is it a stand-alone test or is it one of a series of tests?
- Question 7: If it is part of a series of screening tests, are all tests performed in all instances (parallel) or are some tests performed only on the basis of other results (series)?

DISORDER/SETTING

Question 1: What is the specific clinical disorder being studied?

Summary

- Excluding non-melanoma skin cancer, breast cancer is the most common form of cancer and is the second most common cause of cancer deaths in women
 - 250,000 women will be diagnosed each year
 - 39,400 women will die
 - 809,000 person-years of life will be lost
- 5 to 10 percent of breast cancer cases are associated with an autosomal pattern of inheritance, and one of the causes is known to be mutations in the *BRCA1/2* genes
- *BRCA1/2* mutations are also associated with ovarian cancer, and for this reason, breast cancer and ovarian cancer need to be considered together
- Women identified with a *BRCA1/2* mutation have a predisposition to developing ovarian cancer and/or early onset breast cancer

The primary clinical disorder being studied in this report is breast cancer in women. However, since this report focuses on testing for mutations in the genes *BRCA1* (breast cancer gene 1) and *BRCA2* (breast cancer gene 2) that predispose women to both breast and ovarian cancer, ovarian cancer will also be reviewed.

Excluding non-melanoma skin cancers, breast cancer is the most common form of cancer among women in the United States. The American Cancer Society estimates that in 2002 about 203,500 new cases of invasive breast cancer and 54,300 cases of *in situ* breast cancer will be diagnosed among women in the United States. (2002) It is estimated that 39,400 women will die of breast cancer this year, ranking it second among cancer deaths in women, exceeded only by lung cancer. Although not as common as breast cancer, ovarian cancer accounts for nearly 4 percent of all cancers among women (23,400 diagnosed cases) and is estimated by the American Cancer Society to cause 13,900 deaths in 2002. Ovarian cancer has the highest mortality rate of all reproductive system cancers in women. The public health impact of these two cancers in women is substantial. In 1997, breast cancer ranked second only to lung and bronchus cancer in terms of person-years of life lost (809,000), a measure of total burden of a cancer on society. (Brown *et al.*, 2001) Ovarian cancer ranked ninth, with 232,000 person-years of life lost. Both cancers ranked higher than lung, colon/rectum, and prostate cancer in terms of average years of life lost per person (breast 19.3, ovarian 17.2). This is a measure of burden that gives more weight to cancers that tend to occur in people at relatively younger ages. In terms of financial impact, a direct cost of treatment of 5.98 billion dollars was noted for breast cancer, based on 1996 Surveillance, Epidemiology, and End Results (SEER) Medicare linked data.

According to a report from the National Cancer Institute, it is estimated that about 1 in 8 women in the United States will develop breast cancer, the greatest risk being for women who live longer. (Ries *et al.*, 2002) Although quite rare, breast cancer can occur in men, and is estimated to affect 1,500 men each year. (2002) Most breast cancers occur postmenopausally in women over age 50, and the risk is especially high for women over age 60. While it is uncommon for

women under age 35 to be diagnosed with breast cancer, the course of the disease is more aggressive in that age group. There is also an increased likelihood for an underlying genetic predisposition, but the data are less clear for women whose cancers occur under age 30 (Question 18).

Numerous risk factors for breast cancer have been identified and include advancing age and family history, as well as other endocrine and environmental factors. It has been estimated that 5 to 10 percent of breast cancer cases demonstrate an autosomal dominant pattern of inheritance. The cancer susceptibility syndromes most associated with this pattern are hereditary breast and ovarian cancer due to *BRCA1/2* mutations, Li-Fraumeni syndrome due to *p53* mutations, and Cowden syndrome due to *PTEN* mutations. Most known mutations that increase breast cancer risk also appear to increase risk of ovarian cancer and may also increase risk of other cancers. For instance, mutations in *BRCA1/2* are associated with a 36 to 87 percent lifetime risk for breast cancer, and a 9 to 66 percent lifetime risk of ovarian cancer. Most of the increased risk of breast cancer over background in women with *BRCA1/2* mutations occurs premenopausally. (2000; Antoniou *et al.*, 2000; Antoniou *et al.*, 2002; Brose *et al.*, 2002; Easton *et al.*, 1995; Fodor *et al.*, 1998; Ford *et al.*, 1994; Ford *et al.*, 1998; Hopper *et al.*, 1999; Moslehi *et al.*, 2000; Risch *et al.*, 2001; Satagopan *et al.*, 2001; Schubert *et al.*, 1997; Struewing *et al.*, 1997; Thorlacius *et al.*, 1998; Warner *et al.*, 1999)

DISORDER/SETTING

Question 2: What are the clinical findings defining this disorder?

Summary

- Physical findings associated with breast cancer are relatively specific and well understood. Information about this is widely disseminated. For this reason, many cases of breast cancer are identified at an early stage.
- Physical findings associated with ovarian cancer are not apparent in the early stages. For this reason, many cases of ovarian cancer are identified only at a late stage.
- Diagnosis is by biopsy/pathologic examination. Histologic grading and tumor staging is standardized.

Breast cancer

Breast cancer is defined as the presence of a malignant tumor(s) within the breast tissue. These tumors are made up of groups of abnormal cells that divide without control or order, and can invade and damage other tissues and organs. These features distinguish them from a benign tumor. A definitive diagnosis of breast cancer can be made only after biopsy and pathological examination.

The earliest physical signs of breast cancer typically include:

- a palpable lump
- thickening, swelling, distortion, or tenderness
- skin irritation or dimpling
- nipple pain, ulceration, or retraction.

The malignancy is initially localized. It then spreads to surrounding tissues and lymph nodes. The natural history of breast cancer can be altered by early detection methods, such as mammography, and by early treatment, which provides the best hope for total eradication. A standard histological classification of the various tumor types has been provided by the World Health Organization. Breast cancers can be further graded (1, 2, or 3 based on level of differentiation of the cells on histologic characterization) and staged based on tumor size, involvement of lymph nodes, and presence of metastases. This grading allows standardization for comparison of results of various modes of therapy. Additional information from results of testing regarding the presence of estrogen and progesterone receptors, cancer cell ploidy and proliferation rate, and testing for the HER2/neu protein also aids in determining appropriate treatment.

Epidemiologic data suggest that genetic, endocrine, and environmental factors may be involved in the initiation and/or the promotion of breast cancer growth. It is well known that the risk of breast cancer increases with age. Important other risk factors include early age at onset of menarche, late onset of menopause, first full-term pregnancy after age 30, a history of premenopausal breast cancer in a mother or sister, and a personal history of breast cancer or benign proliferative breast disease.

Ovarian cancer

Unlike breast cancer, signs and symptoms of ovarian cancer often appear late and are non-specific (e.g., general abdominal discomfort and/or pain, loss of appetite, nausea, diarrhea, constipation, frequent urination, weight gain or loss, and occasionally vaginal bleeding). Ovarian cancer can be of three types; epithelial carcinoma, germ cell tumors, or stromal tumors, depending on the specific tissue involved. Epithelial cancer is the most common type. Like breast cancer, the risk for ovarian cancer increases with age and peaks when women are in their late 70s. Most other risk factors for breast cancer are also risk factors for ovarian cancer. Mutations in the *BRCA1/2* genes increase the risk of epithelial ovarian cancer. Increased risk of germ cell and stromal tumors has not been demonstrated.

Further Information

Further information about genetic and environmental factors influencing breast and ovarian cancer can be found in Question 25. More information about the natural history of breast cancer and ovarian cancer can be found in Question 26.

DISORDER/SETTING

Question 3: What is the clinical setting in which the test is to be performed?

Summary

- Screening adult women in the primary health care setting is chosen for this report
- This report does not address women with a personal history of breast/ovarian cancer and does not consider the Ashkenazi Jewish population as a separate group
- Two professional organizations in the U.S. have issued guidelines for breast/ovarian cancer susceptibility testing
- The first step in screening is a family history questionnaire, followed by risk assessment
- Among those identified as being at high risk for carrying a *BRCA1/2* mutation, pre-test education and post-test counseling is recommended

The decision to offer and perform *BRCA1/2* mutation testing is based on the presence of personal and/or family risk factors that determine the probability of finding a deleterious mutation (Question 5). The American College of Medical Genetics (ACMG) published guidelines in 1999, with a recommended protocol for Breast/Ovarian Cancer Genetic Susceptibility Assessment to aid health care providers. (1999) These guidelines stress the importance of all the components of the recommended protocol, including family history risk assessment, pre-test education and post-test counseling. The clinician may choose to manage all aspects, or may work in concert with an expert in cancer genetic counseling and risk assessment. The guidelines state that risk assessment should begin with estimating the likelihood of developing breast or ovarian cancer through a complete personal and three generation family history, including all types of cancer and approximate age at diagnosis for each affected individual. According to ACMG, the likelihood of having a mutation in a known cancer susceptibility gene (e.g. *BRCA1/2*) should be assessed on the basis of number of family members with breast or ovarian cancer, the closeness of the relationship to the patient, the ages at diagnosis, and whether or not an individual is a member of an ethnic group at higher risk for specific mutations.

The ACMG guidelines propose that there is sufficiently increased risk to warrant offering testing for a mutation in the *BRCA1/2* gene if:

- There are three or more affected first or second degree relatives on the same side of the family, regardless of age of diagnosis, or
- There are fewer than three affected relatives, but
 - the patient was diagnosed at age 45 or younger, or
 - a family member is known to carry a detectable mutation, or
 - there are one or more cases of ovarian cancer and at least one relative on the same side of the family with breast cancer (at any age), or
 - there are multiple primary or bilateral breast cancers in the patient or one family member, or
 - there is breast cancer in a male relative, or
 - the patient is at increased risk for specific mutation(s) due to ethnic background (e.g. Ashkenazi Jewish), and has one or more relatives with breast or ovarian cancer

In the absence of these personal and family risk factors, the protocol does not recommend further testing. Before *BRCA1/2* mutation testing is performed, the ACMG guidelines require that women at increased risk undergo a process of pre-test education regarding risks, benefits, alternatives and psychological/social impact of testing, so that they can make an informed choice about whether or not to proceed.

The American Society of Clinical Oncology (ASCO) published a revised statement on Genetic Testing for Cancer Susceptibility. (2003) ASCO recommends that cancer predisposition testing be offered only when:

- 1) the individual has personal or family history features suggestive of a genetic cancer susceptibility condition,
- 2) the test can be adequately interpreted, and
- 3) the results will aid in the diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer.

ACMG recognizes the importance of testing an affected member of the family first to identify the familial mutation. In the absence of knowing the mutation associated with cancer, a negative test in an unaffected family member is uninformative. Table 1-1 contains a comparison of the ASCO and ACMG guidelines with other national guidelines. In general, there is a high degree of consistence between the guidelines.

For the purposes of this report, the Ashkenazi Jewish population is not being considered separately. In addition, the focus is on screening women in the general population without a personal history of breast or ovarian cancer, using family history as the first screening test.

Table 1-1. Guidelines and protocols that have been developed for assessing *BRCA1/2*-related hereditary predisposition to cancer

Group	Date	Screening for <i>BRCA1/2</i> -Related Hereditary Predisposition to Cancer Number of Affected Relatives for Determining High Risk		Age of onset issues	
		Breast Cancer	Ovarian Cancer	Breast Cancer	Ovarian Cancer
American Society of Clinical Oncology (BRCA1 only)	1996	4 or more cases in females < age 50 or sisters diagnosed with breast cancer < 50 years	1 relative with ovarian cancer and 3 or more with breast cancer; or sisters diagnosed with one ovarian cancer and one breast cancer or two ovarian cancers	See number column	None
New York State Department of Health/ACMG	1999	3 cases in females; or 1 in male; or multiple cancers in one individual	1 relative with ovarian cancer and 1 with breast cancer (on the same side of the family).	Onset <45 years (not clear if only one counts)	None noted
NHMRC National Breast Cancer Centre (Australia)	2000	3 cases in females; or 2 cases if 1 was multiple cancers (breast or ovarian), or 1 was a breast cancer in a male, or 2 cases in a family of Jewish ancestry	1 relative with ovarian cancer and 2 with breast cancer	1 case <40 years (with at least 1 other relative with breast or ovarian cancer at any age)	1 case <age 50 years (with at least 1 other breast or ovarian cancer at any age)
Oxford Regional Genetics Service	2001	4 or more cases in females; or 1 case with bilateral disease; or 1 case in a male relative	3 relatives with ovarian cancer; or 1 relative with ovarian cancer and at least 2 with breast cancer	1 case in first degree relative <40 years; or 2 in relatives <50 years; or 3 in relatives <60 years	2 cases in relatives <60 years
Wales Cancer Genetics Service	2002	3 cases in females (same side of family); or 1 in male first degree relative; or 1 in first degree relative with bilateral breast cancer; (see also age of onset)	2 first degree relatives with ovarian cancer; at least 1 being first degree (same side of the family); or 1 first degree relative with ovarian cancer, who also has/had breast cancer; or 1 first degree relative with ovarian cancer and 1 with breast cancer (at < 50 years); or 1 ovarian cancer and 2 or more breast cancer cases in first degree relatives.	1 case in first degree relative <40 years; or 2 cases in first degree relatives <60 years (same side of family)	None

DISORDER/SETTING

Question 4. What DNA test(s) are associated with this disorder?

Summary

- *BRCA1* and *BRCA2* are large genes with thousands of mutations.
- Most *BRCA1/2* mutations are unique, so that each family with a defined history of breast/ovarian cancer tends to have its own mutation.
- Due to the size and complexity of the genes, expensive and time-consuming gene sequencing is often necessary
- Once a family mutation is known, less expensive targeted testing can be performed
- Full gene sequencing for clinical purposes can only be legally done in one laboratory in the U.S., due to patent restrictions
- *BRCA1/2* mutation test results are reported in three categories: deleterious mutation, variant of unknown clinical significance, and no detectable mutation (this last category includes polymorphisms known not to be associated with cancer susceptibility)
- Ongoing studies are helping to resolve some of the variants of unknown clinical significance

Background

Several genes have been identified in which germline mutations are associated with an increased risk for breast and ovarian cancer.

- *BRCA1* is localized on chromosome 17q12-21, spans a genomic region of almost 100 kilobases (kb) in length and contains 24 exons. The full-length messenger RNA (mRNA) is 7.8 kb, encoding a protein of 1,863 amino acids. More than 1,200 mutations and sequence variations have been detected, and not all mutations have yet been discovered.
- *BRCA2* has been isolated on chromosome 13q12-13 and is composed of 27 exons distributed over roughly 70 kb of genomic DNA, encoding a protein of 3,418 amino acids. Approximately 1,400 mutations have been reported for *BRCA2*.

Microinsertions and point mutations are equally common in the *BRCA1* gene, whereas microdeletions predominate in *BRCA2*. Large recurrent rearrangements, ranging from 0.5 to 23.8 kb and spanning the entire *BRCA1/2* genes, have recently been discovered. (Montagna *et al.*, 1999; Nordling *et al.*, 1998; Payne *et al.*, 2000; Petrij-Bosch *et al.*, 1997; Puget *et al.*, 1999; Puget *et al.*, 1997; Rohlf *et al.*, 2000; Swensen *et al.*, 1997; Unger *et al.*, 2000) These rearrangements are not detectable by usual polymerase chain reaction (PCR)-based laboratory methods (including sequencing and scanning). These rearrangements represent an estimated 10 to 15 percent of all mutations in the general population (Puget *et al.*, 1999; Unger *et al.*, 2000) and up to 36 percent in the Dutch population. (Petrij-Bosch *et al.*, 1997). The influence of these rearrangements on clinical validity is discussed later (Question 18). Evidence suggests that the *BRCA1/2* genes are tumor-suppressive via regulation of cellular proliferation and DNA replication and repair. (Holt *et al.*, 1996; Patel *et al.*, 1998; Scully *et al.*, 1997; Scully and Livingston, 2000; Sharan *et al.*, 1997; Zhong *et al.*, 1999)

Forty-eight different deleterious *BRCA1* mutations were found in 102 out of 798 (12.8%) unrelated high-risk women. (Shattuck-Eidens *et al.*, 1997) Overall, 27/102 (27%) of the

mutations were 187delAG, 17 percent were 5385insC (commonly referred to as 185delAG and 5382insC, respectively), and the remaining mutations were found at less than 4 percent frequency. Founder mutations have been described for different ethnic populations: Ashkenazi Jewish women are ten times more likely than non-Jewish Caucasian women to harbor a 185delAG or 5382insC *BRCA1* mutation, or a 617delT *BRCA2* mutation. (Couch and Weber, 1996; Oddoux *et al.*, 1996; Struewing *et al.*, 1997; Tonin *et al.*, 1995) An Ashkenazi Jewish woman's odds of a deleterious *BRCA1* mutation are more than four fold greater than those for a non-Jewish Caucasian woman. Other *BRCA1/2* founder mutations have been identified in the Netherlands, Belgium, Norway, France, Sweden, Denmark, Scotland, Eastern Europe, Iceland, and in French-Canada. (Bergthorsson *et al.*, 2001; Johannesdottir *et al.*, 1996; Martin and Weber, 2000; Petrij-Bosch *et al.*, 1997; Thorlacius *et al.*, 1996; Tonin *et al.*, 1998)

Laboratory testing

Current recommendations call for screened women with a greater than 10 percent likelihood of having a detectable mutation to undergo testing (Questions 5 and 6). Because of patent restrictions, the only facility legally authorized to perform sequencing for *BRCA1/2* mutations for use in patient care is Myriad Genetic Laboratories (Salt Lake City, UT). This laboratory provides several types of *BRCA1/2* analyses. The following list prices were in effect in April 2003.

- For family members of an index case with a known mutation, a single site analysis is provided for that mutation for \$325 (\$490 for results in 10 days).
- For others, a comprehensive full sequence determination is provided in both forward and reverse directions for \$2,760 (\$4,140 for results in 10 days). Beginning in August 2002, this analysis also includes detection of five large recurrent rearrangements. For patients who have previously tested negative by the comprehensive full sequencing, this panel of rearrangements can be ordered for \$325.
- For Ashkenazi Jewish individuals, testing is provided for three specific mutations (187delAG and 5385insC in *BRCA1*, and 6174delT in *BRCA2*) for \$385 (\$575 for results in 10 days). This type of testing can also be obtained at other licensed clinical laboratories in the United States

Polymorphism studies

In an effort to enhance the utilization of *BRCA1/2* mutation test results, Myriad Genetic Laboratories has collaborated with investigators to analyze recurrent variants of uncertain clinical significance in control populations. Those variants identified in the control population at a frequency of two percent are reclassified to polymorphisms of no clinical significance. Amended reports are issued for all patients whose interpretation changes. This ongoing effort continues to reduce the number of indeterminate test results.

Family member testing for uncertain variants

In order to further characterize variants of uncertain clinical significance, Myriad Genetic Laboratories will test additional relatives of the proband for the specific variant identified, in order to determine whether it is co-segregating with cancer in her or his family. This analysis is offered without charge to either parent of the proband, any relative with invasive breast cancer diagnosed before age 60, and any relative diagnosed with ovarian cancer or male breast cancer at any age. Health care providers are given a report with the test result that outlines the option of

testing additional family members. This report summarizes additional information about the uncertain variant, such as the total number of observations, the most common ancestry of the patients, the number of different deleterious mutations seen in the same gene, and whether the variant does not co-segregate with cancer in at least two families. In general, variants that are observed with deleterious mutations in the same gene, and/or do not consistently co-segregate with cancer, are more likely to be of limited clinical significance than to be deleterious.

Changing the status of a mutation

An uncertain variant can be reclassified as a polymorphism of no clinical significance if:

- it is found in two percent of a control population, or
- it is found in equal or greater percentage of a control population, and it does not co-segregate with disease in multiple families, and/or it has been seen with a deleterious mutation in the same gene, or
- it has been shown to have no clinical significance in an association study.

An uncertain variant can be reclassified as a deleterious mutation if:

- it has been statistically linked to cancer in a family, or
- it is an evolutionarily conserved amino acid and the mutant amino acid is chemically different from the wild-type amino acid.

DISORDER/SETTING

Question 5. Are preliminary screening questions employed?

Summary

- Preliminary screening questions are employed among women in the general population for the following reasons:
 - *BRCA1/2* mutations are uncommon
 - financial costs of gene sequencing are high
 - if an unselected population were to be tested, variants of uncertain clinical significance would be far more frequent than positive test results
 - models have been developed to quantify the probability of identifying a *BRCA1/2* mutation
 - guidelines from professional organizations include the types of screening questions and definitions of risk sufficient to warrant consideration of testing
- The reliability of family history questionnaires for breast cancer has not been adequately validated. Summary estimates are:
 - sensitivity ranging from 83 to 95%
 - specificity ranging from 93 to 99%
 - positive predictive value ranging from 83 to 99%
 - negative predictive value is approximately 98%
- Data on the reliability of family history questionnaires for ovarian cancer are limited.
- The reliability of family history questionnaires for identifying candidates for *BRCA1/2* testing has not been validated in the general population for either breast cancer or ovarian cancer

Rationale for preliminary screening questions

Although breast cancer is relatively common, only a small proportion of such cases (Question 18) is associated with mutations detectable by direct sequencing of the *BRCA1/2* genes. This factor, combined with the high cost of testing, provides the rationale for preliminary screening questions to identify appropriate candidates for genetic predisposition testing (Question 3). The aim of testing for *BRCA1/2* mutations is to prevent the morbidity/mortality associated with breast (or ovarian) cancer by providing information to a population of high-risk individuals, so that informed decisions can be made regarding specific risk-reducing activities (Question 29). The areas queried include personal history of breast and/or ovarian cancer, age at diagnosis, family history of breast and/or ovarian cancer and age(s) at diagnosis, menopausal status, and whether the individual to be tested is Ashkenazi Jewish (Question 3). *BRCA1/2* sequencing is not performed on individuals under 18 years of age except in unusual circumstances, as described by the American Society of Clinical Oncology (ASCO). A statement adopted by ASCO in 1996 recommended that breast/ovarian cancer predisposition testing be offered only in the setting of a "strong family history of cancer or very early age of onset of disease", further defined as at least a 10 percent probability of having a *BRCA1/2* mutation. (1996) This threshold, though based on expert opinion, is arbitrary and subject to professional interpretation.

A caveat of *BRCA1/2* mutation testing is that variants of unknown clinical significance are identified in approximately 13 percent of all samples undergoing full sequencing. (Frank *et al.*, 2002) Assuming that these variants are found in the same proportion of the general population, the number of these indeterminate test results would greatly surpass the number of deleterious mutations, if screening questions were not utilized.

Models used to predict risk for carrying a *BRCA1/2* mutation

BRCA1/2 are autosomal dominant genes, meaning that mutations can be inherited equally from the mother's or father's side of the family. Thus, family history and personal disease history increase the probability of finding a *BRCA1/2* mutation in a woman. A possible hereditary risk of breast/ovarian cancer should be considered, if a family includes two or more women with breast cancer at an early age of onset (usually before age 50) and/or ovarian cancer at any age. (Armstrong *et al.*, 2000; Frank *et al.*, 1998) Race/ethnicity is also a consideration (i.e., the mutation prevalence is known to be increased among Ashkenazi Jewish woman). An older age at diagnosis is associated with a lower risk of finding a *BRCA1/2* mutation.

Models have been developed to determine an individual's *a priori* risk of carrying a *BRCA1/2* mutation or to assess risk of breast cancer. Two models were developed to predict the probability of a *BRCA1* mutation, though neither has been validated. (Berry *et al.*, 1997; Couch *et al.*, 1997) An extended model has subsequently been developed to predict the probability of both *BRCA1* and *BRCA2* mutations. (Parmigiani *et al.*, 1998) This model has been developed into a computer program (BRCAPRO). BRCAPRO incorporates the autosomal dominant Mendelian characteristics of the genes, published prevalence and penetrance of *BRCA1/2* mutations, and Bayesian methods. (Iversen *et al.*, 2000) This program has been validated in a population at high risk for breast and/or ovarian cancer. (Berry *et al.*, 2002; Euhus *et al.*, 2002) Empiric data from *BRCA1/2* mutation testing at Myriad Genetic Laboratories have been used to model the probability that an individual carries a *BRCA1/2* mutation. (Frank *et al.*, 1998; Shattuck-Eidens *et al.*, 1997) Empiric models for predicting breast cancer risk have also been developed. (Claus *et al.*, 1994; Gail *et al.*, 1989; Houlston *et al.*, 1992) Each of the above-listed models has strengths and weaknesses and is appropriate for use in certain settings. These models are reviewed in a recent publication. (Domchek *et al.*, 2003) In addition, other methods are utilized in the clinical setting to assess risk of breast cancer and/or risk of carrying a *BRCA1/2* mutation, including check lists provided by insurers or Myriad Genetic Laboratories. (Mackay, 1997) Women may be placed in different risk categories, depending on the method used to estimate risk. (Domchek *et al.*, 2003; Tischkowitz *et al.*, 2000) Given the current status of these models, it is important to involve an experienced health professional (e.g., a genetic counselor) to interpret risk estimates and provide counseling regarding *BRCA1/2* mutation testing.

An example of data upon which these models are based is depicted in Table 1-2. The odds ratios of carrying a deleterious *BRCA1* mutation are derived from a logistic regression model. (Shattuck-Eidens *et al.*, 1997) According to Table 1-2, each year added to the age at diagnosis decreases the risk by 8%. As evidence of this effect, among a population-based sample of women under 35 years of age with breast cancer, unselected for family history, 6 of 80 (7.5%) had *BRCA1* mutations. (Langston *et al.*, 1996) Similar results were seen in another study, where 13 percent of women with very early onset breast cancer, and without a strong family history, had *BRCA1* mutations. (FitzGerald *et al.*, 1996) Both of these findings are higher than the

expected 4 to 5% of *BRCA1* mutations among women with breast cancer under age 55 in a general population. (Question 18).

Example of computing the risk of carrying a *BRCA1* deleterious mutation

“The log odds (L) of an individual carrying a deleterious mutation is estimated by the following equation: $L = -0.08a + 1.41b + 0.0c + 1.29d + 2.08e + 3.39f + 1.68g + 0.31h + 1.06i + 1.68j$, where a is the age at diagnosis of breast and/or ovarian cancer; b is 1 if a patient is of Ashkenazi descent, 0 otherwise; c is 1 if the patient is diagnosed with unilateral breast cancer but not ovarian cancer, 0 otherwise (coefficient of c in the equation is 0 since this case is used as baseline, and it is included for completeness); d is 1 if the patient is diagnosed with bilateral breast cancer but not ovarian cancer, 0 otherwise; e is 1 if the patient is diagnosed with unilateral breast cancer and with ovarian cancer, 0 otherwise; f is 1 if the patient is diagnosed with bilateral breast cancer and with ovarian cancer, 0 otherwise; g is 1 if the patient is diagnosed with ovarian cancer but not breast cancer, 0 otherwise; h is number of relatives with breast cancer, but not ovarian cancer; i is number of relatives with ovarian cancer, but not breast cancer; and j is number of relatives with breast and ovarian cancer. The intercept was estimated to be 0.” (Shattuck-Eidens *et al.*, 1997) The probability that an individual carries a *BRCA1* mutation is: $p = \exp(L)/[1 + \exp(L)]$

Woman with a personal history of cancer Using the model described above, a 50 year old woman diagnosed with ovarian cancer and who has one relative with breast cancer is computed to have an 11.8 percent probability of having a deleterious *BRCA1* mutation. ($-2.01 = -0.08[50] + 1.68[1] + 0.31[1]$ and $0.118 = \exp[-2.01]/[1 + \exp(L)]$)

Woman without a personal history of cancer A woman with no personal history of breast or ovarian cancer who has 3 relatives with breast cancer and 1 relative with ovarian cancer is computed to have an 88 percent probability of having a deleterious *BRCA1* mutation. ($1.99 = 0.31[3] + 1.06[1]$ and $0.88 = \exp[1.99]/[1 + \exp(L)]$)

Table 1-2. Risk factors and Odds Ratios for Carrying a *BRCA1* Deleterious Mutation

Risk Factor	Odds Ratio (95% CI)
Bilateral breast cancer with ovarian cancer	10.9 (5.4 to 21.8)
Unilateral breast cancer with ovarian cancer	8.0 (5.0 to 12.9)
Ovarian cancer but not breast cancer	5.4 (3.2 to 9.0)
Each relative with breast and ovarian cancer	5.3 (3.4 to 8.5)
Ashkenazi descent	4.0 (2.9 to 5.8)
Bilateral breast cancer but not ovarian cancer	3.7 (2.5 to 5.3)
Each relative with ovarian cancer but not breast cancer	2.9 (2.2 to 3.7)
Each relative with breast cancer but not ovarian cancer	1.4 (1.2 to 1.6)
Proband's age at diagnosis of breast and/or ovarian cancer	0.82*

From (Shattuck-Eidens *et al.*, 1997)

* Each year added to the age at diagnosis decreases the risk by 8%

Gap in Knowledge: Validation for specific models predicting *BRCA1/2* risk.

Although some studies have compared the risks predicted by different models, no study has compared the predicted risk for specific selected family histories versus the observed proportion of positive mutation studies found by Myriad Genetic Laboratories.

Accuracy of family history information – breast cancer

Accuracy of family history information for breast cancer has been investigated and is summarized in Table 1-3. Four of the six studies included only breast cancer patients or women who had been referred to a cancer genetics clinic. Accuracy of family history of breast cancer in the general population was assessed in the remaining two studies through the use of controls. These data are of limited use because sensitivity and specificity were not assessed in one study, and personal interview data were compared with those in a population database in the remaining study. This methodology is likely to underestimate sensitivity (the individual does indeed have cancer, but is not included in the registry). It would also likely result in the specificity being overestimated (some individuals not reporting cancer and not in the registry, do indeed have cancer, but were not included in the registry). Incorrect matching could result in over- or under-estimation of sensitivity and specificity. A single study estimated sensitivity and specificity by verifying reported cases of breast cancer with either pathology reports/clinical records, self-reports from the affected and non-affected relatives of the proband, or death certificates. Sensitivity refers to the proportion of reported cases of breast cancer among all cases. Sensitivity reported in two studies ranges from 83 to 95 percent. Specificity refers to the proportion of women reported not to have breast cancer among all those who do not have breast cancer. Specificity reported in three studies ranges from 93 to 99 percent. Positive predictive value is the proportion of women confirmed to have breast cancer among all those reported to have breast cancer. The positive predictive values ranged from 83 to 99 percent. Negative predictive value is the proportion of women without breast cancer among all those reported to not have breast cancer. This was assessed by studies 4 through 6 only. These studies reported a negative predictive value of approximately 98 percent. Figure 1-1 shows the impact of using a family history questionnaire in the screening process for identifying women at increased risk for carrying *BRCA1/2* mutations. The following caveat should be considered. These estimates are based on the total number of reported cases, not on the number of individuals reporting cases. For example, if 35 women each correctly reported one first-degree relative with breast cancer but collectively failed to report two other cases, the sensitivity would be 95 percent (35/37). If these same 35 women each correctly reported two first-degree relatives with breast cancer but collectively failed to report 10 cases, then the sensitivity would be 88 percent (70/80).

Table 1-3. A Summary of Studies Reporting Validation of First-degree Family History of Breast Cancer

Reference	<u>Sensitivity</u>		<u>Specificity</u>		<u>Positive Predictive Value</u>		<u>Negative Predictive Value</u>	
	Number	(%)	Number	(%)	Number	(%)	Number	(%)
1	N/A	N/A	N/A	N/A	78/83	94.0	N/A	N/A
2	N/A	N/A	N/A	N/A	107/115	93.0	N/A	N/A
3	N/A	N/A	100/101	99.0	166/167	99.4	N/A	N/A
4	188/197	95.4	850/873	97.4	188/211	89.1	850/859	98.9
5	53/58	91.4	364/370	98.4	54/60	90	364/369	98.6
6	29/35	82.9	274/296	92.6	29/51	83.0	274/280	97.9

N/A = Not Available

Reference: 1 (Love *et al.*, 1985), 2 (Parent *et al.*, 1995), 3 (Theis *et al.*, 1994), 4 (Ziogas and Anton-Culver, 2003), 5 (Anton-Culver *et al.*, 1996), 6 (Kerber and Slattery, 1997)

Study 1. Wisconsin: Love *et al.* One hundred and twenty-one self-referred patients visiting a cancer prevention clinic at the University of Wisconsin provided a detailed history of cancers occurring in first-, second-, and third-degree relatives. Verification of a positive cancer family history was done by reviewing pathology and operative reports, hospital admission and discharge summaries, death certificates, and autopsy reports. Verification of negative cancer family history was not performed, thus sensitivity and specificity could not be calculated. Participants were correct in 91 percent (143/157, 95% CI 85.5-95.0%) of the cases for all relatives in whom they reported breast as the primary site, 94 percent (78/83, 95% CI 86.5-98.0%) of the cases in first-degree relatives, and 88 percent (65/74, 95% CI 78.2-94.3%) of the cases in second- and third-degree relatives.

Study 2. Canada: Parent *et al.* reported 414 French-Canadian women recently diagnosed with primary breast cancer and 429 age-matched population-based controls, all of whom provided information on relatives affected with any type of cancer. A total of 105 women (68 cases and 37 controls) reported a history of breast cancer in at least one first-degree relative. The accuracy was confirmed via pathological records. Cases correctly reported 74 out of 81 first-degree relatives with breast cancer (positive predictive value of 89 percent - 95% CI 83.0-96.4%), while controls were correct in 33 out of 34 (positive predictive value of 97 percent - 95% CI 84.7-99.9%). The overall positive predictive value was 93 percent (95% CI 86.8-97.0%). Sensitivity and specificity were not assessed. Overall, 11 percent of reports contained errors of more than five years from the real age at diagnosis.

Study 3. Canada: Theis *et al.* reported on 165 breast cancer patients in a Toronto hospital who provided family cancer histories in first- and second-degree relatives. Of the 186 reported cases of breast cancer in first-degree relatives, 167 records were obtained. Confirmation of this diagnosis was made in 166 cases (positive predictive value of 99.4 percent - 95% CI 96.7-99.99). In second-degree relatives, 33 of 39 reported breast cancer cases were correctly identified (positive predictive value of 84.6% - 95% CI 69.5-94.1). Specificity was assessed by randomly sampling 100 first-degree relatives reported as cancer-free. None of these relatives appeared in

the Ontario cancer registry and were assumed to not have cancer (specificity = 99 percent, 95% CI 94.6-99.98%). Data for ovarian cancer were sparse. Only two cases were reported and had records obtained. Both cases were confirmed.

Study 4. California: Ziogas *et al.* studied 670 cases of breast cancer in Orange County, California. Of these cases, 638 were population-based and 32 were clinic-based. Eight male breast cancer cases are included. Validation of family history of breast cancer was done by comparing data obtained by personal interview with pathology reports (474), self-reports (777), or death certificates (2142) on the relatives. The sensitivity of the case individuals' report of their first-degree relatives' histories of breast cancer was 95.4 percent (95 percent CI 92.6-98.3%). The specificity was 97.4 percent (95 percent CI 96.4-98.4). Of the 211 cases of breast cancer reported in the interviews, 188 were confirmed by one of the reference standards (positive predictive value of 89.1 percent (95 percent CI 84.1-93.0%). Predictors of false negative reports of breast cancer were age greater than 70 years, and reports of cancer in 2nd and 3rd degree relatives. Predictors of false positive reports were not broken down by proband cancer type. For all cancers combined, false positives were more likely to be reported by males and clinic-based probands

Study 5. California: Anton-Culver *et al.* validated family history of breast cancer reported by 359 breast cancer probands in Orange County with data contained in a cancer registry. This cancer registry is one of the ten in the California Cancer Reporting System and meets all reporting requirements of the Surveillance, Epidemiology, and End Results program of the National Cancer Institute. Ascertainment of cases has been shown to be 97 percent complete. Using the cancer registry as the standard, the sensitivity of the personal interview data on breast cancer history in mothers and sisters was 91.4% (95% CI 81.0-97.1). The specificity was 98.4% (95% CI 96.5-99.4). Of the 59 cases of breast cancer reported in the interview, 53 were confirmed by the registry (PPV=89.8%, 95% CI 79.2-96.5).

Study 6. Utah: Kerber and Slattery reported on 881 cases and controls from the Diet, Activity, and Reproduction in Colon Cancer study. (Kerber and Slattery, 1997) Of these, 331 (37.6%) could be linked to the Utah Population Database (UPDB), which contains genealogic and cancer information. The proportion of the Utah population in the UPDB falls from about 60 percent between 1920 and 1934 to just over 30 percent by 1960. A comparison was made between self-reporting of family history of breast cancer and data in the UPDB. Sensitivity and specificity for first-degree relative reporting of breast cancer were 82.9 percent (95% CI 66.4-93.4%) and 92.6 percent (95% CI 89.0-95.3%), respectively. Sensitivity and specificity were slightly higher in cases (84.6 and 95.5%, respectively) than in controls (81.8 and 90.8%, respectively). Of the 51 cases of breast cancer reported by participants, 29 were confirmed by the UPDB (positive predictive value of 56.9 percent, 95% CI 42.2-70.6). The positive predictive value for reporting breast cancer cases was 68.7 percent in cases and 51.4 percent in controls.

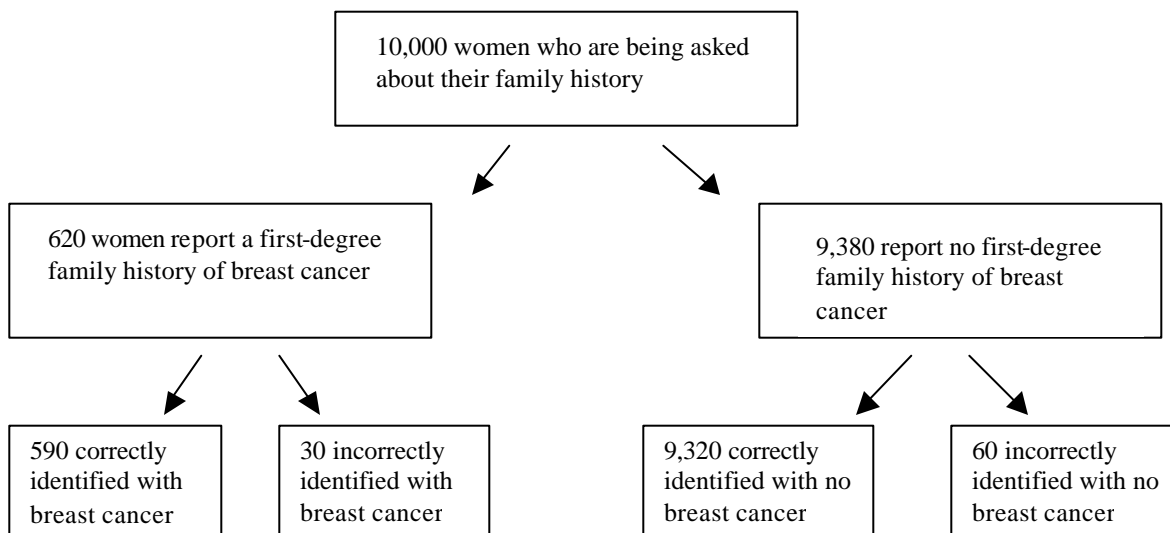
Studies not Included: Another study utilized family history information from 408 confirmed family cancer case notes in two regional cancer genetics departments. Information from cancer registries, death certificates, hospital notes, and histopathological records were used to confirm reported family history of breast cancer. (Douglas *et al.*, 1999) The accuracy of breast cancer

family history was 94 percent. Verification of negative history was not reported. Because no raw numbers or other data were given, this study could not be combined with those in Table 1-2.

Two studies have reported the validation of a personal history of cancers. In the first, the validity of self-reported breast cancer diagnosis (personal history) was compared with population-based cancer registry data in 65,582 men and women aged 39 to 96 years, who were participants in the Cancer Prevention Study II Nutrition survey. (Bergmann *et al.*, 1998) Sensitivity was 91 percent (779/853, 95 percent CI 89.2-93.1%) and specificity was 99.8 percent (64,587/64,729, 95 percent CI 99.7-99.8%) in breast cancer personal history reporting. Positive predictive value was 84.6 percent (95 percent CI 82.1-86.9%). The second study validated self-reported cancers from the California Teachers Study with the California Cancer Registry. (Parikh-Patel *et al.*, 2003) Of the 121,196 teachers included in the study, 3,103 were found in the registry to have breast cancer. Only 2,991 of these teachers reported a personal history of breast cancer (sensitivity = 96.4%, 95% CI 95.6-97.5). Among the 118,093 teachers who did not have a breast cancer found in the registry, 115,849 reported a negative personal history (specificity = 98.1%, 95% CI 98.1-98.2); the remaining 2,244 falsely reported a positive personal history of breast cancer. The positive predictive value was 57.1 percent (95 percent CI 55.8-58.5) and negative predictive value was 99.9 percent. The only statistically significant predictor of accurate reporting was age of less than 45 years. An additional statistically significant predictor of false negative reports was *in situ* stage of cancer at diagnosis (OR = 8.22, 95 percent CI 5.4-12.5).

Gap in Knowledge: Reliability of Sensitivity and Specificity of Family History Questionnaires. Data provided in Table 1-3 show heterogeneity in estimates of sensitivity and specificity. Data from studies 4 and 5 are based on the assumption that cancer registries are 100% accurate. This is unlikely to be true. Incomplete ascertainment will likely cause sensitivity to be underestimated (the individual does indeed have cancer, but is not included in the registry). It would also likely result in the specificity being overestimated (some individuals not reporting cancer and not in the registry, do indeed have cancer, but were not included in the registry). Incorrect matching could result in over- or underestimation of sensitivity and specificity.

Figure 1-1. Predicted Screening Performance of a Protocol Using Family History of Breast Cancer for Identifying Women at Increased Risk for Carrying *BRCA1/2* Mutations.



Assumptions: Prevalence of family history is 6.2% (Question 19, Appendix A)
Sensitivity of family history questionnaire is 91%.

Accuracy of family history information – Ovarian cancer

Limited data are available regarding the validation of ovarian cancer family history. Validation of family history of ovarian cancer was done by comparing data obtained from personal interview with pathology reports, self-reports, or death certificates on the relatives. (Ziogas and Anton-Culver, 2003) Sensitivity and specificity for first-degree relative reporting of ovarian cancer were 83.3 percent (95 percent CI, 68.6-93.0%) and 98.9 percent (95 percent CI, 98.1-99.5%), respectively. The positive predictive value was 76.1 percent (95 percent CI, 61.2-87.4%). Self-reporting of family history of ovarian cancer was compared to genealogic and cancer information in the Utah Population Database. (Kerber and Slattery, 1997) Sensitivity and specificity for first-degree relative reporting of ovarian cancer were 60 percent (95 percent CI, 14.7-94.7%) and 97.6 percent (95 percent CI, 95.2-98.9%), respectively. The positive predictive value was 27.3 percent (95 percent CI, 6.0-61.0%). A study in the UK utilized information from cancer registries, death certificates, hospital notes, and histopathological records to confirm reported family history of ovarian cancer. (Douglas *et al.*, 1999) The positive predictive value of ovarian cancer family history was 83 percent. Verification of negative history was not reported.

DISORDER/SETTING

Question 6. Is it a stand-alone test or one of a series of tests?

BRCA1/2 mutation testing is the second of two tests in a series. Screening questions pertaining to personal and family history of breast/ovarian cancer, age at diagnosis, ethnicity, and the woman's age are used as the first step in assessing a patient's risk for breast cancer. If the responses to these questions confer a 10 percent or higher risk of carrying a *BRCA1/2* mutation, then DNA analysis for breast/ovarian cancer predisposition is the second test of this series (see Question 5 for risk modeling). In some instances, if a single- or multi-site analysis is negative for a mutation, comprehensive full-gene sequencing may be done as a reflexive test. Question 5 lists the reasons for why a preliminary screening question is necessary. About half of the women with a *BRCA1/2* mutation will have a positive family history (Question 18 and 19).

DISORDER/SETTING

Question 7. If it is part of a series of screening tests, are all tests performed in all instances (parallel) or are some tests performed only on the basis of other results (series)?

Breast/ovarian cancer predisposition testing for *BRCA1/2* mutations is usually performed when family history screening questions provide an indication (10 percent or greater risk of carrying a mutation - Question 5). Thus, the screening questions and DNA tests are done in series. If a single- or multi-site analysis is negative for a mutation, full gene sequencing can be done as a reflexive test.

References

1996. Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility, Adopted on February 20, 1996. *J Clin Oncol* **14**(5):1730-6; discussion 1737-40.
1999. Genetic susceptibility to breast and ovarian cancer: assessment, counseling and testing guidelines, American College of Medical Genetics Foundation.
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.
2002. Breast Cancer Fact Sheet, American Cancer Society.
2003. American Society of Clinical Oncology Policy Statement Update: Genetic Testing for Cancer Susceptibility. *J Clin Oncol* **11**:11.
- Anton-Culver H, Kurosaki T, Taylor TH, Gildea M, Brunner D, and Bringman D. 1996. Validation of family history of breast cancer and identification of the BRCA1 and other syndromes using a population-based cancer registry. *Genet Epidemiol* **13**(2):193-205.
- Antoniou AC, Gayther SA, Stratton JF, Ponder BA, and Easton DF. 2000. Risk models for familial ovarian and breast cancer. *Genet Epidemiol* **18**(2):173-90.
- Antoniou AC, Pharoah PD, McMullan G, Day NE, Stratton MR, Peto J, Ponder BJ, and Easton DF. 2002. A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. *Br J Cancer* **86**(1):76-83.
- Armstrong K, Eisen A, and Weber B. 2000. Assessing the risk of breast cancer. *N Engl J Med* **342**(8):564-71.
- Bergmann MM, Calle EE, Mervis CA, Miracle-McMahill HL, Thun MJ, and Heath CW. 1998. Validity of self-reported cancers in a prospective cohort study in comparison with data from state cancer registries. *Am J Epidemiol* **147**(6):556-62.
- Berghthorsson JT, Ejlersen B, Olsen JH, Borg A, Nielsen KV, Barkardottir RB, Klausen S, Mouridsen HT, Winther K, Fenger K, Niebuhr A, Harboe TL, and Niebuhr E. 2001. BRCA1 and BRCA2 mutation status and cancer family history of Danish women affected with multifocal or bilateral breast cancer at a young age. *J Med Genet* **38**(6):361-8.
- Berry DA, Iversen ES, Jr., Gudbjartsson DF, Hiller EH, Garber JE, Peshkin BN, Lerman C, Watson P, Lynch HT, Hilsenbeck SG, Rubinstein WS, Hughes KS, and Parmigiani G. 2002. BRCAPRO validation, sensitivity of genetic testing of BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes. *J Clin Oncol* **20**(11):2701-12.
- Berry DA, Parmigiani G, Sanchez J, Schildkraut JM, and Winer EP. 1997. Probability of carrying a mutation of breast-ovarian cancer gene BRCA1 based on family history. *J Natl Cancer Inst* **89**(3):227-37.
- Brose MS, Rebbeck TR, Calzone KA, Stopfer JE, Nathanson KL, and Weber BL. 2002. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. *J Natl Cancer Inst* **94**(18):1365-72.
- Brown ML, Lipscomb J, and Snyder C. 2001. The burden of illness of cancer: economic cost and quality of life. *Annu Rev Public Health* **22**:91-113.
- Claus EB, Risch N, and Thompson WD. 1994. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer* **73**(3):643-51.
- Couch FJ, DeShano ML, Blackwood MA, Calzone K, Stopfer J, Campeau L, Ganguly A, Rebbeck T, and Weber BL. 1997. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. *N Engl J Med* **336**(20):1409-15.

- Couch FJ, and Weber BL. 1996. Mutations and polymorphisms in the familial early-onset breast cancer (BRCA1) gene. Breast Cancer Information Core. *Hum Mutat* **8**(1):8-18.
- Domchek SM, Eisen A, Calzone K, Stopfer J, Blackwood A, and Weber BL. 2003. Application of breast cancer risk prediction models in clinical practice. *J Clin Oncol* **21**(4):593-601.
- Douglas FS, O'Dair LC, Robinson M, Evans DG, and Lynch SA. 1999. The accuracy of diagnoses as reported in families with cancer: a retrospective study. *J Med Genet* **36**(4):309-12.
- Easton DF, Ford D, and Bishop DT. 1995. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Am J Hum Genet* **56**(1):265-71.
- Euhus DM, Smith KC, Robinson L, Stucky A, Olopade OI, Cummings S, Garber JE, Chittenden A, Mills GB, Rieger P, Esserman L, Crawford B, Hughes KS, Roche CA, Ganz PA, Seldon J, Fabian CJ, Klemp J, and Tomlinson G. 2002. Pretest prediction of BRCA1 or BRCA2 mutation by risk counselors and the computer model BRCAPRO. *J Natl Cancer Inst* **94**(11):844-51.
- FitzGerald MG, MacDonald DJ, Krainer M, Hoover I, O'Neil E, Unsal H, Silva-Arrieto S, Finkelstein DM, Beer-Romero P, Englert C, Sgroi DC, Smith BL, Younger JW, Garber JE, Duda RB, Mayzel KA, Isselbacher KJ, Friend SH, and Haber DA. 1996. Germ-line BRCA1 mutations in Jewish and non-Jewish women with early-onset breast cancer. *N Engl J Med* **334**(3):143-9.
- Fodor FH, Weston A, Bleiweiss IJ, McCurdy LD, Walsh MM, Tartter PI, Brower ST, and Eng CM. 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 DF, Bishop DT, Narod SA, and Goldgar DE. 1994. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Lancet* **343**(8899):692-5.
- Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, Bishop DT, Weber B, Lenoir G, Chang-Claude J, Sobol H, Teare MD, Struewing J, Arason A, Scherneck S, Peto J, Rebbeck TR, Tonin P, Neuhausen S, Barkardottir R, Eyfjord J, Lynch H, Ponder BA, Gayther SA, 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 TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, Gumpfer KL, Scholl T, Tavtigian SV, Pruss DR, and Critchfield GC. 2002. Clinical Characteristics of Individuals With Germline Mutations in BRCA1 and BRCA2: Analysis of 10,000 Individuals. *J Clin Oncol* **20**(6):1480-90.
- Frank TS, Manley SA, Olopade OI, Cummings S, Garber JE, Bernhardt B, Antman K, Russo D, Wood ME, Mullineau L, Isaacs C, Peshkin B, Buys S, Venne V, Rowley PT, Loader S, Offit K, Robson M, Hampel H, Brenner D, Winer EP, Clark S, Weber B, Strong LC, Thomas A, and et al. 1998. Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family history and ovarian cancer risk. *J Clin Oncol* **16**(7):2417-25.
- Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, and Mulvihill JJ. 1989. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* **81**(24):1879-86.
- Holt JT, Thompson ME, Szabo C, Robinson-Benion C, Arteaga CL, King MC, and Jensen RA. 1996. Growth retardation and tumour inhibition by BRCA1. *Nat Genet* **12**(3):298-302.
- Hopper JL, Southey MC, Dite GS, Jolley DJ, Giles GG, McCredie MR, Easton DF, and Venter DJ. 1999. Population-based estimate of the average age-specific cumulative risk of breast

- cancer for a defined set of protein-truncating mutations in BRCA1 and BRCA2. Australian Breast Cancer Family Study. *Cancer Epidemiol Biomarkers Prev* **8**(9):741-7.
- Houlston RS, McCarter E, Parbhoo S, Scurr JH, and Slack J. 1992. Family history and risk of breast cancer. *J Med Genet* **29**(3):154-7.
- Iversen ES, Parmigiani G, and Berry DA. 2000. Genetic susceptibility and survival: Application to breast cancer. *J Am Stat Assoc* **95**:28-42.
- Johannesdottir G, Gudmundsson J, Bergthorsson JT, Arason A, Agnarsson BA, Eiriksdottir G, Johannsson OT, Borg A, Ingvarsson S, Easton DF, Egilsson V, and Barkardottir RB. 1996. High prevalence of the 999del5 mutation in icelandic breast and ovarian cancer patients. *Cancer Res* **56**(16):3663-5.
- Kerber RA, and Slattery ML. 1997. Comparison of self-reported and database-linked family history of cancer data in a case-control study. *Am J Epidemiol* **146**(3):244-8.
- Langston AA, Malone KE, Thompson JD, Daling JR, and Ostrander EA. 1996. BRCA1 mutations in a population-based sample of young women with breast cancer. *N Engl J Med* **334**(3):137-42.
- Love RR, Evans AM, and Josten DM. 1985. The accuracy of patient reports of a family history of cancer. *J Chronic Dis* **38**(4):289-93.
- Mackay J. 1997. The role of genetic testing in breast cancer by the year 2000. *Cancer Treat Rev* **23 Suppl 1**:S13-22.
- Martin AM, and Weber BL. 2000. Genetic and hormonal risk factors in breast cancer. *J Natl Cancer Inst* **92**(14):1126-35.
- Montagna M, Santacatterina M, Torri A, Menin C, Zullato D, Chieco-Bianchi L, and D'Andrea E. 1999. Identification of a 3 kb Alu-mediated BRCA1 gene rearrangement in two breast/ovarian cancer families. *Oncogene* **18**(28):4160-5.
- 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 JS, and Narod SA. 2000. BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. *Am J Hum Genet* **66**(4):1259-72.
- Nordling M, Karlsson P, Wahlstrom J, Engwall Y, Wallgren A, and Martinsson T. 1998. A large deletion disrupts the exon 3 transcription activation domain of the BRCA2 gene in a breast/ovarian cancer family. *Cancer Res* **58**(7):1372-5.
- Oddoux C, Struewing JP, Clayton CM, Neuhausen S, Brody LC, 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**:188-90.
- Parent ME, Ghadirian P, Lacroix A, and Perret C. 1995. Accuracy of reports of familial breast cancer in a case-control series. *Epidemiology* **6**(2):184-6.
- Parikh-Patel A, Allen M, and Wright WE. 2003. Validation of Self-reported Cancers in the California Teachers Study. *Am J Epidemiol* **157**(6):539-45.
- Parmigiani G, Berry D, and Aguilar O. 1998. Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. *Am J Hum Genet* **62**(1):145-58.
- Patel KJ, Yu VP, Lee H, Corcoran A, Thistlethwaite FC, Evans MJ, Colledge WH, Friedman LS, Ponder BA, and Venkitaraman AR. 1998. Involvement of Brca2 in DNA repair. *Mol Cell* **1**(3):347-57.
- Payne SR, Newman B, and King MC. 2000. Complex germline rearrangement of BRCA1 associated with breast and ovarian cancer. *Genes Chromosomes Cancer* **29**(1):58-62.

- Petrij-Bosch A, Peelen T, van Vliet M, van Eijk R, Olmer R, Drusedau M, Hogervorst FB, Hageman S, Arts PJ, Ligtenberg MJ, Meijers-Heijboer H, Klijn JG, Vasen HF, Cornelisse CJ, van't Veer LJ, Bakker E, van Ommen GJ, and Devilee P. 1997. BRCA1 genomic deletions are major founder mutations in Dutch breast cancer patients. *Nat Genet* **17**(3):341-5.
- Puget N, Stoppa-Lyonnet D, Sinilnikova OM, Pages S, Lynch HT, Lenoir GM, and Mazoyer S. 1999. Screening for germ-line rearrangements and regulatory mutations in BRCA1 led to the identification of four new deletions. *Cancer Res* **59**(2):455-61.
- Puget N, Torchard D, Serova-Sinilnikova OM, Lynch HT, Feunteun J, Lenoir GM, and Mazoyer S. 1997. A 1-kb Alu-mediated germ-line deletion removing BRCA1 exon 17. *Cancer Res* **57**(5):828-31.
- Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, and Edwards BKe, 2002, SEER Cancer Statistics Review, 1973-1999, National Cancer Institute, Bethesda, MD.
- Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Kwan E, Jack E, Vesprini DJ, Kuperstein G, Abrahamson JL, Fan I, Wong B, and Narod SA. 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.
- Rohlfes EM, Puget N, Graham ML, Weber BL, Garber JE, Skrzynia C, Halperin JL, Lenoir GM, Silverman LM, and Mazoyer S. 2000. An Alu-mediated 7.1 kb deletion of BRCA1 exons 8 and 9 in breast and ovarian cancer families that results in alternative splicing of exon 10. *Genes Chromosomes Cancer* **28**(3):300-7.
- Satagopan JM, Offit K, Foulkes W, Robson ME, Wacholder S, Eng CM, Karp SE, and Begg CB. 2001. The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Cancer Epidemiol Biomarkers Prev* **10**(5):467-73.
- Schubert EL, Lee MK, Mefford HC, Argonza RH, Morrow JE, Hull J, Dann JL, and King MC. 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 DM. 1997. Association of BRCA1 with Rad51 in mitotic and meiotic cells. *Cell* **88**(2):265-75.
- Scully R, and Livingston DM. 2000. In search of the tumour-suppressor functions of BRCA1 and BRCA2. *Nature* **408**(6811):429-32.
- Sharan SK, Morimatsu M, Albrecht U, Lim DS, Regel E, Dinh C, Sands A, Eichele G, Hasty P, and Bradley A. 1997. Embryonic lethality and radiation hypersensitivity mediated by Rad51 in mice lacking Brca2. *Nature* **386**(6627):804-10.
- Shattuck-Eidens D, Oliphant A, McClure M, McBride C, Gupte J, Rubano T, Pruss D, Tavtigian SV, Teng DH, Adey N, Staebell M, Gumpfer K, Lundstrom R, Hulick M, Kelly M, Holmen J, Lingenfelter B, Manley S, Fujimura F, Luce M, Ward B, Cannon-Albright L, Steele L, Offit K, Thomas A, and et al. 1997. BRCA1 sequence analysis in women at high risk for susceptibility mutations. Risk factor analysis and implications for genetic testing. *JAMA* **278**(15):1242-50.
- Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman MM, Brody LC, and Tucker MA. 1997. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* **336**(20):1401-8.

- Swensen J, Hoffman M, Skolnick MH, and Neuhausen SL. 1997. Identification of a 14 kb deletion involving the promoter region of BRCA1 in a breast cancer family. *Hum Mol Genet* **6**(9):1513-7.
- Theis B, Boyd N, Lockwood G, and Tritchler D. 1994. Accuracy of family cancer history in breast cancer patients. *Eur J Cancer Prev* **3**(4):321-7.
- Thorlacius S, Olafsdottir G, Tryggvadottir L, Neuhausen S, Jonasson JG, Tavgigian SV, Tulinius H, Ogmundsdottir HM, and Eyfjord JE. 1996. A single BRCA2 mutation in male and female breast cancer families from Iceland with varied cancer phenotypes. *Nat Genet* **13**(1):117-9.
- Thorlacius S, Struewing JP, Hartge P, Olafsdottir GH, Sigvaldason H, Tryggvadottir L, Wacholder S, Tulinius H, and Eyfjord JE. 1998. Population-based study of risk of breast cancer in carriers of BRCA2 mutation. *Lancet* **352**(9137):1337-9.
- Tischkowitz M, Wheeler D, France E, Chapman C, Lucassen A, Sampson J, Harper P, Krawczak M, and Gray J. 2000. A comparison of methods currently used in clinical practice to estimate familial breast cancer risks. *Ann Oncol* **11**(4):451-4.
- Tonin P, Serova O, Lenoir G, Lynch H, Durocher F, Simard J, Morgan K, and Narod S. 1995. BRCA1 mutations in Ashkenazi Jewish women. *Am J Hum Genet* **57**:189.
- Tonin PN, Mes-Masson AM, Futreal PA, Morgan K, Mahon M, Foulkes WD, Cole DE, Provencher D, Ghadirian P, and Narod SA. 1998. Founder BRCA1 and BRCA2 mutations in French Canadian breast and ovarian cancer families. *Am J Hum Genet* **63**(5):1341-51.
- Unger MA, Nathanson KL, Calzone K, Antin-Ozerkis D, Shih HA, Martin AM, Lenoir GM, Mazoyer S, and Weber BL. 2000. Screening for genomic rearrangements in families with breast and ovarian cancer identifies BRCA1 mutations previously missed by conformation-sensitive gel electrophoresis or sequencing. *Am J Hum Genet* **67**(4):841-50.
- 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 JS, 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.
- Zhong Q, Chen CF, Li S, Chen Y, Wang CC, Xiao J, Chen PL, Sharp ZD, and Lee WH. 1999. Association of BRCA1 with the hRad50-hMre11-p95 complex and the DNA damage response. *Science* **285**(5428):747-50.
- Ziogas A, and Anton-Culver H. 2003. Validation of family history data in cancer family registries. *Am J Prev Med* **24**(2):190-8.