FAMILY HISTORY OF BREAST/OVARIAN CANCER AND REFERRAL CRITERIA FOR A BRCA1 TESTING PROGRAM

by

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Abstract

Background: Breast and ovarian cancer can arise from genetic predisposition and environmental (i.e., non-genetic) exposures. Family history is the basis for many referrals to a genetic testing program, but family history is expected to depend on a person's age and family structure, the disease risk that is associated with BRCA1 and the sporadic disease risk in the population. Population-based research on BRCA1 is difficult to conduct because of logistic, financial and ethical issues.

Methods: The first phase of the study created a simulation model of BRCA1 and breast/ovarian cancer in a family. The next phase analyzed the effects of age and pedigree size on the relationship between family history and whether someone carried a BRCA1 mutation, and examined the stability of results in relation to estimates of the hereditary and overall rate of breast/ovarian cancer in the population. The third phase combined the simulation results with BC demographic information to examine the implications for a provincial genetic testing program.

Results: The predictive accuracy of family history was strongly dependent on a person's age and pedigree size. The stability of these results also depended on the risk associated with a BRCA1 mutation and the population rate of disease in the model. If 0.12% of people in BC carry a mutation, a province-wide testing program for persons 20 to 69 years of age is estimated to identify 62% of them. About 4% of people who receive

testing will be BRCA1 mutation carriers. Both percentages depend on referral criteria for the program.

Conclusions: The results of these analyses are based on assumptions and observations in other populations. The corresponding information for the British Columbia population is not known. Any criteria that restrict referral to a BRCA1 testing program will exclude some mutation carriers in the population. The part of the population most likely to be affected is young people with small families.

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Acknowledgments

I've developed a love of live opera during the last decade. I like its scale: the dramatic themes, the overdone acting, the dominating sets and the ridiculous stories. There's beautiful music and singing too. It's a lot like graduate school.

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Chapter 1: Introduction

1.1 Breast/ovarian cancer, BRCA1 and family history of disease

More than 2,900 women in British Columbia (BC) were diagnosed with breast or ovarian cancer during the year 2000 (NCIC 2000). Although the incidence of breast cancer is higher than that of ovarian cancer, the latter is more likely to be fatal. There were 28 deaths from breast cancer for every 100 cases diagnosed in 2000 and 60 deaths for every 100 cases of ovarian cancer (NCIC 2000). Cases of breast and ovarian cancer often cluster within a family and have several risk factors in common. In this thesis, the epidemiology of these conditions in women will be considered that of a single disease: breast/ovarian cancer. Unless stated otherwise, breast cancer in men is not considered.

The BRCA1 gene is located on chromosome 17. It is comprised of 23 coding regions that produce a 190kDa protein with 1863 amino acids. The function of BRCA1 is not fully understood, although some mutations are associated with an increased incidence of certain cancers. (Some mutations, particularly those that do not determine an amino acid in the BRCA1 protein, might not affect cancer risk.) A germline genetic mutation is one that is inherited at conception and therefore present in nearly every cell of the body. Someone with a germline BRCA1 mutation is referred to as a carrier. Early studies suggested germline mutations in breast/ovarian cancer susceptibility genes were responsible for 5-10% of these cancers (Claus et al 1996). More recent estimates suggest that less than 3% of breast/ovarian cases are due to BRCA1, and that the percentages for breast and ovarian cancer cases are not necessarily the same (e.g., Whittemore et al 1997, Peto et al 1999, Anton-Culver et al 2000). The exact

proportion of breast/ovarian cases that is due to BRCA1 mutations is unknown and will vary between populations and time periods. If someone has a germline mutation, it is likely to be carried by one of their parents, half of their siblings, a quarter of their aunts and uncles, and one of their grandparents. Because a BRCA1 mutation increases breast/ovarian cancer risk, relatives of mutation carriers often have the disease.

Of course, breast and ovarian cancer can occur for reasons entirely unrelated to BRCA1. In this thesis, cases of breast/ovarian cancer due to germline BRCA1 mutations are called *hereditary* and the remaining cases are called *sporadic*. Note that sporadic disease can occur in women with BRCA1 mutations, and that cancer due to inherited genetic factors other than BRCA1 (e.g., BRCA2) are considered here as sporadic. A family's history of disease can include both hereditary and sporadic cases of cancer.

At a familial breast or ovarian cancer clinic, there is evidence for each patient that he or she carries a BRCA1 mutation prior to testing. This is not true for BRCA1 carriers in the general population, and carriers at a high-risk clinic are not representative of carriers in general. In the Hereditary Cancer Program (HCP) at the BC Cancer Agency (BCCA), genetic counselors determine the likelihood that patients carry a mutation and their eligibility for genetic testing. Family history is the basis on which physicians refer most patients to the program. In this thesis, principal interest lies in referral criteria for a population-based program like the HCP. The ability to identify people who carry BRCA1 mutations can be evaluated according to the sensitivity, specificity and post-test likelihoods that are associated with family history. These parameters are likely to be affected by the definition of family history, a person's age and family structure, the disease risk that is associated with BRCA1 and the overall disease risk in the population.

1.2 Computer simulations

Conducting epidemiological research on BRCA1 is difficult. In most populations, less than 1% of people are expected to carry a BRCA1 mutation and therefore population-based studies require a very large sample. Current practice also requires that a person receive genetic counseling before testing, and again when he or she is given the results. This makes research both expensive and time-consuming. Several studies have considered smaller samples from clinics for people with a high risk of developing disease or carrying some form of genetic susceptibility. The results of these studies cannot be extended to the general population. In particular, few men and few women without a family history attend such clinics. Other problems are that self-reported family histories can be inaccurate and difficult to verify, and the presence of germline BRCA1 mutations is difficult to determine precisely. These issues aside, many people decline participation in genetic research because of ethical concerns (e.g., loss of privacy).

Computer simulation models attempt to mimic phenomena and the relationships between them. More formally, a simulation model comprises structural assumptions, parameter estimates, input variables, decision rules and output variables (Whicker and Sigelman 1991). The models are especially useful when the real phenomena are difficult to observe, when there are feedback mechanisms in relationships between phenomena, and when attempting to study changes in the relationships. Simulation studies provide a method to study BRCA1 epidemiology and avoid many of the problems associated with population-based research. Perhaps most importantly, a simulation model allows us to consider BRCA1 mutations in families where there is no history of disease. Simulation studies can be inexpensive despite involving large samples, and information regarding BRCA1 mutations and family histories in a simulation study is known to

be correct (i.e., the information is specified by the researchers, not observed). If little is known about a parameter estimate in a simulation model, stability analyses can evaluate the extent to which results depend on that estimate. Simulation studies are also useful when a system involves several underlying relationships. In such scenarios, a model typically combines results from separate specialties in science. The aggregation of results can identify assumptions that are necessary in the larger model. Because the data generated in a simulation are independent, parameter estimates and confidence intervals are statistically sound. This is not always true for population-based samples.

1.3 Research questions

A person's family history of disease is expected to depend on his or her age and family structure. A 20-year-old might have no family history of breast/ovarian cancer but have several affected relatives by the time he or she is 40. Someone is more likely to have a family history if he or she has a large family than a small one, unless increased family size is somehow associated with a reduced disease risk. The accuracy of family history as a predictor of BRCA1 mutation carrier status is also expected to depend on the rate of disease in the population. Breast/ovarian cancer is more than 10 times as common in BC than in Korea (Parkin et al 1997) and so a family history of cancer in Korea would be more likely to reflect genetic susceptibility. Finally, the breast/ovarian cancer risk that is associated with a germline BRCA1 mutation is expected to determine how well family history can identify families in which there is a mutation. This risk is not the same in all populations and will depend on other genes and environmental exposures.

This thesis will examine family history of breast/ovarian cancer as a basis for referral to a BRCA1 testing program. To do so, family history is evaluated as a predictor of whether someone carries a BRCA1 mutation. In particular, the thesis considers three questions:

- Is the predictive accuracy of family history affected by a person's age and family size?
- Is the accuracy affected by the risk of hereditary breast/ovarian cancer in the population?
- Is the accuracy affected by the overall risk of breast/ovarian cancer in the population?

The accuracy of predictions will be measured by the sensitivity, specificity and post-test likelihoods (both positive and negative) that are associated with family history as a clinical test of whether someone is a BRCA1 mutation carrier. The thesis addresses these questions in the context of a general population as opposed to a subpopulation like breast or ovarian cancer patients.

1.4 Thesis outline

Methods have been developed to estimate the probability that someone carries a BRCA1 mutation based on their family history of disease (Shattuck-Eidens et al 1997, Couch et al 1997, Berry et al 1997, Parmigiani et al 1998) and computer software is available to calculate these (Duke University Institute of Statistics and Decision Sciences, 2000). The calculations are often carried out by health care professionals who have access to a computer and appropriate

software, but cannot be performed by many people not associated with a hereditary cancer clinic. This thesis examines criteria for determining who should be referred to such a clinic. Unlike the probability estimates, these criteria should be simple enough to be assessed by people and health care workers in general.

The family history criteria in this thesis address the likelihood that one of a person's parents is a BRCA1 mutation carrier. If germline BRCA1 mutations are rare in the population, then Mendelian inheritance implies the probability that someone carries a mutation is about half the probability that one of their parents is a carrier. The family history criteria do not incorporate a person's own disease history.

Following a review of the published literature, a simulation model was developed to mimic family incidence of breast/ovarian cancer in persons with and without germline BRCA1 mutations. In the next phase, analyses were conducted to examine the accuracy of family history as a predictor of BRCA1 mutation carrier status, and the effects of a person's age and family structure on predictions. Analyses were performed to examine the stability of results with respect to the estimated rate of cancer in the population and the risk of cancer associated with mutations. The aim of these analyses is not to quantify the predictive capability of family history in each situation, but to determine whether the predictive ability is constant under a range of scenarios. The thesis concludes by considering family history criteria as a basis for referrals to a BRCA1 testing program in BC.

Chapter 2: Literature Review

2.1 Breast/ovarian cancer epidemiology

Breast and ovarian cancer can arise from both genetic predisposition and environmental (i.e., non-genetic) exposures. The Online Mendelian Inheritance in Man (OMIM) database lists 42 entries referring to breast cancer, 18 entries referring to ovarian cancer and 7 entries referring to both in either the entry's title, clinical synopsis or list of allelic variants (www.ncbi.nlm.nih.gov/omim/ on November 30, 2000). For example, some variations of the BRCA2 gene (OMIM 600185) have been observed more frequently in people with cancer of the breast, ovary, larynx, prostate, colon, stomach, thyroid and cervix. The BARD1 protein (OMIM 601593) appears to interact with other proteins linked to breast/ovarian cancer and mutations in BARD1 might thereby affect breast and ovarian cancer risk. Environmental exposures suggested to affect ovarian cancer risk include chemical exposures such as asbestos (Weiss et al 1996). Environmental exposures suggested to affect breast cancer risk include and lifestyle factors such as the length of time that a mother breast-feeds her children (Henderson et al 1996). Many variables associated with breast and ovarian cancer are also related to hormones, and so causal factors for breast and ovarian cancer are difficult to identify. Risk factors such as age at menarche, parity and breast tissue density are likely combinations of genetic and environmental variables. The interactions between genetic and environmental variables are not well understood.

The age-standardized incidence of breast cancer in Canadian women rose from 81 to 106 cases per 100,000 between 1970 and 2000 (NCIC 2000). The age-standardized incidence of ovarian

cancer was more stable during this period, with an annual average of about 14 cases per 100,000 women (NCIC 2000). In most populations, the youngest women to be diagnosed with breast cancer are in their late teens and disease incidence increases for older age groups. The age-specific incidence rate increases most rapidly until women are about age 50. The rate continues to climb after age 50 but at a slower pace. An inflection in the incidence rate when plotted against age was first remarked upon by Clemmensen (1948) and is now commonly referred to as Clemmensen's hook. Ovarian cancer is first seen amongst women in their teens and the risk of disease increases as they grow older.

Most factors associated with breast cancer risk are related to either previous disease or to hormones. Types of previous breast disease include hyperplasia, *in situ* breast cancer and non-specific conditions characterized by nodular density in mammograms. Hormone-related factors include nulliparity, late age at first childbirth, shortened periods of breast-feeding, menarche occurring before age 12 years and menopause beginning after age 49. Some studies have shown increased breast cancer risk is associated with prolonged use of oral contraceptives, obesity, tallness, ionizing radiation, alcohol consumption, diet and socioeconomic status. Stoll (1995) provides a review of breast cancer risk factors. Henderson et al (1996) provides a review that emphasizes the role of hormones. Risk factors for ovarian cancer include low parity, infertility and exposure to ionizing radiation, talc and asbestos – although the conclusions from various studies are inconsistent. As with breast cancer risk, some of these factors are related to hormones. A review of ovarian cancer risk is provided in Weiss et al (1996).

The first published report of familial clustering of breast cancer is often attributed to Broca in 1866 (e.g., Garber 1991, King et al 1993, Ford and Easton 1995, Newman et al 1997) although earlier reports have been cited (e.g., in Eisinger et al 1998). A recent meta-analysis estimated

the relative risk of breast cancer as 2.0 in women with an affected mother, 2.3 in women with an affected sister and 1.8 in women with an affected daughter (Pharoah et al 1997). The review noted that there was a higher risk for early-onset breast cancer (i.e., breast cancer diagnosed before age 50) than for late-onset breast cancer, and risks were increased if the affected relative had early-onset (as opposed to late-onset) disease. The familial risk was highest for early-onset breast cancer when early-onset breast cancer had been diagnosed in a relative. A summary of ovarian cancer research estimated the relative risk associated with a family history as 3.6 (Amos and Streuwing 1993). As in breast cancer, there was also evidence that early-onset ovarian cancer is more common among cases of familial disease. A review of both breast and ovarian cancer noted the association between breast cancer and family history was stronger in women from families that included bilateral disease and more than one affected first-degree relative (Newman et al 1997). The review also noted that breast and ovarian cancer risks were associated with a family history of either disease. Recent evidence suggests that the familial risks of breast and ovarian cancer depend on a family's ethnicity (Ziogas et al 2000).

The BRCA1 gene (OMIM 113705) is located at 17q21 and was first cloned in 1994 (Miki et al 1994). BRCA1 is hypothesized to be a tumor suppressor, meaning cancer can occur if both copies of the gene are mutated or deleted, and the risk of cancer increases if one copy is mutated or deleted. Not all BRCA1 mutations confer the same risk of disease. Mutations that lead to an alteration in the BRCA1 protein are most likely to increase disease risk. Shattuck-Eidens et al (1995) and Gayther et al (1995) suggested that mutations nearer the 3' end of the gene might be associated with families in which there is a lower proportion of ovarian cancers among the affected women. Some BRCA1 mutations are less likely to affect cancer risk and a "benign" mutation can be considered another normal allele. Polymorphism is defined to occur when two or more alternative alleles exist in a population, each having a carrier frequency greater than

2%. Following Scriver et al (1999), here I define a mutation as an allele carried by less than 2% of the population. The carrier frequency in the general population is estimated based on current data, and might be re-estimated when new data become available. BRCA1 mutations detected around the world are reported in the Breast Information Core database that is hosted by the National Human Genome Research Institute (www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic/). On 1 December 2000, 864 distinct BRCA1 germline alterations had been reported.

The risk associated with deleterious mutations in a gene can be estimated before the gene has been identified. Segregation analysis considers the pattern of disease occurrence in a set of families and whether that pattern is consistent with various modes of inheritance: autosomal dominant, autosomal recessive or X-linked inheritance of a single gene, inheritance of more than one gene, non-genetic factors or a mixture of these mechanisms. Segregation analysis doesn't involve explicit genetic information about the people in a family, and estimates age-specific disease probabilities associated with the hypothetical genes and their prevalence in the population. Linkage analysis considers the pattern of disease occurrence in a set of families and explicit values of genetic markers in the family members. (A genetic marker is a segment of DNA with a known physical location in the genome. A gene of known location is a marker, but so are smaller DNA sequences that occur between genes or within them.) Cosegregation between disease occurrence and marker status suggests the marker is near the gene associated with the disease. Linkage models involve estimates of age-specific disease risk and the frequency of hypothetical genes in the population. A more thorough explanation of segregation analysis and linkage analysis is given in Khoury et al (1993). Neither analysis requires knowledge about the disease gene, but both analyses produce estimates of the risk associated with it.

A large multi-centre case-control study was undertaken during the early 1980s to examine oral contraceptive use in relation to breast, endometrial and ovarian cancer. The Cancer and Steroid Hormone (CASH) study interviewed 5763 women who were newly-diagnosed with cancer, and 4754 healthy controls, from centres in the US (Wingo et al 1988). Initial analyses found that the risk of breast cancer in cases' mothers and sisters increased as the case's age of diagnosis decreased, and the risk was higher still in women with another affected relative (Claus et al 1991). Segregation analysis of the CASH data suggested there was a rare autosomal dominant allele in the population that conferred a 92% lifetime risk of breast cancer (Claus et al 1991). The Breast Cancer Linkage Consortium (BCLC) in Great Britain ascertained families from parts of Europe, Iceland and North America on the basis of family history of breast or breast/ovarian cancer. Easton et al (1993) reported linkage of markers on chromosome 17 with breast and ovarian cancer in 45% of 214 BCLC families. Results from the BCLC were interpreted to estimate the probability that a particular constellation of familial breast/ovarian cancer cases were the result of a germline BRCA1 mutation (Shattuck-Eidens et al 1995). These estimates suggested that the probability of a germline BRCA1 mutation was increased in a breast cancer patient who had a sister affected with breast/ovarian cancer, or a family with three or more cases of breast/ovarian cancer. The risk of familial clustering was higher for families in which relatives had earlier ages at diagnosis.

The CASH studies did not concern BRCA1 explicitly, but rather cases of breast cancer that likely involved autosomal dominant inheritance. The BCLC studies examined cancer for which there was evidence of linkage with 17q21, but not direct evidence of BRCA1 mutations. The CASH studies were based on a population-based sample of US women that had been diagnosed with breast, ovarian or endometrial cancer at any time during a 25-month period. The BCLC studies were based on families from several centres that were ascertained on the basis of

multiple cases of (male or female) breast cancer and ovarian cancer. All participants in the BCLC had some sort of family history of breast/ovarian cancer, often a strong one.

2.2 Models of BRCA1 and family history

After BRCA1 was cloned, many reports were published regarding the prevalence of germline mutations in different populations. A PubMed search revealed 356 entries on human research reported since 1994 with the words "BRCA1" and "mutations" in the title (www.ncbi.nlm.nih/ pubmed/ on December 1, 2000). Those articles were almost exclusively concerned with cancer patients and their families, and from populations defined by ethnicity or geography. Examples include studies conducted among Ashkenazi Jews (Struewing et al 1995), Germans (Jandrig et at 1996), Hungarians (Ramus et al 1997), Russians (Gayther et al 1997), Scandinavians (Hakansson et al 1997), Chinese (Tang et al 1999), British (Peto et al 1999), Welsh (Lancaster et al 1998), African Americans (Gao et al 1997) and French-Canadians (Tonin et al 1998). Although the number of BRCA1 carriers was often small, most reports noted whether the patients had relatives with breast or ovarian cancer. Studies with few mutation carriers cannot examine the relationship between family history and BRCA1 in much detail, but they are valid case series and offer important anecdotal evidence concerning family history and BRCA1. Studies that reported fewer than 25 BRCA1 mutation carriers are not considered further in this review.

Gayther et al (1995) considered BRCA1 mutations in 60 families "primarily of British origin" for which there was a family history of breast or ovarian cancer. In particular, each family included at least 4 cases of either breast cancer diagnosed before age 60, or cancer of the

ovarian epithelia. The study did not comment upon the relationship between family history and BRCA1, but reported a significant difference in the proportion of breast cancer and ovarian cancer cases in a family depending on whether the BRCA1 mutation was nearer the 3' or 5' end of the gene.

Another early report concerned the BRCA1 status of 160 women from the Institute Curie in Paris (Stoppa-Lyonnet et al 1997). Women in the study did not necessarily have cancer but were included if they had a family history of breast or ovarian cancer, and a blood sample was potentially available from an affected family member or obligate carrier. (An obligate carrier is someone with a child who has a germline mutation and the child's other parent is known not to be a carrier.) A family history of cancer was defined if a participant had two first-degree relatives with breast cancer diagnosed before age 41 or ovarian cancer (diagnosed at any age), or three relatives with breast/ovarian cancer from the same side of the family. (First-degree relatives share 50% of genetic material on average and include a person's siblings, parents and children. Second-degree relatives share 25% of genetic material on average and include a person's half-siblings, aunts, uncles, nieces, nephews, grandparents and grand-children.) The study found that germline BRCA1 mutations were more likely if women had a relative with ovarian cancer and still more likely if women had more than one relative with ovarian cancer.

Robson et al (1997) examined BRCA1 and family history in 236 Ashkenazi Jewish women with breast cancer. It is not clear where the patients were ascertained but many were identified through the Clinical Genetics Service at Memorial Sloan-Kettering Cancer Center in New York. A family history was defined as having a first-or-second-degree relative with breast or ovarian cancer. Earlier research by another group (Roa et al 1996) had established that BRCA1 mutations in Ashkenazi Jews were mostly of two kinds. Forty-three carriers of 185delAG or

5382insC mutations were identified and more likely in women with a family history of breast cancer. Mutations were most likely to occur in women with a family history of both breast and ovarian cancer.

Shattuck-Eidens et al (1997) reported findings on 798 women with breast or ovarian cancer who attended clinics in parts of the US and Europe for persons with a high risk of carrying a BRCA1 mutation. Eighty-four women in the sample had bilateral breast cancer, 40 women had ovarian cancer and 30 women had both breast and ovarian cancer. Women whose families were known to carry genetic markers associated with BRCA1 were excluded from the sample. Logistic regression was used to predict whether women carried BRCA1 mutations based on their family history and other variables. Several variables significantly increased the probability of being a carrier, including the number of relatives with breast cancer and the number with ovarian cancer.

Couch et al (1997) considered 263 women who were ascertained at a clinic for persons with a high risk of genetic susceptibility or at a general oncology practice. All participants had been diagnosed with breast cancer and the study examined measures of personal and family history as indicators of whether women carried a germline BRCA1 mutation. The probability of a mutation was predicted using a logistic regression model that incorporated whether the family was Ashkenazi Jewish, the average age of breast cancer diagnosis amongst affected family members, and whether the family history included breast cancer, ovarian cancer, both, or someone with breast cancer and ovarian cancer. The number of women in the family age 20 years or older was not significant when added to this model. The authors concluded that the majority of women that attend a clinic for high-risk families do not carry a BRCA1 mutation.

The report did not state where the participants were from, but it is likely the Pennsylvania area where the study was conducted.

Berry and colleagues described a mathematical model to estimate the probability that someone carries a BRCA1 mutation based on his or her family history of disease (Berry et al 1997). The probability is estimated using Bayes theorem and the probability of the observed family history, conditional on whether the person carries a mutation:

$$prob(M|fh) = \frac{prob(fh|M)*prob(M)}{prob(fh)}$$

where *M* indicates that the proband carries a BRCA1 mutation and *fh* represents the family history of disease.

In the numerator, *prob(fh|M)* is determined as a product of probabilities for individual family members. These probabilities are based on the family member's age, the likelihood that they carry a BRCA1 mutation and whether or not they have breast or ovarian cancer. The "prior" probability of being a mutation carrier (i.e., *prob(M)*) is estimated as the proportion of BRCA1 mutation carriers in the population. The probability of a family history is determined as

$$prob(fh) = prob(fh|M)*prob(M) + prob(fh|N)*prob(N)$$

where *N* indicates the conjugate of *M* (i.e., *N* indicates that the proband does not carry a BRCA1 mutation) and *prob(N)* is *1-prob(M)*.

The family history includes female breast and ovarian cancer, the current age or age of death for each relative without cancer, and the age at diagnosis for each relative with cancer. The family history can include any number of people and there are no restrictions as to how they are related (although this information must be provided). In particular, the family history usually includes the disease history of the proband. Schaid (1997) commented that the estimates were a specific application of Bayesian pedigree analysis and could be calculated using other software.

Within a year, Berry and colleagues expanded the model to incorporate mutations in both BRCA1 and BRCA2 (Parmigiani et al 1998) and a computer program was developed to implement that model (Duke University Institute of Statistics and Decision Sciences, 2000). The BRCAPRO program calculates the probability that someone carries a BRCA1 or BRCA2 mutation based on his or her family history. A copy of the program can be requested from the BRCAPRO web page (www.isds.duke.edu/~gp/brcapro.html).

Myriad Genetics is a biopharmaceutical company in Salt Lake City, Utah that conducts genetic research and offers commercial testing for BRCA1 and other genes. Myriad provides genetic testing for groups and individuals around the world. A group of researchers from Myriad considered BRCA1 mutations in 238 women who had been diagnosed with breast cancer prior to age 50 or ovarian cancer at any age (Frank et al 1998). The report does not identify the institutions from which the cases were ascertained. In the study, investigators sought information about all of a woman's first-degree relatives and any additional relatives who had been diagnosed with cancer. Logistic regression was used to model the probability that a woman carried either a BRCA1 or BRCA2 mutation. The analysis showed significant effects for having a relative with ovarian cancer and for having a relative with breast cancer diagnosed before age 50. There was also a significant increase in the probability for women who were

diagnosed prior to age 40 and for women with both breast and ovarian cancer. Not all of the study's results agreed with studies reported before or after. In particular, no difference in carrier probabilities was found for women of Ashkenazi Jewish ancestry.

Myriad's web site provides mutation prevalences for BRCA1 and BRCA2 (www.myriad.com/gtmp.html viewed January 24, 2001). The prevalence values are based on data routinely collected by Myriad Genetic Laboratories and the current data are dated August 23, 2000. The data suggest that, for people with at least one first-or-second-degree affected relative, the prevalence of mutations is increased amongst women with breast cancer diagnosed before age 50, people with ovarian cancer, people with both breast and ovarian cancer, people with more that one affected relative and people of Ashkenazi Jewish ancestry. The prevalence values are based on observations and do not appear to assume any model. In some categories, the number of observations is small.

Malone et al (1998) tested for germline BRCA1 mutations in two groups of women from three counties in western Washington State (USA). The first group was comprised of 193 breast cancer patients who were diagnosed before age 35 years. The second group was comprised of 208 breast cancer patients who were diagnosed before age 45 years and who had a first-degree relative with breast cancer. About 6% of the first group and 7% of the second group were found to have germline BRCA1 mutations. Mutations were more likely in women as their number of affected relatives increased and if there was a case of ovarian cancer in the family. A later analysis (Malone et al 2000) revealed that BRCA1 mutations were more likely in women who had a mother or sister with ovarian cancer compared to women who had an aunt or grandmother with ovarian cancer. That result is consistent with cancer risk being inherited genetically, but

illustrates that the relationship between BRCA1 and family history might not be so straightforward.

Rubin et al (1998) examined 116 consecutive epithelial ovarian cancer patients from a Pennsylvania hospital. Of 22 family history criteria, only maternal family history of breast cancer and maternal family history of breast/ovarian cancer were significantly different between BRCA1 mutation carriers and non-carriers. Paternal family history of neither cancer was significantly different between carriers and non-carriers. The difference in results for maternal and paternal family history might be due to genetic imprinting (where the effects of a gene is dependent on whether it was inherited from the mother or the father) or because there is one less female relative on average in someone's paternal family history than in his or her maternal family history. This difference is small, but the effect can be substantial. The authors suggested that the difference is likely due to a lessened awareness of women regarding disease in their fathers' families. There was not a one-to-one correspondence between family history and BRCA1 mutation carrier status. A large number of women without a BRCA1 mutation had a family history of cancer, and a large number of BRCA1 mutation carriers did not have a family history of cancer. The authors concluded family history was hence an unreliable criterion for identifying mutation carriers. In a discussion that accompanied the paper, Holly Gallion calculated that the sensitivity and specificity of the maternal family history in predicting mutations were 70% and 66% respectively. In the same discussion, both she and Carolyn Runowicz noted that family size affected the probability of family history. Again, these comments suggest the association between BRCA1 and family history might not be a simple one.

In 1999, researchers from the Myriad Genetics company considered a sample of 440 women who had been diagnosed with breast cancer prior to age 45 (Frank et al 1999). Women with any family history of ovarian cancer were excluded from all analyses, and the report does not indicate from which population the patients were ascertained. Women with a first-degree relative who was diagnosed with breast cancer were more likely to carry a BRCA1 mutation than were women with no affected relatives. Furthermore, women with a relative diagnosed prior to age 50 were more likely to carry a mutation than were women with a relative diagnosed at age 50 or later.

Peto et al (1999) examined 617 women diagnosed with breast cancer before age 46 years who were ascertained at registries throughout Britain. The study's aim was to estimate the proportion of BRCA1 and BRCA2 mutation carriers in the UK population. Conclusions regarding family history were limited, but families with multiple cases of breast cancer diagnosed before age 60 and families with cases of ovarian cancer favored the presence of a BRCA1 or BRCA2 mutation. The authors noted that women with many daughters were more likely to have a daughter with breast cancer, and so mothers of women with breast cancer will tend to have high parity. This again suggests that the association between genetic susceptibility and family history depends on family size and structure.

Two major studies have examined family history and BRCA1 in women without breast or ovarian cancer. Hodgson et al (1999) considered a logistic model to predict the probability of the common germline BRCA1 mutations 185delAG and 5382insC in Ashkenazi women. They examined 184 women with breast/ovarian cancer who responded to advertisements in lectures, during broadcasts and printed in newspapers. The study's final model included variables describing the woman's own cancer and whether her family included a first-or-second degree

relative with breast cancer, a first-degree relative diagnosed with breast cancer before age 60, or any relative with ovarian cancer. If a test of BRCA1 mutation carriers were based on whether the model predicted a probability of 0.1 or higher, the test would have 85% sensitivity and 59% specificity in this sample.

The other major study of family history and BRCA1 in people without cancer was also conducted amongst Ashkenazi Jews. Hartge et al (1999) reported a study of common germline mutations in BRCA1 and BRCA2 for a large sample of Ashkenazim living in Washington DC. The sample was comprised of 5318 men and women who responded to posters, advertisements and radio announcements. Mutations were predicted using a classification and regression (CART) analysis that identified carriers based on whether a woman had a previous diagnosis of breast/ovarian cancer, whether a man or women had a first-degree relative with breast, ovarian or prostate cancer, and whether the affected relative was diagnosed prior to age 50. The results were not reported separately for BRCA1 and BRCA2. The frequencies reported in that study were re-analyzed using a logistic regression model (Hopper and Jenkins 1999) and again using Mantel-Haenszel odds ratios in strata defined by the study subject's age (Foulkes et al 1999). Both re-analyses concluded that a family history of breast/ovarian cancer and a woman's personal history of breast/ovarian cancer were the most important predictors of whether he or she carried a mutation.

Gayther et al (1999) considered BRCA1 and BRCA2 mutations in 112 ovarian cancer patients from the Familial Ovarian Cancer Registry in the UK. Each woman in the study had ovarian cancer and at least one first-or-second-degree relative with ovarian cancer. The authors modeled the probability that a woman carried a BRCA1 mutation and found the number of

breast cancer diagnoses and the number of ovarian cancer diagnoses in her family were significant predictors.

Warner et al (1999) examined 185delAG and 5382insC mutations in 4123 breast cancer patients with Ashkenazi Jewish ancestry. The study group was ascertained between November 1996 and May 1998 from patients at six oncology centers in Toronto and Montreal. Women provided a complete three-generation pedigree and information about all third-degree or closer relatives with breast or ovarian cancer. Mutations were more frequent in women who were diagnosed prior to age 50, women with a family history of ovarian cancer, and in women who had a relative with breast cancer that was diagnosed before age 50. This was one of few large studies to examine BRCA1 and family history in a Canadian population.

Gershoni-Baruch et al (2000) considered 185delAG and 5382insC mutations in 172 Jewish women who had been diagnosed with breast cancer prior to age 42. The women were ascertained from the oncology departments at two hospitals in Israel. Women were categorized according to whether they had a first-degree relative with breast/ovarian cancer, or a second-degree relative with breast/ovarian cancer. Forty-two of the women were found to carry a BRCA1 mutation and the proportion of carriers was higher amongst women with a second-degree family history and higher still amongst women with a first-degree family history.

Anton-Culver et al (2000) reported an analysis of 793 consecutively-diagnosed female breast and ovarian cancer patients from Orange County, California. They defined a positive family history as one in which a woman had a first-degree relative with breast or ovarian cancer, or two second-degree relatives from the same side of the family with breast or ovarian cancer. They

found a positive family history was associated with whether a woman had a germline BRCA1 mutation, as was the number of affected first-and-second-degree relatives.

Whittemore et al (1997) used a simulation model to examine the prevalence and contribution of BRCA1 mutations to breast and ovarian cancer incidence. Gong and Whittemore (1999) used a similar model to examine the estimates of BRCA1 risks as obtained from case-control data. Siegmund and McKnight (1998) developed a model for simulating breast cancer incidence in a woman, her mother and a single sister, where disease could occur as the result of genetic susceptibility or environmental exposures. Their analyses compared estimates of the genetic mutations' population frequency and the risk associated with them for biased and unbiased samples. Cui and Hopper (1999) performed simulations of family history in BRCA1 and BRCA2 mutation carriers using estimates of family size and cancer risk as determined from Australian population data. They found that family history of breast cancer was not a strong predictor of a woman's mutation status.

2.3 Limitations

The only studies to consider a general population have addressed Ashkenazi Jews (i.e., Hodgson et al 1999 and Hartge et al 1999) and results should not be extended to other populations. The Hodgson and Hartge studies were conducted amongst volunteers and some people might have declined to participate in genetic testing for fear of employment restrictions, difficulties in acquiring life insurance or loss of confidentiality (Lerman et al 1997, Goelen et al 1999). The paucity of information about BRCA1 for the Canadian general population was a major theme in a recent review (Elwood 1999a,b,c).

In other large studies, there usually have been only a small number of cases with germline BRCA1 mutations. Researchers have attempted to overcome this by focusing on groups that are expected to have a high proportion of carriers. Studies of women attending high-risk clinics, women with familial cancer risk factors and volunteers are likely to over-represent women with a family history of disease. Furthermore, many people in these groups are likely to have other evidence that suggests they carry a BRCA1 mutation (e.g., relatives' test results, personal history of disease). In some clinics, testing is available only when an affected family member is willing to participate in genetic testing as well. Studies using people likely to carry a BRCA1 mutation cannot be applied to the general population, but people attending high-risk clinics are sometimes the group of primary concern. Unfortunately, it is difficult to assess the effects of BRCA1 on family history without considering both cancer patients and healthy controls (both related and unrelated to the patient group).

Some studies have involved diverse populations or used complicated ascertainment schemes. The populations might come from different geographical areas or have different ethnic backgrounds, and can be expected to differ in both genotypic characteristics and environmental exposures. To address early-onset disease, some studies have targeted patients diagnosed prior to age 35, while other have considered all cases diagnosed prior to age 50 as a single group. The most appropriate definition of early-onset disease is likely to depend on diagnostic and reporting policies within the population.

For any study, all family history information should be verified by medical records. A proband might not know, recall or honestly report information about his or her relatives. The accuracy of information depends on whether it was obtained in an interview or from a self-administered questionnaire, and on the demographic and disease characteristics of the proband and his or her

relatives (Love et al 1985, Floderus et al 1990, Slattery and Kerber 1993, Theis et al 1994, Aitken et al 1995). Information about relatives from previous generations might be less accurate than for relatives from current or subsequent ones because a person's memory of family history information is likely to depend on how long ago it happened. Unfortunately, medical records can be incomplete, inaccurate, or unobtainable (Love et al 1985, Novakovic et al 1996), especially if the proband has been adopted or separated from their family. It is possible to use interviews and record searches in combination (Anton-Culver et al 1996). Family history information can be obtained in an interview and verified by medical records, but cases not identified in the interview will go undetected. Family histories can be constructed from medical records of relatives and then verifying information through interviews, but this can produce errors if there are problems with record linkage.

The relatives included in a family history measure were not always the same in earlier studies. The CASH analyses were restricted to the mother and sisters in a family; the BCLC studies involved pedigrees that sometimes spanned several generations. The analyses by Couch et al (1997) and Shattuck-Eidens et al (1997) were not clear as to which relatives in a family were included. In studies where the family history included a variety of relatives, the degrees of relationship between them were not always reported. Some studies did not specify whether the father's family was considered or distinguished from the mother's. Few studies considered the presence of BRCA1 mutations in men. There is also confusion between a person's own history of disease and the history of disease in his or her family.

Not all studies have examined every mutation of BRCA1. In particular, several groups have focused on mutations believed to be more common in the population (e.g., 185delAG and 5382insC) or mutations believed more likely to affect cancer risk (e.g., mutations in coding

regions). Different laboratory techniques also have varying abilities to detect BRCA1 mutations. Direct sequencing has been used in several studies and the method identifies each base pair in the gene's exons and splice sites. Ford et al (1998) estimated that standard laboratory methods, including direct sequencing, detected only 63% of BRCA1 mutations.

A family history of disease will depend on a person's age and the size of his or her family. Except for the mathematical models of Berry et al (1997) and Parmigiani et al (1998), none of the models in the literature considered this explicitly. Several studies have been restricted to patients diagnosed with cancer at an early age, but interpretation of results is typically concerned with the characteristics of early-onset disease and not the characteristics of young women. A person's cancer risk and family history will also depend on the rate of sporadic cancer in the population and the risk of cancer associated with a BRCA1 mutation. These factors are expected to vary among populations. Studies in the literature have been conducted in many parts of the world and have involved different target populations. No population-based studies of BRCA1 have been conducted in BC.

Chapter 3: Simulation Model and Analysis Methodology

3.1 Introduction

The first phase of this study develops a model to simulate cancer incidence in the family of someone with a germline BRCA1 mutation. Whether a person has a family history of disease depends on several factors. As pictured in Figure 3.1, a person's cancer family history depends on whether he or she carries a BRCA1 mutation, the person's age and family size, and the risk of hereditary (i.e., BRCA1-related) and sporadic (i.e., other) breast/ovarian cancer in the population. Note that the frequency of a mutation in the population and the risk associated with it are separate. A mutation might be common in a population but have only a small risk associated with it. The same mutation might be rare in another population but have a high risk associated with it. The ability of family history to predict whether someone carries a BRCA1 mutation will depend on all of the other factors that determine family history. The model in Figure 3.1 does not incorporate all of those determinants or the relationships between them, but it does identify some of the major factors. When possible, parameters in the model were estimated using data from BC and mathematical descriptions of phenomena were evaluated by comparison with what is known about them. A computer program to implement the model (Bajdik et al 2001) was developed in S-Plus (Mathsoft Inc. 1997). That program and instructions to perform the example in section 3.5 are provided in the Appendix. Data generated by this model will be used to examine the relationship between family history and BRCA1 in Chapter 4.

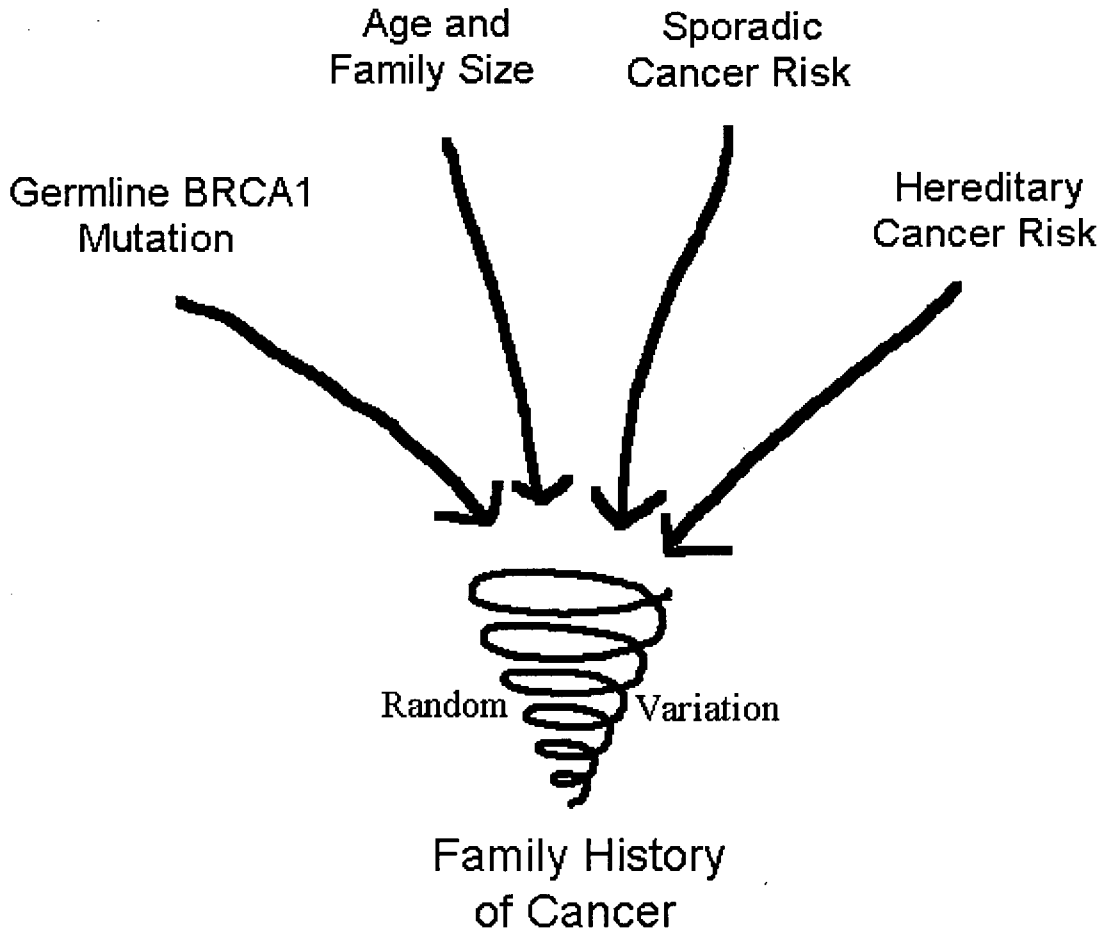


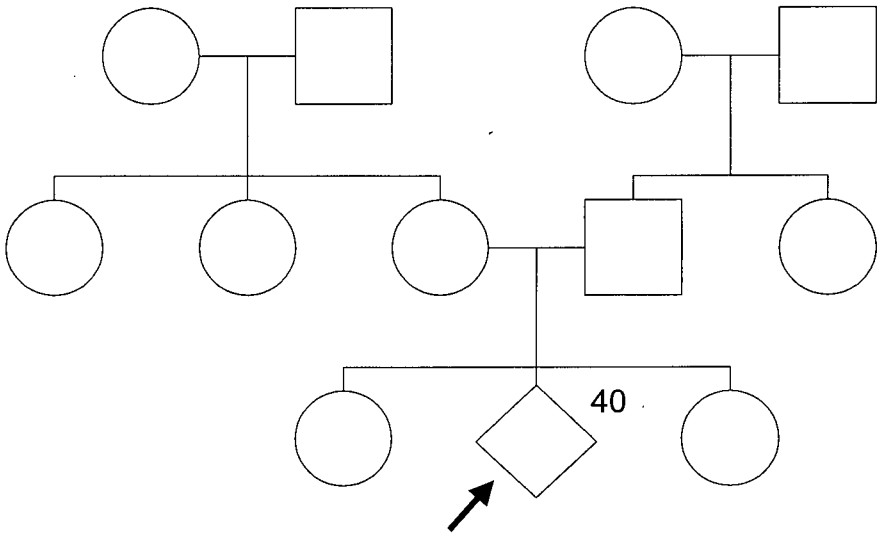
Figure 3.1 Determinants of a cancer family history.

3.2 Model formulation

A pedigree diagram is a schematic representation of the people in a family and the relationships between them. The pedigree can include close and distant biological relatives, adopted family members, and people who entered the family through marriage. For each person represented, a pedigree can record his or her age, gender, vital status and other characteristics. In particular, the details of disease occurrence can be recorded. One person in a pedigree (usually the person who brought the family to our attention) is identified as the proband and this will be the person whose BRCA1 mutation carrier status is predicted. The model developed in this thesis simulates the incidence of breast/ovarian cancer in a pedigree based on the age, gender and BRCA1 carrier status of family members and the relationships between them. The model begins with a hypothetical family in which the age of the proband and his or her number of sisters, maternal aunts and paternal aunts are specified. Given this information, the model simulates family history in three steps: (1) determine which family members in the pedigree carry the mutation, (2) determine the ages of family members in the pedigree and (3) determine the incidence of breast and ovarian cancer in each female family member represented in the pedigree. An illustration of the model is shown in Figure 3.2, where the proband's family includes two sisters, two maternal aunts and one paternal aunt. The BRCA1 mutation carried by the proband is also carried by the mother, a maternal aunt and the maternal grandmother. The ages of the family members were determined in Step 2 and, in particular, one of the maternal aunts died at age 12 and both the paternal grandparents died at age 87. In Step 3, the proband's mother, maternal grandmother and paternal aunt have cancer.

The model was formulated so as to ignore details of a pedigree that will have little effect on the family history, but not overlook variations that might be important. Accordingly, the model

Initialization: specify proband's age and pedigree structure



Step 1: determine mutation carriers

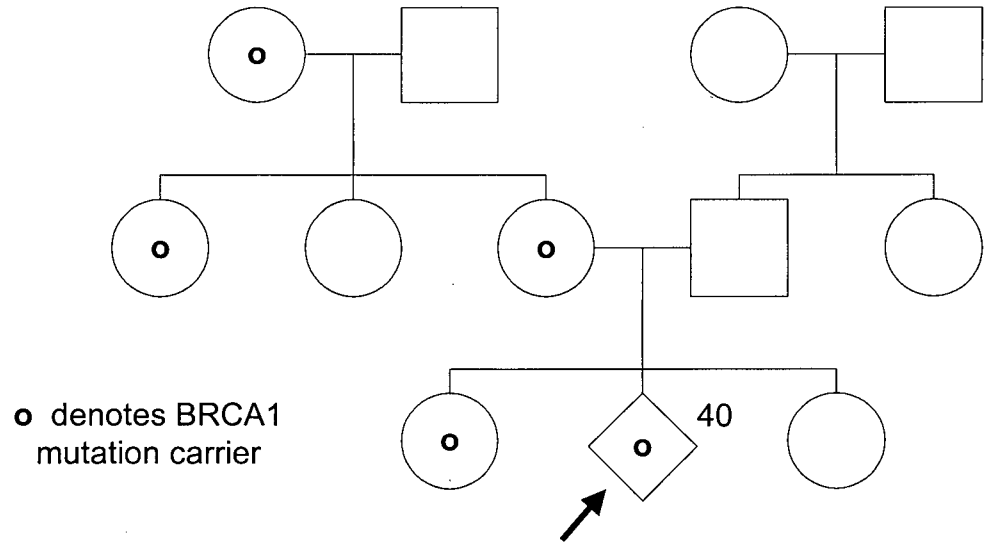
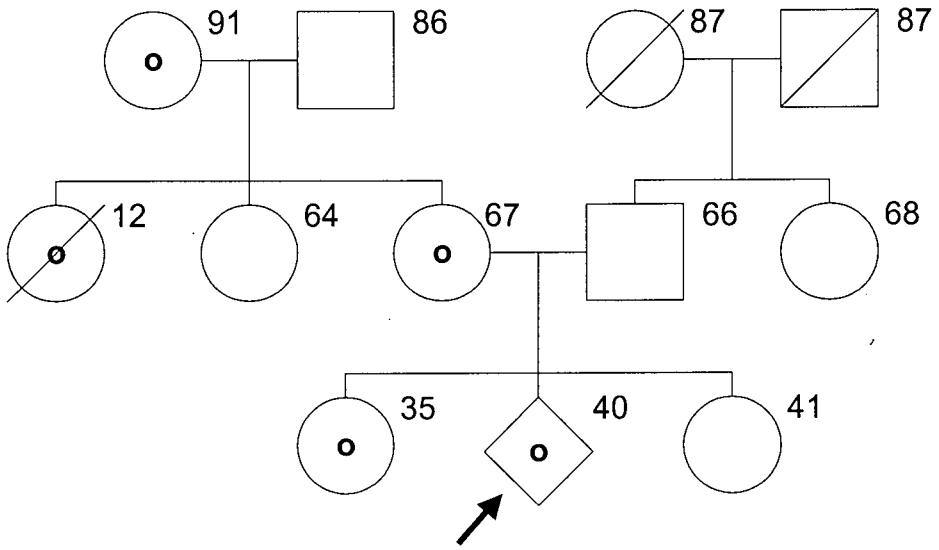


Figure 3.2 Simulation model of breast/ovarian cancer in families of BRCA1 mutation carriers. Initial information (provided by user) is proband's age and number of sisters, maternal aunts and paternal aunts. Step 1 determines who else in the family carries the mutation. (continued)

Step 2: determine ages



Step 3: determine cancer incidence

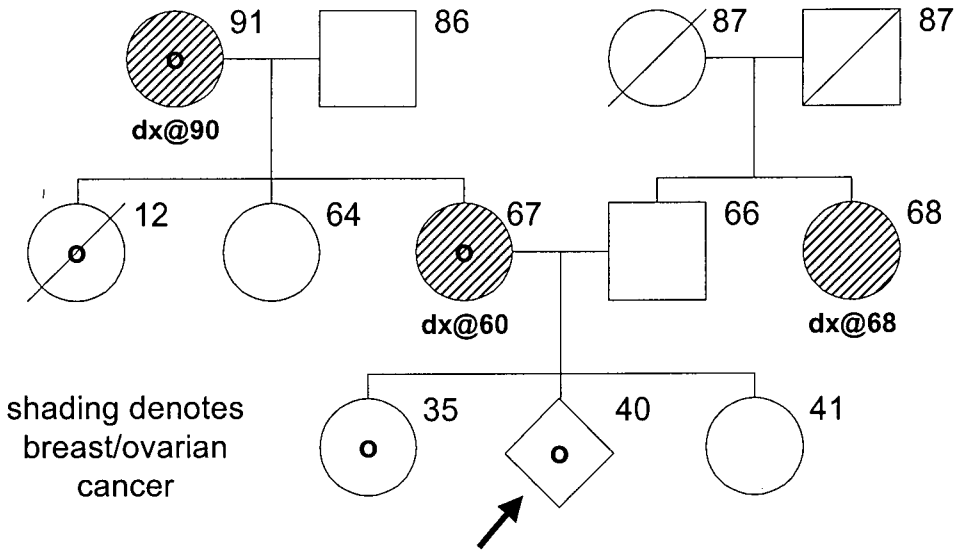


Figure 3.2 (continued) Simulation model of breast/ovarian cancer in families of BRCA1 mutation carriers. Step 2 determines the age and survival of each family member. Step 3 determines the incidence of breast and ovarian cancer in each family member (except the proband).

specifies pedigrees which include the proband's parents, sisters, maternal aunts, paternal aunts and grandparents. The model does not consider the disease history of the proband, the brothers or uncles in a family, or the proband's daughters, granddaughters or nieces. The disease status of the proband was not included in the model because it is considered part of the proband's personal disease history and not their family history. Brothers and uncles were not included in the simulations because male breast cancer was not part of the family history measures being considered.

The model does not consider the proband's children, grandchildren, nieces or nephews. Family members from generations following the proband's are typically (i.e., the proband's nieces and nephews), or necessarily (i.e., the proband's children and grandchildren), younger than the proband and are expected to have little influence on family history of breast/ovarian cancer. (The proband's sisters may nonetheless be younger than the proband.) Breast and ovarian cancer are rare in women under age 30, but disease occurring in young women is especially suggestive of genetic susceptibility. Like the disease history of the proband, disease in very young relatives might be considered independently of family history for predicting BRCA1 carriers. For simplicity, families in this model do not include multiple births, half-siblings, third-and-higher-degree relatives, or consanguineous parents.

Step 1 of the model determines who in a proband's family is a BRCA1 mutation carrier. Either the mother or the father is assumed to be a carrier, but not both, each with equal probability. Likewise, the parents of the mother or father that carries the mutation each have a 50% probability of being a carrier. For whichever grandparent is a mutation carrier, each of their offspring has a 50% probability of inheriting the mutation (except the child who is the parent of the proband, who is already known to carry the mutation). This determines which of the

proband's aunts are mutation carriers. Finally, each of the proband's siblings can inherit the mutation with a probability of 50%.

Step 2 of the model determines family members' current ages or the ages at which they died. The minimum and potential age of each family member was calculated based on the age of the proband, and the actual ages were determined using a survival function within that interval. The potential age (in years) of each sister is

$$\textit{proband's age} \pm \xi_1 \qquad [3.1]$$

where ξ_1 is a Poisson random variable with mean 2, and restricted such that that all sisters' potential ages are non-negative and unique within a kindred. The potential ages of aunts are determined in the same way – relative to the proband's mother or father. The mean age of first-time mothers in BC during 1995 was about 26 years and the average age of first-time mothers in Canada has increased roughly three years during the last two decades (Statistics Canada 1995b). The mother's potential age (in years) is calculated as

$$\textit{potential eldest child's age} + 23 \pm \xi_2 \qquad [3.2]$$

where ξ_2 is a Poisson random variable with mean 3. A mother's minimum age is her age at the birth of her most-recently born child, and a father's minimum age is

$$\textit{mother's minimum age} + \xi_3 \qquad [3.3]$$

where ξ_3 is a Poisson random variable with mean 2. The grandmothers' ages were calculated in the same manner as the mother's. Relatives without children could have died anytime and have a minimum age of zero.

Survival between a person's minimum and potential age was determined as a stochastic process with annual survival probabilities taken from 1990-1992 BC life tables (Statistics Canada 1995a). Annual estimates of the survival probability between ages 85 and 99 were assumed to be constant and survival past age 100 was assigned probability 0. A plot of the annual male and female probabilities of death are given in Figure 3.3.

Step 3 of the model determines the incidence of hereditary and sporadic cancer for each woman in the family (not including the proband). The incidence was modeled as a stochastic process for each year in a woman's life. Breast and ovarian cancer were simulated as separate processes. For BRCA1 mutation carriers, hereditary cancer incidence was determined as a random event with annual age-specific probabilities as reported in Berry et al (1997). For all family members (i.e., both BRCA1 mutation carriers and non-carriers), additional cancer incidence was determined as a stochastic process with annual age-specific probabilities taken from population rates in BC during 1993-1997. Plots of these probabilities are shown in Figure 3.4. The risk estimates for hereditary cancer are highest for women in their late 50's, and decrease symmetrically for earlier and later ages. The risk estimates for breast/ovarian cancer in the population continue to rise throughout a woman's life but, until she in her eighties, are lower than the estimates of hereditary cancer risk for BRCA1 mutation carriers. In the simulation model, if cancer occurred more than once in an individual, only the first diagnosis was recorded.

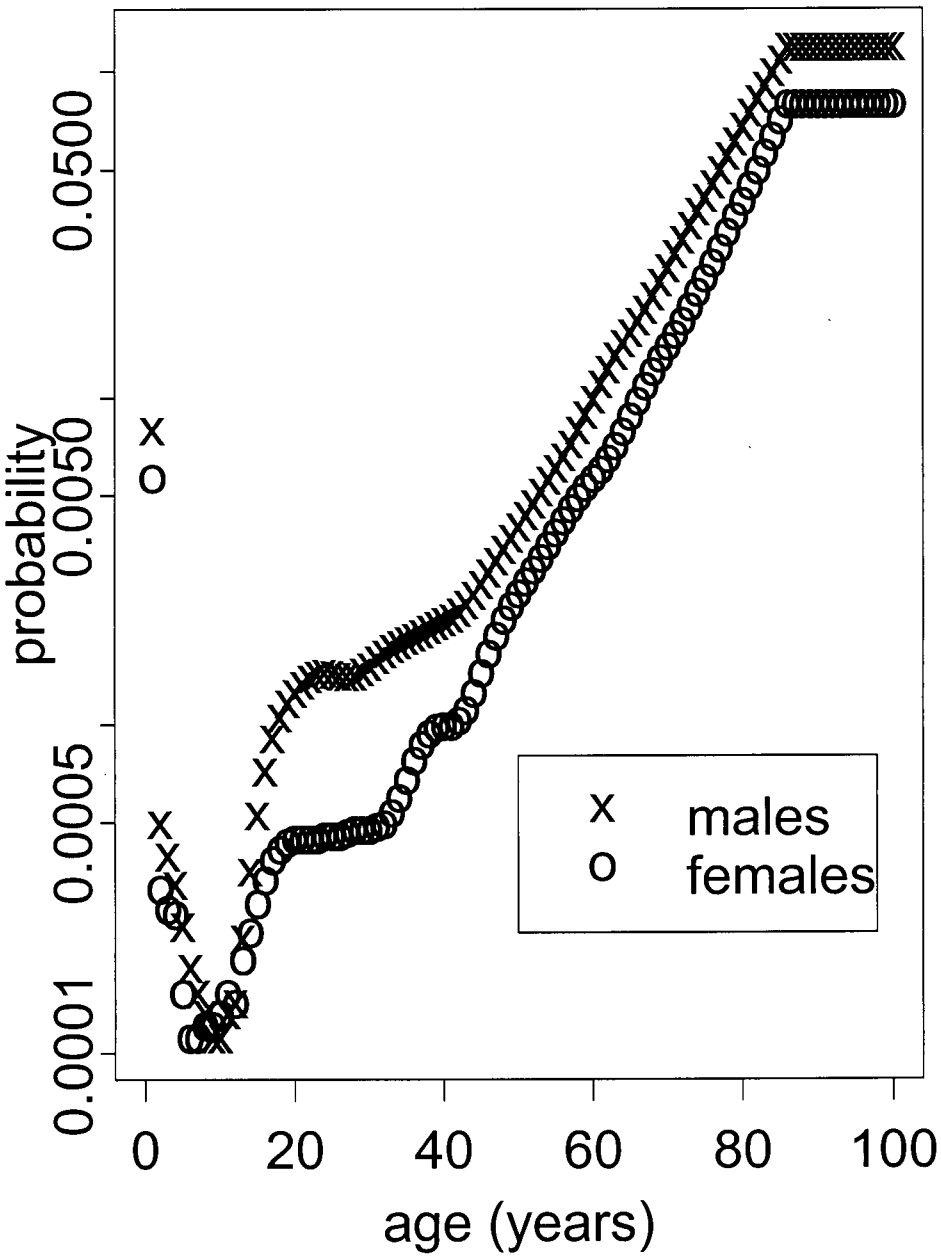


Figure 3.3 Annual probability of death: males and females ages 0 to 85 in British Columbia 1990/92 (Statistics Canada 1995a).

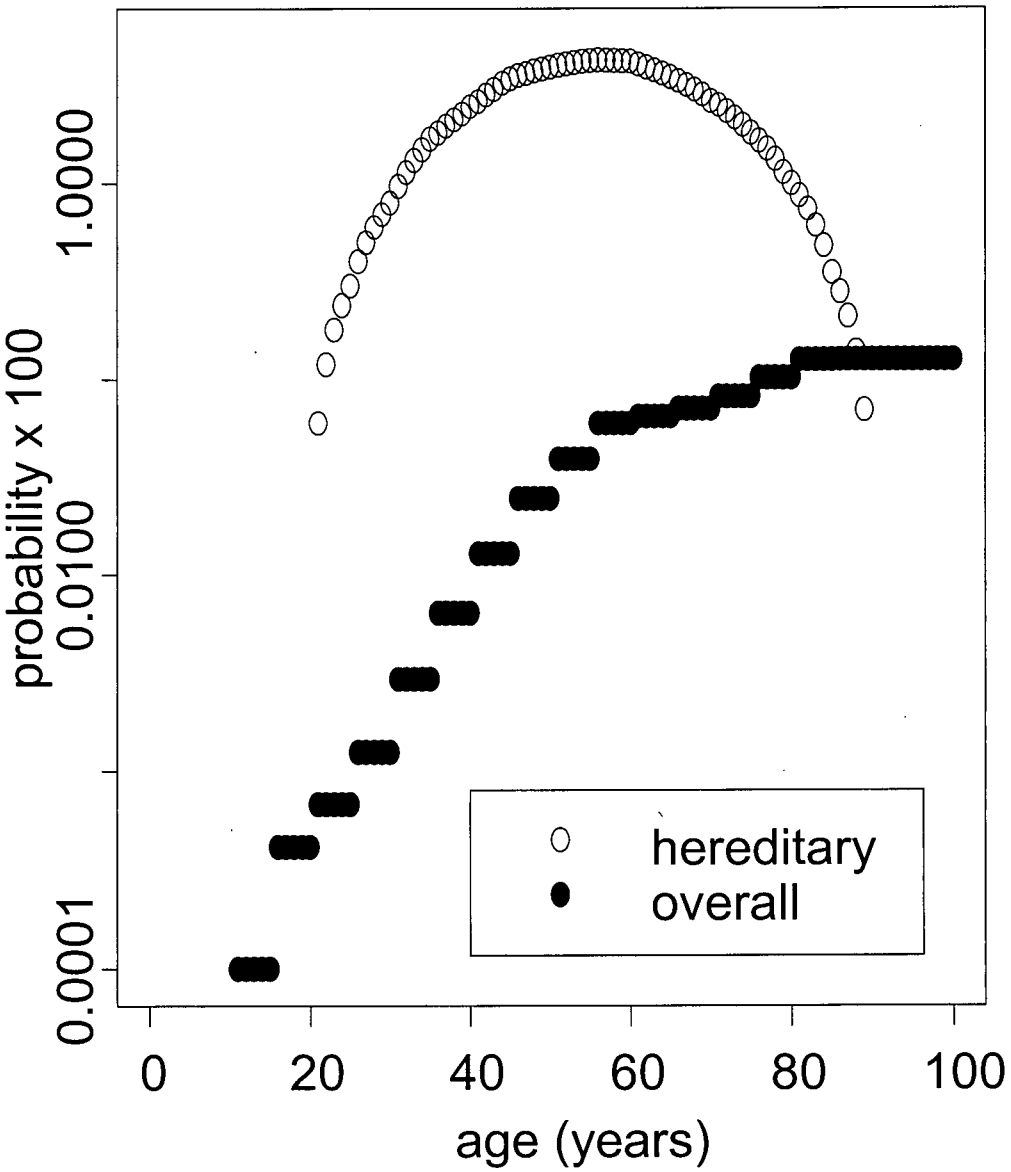


Figure 3.4 Probability of hereditary breast/ovarian cancer (due to BRCA1) as estimated by Berry et al (1997) and overall probability of breast/ovarian cancer based on rates in British Columbia between 1993 and 1997 (personal communication, BC Cancer Registry).

Each step in the model incorporates random variation. If 100 families are simulated with the same age and pedigree structure, 100 different family histories can result. Because the outcomes are independent, parameter estimates and standard errors based on the simulation output are unbiased.

Much of the family information determined by the model would be unavailable in other situations. In particular, the carrier status of each family member is rarely known. Likewise, information as to whether an observed case of breast/ovarian cancer is hereditary or sporadic is usually unavailable. The assessment of a person's family history is based on clinical observations (including a person's reports of cancer diagnoses in his or her relatives) that correspond to information available upon the completion of step 3, not on information determined before then.

The model was implemented in the computer language S-Plus (Mathsoft Inc. 1997) and a copy of the program is provided in the Appendix. Parameters in the program are age-specific probabilities for developing breast and ovarian cancer, and age-specific survival probabilities for men and women. Input for the program consists of the proband's age, the proband's number of sisters, the proband's number of maternal aunts, the proband's number of paternal aunts, and the number of pedigrees to be simulated. Output created by the program includes each relative's current age or age at death, and the age at time of breast/ovarian cancer diagnosis. An example using the program is provided in section 3.5 and S-plus commands to perform that analysis are included in the Appendix.

3.3 Assessing the relationship between BRCA1 and family history

Family history is to be assessed for the proband in a pedigree. The predictive ability of family history can be considered in 2 ways:

- What proportions of BRCA1 mutation carriers and non-carriers are correctly identified by their family history of breast/ovarian cancer?

- What proportions of persons with and without a family history of breast/ovarian cancer will carry a BRCA1 mutation?

The sensitivity of a family history measure is the probability of a positive family history in someone who is a BRCA1 mutation carrier. The specificity of a measure is the probability of a positive family history in someone who is not a carrier. These parameters are important for evaluating the success of a genetic testing program. Sensitivity and specificity take values between 0 and 1, and the values that are considered acceptable depend on the consequences of a false positive or false negative result (i.e., a positive family history when there is no germline BRCA1 mutation, or a negative family history when there is one). When studying these estimates, remember that sensitivity is only concerned with those people in the population who carry a BRCA1 mutation, and specificity concerns only those people who do not.

If n is the number of simulated pedigrees with a germline BRCA1 mutation, then sensitivity can be estimated as

$$sensitivity = (\#\ of\ probands\ with\ a\ family\ history)/n \quad [3.4]$$

The specificity can be estimated from the same families by ignoring cases of hereditary cancer determined in step 3 – because these cases would not have occurred if the person did not inherit a germline BRCA1 mutation.

$$specificity = (n - \#\ of\ probands\ with\ a\ non\text{-}hereditary\ family\ history)/n \quad [3.5]$$

Of course, some relatives of a non-carrier proband will have a germline mutation, but the population rates of disease include those people.

In considering whether someone is likely to carry a BRCA1 mutation, the parameters of interest are typically the post-test likelihoods. The positive post-test likelihood (PTL+) is the probability that someone with a family history of breast/ovarian cancer carries a BRCA1 mutation. The negative post-test likelihood (PTL-) is the probability that someone without a family history carries a mutation. These parameters might be considered more relevant than sensitivity and specificity in a clinical setting. The post-test likelihoods depend on the sensitivity and specificity of family history and the prevalence of germline BRCA1 mutations in the population. The post-test likelihoods can be estimated as

$$PTL+ = \tfrac{1}{2} * \frac{p_c LR+}{(1-p_c) + p_c LR+} \quad [3.6]$$

$$PTL- = \tfrac{1}{2} * \frac{p_c LR-}{(1-p_c) + p_c LR-} \quad [3.7]$$

where p_c is the probability that one of two parents selected from the population are BRCA1 mutation carriers and LR+ and LR- are the positive and negative likelihood ratios. Recall that the simulation model assumes that one of the proband's parents is a mutation carrier. If one parent is a carrier, then only half of their children will inherit the mutation. If mutations are rare in the population, p_c is twice the probability that anyone in the population is a carrier. LR+ is the probability of a family history in someone with a germline BRCA1 mutation, divided by the probability of a family history in someone without a germline BRCA1 mutation. LR- is the probability of no family history in someone with a germline BRCA1 mutation, divided by the probability of no family history in someone without a germline BRCA1 mutation. The likelihood ratios can be estimated as

$$LR+ = sensitivity / (1\text{-}specificity) \quad [3.8]$$

$$LR- = (1\text{-}sensitivity) / specificity \quad [3.9]$$

to emphasize the relationship between the post-test likelihoods and sensitivity and specificity.

The proportion of BRCA1 mutation carriers in BC is not known. Unless specified otherwise, the post-test likelihoods in this thesis are based on the prevalence of mutation carriers as estimated by Ford et al (1995) using data from England and Wales: $p=0.0012$ (i.e., 0.12% of people in the population carry a BRCA1 mutation).

Finally, it is of some interest to consider the relative probability of carrying a BRCA1 mutation for someone with a positive family history compared to someone without one. This relative probability (RP) can be estimated as the ratio of positive and negative post-test likelihoods.

$$RP = PTL+ / PTL- \qquad [3.10]$$

Despite the similar interpretation, RP is not the relative risk of breast/ovarian cancer in someone with a germline BRCA1 mutation. A RP of 1 implies that a positive family history is not associated with a germline BRCA1 mutation. A RP greater than 1 implies a person with a positive family history is more likely to be a mutation carrier than someone without a family history. Regardless of the absolute probability of carrying a BRCA1 mutation, RP indicates the extent to which the probability is modified by measuring family history.

3.4 Example

The simulation model and the parameters that assess predictive value are demonstrated by simulating family histories of breast/ovarian cancer in BRCA1 mutation carriers who have two sisters, two maternal aunts and two paternal aunts. Simulations were performed involving each of 1000 independent probands with ages 20, 30, 40, 50 and 60 years. The population risk of breast/ovarian cancer is based on the incidence rates of breast and ovarian cancer observed in BC during 1993-1997. The risk of hereditary breast/ovarian cancer is based on the rates reported in Berry et al (1997). A positive family history occurred if breast/ovarian cancer was diagnosed in the two of the proband's close relatives from the same side of the family, or was diagnosed in one close relative before age 50. Close relatives are the proband's mother, sisters, aunts and grandmothers.

The age distributions of the probands' sisters and mothers in the simulations are shown in Figure 3.5. Note that a person's age is not the same as his or her potential age. A sister born one year before the proband will have a potential age that is one year greater than the proband's age. However if the sister dies at age 10, her age remains 10 – regardless of what her age would have been today. Mothers' ages are likewise affected, but mothers are known to have been alive if one or more children were born after the proband. As a result of these conventions, pedigrees may have probands with apparently much younger siblings (even siblings age 0) and mothers whose ages suggest they are younger than their daughters. In general, parents with lower ages than their children's are men and women who are deceased. In Figure 3.5, the ages of the proband's sisters are generally symmetric about the proband's age, but the distribution includes the ages of several women who died prior to their potential age. Probands with a greater number of sisters would be expected to have sisters with a wider age range. The age of mothers in Figure 3.5 range from the early thirties up to 100 (the maximum achievable age in these simulations) with the mean depending on the age of the proband. As with the distribution of sisters' ages, the distribution includes the ages of several women who died prior to their potential age. Among probands with more than two sisters, some of those sisters would, on average, be younger, and hence the expected minimum age of the mothers would be higher and their age range would be narrower. For probands of each age, the sensitivity and specificity of the family history measure as a test of mutation carrier status were calculated. A plot of the sensitivity and specificity is shown in Figure 3.6. As the proband's age increased, the sensitivity became greater and the specificity decreased. The post-test likelihoods and RP are shown in Table 3.1. Note that the post-test likelihoods are not strict monotonic functions of age, likely because they are defined by ratios of functions involving sensitivity and specificity. Both post-test likelihoods became smaller as the percentage of BRCA1 mutation carriers in the

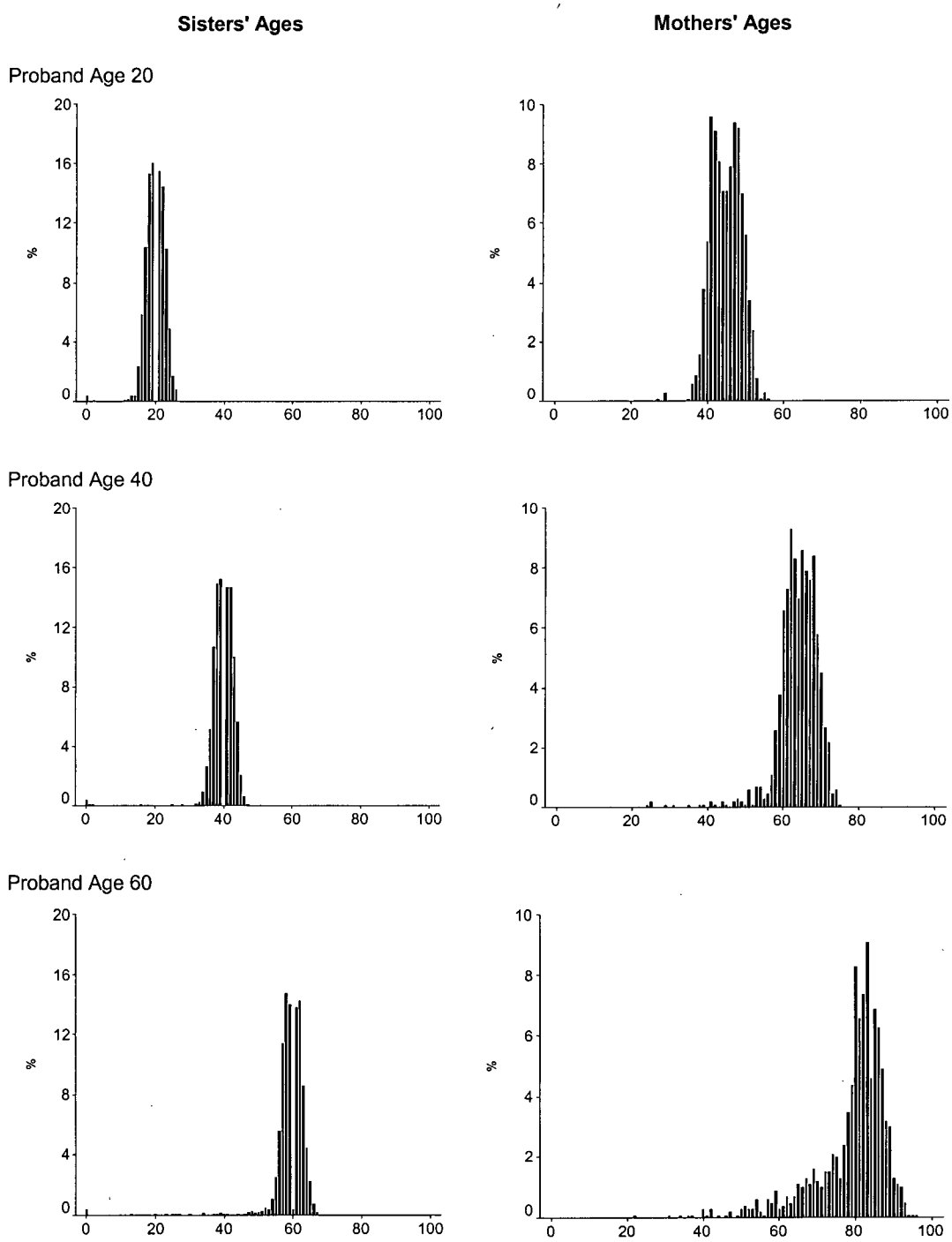


Figure 3.5 Histograms of mothers' and sister's ages in simulated families of 1000 people ages 20, 40 and 60 years. Age at death is used if the relative is deceased. Each proband in the simulations had a mother and two sisters.

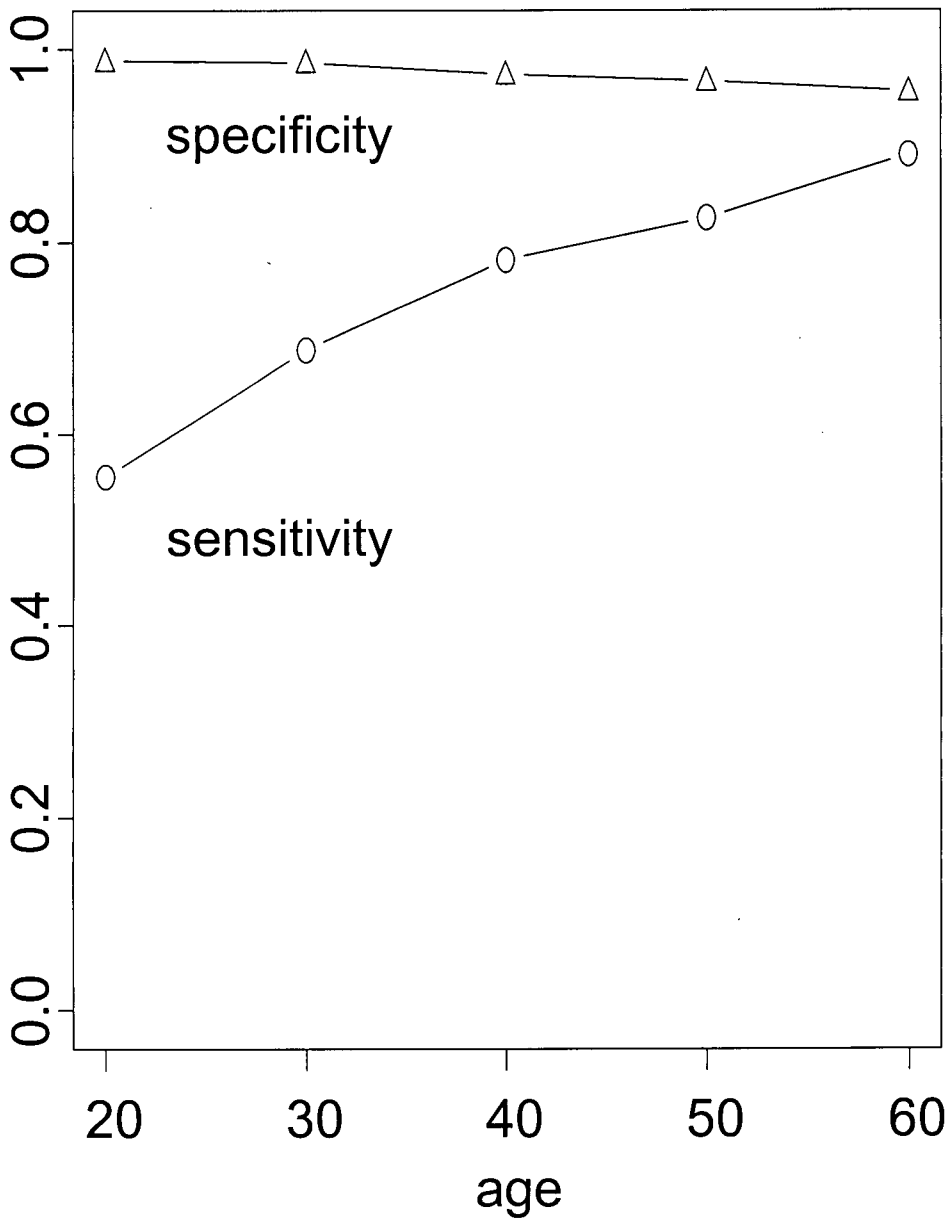


Figure 3.6 Simulation estimates of sensitivity and specificity for family history as a predictor of BRCA1 mutation carriers. Each proband in the simulations had a mother, two sisters, two maternal and two paternal aunts, and a maternal and paternal grandmother. A positive family history was declared if breast/ovarian cancer had been diagnosed in either the proband's mother, sister, two aunts on the same side of the family, an aunt plus the grandmother on the same side of the family, or any aunt or grandmother under age 50.

Table 3.1 From example (section 3.5): Simulation estimates of positive and negative post-test likelihoods (PTL+ and PTL- respectively) and relative probability (RP) for probands age 20 to 60 years with a mother, two sisters, two maternal and paternal aunts, and two grandmothers.

Proband's Age (years)	Mutation Carriers in Population (%)	PTL+ (%)	PTL- (%)	Relative Probability (PTL+/PTL-)
20	1.0	23.4	0.49	48
	0.5	15.2	0.24	62
	0.1	4.0	0.05	82
30	1.0	22.4	0.38	60
	0.5	14.3	0.19	77
	0.1	3.7	0.04	99
40	1.0	17.3	0.31	56
	0.5	10.4	0.15	67
	0.1	2.5	0.03	80
50	1.0	23.3	0.19	120
	0.5	15.1	0.10	156
	0.1	3.9	0.02	205
60	1.0	18.6	0.16	115
	0.5	11.4	0.08	141
	0.1	2.8	0.02	173

population decreased. RP is the ratio of the post-test likelihoods and its behavior is somewhat erratic in relation to proband's age. Generally, RP increased as the proportion of BRCA1 mutation carriers in the population decreased.

3.5 Summary

This chapter presented a model to simulate the family history of breast/ovarian cancer in someone who has a germline BRCA1 mutation. Step 1 of the model used basic concepts from genetics to determine which members of a family carry a BRCA1 mutation. Step 2 of the model used demographic observations of women's ages at childbirth and overall survival in BC to determine the ages of a proband's family members. Step 3 of the model used the published reports of previous investigators and data from the BC Cancer Registry to mimic the incidence of breast/ovarian cancer in family members. The model was useful in combining separate results from earlier studies to create a larger system. In particular, the assumptions necessary to connect the parts were clearly identified.

The simulation model generates data but it does not examine the predictive ability of family history with respect to germline BRCA1 mutations. The example in section 3.5 considered the predictive ability for probands with a specific family structure and age range, but other types of pedigrees and definitions of family history can be addressed.

Some parameters in the model were estimated using BC population data on women's ages at childbirth, survival and cancer incidence rates. With appropriate data, the model can be modified to simulate family history in other populations. It also should be possible for the

model to simulate family histories of other complex diseases, including other forms of cancer. This would require knowledge or assumptions regarding the pattern of inheritance for genetic susceptibility and the disease risk associated with it.

Chapter 4: Simulations of Family History and BRCA1

4.1 Introduction

A family history of breast/ovarian cancer is sometimes the result of a germline BRCA1 mutation but also can be caused by other genetic variables, environmental exposures shared amongst family members or by random clustering of sporadic cases. Nonetheless, recommendations for BRCA1 testing and genetic counseling are required in both a population health program and clinical setting, and it would be useful to base such recommendations on a person's family history of breast/ovarian cancer. The aim of this chapter is to study how the relationship between family history and BRCA1 depends on a person's age, family size, the risk of hereditary disease and the overall risk of breast/ovarian cancer in the population. The model from Chapter 3 is used to generate data for each of the analyses. Section 4.2 considers a series of family history measures and some properties of them, and section 4.3 examines the effects of changes in a proband's age and pedigree size. Sections 4.4 and 4.5 examine the stability of the model under variation in the estimates of hereditary and overall breast/ovarian cancer risk. In each of sections 4.3 to 4.5, effects are considered with respect to sensitivity, specificity and the post-test likelihoods. Section 4.6 compares the predictions of the family history measures with the estimates of the model by Berry et al (1997).

4.2 Measures of family history

It is useful to refer to someone's pedigree when discussing his or her family history of disease. The proband is the person who brings the family to our attention and, here, will be the person for whom we predict whether he or she carries a BRCA1 mutation. Other members of a family are referred to by their relationship with the proband. A pedigree may include first-degree relatives (parents, siblings and children), second-degree relatives (grandparents, aunts, uncles, half-siblings, nieces, nephews and grandchildren), other biological relatives such as great-aunts, cousins, etc. and non-biological relatives such as in-laws and adopted children.

The ability of family history to identify BRCA1 mutation carriers will depend on how family history is measured. The definitions considered here are binary. Continuous variables could be used, but a binary measure implies a decision rule and hence is more applicable to the circumstance under consideration. There are five properties of a family history measure that will be considered useful. An ideal family history measure should

- account for biologic relationships between family members
- account for the ages at diagnosis of affected family members
- account for family size and structure
- account for the rate of disease incidence in the population
- be simple to determine

Accounting for biologic relationships is important because first-degree relatives share twice as much genetic material on average as second-degree relatives, and relatives from the same

generation are likely to share more environmental exposures than relatives one or more generations apart. However, most people have more distant relatives than close relatives (e.g., more cousins than siblings), so the inclusion of distant relatives might substantially improve the predictive ability of family history (as emphasized in Slattery and Kerber 1993). Accounting for disease characteristics in the family history measure depends on the current state of knowledge regarding BRCA1. Current data suggest that cancer onset occurs earlier, and is hence diagnosed earlier, amongst BRCA1 mutation carriers. Thirdly, it is important to account for family size and structure in a family history measure because this affects the probability that some member of the family has breast/ovarian cancer – regardless of whether the family includes persons who carry a BRCA1 mutation. Fourth, the rate of disease incidence in the population is important because the interpretation of family history will depend on whether the disease is common. Finally, some measures of family history are simpler to determine. This affects the resources that are necessary and level of knowledge that is required for persons assessing family history. Simplicity might be especially important in defining family history criteria for referring people to a BRCA1 testing program.

Four family history measures are proposed.

Definition: FHS ("family history – simple") is positive if breast/ovarian cancer has been diagnosed in the proband's mother or sister. FHS is otherwise negative.

Definition: FH ("family history") is positive if breast/ovarian cancer has been diagnosed in two of the proband's close relatives or one close relative before age 50. Close relatives are defined as the proband's mother, sisters, aunts and

grandmothers. FH is otherwise negative.

Definition: OE is based on a ratio of the observed and expected number of breast/ ovarian cancer diagnoses in a family. The expected number is calculated according to the incidence rate for breast/ovarian cancer in the population. OE is positive if the observed-expected ratio exceeds some pre-determined cutoff. OE is otherwise negative.[1]

Definition: For NDX ("index"), a denominator is determined based on the number of female relatives in the family and a numerator is determined using only the female relatives with breast/ovarian cancer. NDX is positive if the ratio of the numerator and denominator exceeds some pre-determined cutoff value. NDX is otherwise negative[2].

Assessment of the family history measures is subjective. A summary is presented in Table 4.1.

FHS is simple to determine because it depends on only basic information about the disease in the proband's mothers and sisters, and is often used as a marker of increased cancer risk. The mother and sisters each have about 50% of the same genetic material as the proband, although the proband's environmental exposures are likely to be more similar to a sibling's than the

[1] The variable OE is based on the observed/expected ratio but should not be confused with it. In particular, the observed/expected ratio is continuous whereas OE is not.

[2] The variable NDX is based on the family history index but should not be confused with it. In particular, the family history index is continuous whereas NDX is not.

Table 4.1 Characteristics of family history measures. None, one or two crosses designate a non-existent, moderate or strong value.

Family History Measure	Accounts For Biologic Relationships	Accounts For Ages of Diagnoses	Accounts For Family Size	Accounts For Disease In Population	Simple To Determine
FHS					++
FH	+	+			+
OE		++	++	++	
NDX	+		++	+	

mother's. The measure does not incorporate information about second-degree relatives such as aunts and grandmothers, the size of the proband's family, ages of the family members at the time they were diagnosed with cancer, nor the rate of breast/ovarian cancer incidence in the population.

The measure FH is similar to the family history criteria that are used to determine if someone can be referred to the Hereditary Cancer Program at the BC Cancer Agency. FH is reasonably easy to determine, although information about aunts and grandmothers can be more difficult to obtain and verify than information about sisters and the mother. The measure does not acknowledge the difference in the genetic similarity for first-degree and second-degree relatives, but it does require that two affected relatives are from the same side of the family in order to determine a positive family history. Diagnoses of cancer occurring before age 50 have more influence on FH than diagnoses occurring at later ages. FH does not account for family size or the breast/ovarian cancer incidence rate in the population.

OE is not restricted to any particular subset of relatives. It can include the proband's cousins and exclude the proband's mother. This is important because some probands, particularly immigrants and otherwise displaced individuals, might be unaware of the disease history in even their close relatives or there might be no way to verify the information they report. OE specifically accounts for the size of the proband's family and the breast/ovarian cancer incidence rate in the population but it does not recognize differences between types of relatives or whether relatives are from the same side of the family. The variable is therefore likely to be more indicative of disease clustering in the family than the presence of genetic susceptibility. The expected number of cases in a family can be calculated using the probability of a relative having developed cancer by age X

$$P_X = 1 - \prod_1^X (1 - p_i)$$

where p_i is the cancer rate in the population for someone age i years, and then summing these probabilities over all members of the family. Population-based disease incidence rates are available for breast and ovarian cancer in many parts of the world and for some ethnic subpopulations, but the calculation of OE is still difficult. It requires age-specific estimates of population disease risk, an estimate of an appropriate cutoff for the observed-expected ratio, and typically a computer to perform the computations.

NDX can be calculated using a form like that in Figure 4.1 and can include or exclude any types of relatives if the form is modified appropriately. NDX incorporates information about the size of the family and assigns twice the weight to first-degree relatives (i.e., the mother and sisters) than it does to second-degree relatives (i.e., aunts and grandmothers), but does not recognize whether cancer diagnoses are on the same side of the family. The latter characteristic is

NDX

A family history index

Relatives with breast or ovarian cancer		All relatives	
mother	__ x2 = ___	mother	__ x2 = ___
sisters	__ x2 = ___	sisters	__ x2 = ___
aunts	__ x1 = ___	aunts	__ x1 = ___
grandmothers	__ x1 = ___	grandmothers	__x1 = ___
Totals	R_{CA}		R_A

If R_{CA}/R_A is greater than 0.15 → NDX is positive.

Otherwise → NDX is negative.

Figure 4.1 A form to calculate the family history measure NDX.

expected to make NDX behave like a measure of familial clustering, similar to OE. The use of a cutoff adjusts OE for the population incidence rate, but only slightly. The computation of NDX is more complicated than FHS or FH, but less difficult than that of OE, and probably can be determined using a hand calculator.

4.3 Proband age and family size

The ability of family history to predict a BRCA1 mutation carrier is expected to depend on the person's age and the number of females in his or her family. The risk of breast/ovarian cancer is largely dependent on age, and the number of sisters and the number of aunts in a family will affect predictions differently. The effects of family size will depend on the age difference between the proband and his or her parents, and the smallest effects are anticipated where the proband's generation has an age range for which the risk of breast/ovarian cancer is small compared to that for the parent's generation.

The analyses in this section will examine the effects of proband age and family size on the predictive ability of the family history measures presented in section 4.2. Assessments will be based on the sensitivity, specificity and post-test likelihoods for each measure as a predictor of BRCA1 mutation carrier status. Comparisons of the predictive ability between the measures are not valid because OE and NDX are defined using subjective cutoff values.

Methods

Data were generated using the simulation model described in Chapter 3. The analyses consider

probands with an equal number of sisters, maternal and paternal aunts, and this number is referred to as the pedigree size. Data were generated for 2500 independent probands 20, 30, 40, 50 and 60 years of age, with pedigrees of size 0, 1, 2, 3, 4 and 5 (75,000 simulations in total). Each proband's family history was measured according to the variables FHS, FH, OE and NDX. For OE, expected values were calculated according to the age-specific rates of breast and ovarian cancer in BC during the period 1993-1997. These expected values are based on the same probabilities used to determine cancer incidence in the simulation model. For both OE and NDX, cutoff values were determined as the midpoint of the median values from 200 preliminary simulations for probands having pedigree sizes between 0 and 5 (1200 simulations total). Amongst probands with a germline BRCA1 mutation, the number with a positive family history is assumed to follow a binomial distribution where each proband has a positive family history with probability p. Sensitivity was estimated as the proportion of carriers having a positive family history. This estimate has variance $p(1-p)/n$, where n is the number of families in the simulation. Specificity was estimated using the same data but determining family history from only the non-inherited cancer cases in the pedigree. Each sensitivity and specificity estimate in this analysis has a standard error of less than 0.01. Post-test likelihoods and RP were calculated according to the formulae in section 3.4, and assuming 0.12% of the population carry a BRCA1 mutation. For each of sensitivity, specificity, the post-test likelihoods and RP, the optimal behavior is considered one that is constant for probands of different ages and pedigree sizes.

Results: cutoff values for OE and NDX

Data and median values for the observed-expected ratio from preliminary simulations are plotted in Figure 4.2. There was considerable overlap between the range of values for carriers and non-carriers, although median values were consistently separated for each pedigree size. The midpoint of the carrier and non-carrier median values was 6.16 and this was used as the cutoff to define a positive value of OE. Data and median values of the family history index from preliminary simulations are plotted in Figure 4.3. There were fewer distinct values in comparison to the observed-expected ratio and the number of distinct values increased with the size of the pedigree. (A pedigree of size 0 includes the proband and three female relatives: the mother and two grandmothers. A pedigree of size 5 includes the proband and 18 female relatives: five sisters, 10 aunts, the mother and two grandmothers.) As with OE, there was considerable overlap between the range of values for carriers and non-carriers, although the median values were consistently separated for each pedigree size. The midpoint of the carriers and non-carrier median values was 0.0625 and this was used as the cutoff to define a positive value of NDX.

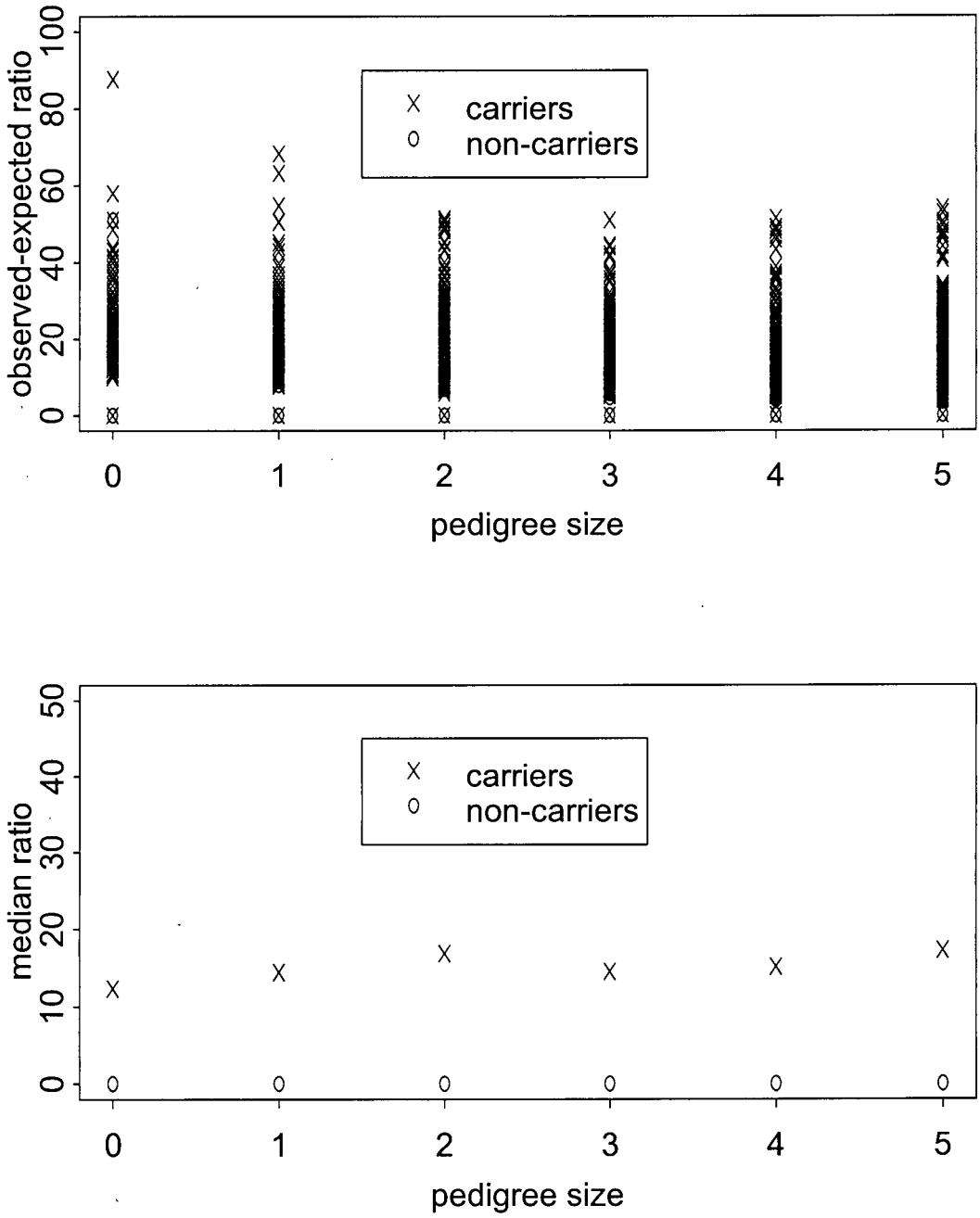
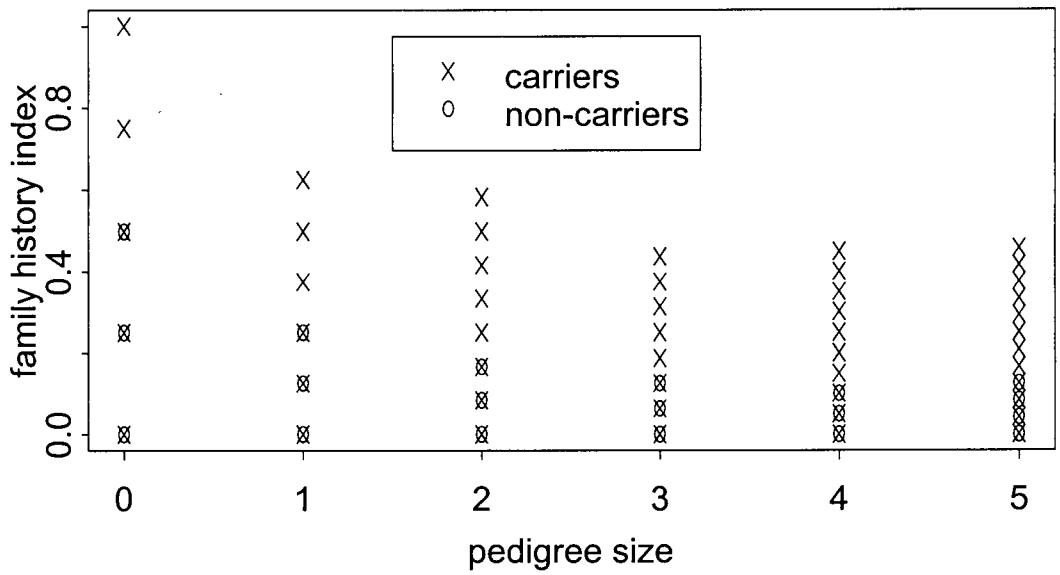


Figure 4.2 Individual and median values of the observed-expected ratio versus pedigree size. All probands are age 40 years. Pedigree size is the proband's number of sisters, maternal aunts and paternal aunts.



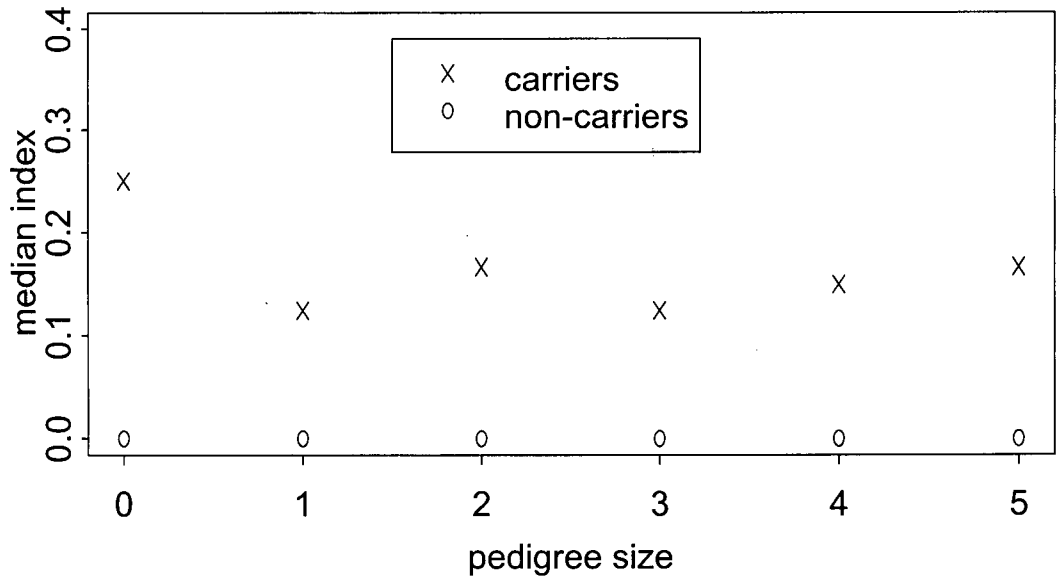


Figure 4.3 Individual and median values of the family history index versus pedigree size. All probands are age 40 years. Pedigree size is the proband's number of sisters, maternal aunts and paternal aunts.

Results: sensitivity and specificity

The sensitivity for FHS, FH, OE and NDX is plotted in Figure 4.4. For each measure, sensitivity was usually highest in the oldest probands and in probands with the largest pedigree size. Recall that pedigree size refers to the number of sisters, maternal aunts and paternal aunts in the person's family, so a unit increase in pedigree size is an increase of three relatives. However, aunts are ignored by the family history FHS and so, for that measure, a unit increase in pedigree really only implies one extra relative.

For FHS, the sensitivity was less than 0.2 in probands age 20 years and changed little among probands with different pedigree sizes. The consistency with respect to pedigree size was not surprising because FHS only considers the incidence of disease in the proband's mother and sisters, and the sisters of a proband age 20 share an age range in which there is only a small probability of developing breast/ovarian cancer. However, as the number of sisters increases, the age of the eldest sister is also likely to increase, implying the age of the mother and her risk of developing breast/ovarian cancer is greater. Among probands age 60 years, the sensitivity of FHS more than doubled for pedigrees of size 5 compared to size 0, largely because the sisters of a 60 year-old proband are in an age range where breast/ovarian cancer is more common.

For FH, the highest sensitivity was observed in the oldest probands and the effect of age was roughly constant for pedigrees of different size. The sensitivity for FH roughly doubled in pedigrees of size 5 compared to size 0. The effect of pedigree size was more pronounced for FH than for FHS because the former considers disease in second-degree relatives, and the ages of the proband's aunts and grandmothers are in a range for which there is a greater risk of breast/ovarian cancer.

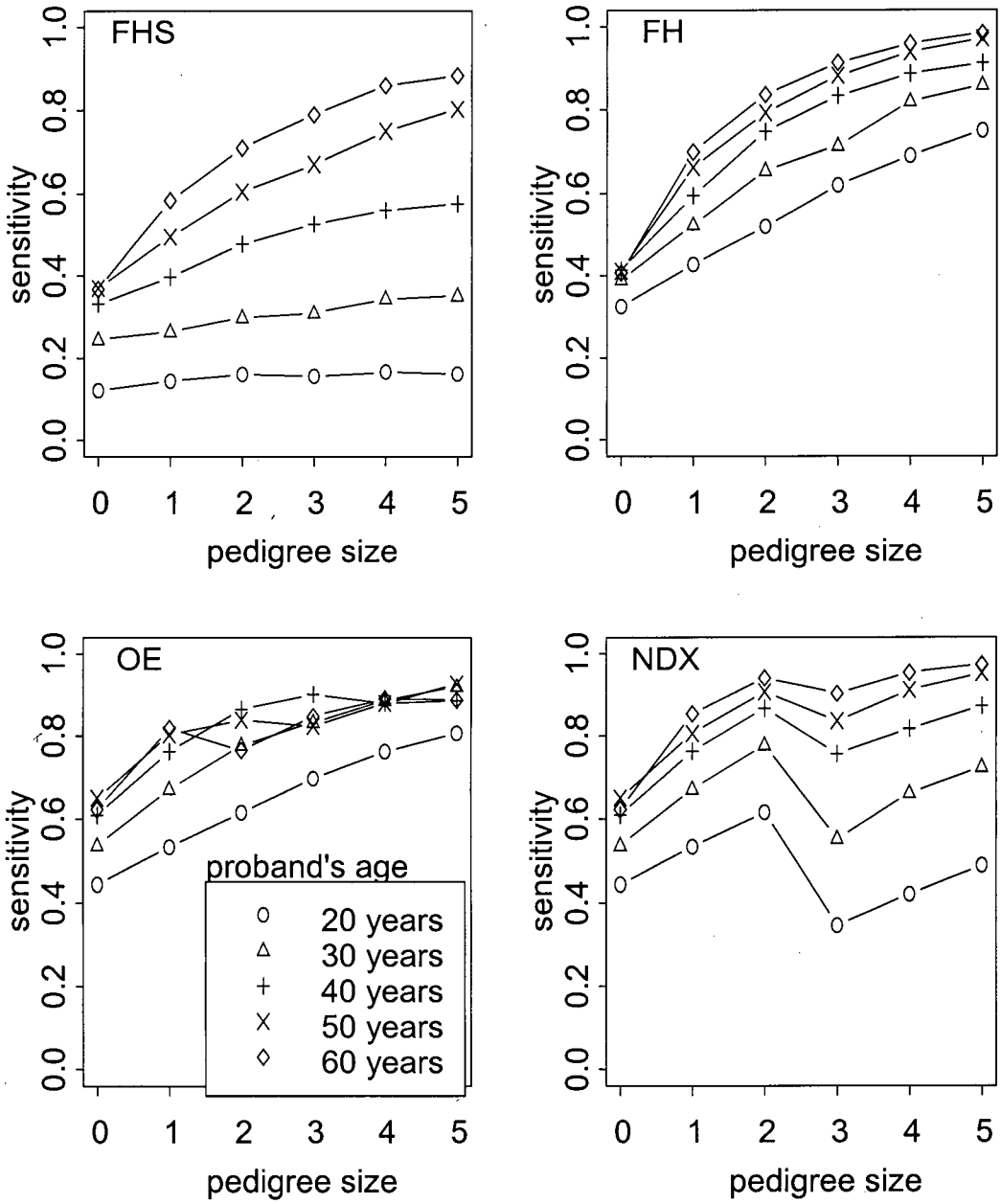


Figure 4.4 Sensitivity of four family history measures as predictors of BRCA1 mutation carrier status. Pedigree size is the proband's number of sisters, maternal aunts and paternal aunts.

The sensitivity of OE was generally highest in the oldest probands and in those with the largest pedigrees. Effects were generally smaller and somewhat erratic compared to those observed for FHS and FH, possibly because sensitivity has an upper bound of 1. Note that if a lower or higher cutoff value of the observed-expected ratio had been used, the sensitivity of OE would be affected.

For NDX, sensitivity was highest for the oldest probands. Regardless of the proband's age, sensitivity increased from pedigree size 0 to 2, dropped for pedigrees of size 3, and then increased for pedigrees of size 4 and 5. The up-and-down behavior of sensitivity results from the use of a cutoff value to make a continuous outcome (the family history index) into a dichotomous one (NDX). For example, NDX is positive (i.e., the family history index is greater than the cutoff) in pedigrees of size 1 if any relative has cancer. In pedigrees of size 3, NDX is only positive if two or more of the mother and sisters have cancer, or three or more of the aunts and grandmothers have cancer. Despite being continuous, the family history index depends on a count of events. If a lower or higher cutoff value of the family history index had been used, the sensitivity of NDX would be affected.

The specificity for FHS, FH, OE and NDX is plotted in Figure 4.5. Specificity varied depending on the proband's age and pedigree size, but much less so than sensitivity. The greatest specificity tended to occur in the youngest probands and probands with small families, opposite to the effects observed in sensitivity.

None of the family history measures produced constant values of sensitivity or specificity across all values of proband age and pedigree size.

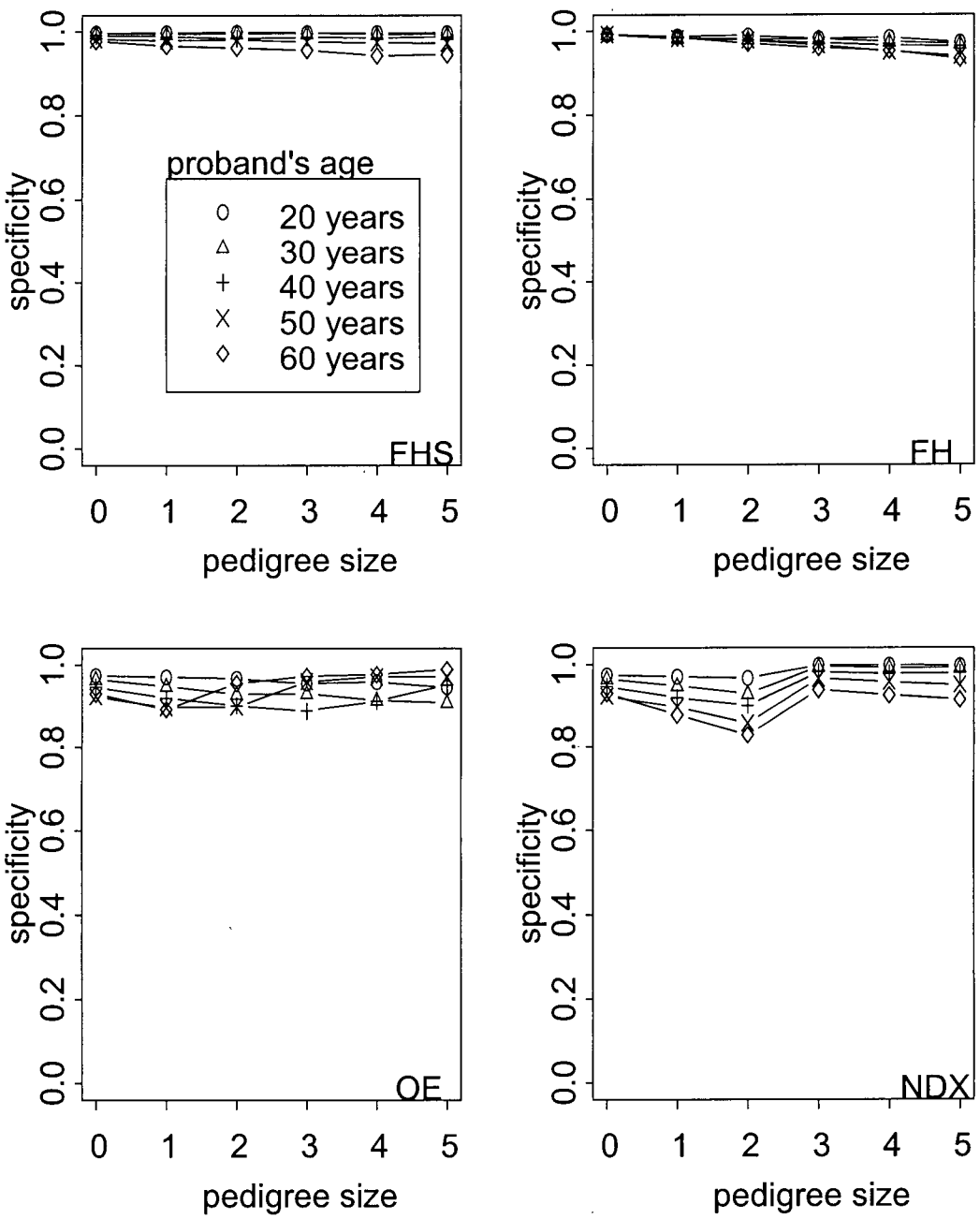


Figure 4.5 Specificity of four family history measures as predictors of BRCA1 mutation carrier status. Pedigree size is the proband's number of sisters, maternal aunts and paternal aunts.

Results: post-test likelihoods

For a population in which 0.12% of people carry a BRCA1 mutation, the post-test likelihoods associated with each family history measure are plotted in Figure 4.6. PTL+ and PTL- were generally higher for young probands in comparison to older ones, implying a germline BRCA1 is (1) more likely when a positive family history is observed in young people and (2) less likely when no family history is observed in older people. PTL+ was fairly constant across pedigree size for the measures FHS and FH, but PTL- was generally lower for probands with larger pedigree sizes. The sometimes-erratic behavior of the post-test likelihoods for OE and NDX is explained by the behavior of sensitivity and specificity from which PTL+ and PTL- were derived. As with sensitivity and specificity, a lower or higher cutoff value of the observed-expected ratio or family history index would affect the post-test likelihoods associated with OE and NDX.

The RP associated with a positive family history is the ratio of the positive and negative post-test likelihoods, and is plotted in Figure 4.7. The effects of the proband's age and family size were pronounced. The largest effects were seen for FH, where the RP associated with a positive family history was 10 times greater in persons age 60 years with a large family compared to persons age 20 years with a small family. This implies that the ability of family history to distinguish BRCA1 mutation carriers from non-carriers is greatest in older probands with large families.

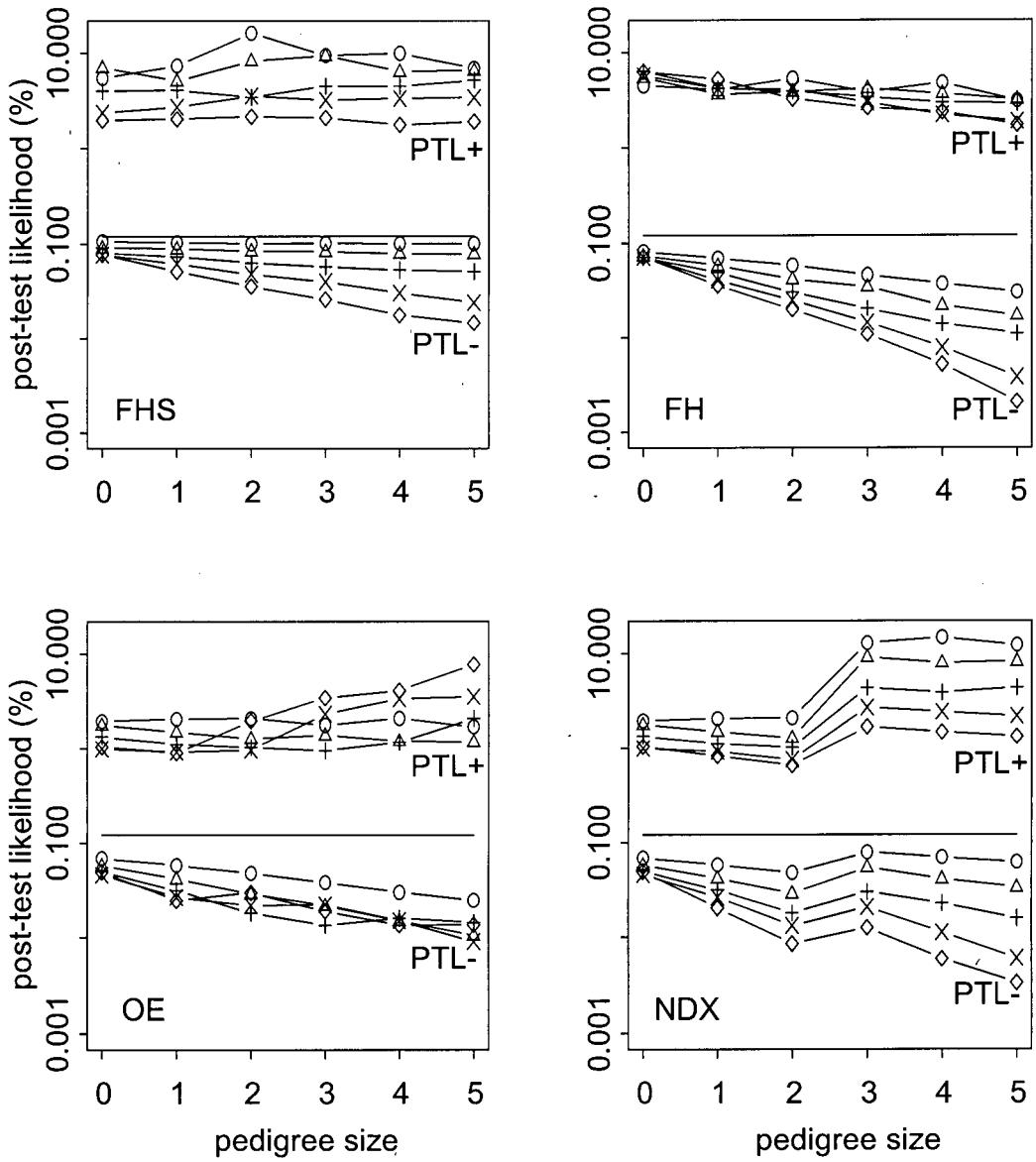


Figure 4.6 Positive and negative post-test likelihoods (PTL+ and PTL- respectively) for four family history measures as predictors of BRCA1 mutation carrier status. Pedigree size is the proband's number of sisters, maternal aunts and paternal aunts. The pre-test likelihood of carrying a BRCA1 mutation is 0.12%. The age of the proband is identified by the plotting symbol: probands age 20 years are represented by circles, probands age 30 years are represented by triangles, probands age 40 years are represented by crosses, probands age 50 years are represented by x's and probands age 60 years are represented by diamonds.

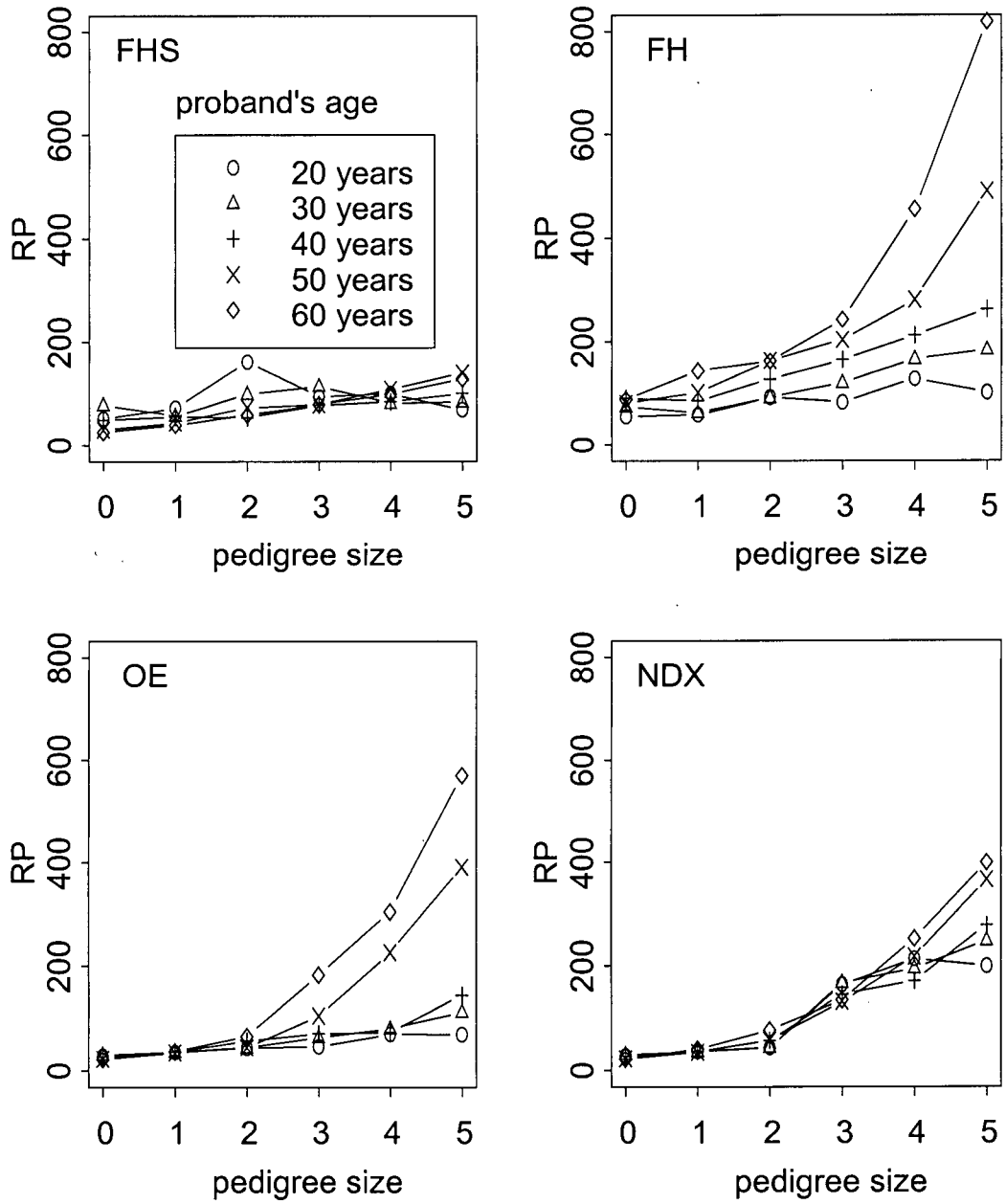


Figure 4.7 Relative probability (RP) associated with four family history measures as predictors of germline BRCA1 mutation carrier status. Pedigree size is the proband's number of sisters, maternal aunts and paternal aunts. The pre-test likelihood of carrying a BRCA1 mutation is 0.12%.

4.4 Stability: hereditary disease risk

If the risk of hereditary breast/ovarian cancer (in BRCA1 mutation carriers) was the same as that of sporadic cancer, it might be difficult to distinguish the family histories of BRCA1 mutation carriers and non-carriers. In the analyses considered thus far, the estimates of hereditary cancer risk were based on the estimates of cancer risk in mutation carriers that were reported by the BCLC (Easton et al 1995) and modified in Berry et al (1997). Other estimates have been reported by Claus et al (1991), Whittemore et al (1997) and Hopper et al (1999). The following analyses examine the stability of the output parameters for estimates of hereditary cancer risk that are proportional to the estimates of Berry et al (1997). As before, assessments will be based on the sensitivity, specificity and post-test likelihoods that are associated with each of the family history measures in section 4.1, and 0.12% of the population will be assumed to carry a mutation. The aim of these analyses was not to measure the change in outcomes that result from different parameter estimates, but rather to observe the variation in outcomes for a spectrum of estimates.

Methods

Data were generated using the simulation model described in Chapter 3. Simulations were performed in which age-specific hereditary cancer risk estimates were 50% to 150% of those reported in Berry et al (1997) (i.e., ½ to 1½ times the estimates from Berry et al (1997)). All other parameter estimates in the model remained as before. Simulations were performed for probands age 40 years with pedigree sizes 0, 1, 2, 3, 4 and 5, and each proband was classified according to the family history measures defined in section 4.2. For both OE and NDX, cutoff values were determined in 200 preliminary simulations for each estimate of hereditary disease

risk (1000 simulations total). Amongst probands with a germline BRCA1 mutation, the number with a positive family history is assumed to follow a binomial distribution where each proband has a positive family history with probability p. Sensitivity was estimated as the proportion of carriers having a positive family history. This estimate has variance $p(1-p)/n$, where n is the number of families in the simulation. Specificity was estimated using the same data but determining family history from only the non-hereditary cancer cases in the pedigree. Sensitivity and specificity estimates in the main analyses were each generated from 2500 simulations (15,000 simulations total) and have standard errors of less than 0.01. Post-test likelihoods and RP were calculated according to the formulae in section 3.4.

Results

Data and median values of the observed-expected ratio from the preliminary simulations are plotted in Figure 4.8. There was overlap between the range of values for carriers and non-carriers, but the median values were clearly separated for each estimate of hereditary cancer risk. The medians of the observed-expected ratio for carriers and non-carriers were further apart as estimates of the hereditary cancer risk increased. The overall midpoint of the medians for carriers and non-carriers was about 6 and, to be consistent with earlier analyses, 6.16 was chosen as the cutoff for positive values of OE. Data and median values of the family history index from the preliminary simulations are plotted in Figure 4.9. These values were more discrete than the observed-expected ratios. There was overlap between the range of values for carriers and non-carriers, but the median values were clearly separated for each estimate of hereditary cancer risk. Like the observed-expected ratios, the medians of the family history index for carriers and non-carriers were further apart as estimates of the hereditary cancer risk

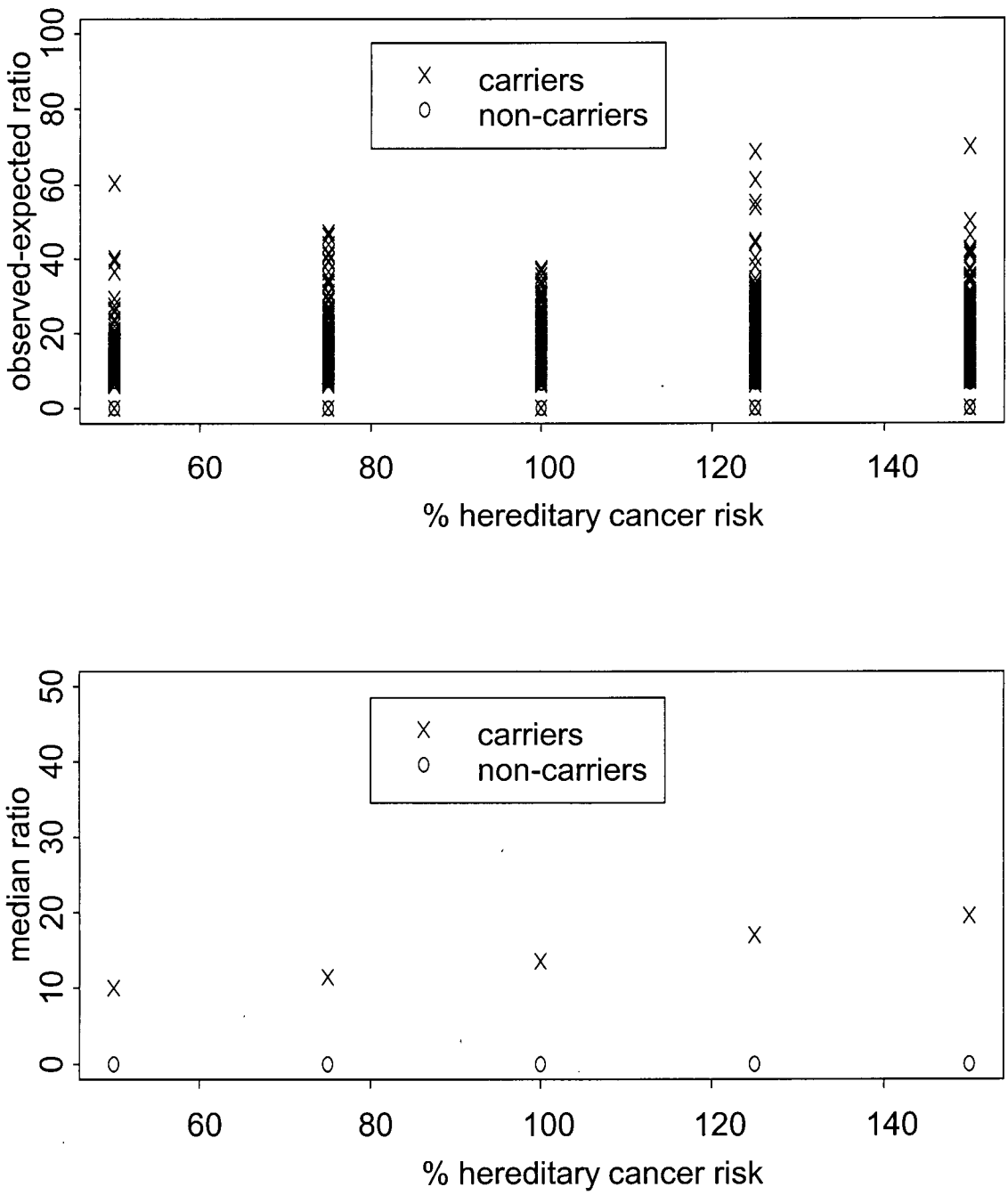


Figure 4.8 Individual and median values of the observed-expected ratio versus estimates of hereditary cancer risk in BRCA1 mutation carriers. All probands are age 40 years. 100% hereditary cancer risk refers to the age-specific estimates of Berry et al (1997); 150% risk is 1½ times those estimates.

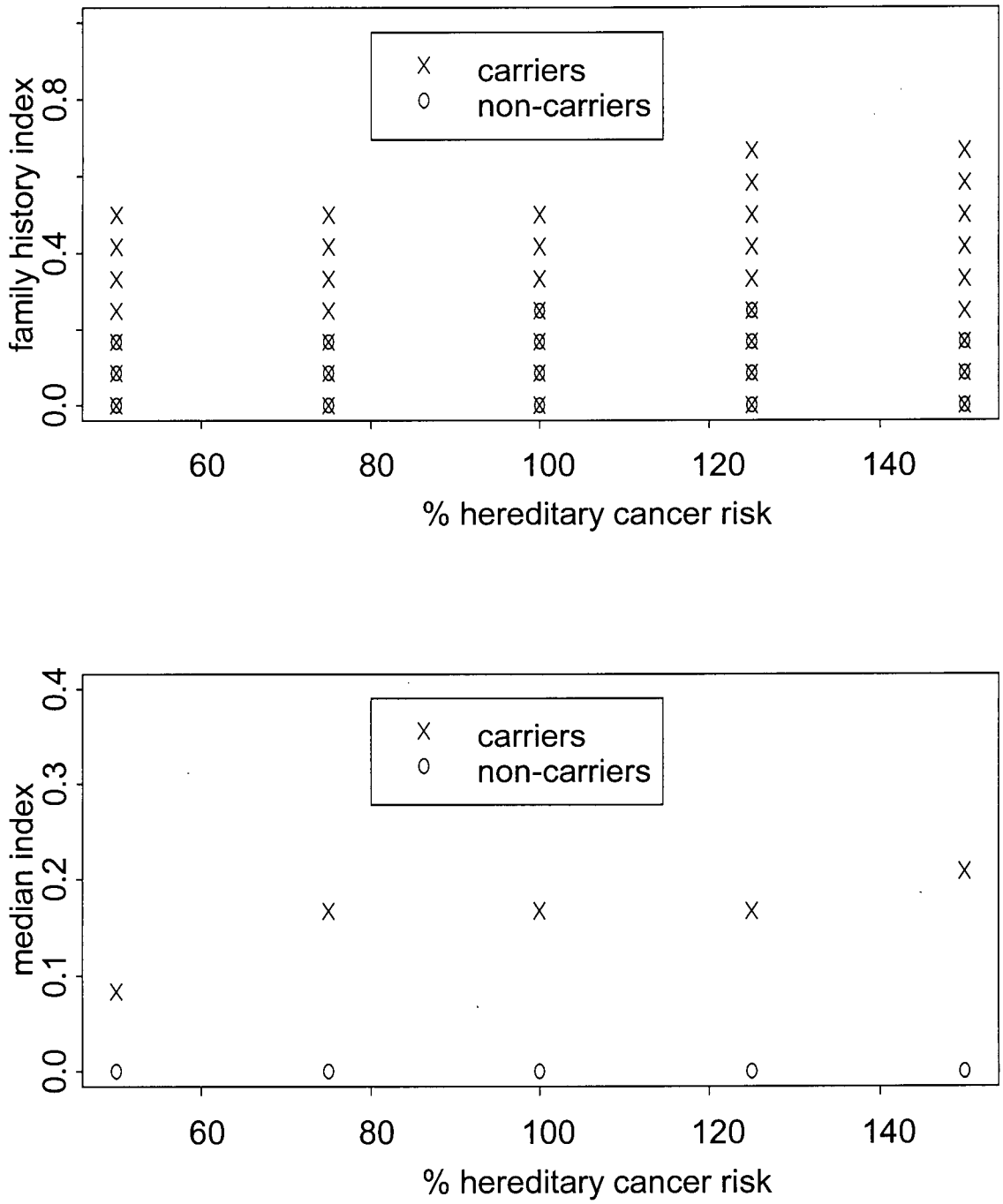


Figure 4.9 Individual and median values of the family history index versus estimates of hereditary cancer risk in BRCA1 mutation carriers. All probands are age 40 years. 100% hereditary cancer risk refers to the age-specific estimates of Berry et al (1997); 150% risk is 1½ times those estimates.

increased. The midpoint of the medians for carriers and non-carriers was about 0.06 and, to be consistent with earlier analyses, 0.0625 was chosen as the cutoff for positive values of NDX.

The sensitivity for FHS, FH, OE and NDX is plotted in Figure 4.10. The lowest sensitivity was observed when the estimate of hereditary cancer risk was lowest and hence nearest sporadic cancer risk. The sensitivity depended on the proband's pedigree size as before, with sensitivity increasing as pedigree size increased. The specificity for FHS, FH, OE and NDX is plotted in Figure 4.11. The estimate of hereditary cancer risk had little effect upon specificity, which is not surprising because specificity concerns only people who do not carry a BRCA1 mutation.

For a population in which 0.12% of people carry a BRCA1 mutation, the post-test likelihoods associated with each family history measure are plotted in Figure 4.12. PTL+ was largely unaffected by changes in the hereditary cancer risk estimate. (The effect appears particularly small in Figure 4.12 because of the logarithmic scale.) Conversely, lowering the estimate of hereditary cancer risk produced an increase in PTL-. The RP associated with a positive family history is plotted in Figure 4.13 and the effect of the hereditary cancer risk estimate is dramatic. For FH, OE and NDX, the RP associated with a positive family history in a large pedigrees were roughly 10 times greater when estimates of hereditary cancer risk were 150% compared to 50% of those in Berry et al (1997). The variation in RP also increased with pedigree size.

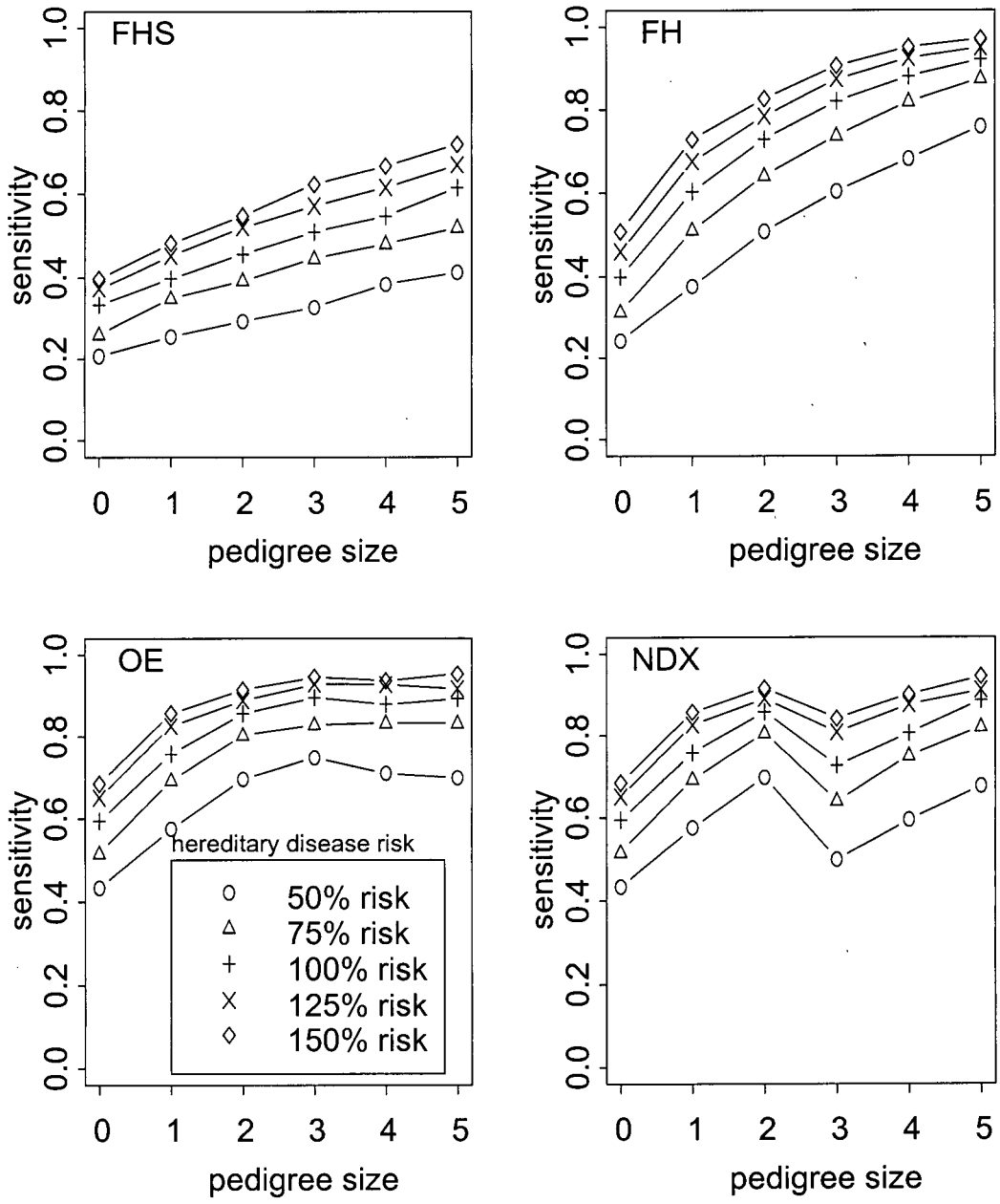


Figure 4.10 Sensitivity of four family history measures as predictors of BRCA1 mutation carrier status for different estimates of hereditary breast/ovarian cancer risk. All probands are age 40 years. Pedigree size is the proband's number of sisters, maternal aunts and paternal aunts. 100% hereditary cancer risk refers to the estimates of Berry et al (1997); 150% risk is 1½ times those estimates.

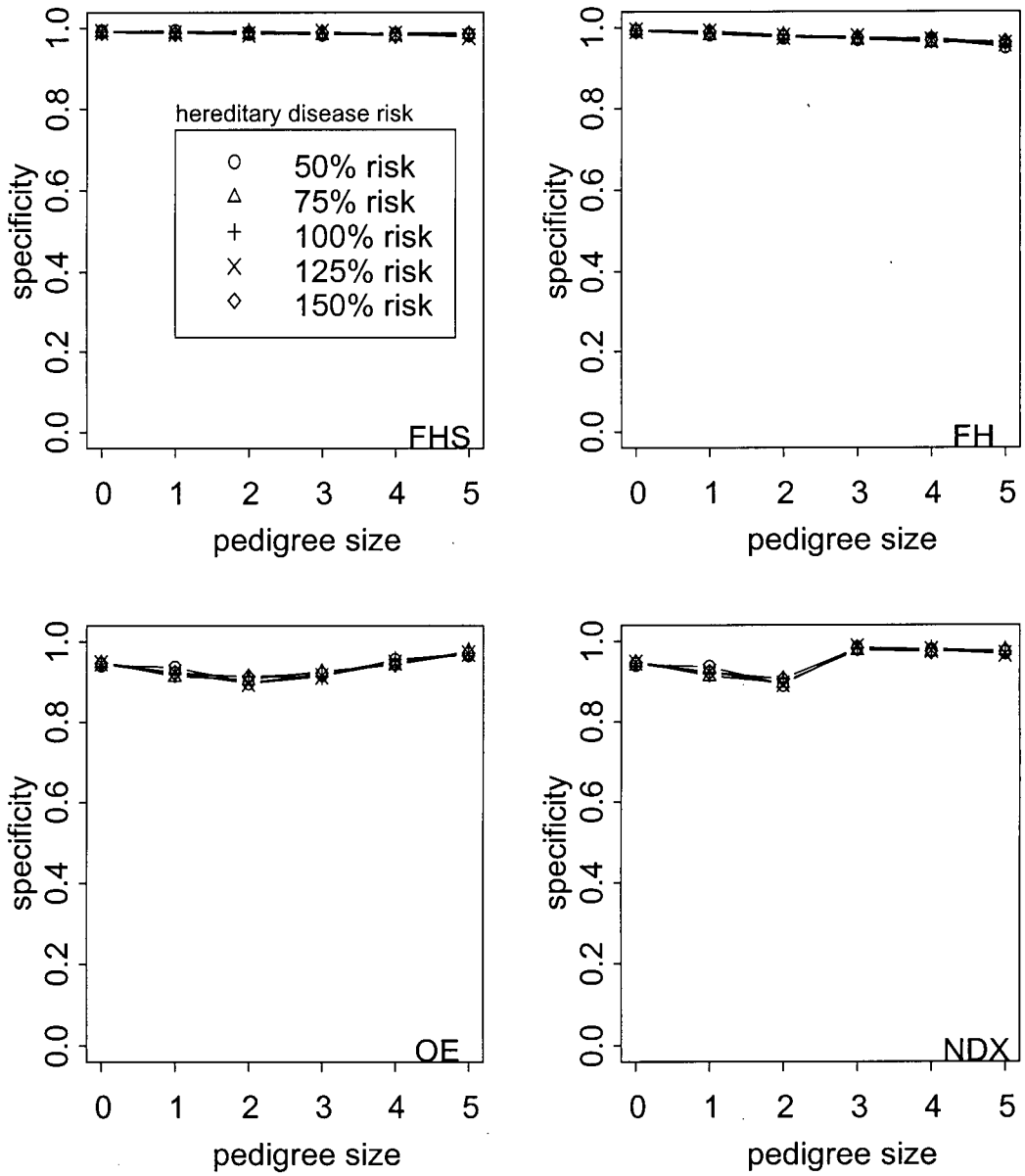


Figure 4.10 Specificity of four family history measures as predictors of BRCA1 mutation carrier status for different estimates of hereditary breast/ovarian cancer risk. All probands are age 40 years. Pedigree size is the proband's number of sisters, maternal aunts and paternal aunts. 100% hereditary cancer risk refers to the estimates of Berry et al (1997); 150% risk is 1½ times those estimates.

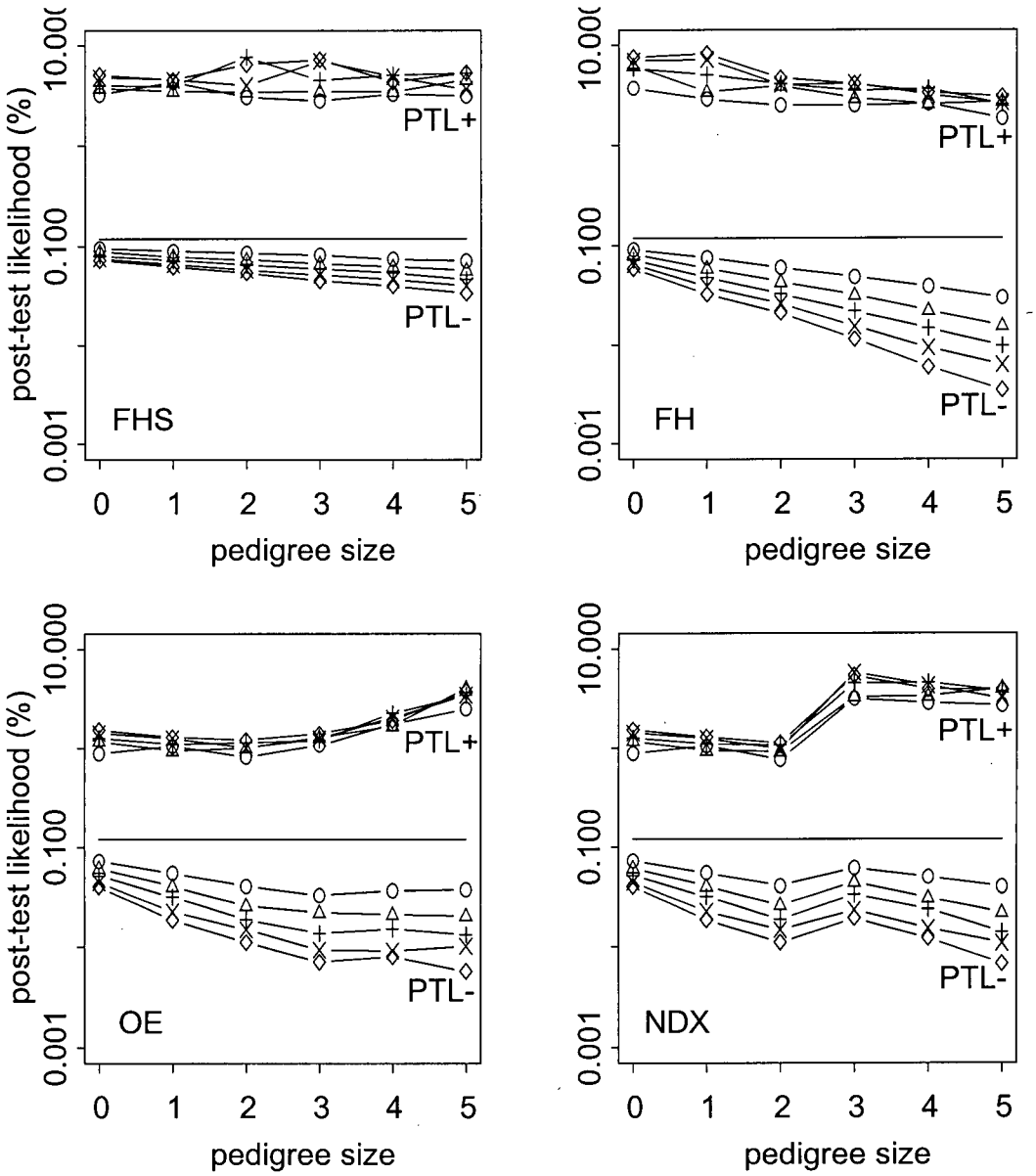


Figure 4.12 Positive and negative post-test likelihoods (PTL+ and PTL- respectively) associated with four family history measures as predictors of germline BRCA1 mutation carrier status for different estimates of hereditary breast/ovarian cancer risk. All probands are age 40 years. Pedigree size is the proband's number of sisters, maternal aunts and paternal aunts. The hereditary breast/ovarian cancer risk estimate is indicated by the plotting symbol: probands with 50% risk are represented by circles, probands with 75% risk are represented by triangles, probands with 100% risk are represented by crosses, probands with 125% risk are represented by x's and probands with 150% risk are represented by diamonds. 100% hereditary cancer risk refers to the estimates of Berry et al (1997); 150% risk is 1½ times those estimates.

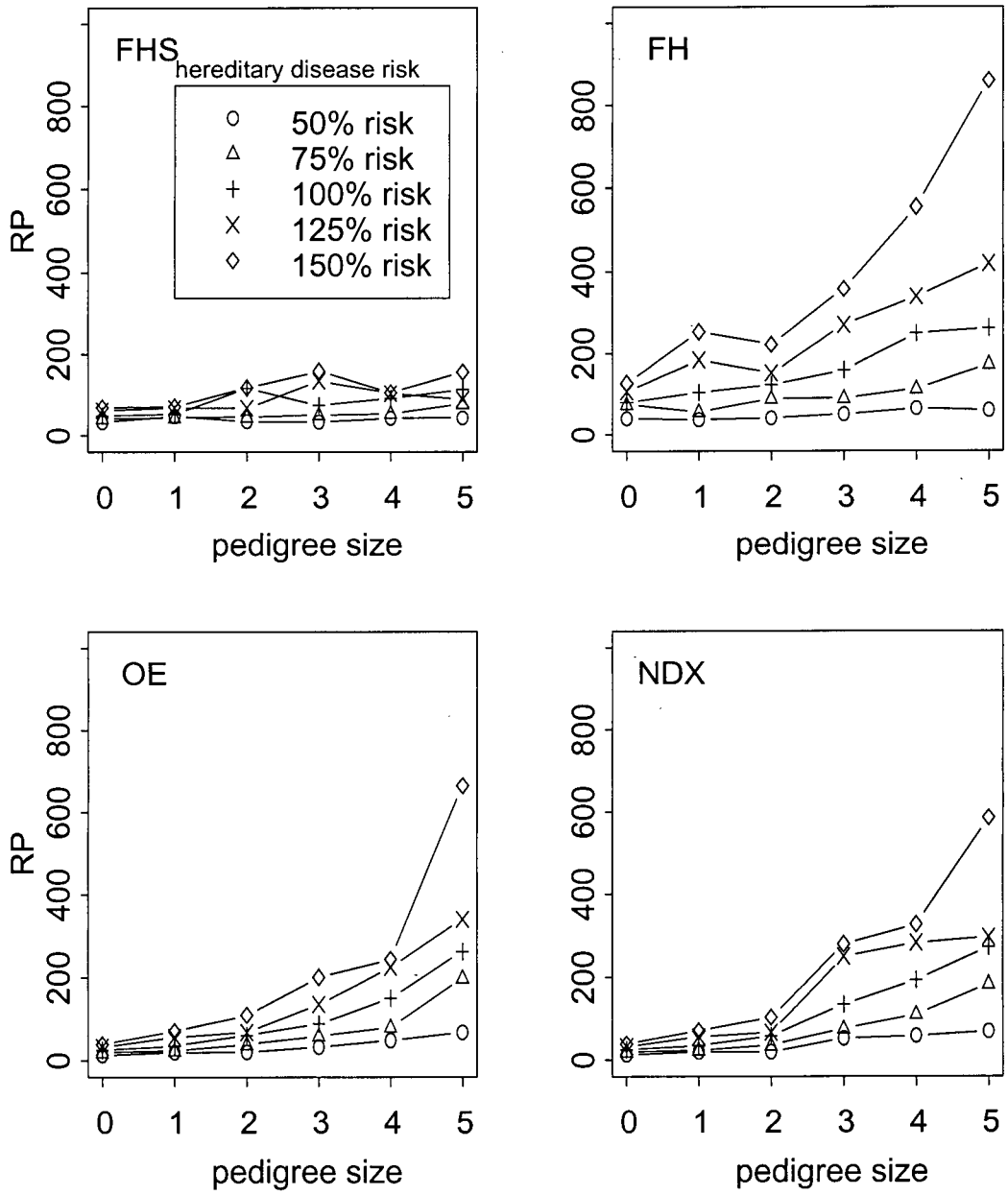


Figure 4.13 Relative probability (RP) associated with four family history measures as predictors of BRCA1 mutation carrier status for different estimates of hereditary breast/ovarian cancer risk. All probands are age 40 years. Pedigree size is the proband's number of sisters, maternal aunts and paternal aunts. 100% hereditary cancer risk refers to the estimates of Berry et al (1997); 150% risk is 1½ times those estimates.

4.5 Stability: disease risk in the population

As stated earlier, if the risk of hereditary breast/ovarian cancer was the same as that of sporadic cancer, it might be difficult to distinguish between the family histories of BRCA1 mutation carriers and non-carriers. The incidence of overall breast and ovarian cancer in the simulation model was based on BC data, but cancer incidence varies widely around the world and among different ethnic groups. In Los Angeles between 1988 and 1992, the age-standardized incidence rate of breast cancer was nearly five times higher in non-Hispanic White women compared to Korean women, and the rate of ovarian cancer was two to three times higher (Parkin et al 1997). Some of this variation is due to diagnostic and reporting practices (including screening programs), and some is the result of different environmental exposures and genetic differences between the populations.

The simulation model assumed that the overall risk of breast/ovarian cancer can be estimated using population disease rates in BC. These are not estimates of purely sporadic cancer rates because some of the cases in BC are hereditary (i.e., the result of germline BRCA1 mutations). Ford et al (1995) estimated the proportion of breast cancer cases due to germline BRCA1 mutations as 7.5% for cases diagnosed between ages 20 and 29, 5.1% for cases diagnosed between ages 30 and 39, 2.2% for cases diagnosed between ages 40 and 49, 1.4% for cases diagnosed between ages 50 and 59, and 0.8% for cases diagnosed between 60 and 69 years. The corresponding percentages of ovarian cancer cases due to BRCA1 mutations are 5.9%, 5.6%, 4.6%, 2.6% and 1.8% respectively. Overall, 1.7% of breast cancer cases and 2.8% of ovarian cancer cases diagnosed between ages 20 and 69 were due to BRCA1.

In the following analyses, simulations were performed to examine the stability of the output parameters for varying estimates of the population cancer risk. In the first set of simulations, estimates of risk that are proportional to the original estimates (i.e., estimates that are multiples of those based on BC data) are considered. As in the previous section, the aim of these analyses was not to measure the change in outcomes that result from two or more different parameter estimates, but rather to observe whether there was variation in the outcomes for a spectrum of estimates. In a second set of simulations, sporadic cancer estimates are estimated using BC population rates with a correction for an age-specific portion of hereditary cases.

Methods I

Data were generated using the simulation model described in Chapter 3. Simulations were performed in which population cancer risk estimates were 50% to 150% of those based on rates observed in BC during 1993-1997 (i.e., ½ to 1½ times the BC estimates). All other parameter estimates in the model remained as before. Simulations were performed for probands age 40 with pedigree sizes 0, 1, 2, 3, 4 and 5, and each family was classified according to the family history measures defined in section 4.2. For both OE and NDX, cutoff values were determined in 200 preliminary simulations for each estimate of population disease risk (1000 simulations total). Amongst probands with a germline BRCA1 mutation, the number with a positive family history is assumed to follow a binomial distribution where each proband has a positive family history with probability p. Sensitivity was estimated as the proportion of carriers having a positive family history. This estimate has variance $p(1-p)/n$, where n is the number of families in the simulation. Specificity was estimated using the same data but determining family history from only the non-inherited cancer cases in the pedigree. Sensitivity and specificity estimates in the main analyses were each generated from 2500 simulations (15,000 simulations total) and

have standard errors of less than 0.01. Post-test likelihoods and RP were calculated according to the formulae in section 3.4 and assuming 0.12% of the population were mutation carriers.

Results I

Data and median values of the observed-expected ratio from the preliminary simulations are plotted in Figure 4.14. There was overlap between the range of values for carriers and non-carriers, and more variation for low population risk estimates. This is not surprising because the denominator of the ratio is determined by the population risk estimate and lowering the denominator will increase the ratio and its variation. The median values were clearly separated for each population risk estimate, but nearest for low estimates. The midpoint of the medians for carriers and non-carriers was about 6 and, to be consistent with earlier analyses, 6.16 was chosen as the cutoff for positive values of OE. Data and median values of the family history index from the preliminary simulations are plotted in Figure 4.15. There were fewer distinct values of the index compared to the observed-expected ratio. There was overlap between the range of values for carriers and non-carriers, but the median values were clearly separated for each estimate. The midpoint of the medians for carriers and non-carriers was about 0.06 and, to be consistent with earlier analyses, 0.0625 was chosen as the cutoffs for positive values of NDX.

The sensitivity for FHS, FH, OE and NDX is plotted in Figure 4.16. The only family history measure affected by changes in the estimate of population cancer risk was OE, which reflects the dependence of the observed-expected ratio denominator on population disease risk. The specificity for various estimates of sporadic cancer risk is plotted in Figure 4.17. For each

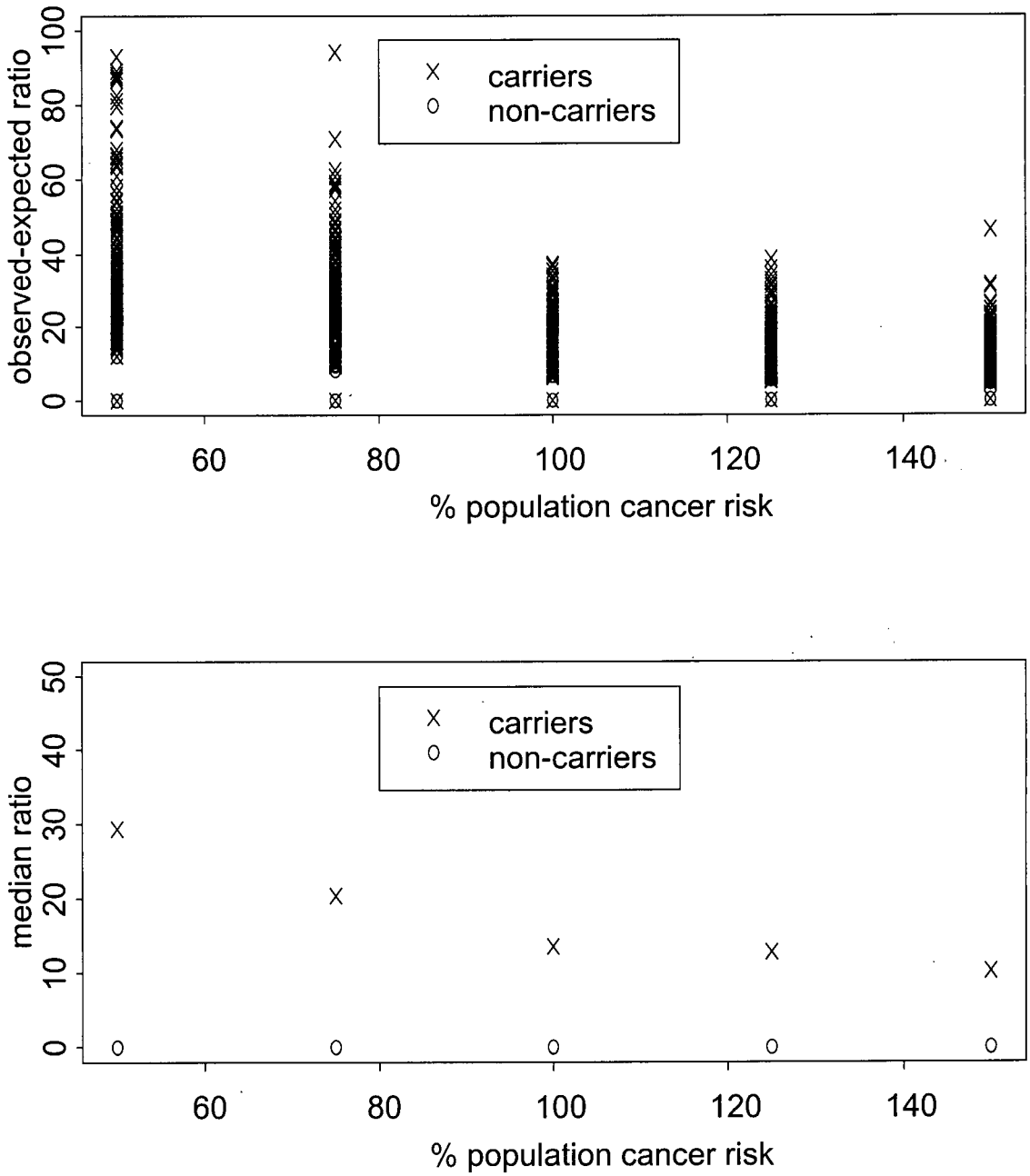
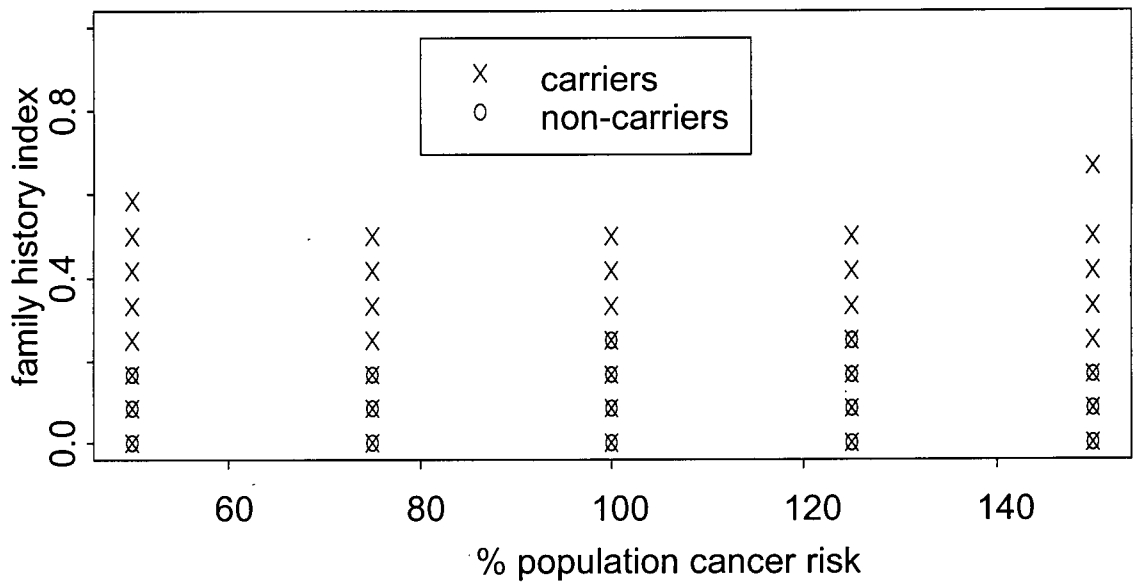


Figure 4.14 Individual and median values of the observed-expected ratio versus cancer risk in the population. All probands are age 40 years. 100% population cancer risk refers to the age-specific risks estimated by observed breast and ovarian cancer rates in BC during 1993-1997; 150% risk is 1½ times those estimates.



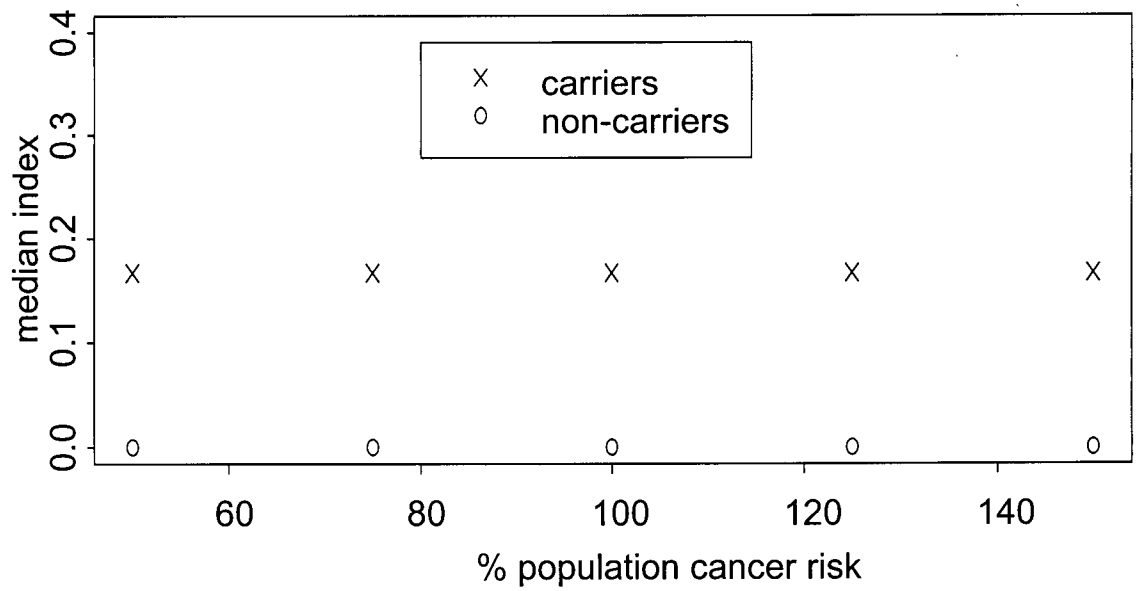


Figure 4.15 Individual and median values of the family history index versus cancer risk in the population. All probands are age 40 years. 100% population cancer risk refers to the age-specific risks estimated by observed breast and ovarian cancer rates in BC during 1993-1997; 150% risk is 1½ times those estimates.

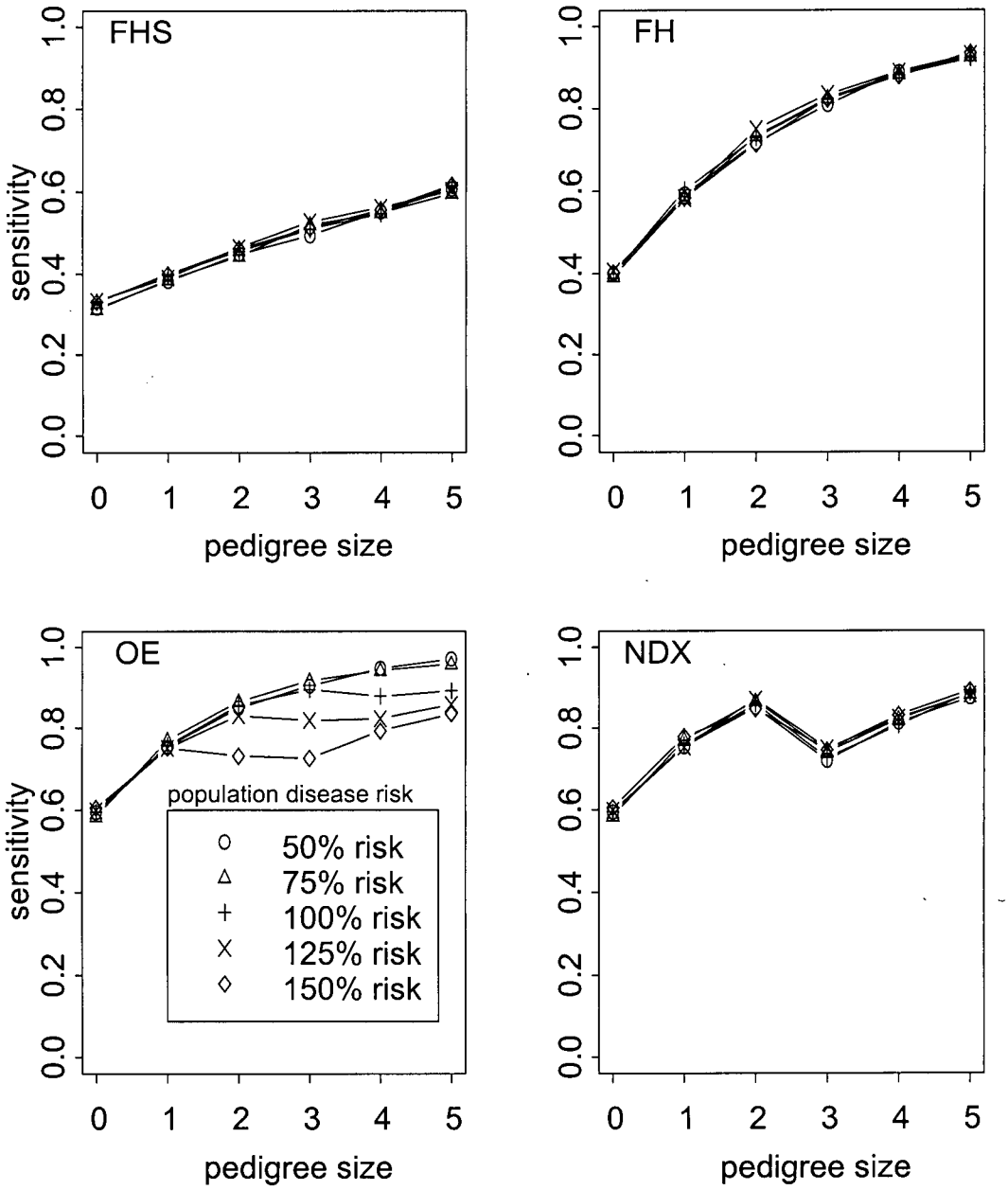


Figure 4.16 Sensitivity of four family history measures as predictors of BRCA1 mutation carrier status in populations with different rates of breast/ovarian cancer. All probands are age 40 years. Pedigree size is the proband's number of sisters, maternal aunts and paternal aunts. 100% population cancer risk refers to the age-specific risks estimated by observed breast and ovarian cancer rates in BC during 1993-1997; 150% risk is 1½ times those estimates.

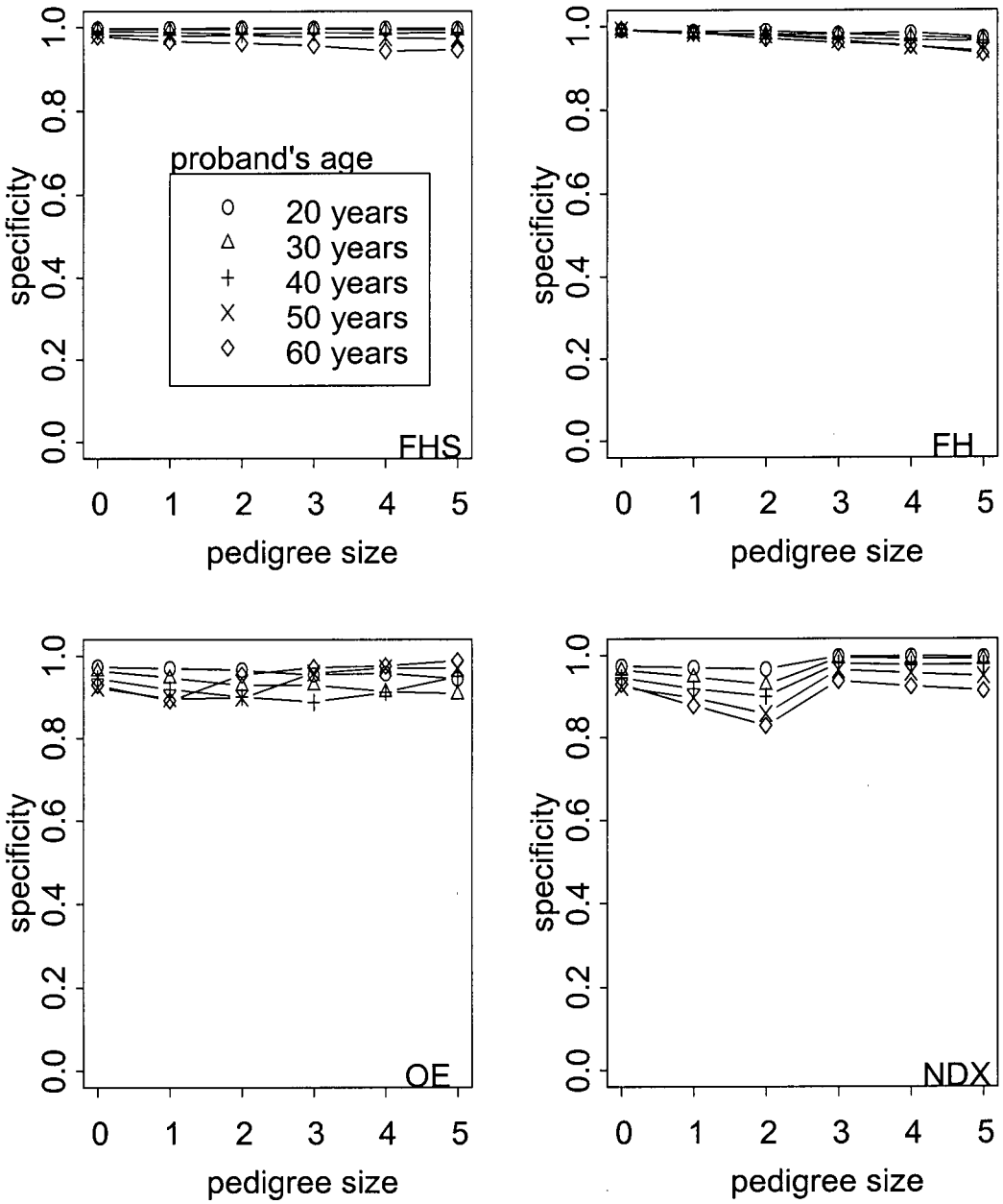


Figure 4.17 Specificity of four family history measures as predictors of BRCA1 mutation carrier status in populations with different rates of breast/ovarian cancer. All probands are age 40 years. Pedigree size is the proband's number of sisters, maternal aunts and paternal aunts. 100% population cancer risk refers to the age-specific risks estimated by observed breast and ovarian cancer rates in BC during 1993-1997; 150% risk is 1½ times those estimates.

family history measure, specificity was reasonably stable with respect to changes in the population cancer risk estimate.

For a population in which 0.12% of people carry a BRCA1 mutation, the post-test likelihoods associated with each family history measure are plotted in Figure 4.18. Except in the case of OE, the estimated population risk affected only the positive post-test likelihood. PTL+ was generally highest for small estimates of population risk, implying that a positive family history more strongly suggests a BRCA1 mutation in a population that has less breast/ovarian cancer. For OE, the population risk affected both the positive and negative post-test likelihoods, presumably because the denominator of OE (the "expected" family history) was calculated using the population risk estimate. The behavior of PTL+ was the same as for FHS, FH and NDX; PTL- for OE was greatest for the smallest estimates of population risk.

The RP associated with a positive family history is plotted in Figure 4.19 and the effect of the population risk estimate is again substantial. The RP associated with a positive family history was 2 to 10 times greater when the risk was 150% compared to 50% of that in BC. For all measures except FHS, the variation in RP increased with pedigree size.

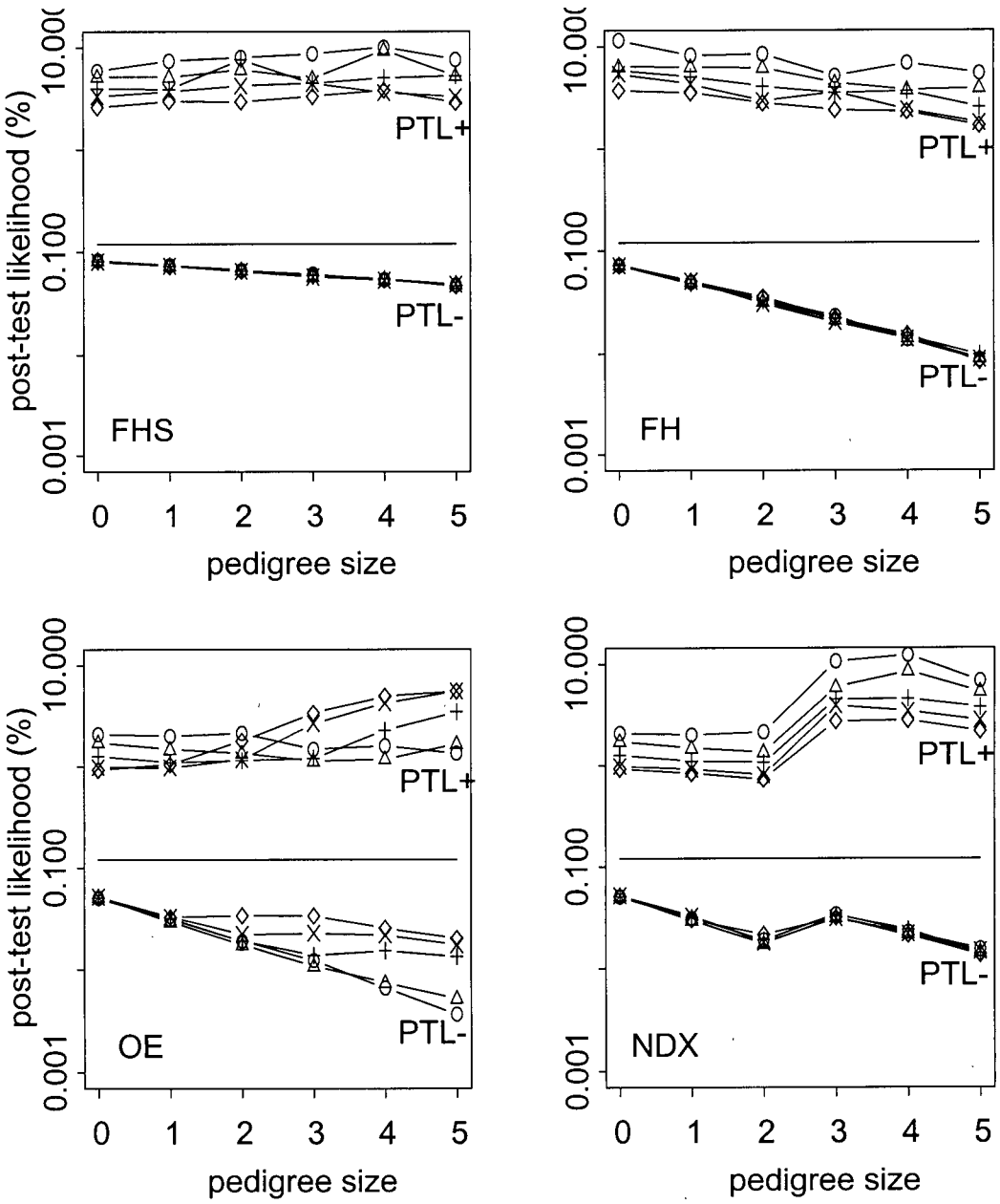


Figure 4.18 Positive and negative post-test likelihoods (PTL+ and PTL- respectively) associated with four family history measures as predictors of BRCA1 mutation carrier status in populations with different rates of breast/ovarian cancer. All probands are age 40 years. Pedigree size is the proband's number of sisters, maternal aunts and paternal aunts. The population breast/ovarian cancer risk estimate is indicated by the plotting symbol: probands with 50% risk are represented by circles, probands with 75% risk are represented by triangles, probands with 100% risk are represented by crosses, probands with 125% risk are represented by x's and probands with 150% risk are represented by diamonds. 100% population cancer risk refers to the age-specific risks estimated by observed breast and ovarian cancer rates in BC during 1993-1997; 150% risk is 1½ times those estimates.

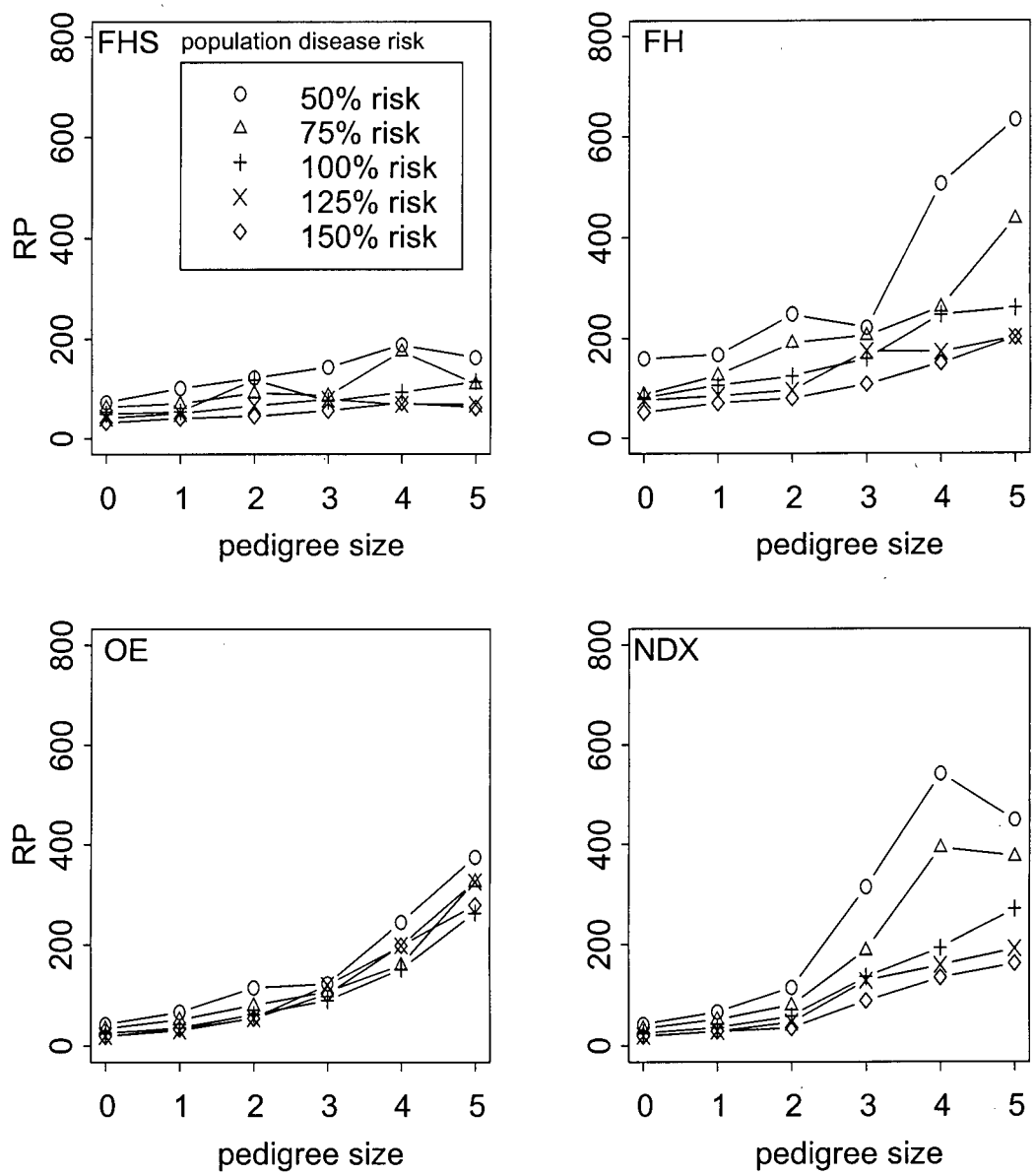


Figure 4.19 Relative probability (RP) associated with four family history measures as predictors of BRCA1 mutation carrier status in populations with different rates of breast/ovarian cancer. All probands are age 40 years. Pedigree size is the proband's number of sisters, maternal aunts and paternal aunts. 100% population risk refers to the age-specific risks estimated by observed breast and ovarian cancer rates in BC during 1993-1997; 150% risk is 1½ times those estimates.

Methods II

Data were generated using the simulation model described in Chapter 3. Simulations were performed in which population risk estimates were based on rates observed in BC during 1993-1997 minus the portion of cases that are believed due to BRCA1. The portion of breast cancer cases due to BRCA1 was estimated to be 7.5% for cases diagnosed before age 30, 5.1% for cases diagnosed between ages 30 and 39, 2.2% for cases diagnosed between ages 40 and 49, 1.4% for cases diagnosed between ages 50 and 59, and 0.8% for cases diagnosed between 60 and 69 years (Ford et al 1995). The corresponding portions of ovarian cancer cases due to BRCA1 mutations are 5.9%, 5.6%, 4.6%, 2.6% and 1.8% respectively (Ford et al 1995). All other parameter estimates in the model remained as before. Simulations were performed for probands age 40 with pedigree sizes 0, 1, 2, 3, 4 and 5, and each family was classified according to the family history measures defined in section 4.2. For both OE and NDX, cutoff values were determined in 200 preliminary simulations. Amongst probands with a germline BRCA1 mutation, the number with a positive family history is assumed to follow a binomial distribution where each proband has a positive family history with probability p. Sensitivity was estimated as the proportion of carriers having a positive family history. This estimate has variance $p(1-p)/n$, where n is the number of families in the simulation. Specificity was estimated using the same data but determining family history from only the non-inherited cases in the pedigree. Sensitivity and specificity estimates in the main analyses were each generated from 2500 simulations (15,000 simulations total) and have standard errors of less than 0.01 .

Results II

Data and median values of both the observed-expected ratio and family history index were almost identical to those of a 40 year-old proband in the original simulations from section 4.3. Using the same cutoff values for OE and NDX, the sensitivity and specificity estimates were almost identical to the original estimates for a 40-year-old proband from section 4.3.

4.6 Including cousins in the family history

Patients attending the HCP have been referred there by a physician – often according to their family history of disease. The HCP referral criteria do not mention the proband's cousins but genetic counselors often use this information when assessing the likelihood that someone carries a BRCA1 mutation. This section considers the change in sensitivity, specificity and post-test likelihoods that result from a family history measure that incorporates information about a proband's cousins.

Methods

The simulation model in Chapter 3 was modified to incorporate the proband's cousins. This required that the original model be changed to include the proband's uncles as well as his or her aunts. Uncles' ages were determined in the same way as the aunts' ages. The number of daughters for aunts and uncles was determined as a random variable from a Poisson distribution with mean 0.85 (separately for each aunt and uncle). This distribution was chosen because the number of children is a discrete variable, the average number of children per woman in BC is

1.7 and because the Poisson distribution accords with the observed distribution (Statistics Canada 1993). Aunts and uncles younger than 17 were assumed to have had no children.

A new family history measure was defined to incorporate information about the proband's cousins.

> Definition: FHC ("family history including cousins") is positive if breast/ovarian cancer has been diagnosed in two of the proband's close relatives from the same side of the family, or any close relative before age 50 years. Close relatives comprise the proband's mother, sisters, aunts and grandmothers. FHC is also positive if breast/ovarian cancer has been diagnosed in three cousins from the same side of the family, or in any cousin before age 50. FHC is otherwise negative.

The measure FHC is the same as the earlier measure FH but it is also positive if three or more cousins from one side of the proband's family have been diagnosed with breast/ovarian cancer, or a cousin has been diagnosed with cancer before age 50.

Simulations were run for 1000 probands age 20, 30, 40, 50 and 60 years with pedigree sizes between 0 and 5 (30,000 simulations total). In these analyses, the pedigree size refers to the number of a proband's aunts and the number of uncles on each side of the family. For example, a pedigree of size 2 implies the proband has two sisters, two maternal aunts, two maternal uncles, two paternal aunts and two paternal uncles. Family history was assessed according to the measures FH and FHC. The standard error of the sensitivity and specificity estimates will be less that 0.016 and 95% confidence intervals will have widths less than $\pm$ 0.032.

Results

There was little difference in the estimates of sensitivity or specificity for the family history measures FH and FHC (Table 4.2). Sensitivity and specificity were sometimes slightly higher when cousins were included in the family history. Because the inclusion of cousins had little effect on sensitivity and specificity, there will be little change in the post-test likelihoods or RP.

4.7 Comparing predictions with those of the Berry model

The post-test likelihood associated with a family history measure is the probability that one of the proband's parents is a BRCA1 mutation carrier. The probability that the proband carries a mutation is half of that, and can be compared with the probability estimated by the Berry model. The analyses in this section use family history defined by FHS and FH, although the same analyses could be performed for other measures.

Methods

The simulation model was used to generate 2500 families with probands age 20, 30, 40, 50 and 60 years and pedigree sizes 0 to 5 (75,000 families total). For each family, estimates that the proband carried a BRCA1 mutation were calculated assuming 0.12% of the population carry a BRCA1 mutation. The Berry model was implemented using S-Plus and the cancer risk estimates for BRCA1 mutation carriers that are given in Berry et al (1997). Cancer risk estimates for non-carriers were based on BC population rates.

Table 4.2 The sensitivity and specificity of family history as a predictor of germline BRCA1 mutation carrier status when including and excluding the proband's cousins. Estimates that include cousins are based on the family history measure FHC. Estimates that ignore cousins are based on the measure FH.

Proband Age	Pedigree Size	Sensitivity		Specificity	
		Including Cousins	Ignoring Cousins	Including Cousins	Ignoring Cousins
20	0	0.33	0.33	0.99	0.99
	1	0.42	0.42	0.99	0.99
	2	0.55	0.54	0.99	0.99
	3	0.65	0.64	0.99	0.99
	4	0.71	0.70	0.98	0.98
	5	0.76	0.75	0.98	0.98
30	0	0.40	0.40	1.00	1.00
	1	0.55	0.54	0.99	0.99
	2	0.65	0.63	0.97	0.97
	3	0.77	0.74	0.98	0.98
	4	0.83	0.81	0.97	0.97
	5	0.86	0.85	0.98	0.98
40	0	0.40	0.40	0.99	0.99
	1	0.61	0.58	0.99	0.99
	2	0.73	0.69	0.98	0.98
	3	0.87	0.84	0.97	0.97
	4	0.92	0.89	0.97	0.97
	5	0.95	0.91	0.96	0.96
50	0	0.41	0.41	0.99	0.99
	1	0.68	0.64	0.99	0.99
	2	0.84	0.81	0.98	0.98
	3	0.93	0.90	0.96	0.96
	4	0.96	0.93	0.96	0.96
	5	0.99	0.97	0.95	0.95
60	0	0.42	0.42	0.99	0.99
	1	0.72	0.69	0.99	0.99
	2	0.88	0.85	0.98	0.98
	3	0.94	0.92	0.96	0.96
	4	0.97	0.95	0.95	0.95
	5	0.99	0.98	0.94	0.94

The average probability from the Berry model was calculated separately for families in which the disease history was positive and for families in which the disease history was negative. The mean from families with a positive history was compared to PTL+. The mean from families with a negative history was compared to PTL-. Separate analyses were performed using FHS and FH to define family history of disease.

Results

Mean estimates from the Berry model are given alongside the post-test likelihoods for FHS and FH in Tables 4.3 and 4.4 respectively.

In families where there is no history of cancer, the Berry estimates and post-test likelihoods are in close agreement. The probabilities (both the PTL and the Berry estimate) are between 0.001% and 0.05%, and generally decrease as the proband's age and pedigree size increase.

When there is a family history of cancer, the post-test likelihoods are up 30 times greater than the probabilities estimated by the Berry model. The post-test likelihoods take values between 0.88% and 6.7%; the estimates from the Berry model take values between 0.032% and 2.5%. The probabilities associated with FHS generally decrease as the proband's age and pedigree size increase, but the probabilities associated with FH are more constant with respect to these factors.

Table 4.3 Estimates of the probability (%) that someone carries a BRCA1 mutation based on their family history of breast/ovarian cancer. Estimates were determined according to the post-test likelihoods associated with the family history measure FHS and according to predictions from the Berry model (Berry et al 1997). All estimates assume 0.12% of the population are carriers. Each post-test likelihood estimate was based on 2500 simulated families from section 4.3. For each proband age and pedigree size, estimates for the Berry model were the average probability in 2500 simulated families.

Proband Age	Pedigree Size	FHS is Positive		FHS is Negative	
		PTL+	Berry	PTL-	Berry
20	0	6.699	2.524	0.053	0.040
	1	3.908	1.431	0.051	0.035
	2	4.523	0.830	0.050	0.030
	3	3.664	0.601	0.051	0.026
	4	3.681	0.590	0.050	0.023
	5	5.409	0.495	0.050	0.021
30	0	3.792	0.859	0.045	0.035
	1	2.691	0.613	0.044	0.028
	2	4.544	0.701	0.042	0.022
	3	5.217	0.519	0.042	0.018
	4	3.443	0.265	0.040	0.016
	5	3.510	0.276	0.039	0.013
40	0	2.080	0.872	0.040	0.031
	1	2.115	0.460	0.037	0.022
	2	1.772	0.340	0.032	0.016
	3	2.353	0.225	0.029	0.012
	4	2.358	0.370	0.027	0.009
	5	2.724	0.179	0.026	0.007
50	0	1.205	0.563	0.038	0.030
	1	1.389	0.380	0.031	0.018
	2	1.826	0.197	0.024	0.012
	3	1.652	0.174	0.020	0.008
	4	1.726	0.121	0.015	0.005
	5	1.762	0.100	0.012	0.004
60	0	1.003	0.686	0.039	0.030
	1	1.036	0.237	0.026	0.016
	2	1.098	0.144	0.018	0.009
	3	1.065	0.119	0.013	0.006
	4	0.893	0.059	0.009	0.003
	5	0.965	0.032	0.007	0.002

Table 4.4 Estimates of the probability (%) that someone carries a BRCA1 mutation based on their family history of breast/ovarian cancer. Estimates were determined according to the post-test likelihoods associated with the family history measure FH and according to predictions from the Berry model (Berry et al 1997). All estimates assume 0.12% of the population are carriers. Each post-test likelihood estimate was based on 2500 simulated families from section 4.3. For each proband age and pedigree size, estimates for the Berry model were the average probability in 2500 simulated families.

Proband Age	Pedigree Size	FH is Positive		FH is Negative	
		PTL+	Berry	PTL-	Berry
20	0	3.745	0.401	0.041	0.040
	1	2.485	0.285	0.035	0.033
	2	2.408	0.195	0.029	0.028
	3	2.195	0.187	0.023	0.024
	4	1.869	0.158	0.019	0.021
	5	1.556	0.120	0.015	0.018
30	0	2.897	0.628	0.037	0.035
	1	1.887	0.312	0.029	0.028
	2	2.008	0.157	0.021	0.021
	3	2.180	0.147	0.018	0.017
	4	1.908	0.167	0.011	0.014
	5	1.642	0.075	0.009	0.012
40	0	3.401	0.420	0.035	0.035
	1	2.188	0.420	0.025	0.026
	2	2.032	0.214	0.015	0.016
	3	1.750	0.082	0.010	0.013
	4	1.536	0.098	0.007	0.009
	5	1.492	0.056	0.006	0.008
50	0	3.043	0.711	0.036	0.035
	1	2.164	0.317	0.021	0.021
	2	2.148	0.121	0.013	0.013
	3	1.529	0.157	0.007	0.008
	4	1.128	0.043	0.004	0.006
	5	0.959	0.044	0.002	0.004
60	0	3.352	0.405	0.036	0.038
	1	2.757	0.265	0.018	0.020
	2	1.685	0.136	0.010	0.011
	3	1.348	0.057	0.005	0.006
	4	1.211	0.041	0.003	0.004
	5	0.879	0.040	0.001	0.003

4.8 Summary

An ideal family history measure should be simple to determine and account for the biologic relationships between family members, disease characteristics associated with BRCA1, family size and the disease incidence rate in the population. The measures FHS and FH were easy to determine but neither adjusted for family size or the population disease rate. The measure OE adjusted for family size and the population disease rate but was difficult to determine. NDX attempted to incorporate the benefits of the other family history measures: it was simpler to determine than OE (but not as simple to determine as FHS or FH) and it adjusted for the proband's pedigree size (but not his or her age).

Generally; the highest sensitivity was observed in the oldest probands and those with the largest families, and the highest specificity was observed in the youngest probands and those with the smallest families. The estimate of hereditary disease risk affected sensitivity but not specificity. The estimate of population disease risk had little effect on sensitivity and specificity except in the case of OE, where lower estimates of hereditary cancer risk produced lower values of sensitivity. For NDX, the effects of the proband's pedigree size were inconsistent and partly due to the use of a cutoff for making a dichotomous outcome from a continuous one. The sensitivity and specificity of FH were slightly higher than for FHS, but FH requires disease information about more of the proband's relatives. The sensitivity and specificity of OE and NDX cannot be compared to one another or the other family history measures because OE and NDX are based on arbitrary cutoff values.

The post-test likelihoods depended on the proband's age and family size, but PTL+ and PTL- were clearly separated for each measure. The somewhat erratic behavior of PTL+ with respect

to changes in the proband's age and pedigree size can be attributed to the behavior of sensitivity and specificity from which the post-test likelihoods were calculated. PTL- was usually lowest for older probands and probands with large pedigrees, and when the estimate of hereditary cancer risk was highest. PTL+ was usually highest when the estimate of population risk was lowest. The adjustment to the population risk estimates to adjust for hereditary disease did not affect sensitivity or specificity, and hence will not affect the post-test likelihood estimates.

The RP associated with family history depended on the proband's age and family size, the estimate of hereditary cancer risk and the risk of sporadic disease in the population. The highest values of RP generally occurred amongst the oldest probands and those with large families, and when the estimate of hereditary cancer risk was high or the estimate of population risk was low.

Including someone's cousins when assessing his or her family history had little effect on the sensitivity or specificity of the family history as a predictor of BRCA1 mutation status.

The post-test likelihoods were compared with the Berry model predictions that someone is a carrier. The probabilities estimated by the Berry model were consistently lower than PTL+ in families where there was a history of cancer, but similar to PTL- in families where there was no history of cancer. An elaboration of these results is given in the discussion.

Chapter 5: Family history and referral criteria for a BRCA1 testing program in BC

5.1 BC demographics and breast/ovarian cancer epidemiology

About 4.1 million people live in BC (www.bcstats.bc.gov.bc.ca/data/pop/popstart.html/ on November 30, 2000). The median age is 37 years and there are 99 men for every 100 women. About 25% of the population are under 20 and about 9% are over 69. In a 1996 survey conducted by Statistics Canada (www.statcan.ca/start.html on November 30, 2000), about 56% of people in BC reported a single ethnic origin. One quarter of these people were British (including English, Irish, Scottish and Welsh), one quarter were European, and one quarter were of Southern or Southeastern Asian ancestry. Other people having a single ancestry reported being Arab, African, West Asian, Latin American, Central American, South American, Caribbean or Canadian. Forty-four percent of people in the survey reported multiple ethnic origins, the majority of which included British. About 2% of people reported Aboriginal ancestry.

The estimated breast/ovarian cancer rate and number of incident cases for BC women in the year 2000 are shown in Table 5.1. The incidence rate is highest in women 80 years of age and older, but the frequency of new cases is highest in women age 60 to 79.

Table 5.1 Breast/ovarian cancer incidence rates and estimated number of new cases that will be diagnosed in BC during the year 2000. Incidence rates are from 1997 (www.bccancer.bc.ca); estimated new cases based on population estimates for 2000 (www.bcstats.gov.bc.ca).

Age Group	Breast Cancer Incidence*	Ovarian Cancer Incidence*	Combined Incidence*	Estimated New Cases
0-19	0.2	0.4	0.6	5
20-39	22.2	5.2	27.4	164
40-59	176.3	20.5	196.8	1143
60-79	377.1	51.1	428.6	1267
80+	420.3	58.1	478.4	402
Total	122.9	16.6	139.5	2981

* diagnoses per 100,000 women annually

The ethnicity of persons diagnosed with cancer is not recorded by the BC Cancer Registry. The age-adjusted incidence rates for breast and ovarian cancer vary around the world (Table 5.2) and might be considered estimates for the corresponding ethnic populations in BC. Breast cancer incidence in England and Wales is more than twice as common as it is in India. Ovarian cancer incidence in Poland is more than twice as common as in Japan. The rates in Table 5.2 are based on data from the late 1980s and early 1990s and were estimated using a different standard population than the rates in Table 5.1 .

The age-standardized mortality rate (ASMR) for female breast cancer in BC Status Indians is about 12% higher than the provincial average, and the ASMR for female reproductive system cancers (ICD-9 codes 179-184) is 21% higher than the provincial average (British Columbia Vital Statistics Agency 1998). Differences in disease mortality do not imply differences in disease incidence, and could reflect changes in diagnostic and reporting practices, treatment and survival.

Table 5.2 Annual age-adjusted breast and ovarian cancer incidence rates in selected populations. (From Parkin et al 1997.)

Population	Age-adjusted Incidence Rate*		
	Breast Cancer	Ovarian Cancer	Combined
British Columbia	84.3	10.3	94.6
England and Wales	68.8	12.4	81.2
Italy (Florence)	67.0	9.4	76.4
Poland (Warsaw)	43.2	13.3	56.5
China (Shanghai)	26.5	5.8	32.3
Japan (Osaka)	24.3	5.6	29.9
India (Bombay)	28.2	7.2	34.4

* per 100,000 women annually

It is difficult to estimate the distribution of family size in BC because available statistics define a family as the persons living together in a household. These can be quite different from statistics pertaining to the biological family. In 1993, Statistics Canada published results of the 1991 census regarding fertility patterns (Statistics Canada 1993). Women in BC gave birth to an average of 1.7 children, although a third of women over age 15 reported no births and 6% had given birth 5 times or more. Excluding single women and women under 15, the average number of births for women was 2.3. While many single women had children, the average number was not reported. Fertility rates between 1950 and 1999 have shown a substantial decline (Statistics Canada 2000). The highest rates occurred around 1960, when women in BC had an average of 3.9 children. Fertility also depended on a woman's ethnicity. At the extremes, married Aboriginal women in 1991 (age 15 years and older) had an average of 3.6 children, and married women (age 15 years and older) with mixed ethnic origins had an average of 2.1 children. Assuming half of children are female, and using the mean number of a person's

sisters, maternal and paternal aunts, the average pedigree size for persons age 20 to 60 in BC is probably less than two.

There is little data on the proportion of people in BC with a family history of breast/ovarian cancer. The BC Women's Health Study collected information from women under age 75 who had been diagnosed with breast cancer between 1 June 1988 and 30 June 1989, and a group of healthy controls who were selected from the Provincial Voters List (Yang et al 1992, 1993). Of 1025 controls, 11% reported a mother or sister who had been diagnosed with breast cancer. (Of 1017 women with breast cancer, 17% reported a mother or sister who also had been diagnosed with breast cancer.) Information about other relatives was not collected nor was information about ovarian cancer, and diagnoses were not confirmed by medical records.

The analyses in Chapter 4 examined family history of breast/ovarian cancer as a predictor of BRCA1 mutation carrier status, and demonstrated the accuracy of predictions depended on a person's age and family size. In this chapter, the implications of those results are considered for a BRCA1 testing program in BC. The section considers a program with referral criteria based on family history of disease and restrictions based on age and family size.

5.2 Referral criteria for a BRCA1 genetic testing program

The potential benefit of a program depends on the population at which it is aimed. In BC, genetic testing is available from the Hereditary Cancer Program (HCP) at the BC Cancer Agency. Referral to the program does not imply genetic testing will be offered. When someone is referred to the HCP, his or her family history of disease is evaluated to determine the

probability they carry a BRCA1 mutation. In some situations (e.g., when no relatives' medical records can be obtained), the probability of carrying a BRCA1 mutation is not estimated. Genetic testing is considered if the probability is sufficiently high. People in the population can be categorized according to whether they carry a mutation and whether they would be referred to the program. A two-way classification of the population is presented in Figure 5.1.

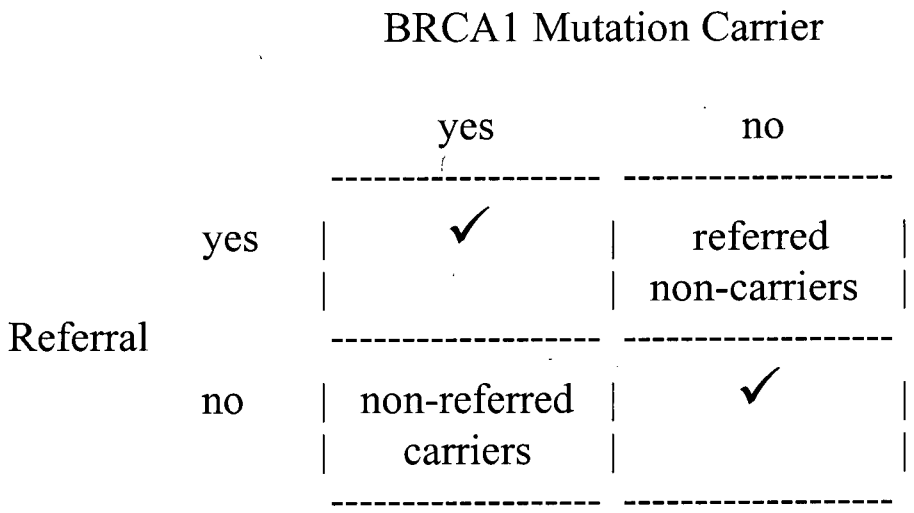


Figure 5.1 Referral and BRCA1 mutation carrier status in a genetic testing program.

Genetic testing is considered beneficial for anyone who has evidence that he or she might be genetically susceptible to cancer – and who wants to be tested. The types of interventions will change as more is learned about BRCA1 and cancer, but current options for people with BRCA1 mutations include frequent surveillance to detect cancer (e.g., physical examination, mammography or transvaginal ultrasound), chemopreventive agents (e.g., tamoxifen or raloxifene) or prophylactic surgery (e.g, mastectomy or oophorectomy). Non-carriers (of

BRCA1) who receive testing will learn that they do not have a germline BRCA1 mutation. This is only completely informative if disease in relatives is known to have been caused by a particular mutation. People who would not be referred for genetic testing are unlikely to carry a BRCA1 mutation, and probably do not consider themselves as genetically susceptible. Unfortunately, BRCA1 mutation carriers who are not referred for genetic testing will miss the program's benefits.

The cost of a provincial genetic program will be proportional to the number of people who are referred – both mutation carriers and non-carriers. The number of referred BRCA1 mutation carriers divided by the total number of carriers is the *program sensitivity*. This indicates the proportion of carriers that can be referred to the program and is at most 1.0 or 100%. The number of referred carriers divided by the total number of referrals is the *program PTL+*, which is sometimes referred to as the program positive predicted value, and indicates the proportion of referrals who will be found to carry a mutation. The most efficient program can only have a PTL+ of 0.5 or 50% because, if family history perfectly predicted whether someone had a parent who was a carrier, only 50% of the probands would be carriers.

There are about 2,660,000 people age 20-69 years in BC. This thesis does not consider genetic testing for people under age 20 or older than age 69. The psychological and emotional effects of genetic testing are not well understood, especially for young people. The risk of breast/ ovarian cancer in women younger than 20 is small and the risk in women older than 70 is approximately the same for carriers and non-carriers. The distribution of family size in the population is assumed to 20%, 25%, 35%, 15%, 3% and 2% for pedigrees of sizes 0 to 5 respectively. This assumption was based on BC population data regarding the distribution of childbirths for women (Statistics Canada 1995b). If 0.12% of people in BC carry a BRCA1

mutation, 1991 of these people would be expected to have a family history of disease. A genetic testing program with eligibility based on FH* would have a program sensitivity of roughly 62% and about 4% of people tested would be found to be carriers. This does not imply 62% of carriers in the population would be identified. Genetic testing of 20 to 69 year-olds would identify about 50% of mutation carriers overall.

If 0.12% of people in BC are BRCA1 mutation carriers and program eligibility is defined by family history measured by the variable FH, the number who are expected to have a family history of disease and the number of those who are mutation carriers are given in Table 5.3. These numbers are based on the sensitivity and specificity estimates of Chapter 4. The number of people who are eligible for the program will determine both the program cost and the number of people who might benefit from it. As greater restrictions to referral are introduced, the population that is eligible for referral (and hence the cost of the program) decreases. Clearly, the least expensive program in one where nobody is eligible for referral. The program sensitivity and PTL+ depend on the age and pedigree size of the population. If the restrictions exclude younger people, the proportion of carriers that can be referred for testing (i.e., the program sensitivity) is increased, but the proportion of referrals who carry a mutation (i.e., the program's PTL+) is reduced. Alternatively, restrictions might be chosen to exclude older probands, in which case the program sensitivity is reduced and the program PTL+ is increased. If program restrictions exclude people with small families, the sensitivity of the program is increased and the PTL+ is reduced.

* FH is positive if two or more of the proband's close relatives from the same side of the family have been diagnosed with breast/ovarian cancer, or if any close relative has been diagnosed before age 50 years. Close relatives of the proband include the mother, sisters, aunts and grandmothers.

Table 5.3 Family history of breast/ovarian cancer and BRCA1 mutation carrier status in BC assuming 0.12% of people are carriers. A family history is positive if someone has two close relatives from the same side of the family with breast/ovarian cancer or one close relative who was diagnosed before age 50. Close relatives include the mother, sisters, aunts and grandmothers. There are assumed to be 20%, 25%, 35%, 15%, 3% and 2% of the population with pedigree sizes 0 to 5 respectively.

Proband Age	Pedigree Size	People With a Family History	Carriers With a Family History	Program Sensitivity	Program PTL+
20-69	any	49,006	1,991	62.4	4.1
	> 0	45,184	1,743	68.3	3.9
	> 1	34,879	1,288	73.3	3.7
30-69	any	42,313	1,665	65.8	3.9
	> 0	39,063	1,461	72.2	3.7
	> 1	30,267	1,080	77.6	3.6
40-69	any	30,542	1,192	69.2	3.9
	> 0	28,377	1,050	76.2	3.7
	> 1	22,374	775	81.8	3.5
50-69	any	17,857	670	71.7	3.7
	> 0	16,649	593	79.4	3.6
	> 1	13,322	435	84.7	3.3
20-59	any	41,284	1,713	60.9	4.1
	> 0	37,920	1,497	66.5	3.9
	> 1	28,813	1,107	71.5	3.8
20-49	any	31,149	1,321	58.5	4.2
	> 0	28,535	1,150	63.7	4.0
	> 1	21,577	853	68.6	4.0
20-39	any	18,464	799	54.3	4.3
	> 0	16,808	693	58.9	4.1
	> 1	12,506	512	63.4	4.1

Eligibility for referral to a testing program might depend on factors other than family history, and this can affect both the program sensitivity and PTL+. Current referral criteria for the HCP are shown in Table 5.4. The first two criteria are based on aspects of a person's own history of breast/ovarian cancer. The third criterion is based on studies that demonstrate Ashkenazi Jews are more likely to carry a BRCA1 mutation. The fourth criterion reflects the HCP providing tests for genes other than BRCA1, and the fifth criterion reflects evidence that someone is more likely to carry a genetic mutation if they have a relative who is a carrier. The referral criteria concerning family history might appear broad for BRCA1 testing, but genetic counseling is considered important for a wider group of patients. In addition, the HCP conducts research on the relationship between genes and family history and this requires consideration of novel constellations of disease amongst family members. The referral criteria will change as knowledge about genetic susceptibility, cancer and genetic testing increase. Other referral criteria might be used in a program to reduce the total number of people who are eligible for testing, but not affect the program sensitivity or PTL+. For example, men may not be eligible for the program if they are not considered at risk of disease. Regardless of its association with disease risk, BRCA1 testing might be beneficial to men for determining disease risk in their children.

5.3 Comparison of simulation results with observations from the Hereditary Cancer Program at the BC Cancer Agency

Upon his or her first visit to the HCP, each patient is interviewed by a geneticist or genetic counselor to determine details of the family. The interview includes questions about each relative's age, history of cancer and history of other diseases. Additional questions about

female relatives address pregnancy history, menopausal status and exposure to factors associated with breast and ovarian cancer risk. For each relative that has been diagnosed with cancer, a pathology report is sought to verify details of the diagnosis.

Table 5.4 Criteria for referral to the Hereditary Cancer Program (HCP) at the BC Cancer Agency (www.bccancer.bc.ca/ on July 3, 2000). Note that "genetic risk assessment" is a reference to genetic counseling and does not imply an offer of genetic testing.

Genetic risk assessment may be appropriate for an individual who meets the following criteria:

- a woman diagnosed with breast cancer at age 35 or younger, **or**
- a woman with ovarian cancer diagnosed at age 50 or younger, **or**
- an Ashkenazi Jewish woman with breast or ovarian cancer diagnosed at any age, **or**
- a man or woman with colon cancer diagnosed age 50 or younger, **or**
- a blood relative with a confirmed mutation of a cancer susceptibility gene

***Or* whose family history includes any *two* (2) of the following:**

- cancer in two (2) or more closely related family members (parents, siblings, children, grandparents, aunts, uncles) on the same side of the family
- cancers at an earlier age than expected in the general population (e.g., breast cancer before menopause or colon cancer before age 50)
- multiple primary cancers in one (1) individual
- cancers associated with known hereditary syndromes (e.g., breast/ovary, colon/uterus)
- male breast cancer

If a HCP patient has an increased probability of carrying a BRCA1 mutation, genetic testing is considered for the patient or a family member who has been diagnosed with breast or ovarian cancer. This family member is the index case. If tests indicate the index case is a carrier, the proband is offered testing for that same mutation. If tests indicate the index case is not a carrier, another relative who has been diagnosed with breast or ovarian cancer might become the index

case. If no index case with a germline mutation is found, genetic testing is not offered to the proband. Test results for the index case are used to classify the family as BRCA1-positive or BRCA1-negative, although the proband in a BRCA1-positive family does not necessarily carry a mutation.

The simulation model in Chapter 3 attempts to mimic breast and ovarian cancer incidence for typical families from BC. People at the HCP are not representative of the BC population, and patients for whom the family's BRCA1-status is known might not be typical of other HCP patients. The HCP sample is clearly different from the general BC population, but a comparison of the groups is nonetheless interesting.

Methods

Anonymized family pedigrees were obtained for a random sample of 110 HCP patients. Families were classified as BRCA1-positive or BRCA1-negative based on genetic test results for the index case. (A family was BRCA1-positive if the index case carried a mutation. A family was BRCA1-negative if the index case did not carry a mutation.) Family history was considered positive if breast or ovarian cancer had been diagnosed in two of the proband's close relatives from the same side of the family, or any close relative before age 50. Close relatives include the proband's mother, sisters, aunts and grandmothers. This definition corresponds to the measure FH in Chapter 4. Note that a proband could be the index case for her family. The sample comprised pedigrees for 55 BRCA1-positive and 55 BRCA1-negative families, but the status of each family was not revealed until the predictions based on family history were complete. A cross-tabulation of FH and the BRCA1 status of each family is given in Figure 5.2.

		Family BRCA1 Status: Positive	Family BRCA1 Status: Negative
Family History (FH)	Positive	49	45
	Negative	6	10
		55	55

Figure 5.2 Family history (FH) and family BRCA1 status for patients attending the Hereditary Cancer Program (HCP) at the BC Cancer Agency. Family history was positive if breast or ovarian cancer had been diagnosed in two of the proband's close relatives from the same side of the family, or any close relative before age 50. Close relatives include the mother, sisters, aunts and grandmothers. Families were classified as BRCA1-positive or BRCA1-negative based on genetic test results for the index case. (See text for details.)

Ninety-three (85%) of the probands had a positive family history of breast/ovarian cancer as measured by the variable FH. (This is not a result of the analysis but a characteristic of the sample.) As a predictor of the family BRCA1 status, family history had a sensitivity of 89% and a specificity of 18% for the sample of patients from the HCP. Many people with a BRCA1-negative family had a positive family history of breast/ovarian cancer.

A simulation of 2500 families was generated with the proband's age and numbers of sisters, maternal aunts and paternal aunts corresponding to each of the HCP patients (275,000 simulations total). All data were generated using the simulation model and parameter estimates in Chapter 3. Sensitivity was estimated as the proportion of (simulated) carriers having a positive family history. Specificity was estimated using the same data but determining family history from only the non-inherited cases in the (simulated) pedigree. Post-test likelihoods were estimated as functions of sensitivity and specificity as given in section 3.3 (equations 3.6 and 3.7) and assumed 0.12% of the population are BRCA1 mutation carriers. Standard errors for sensitivity and specificity are less than 0.01.

The American Society of Clinical Oncology (ASCO) recommends genetic testing for BRCA1 be offered to people with greater than 10% probability of carrying a BRCA1 mutation (ASCO 1996). The family history measures in this thesis do not include information about the proband, and 0.05 (i.e., 5%) was added to a women's probability of carrying a BRCA1 mutation if she had been diagnosed with breast or ovarian cancer.

Results

For each patient, genetic counselors at the HCP attempt to obtain family pedigrees that include all first-and-second-degree relatives. This is not always possible and results provided here are based on information that is stored in patient charts at the HCP. Some pedigrees included notes to indicate where details were uncertain. Information marked as such was omitted from the analysis.

All of the families in the sample had a female proband. This was not a requirement for referral to the HCP or inclusion in the sample. The age of the proband was not known in one instance and that family was excluded from further analyses. The average proband age was 50.0 years (standard error 1.1, minimum 24, maximum 81, median 48) and 91 (84%) of probands had a diagnosis of breast/ovarian cancer.

The median number of sisters for a proband was 2 (minimum 0, maximum 8). The median number of maternal aunts was 2 (minimum 0, maximum 6) and the median number of paternal aunts was 1 (minimum 0, maximum 6). Almost none of the probands had an equal number of sisters, maternal and paternal aunts (i.e., a balanced pedigree). Twenty-two (20%) of the pedigrees included a relative who had been adopted into the family. In one family, the proband was adopted (the family pedigree pertained to the proband's birth family). In one family, consanguinity was reported. There were two families for which the pedigree included two probands (i.e., the family was brought to the attention of the HCP by two people) and the proband used for this analysis was determined by a coin toss. Almost all of the families included someone with breast or ovarian cancer diagnosed prior to age 50, and 61 (55%) of the families included someone with multiple primary tumors (e.g., bilateral breast cancer).

		Family BRCA1 Status: Positive	Family BRCA1 Status: Negative	
Predicted BRCA1 Carrier Status	Positive	12	8	20
	Negative	42	47	89
		54	55	

Figure 5.3 Predicted BRCA1 carrier status and observed family BRCA1 status for patients attending the Hereditary Cancer Program (HCP) at the BC Cancer Agency. Predictions were based on whether the probability of being a carrier exceeded 10% according to the family history measure FH. FH was positive if breast or ovarian cancer had been diagnosed in two of the proband's close relatives from the same side of the family, or any close relative before age 50. Close relatives include the mother, sisters, aunts and grandmothers. Post-test likelihoods assumed 0.12% of the population are BRCA1 mutation carriers. Families were classified as BRCA1-positive or BRCA1-negative based on genetic test results for the index case. (See text for details.)

Only one pedigree included male relatives with breast cancer. This family was found to carry both a BRCA1 and a BRCA2 mutation.

A cross-tabulation of the predicted BRCA1 carrier status and observed family BRCA1 status for people in the HCP sample is given in Figure 5.3. Overall, the predicted carrier status corresponded to the observed family status in 59 (54%) of patients. No population inference can be drawn from this because it depends largely on the proportion of BRCA1-positive and BRCA1-negative families in the sample. BRCA1 status was correctly predicted for 12 (22%) of BRCA1-positive families and 47 (86%) of BRCA1-negative families. The prediction of positive carrier status was not significantly different between the groups (2-tailed Fisher's exact test, p=0.4). Despite the presence of a family history, few proband's from BRCA1-positive families were predicted to carry a BRCA1 mutation (i.e., based on whether the probability of a mutation was greater than 10%). Some of these people will indeed be BRCA1-negative despite having a BRCA1-positive family.

5.4 Summary

Subgroups in a population can be classified as to whether they carry a BRCA1 mutation and whether they meet referral criteria for a genetic testing program. Everyone in the population is assumed to share the program's cost, and anyone who receives genetic testing is assumed to benefit.

There are currently 4.1 million people in BC. The population has diverse ethnic origins and the incidence of breast and ovarian cancer might differ amongst these groups. The overall

distribution of family size in the BC population is not known, but fertility rates suggest women have two or three children on average. Assuming 20%, 25%, 35%, 15%, 3% and 2% of people in BC have pedigree sizes of 0 to 5 respectively, a province-wide genetic testing program for persons 20 to 69 years of age, with eligibility criteria based strictly on family history, would be expected to identify 62.4% of BRCA1 carriers. If 0.12% of people in BC are mutation carriers, 4% of people who are referred for testing will carry a BRCA1 mutation. Restrictions to referral criteria based on age and family size will affect the program's sensitivity and PTL+. Referral restrictions that exclude men will affect the program's costs, but are not expected to change the sensitivity or PTL+.

At the HCP, 89% of BRCA1-positive families and 82% of BRCA1-negative families had a family history of breast/ovarian cancer. BRCA1 status was correctly predicted for 12 (22%) of BRCA1-positive families and 47 (86%) of BRCA1-negative families. The prediction of positive carrier status was not significantly different between the groups. The HCP sample is not comparable to the general BC population and these results should not be used to draw population inferences.

Chapter 6: Discussion

6.1 Overview

An understanding of the relationship between BRCA1 and family history should provide insight regarding genes and cancer in general. A simulation model requires assumptions, but observations of family history and BRCA1 mutation status are difficult to collect, and data from patients at a clinic are not representative of the general population.

A simulation model was created to combine results from previous studies and generate data on BRCA1 and family history of breast and ovarian cancer. The model incorporates results about the autosomal dominant inheritance of BRCA1, the age distribution of family members, the rate of breast/ovarian cancer in the population and the risk of breast/ovarian cancer associated with germline mutations in BRCA1. An analysis of simulated data examined the relationship between family history and BRCA1. Results from that analysis were combined with BC demographic information to study the potential performance of a provincial BRCA1 testing program.

As suspected, the ability of family history to predict BRCA1 mutation carrier status was strongly dependent on age and family size. Predictions further depended on the hereditary disease risk associated with BRCA1 and the general disease risk in the population. A family history implied something quite different when observed in a young person, an elderly person, someone from a large family, someone from a small family, in a population where breast/ovarian cancer is common and in a population where it is rare. A family history was

more likely if someone carried a BRCA1 mutation, but many carriers did not have a family history of disease. None of the family history measures produced constant values of sensitivity or specificity for all values of proband age and pedigree size.

Restricting referrals to a BRCA1 testing clinic based on peoples' age and pedigree size will affect the program's cost and benefit. The average person in BC was estimated to have a pedigree size of less than two. If 0.12% of people carry a BRCA1 mutation, a province-wide testing program for persons 20 to 69 years of age with referrals based only on family history of disease* would identify 62% of mutation carriers. About 4% of people referred to the program would be carriers. Both percentages will be affected by restrictions regarding age, family size and other criteria. Most importantly, any referral criteria will exclude some BRCA1 mutation carriers from the program. The subpopulation most likely to be affected is young people with small families.

6.2 Family history measures

Family history is a useful marker of genetic susceptibility. It is easier to observe family history than it is to assess genetic variables because the former does not require sophisticated laboratory resources and expertise. In addition, assessing family history does not require that the gene or genes leading to susceptibility have been identified. This thesis focuses on family history as the basis for referring people to a genetic testing program.

* Two close relatives from the same side of the family diagnosed with breast or ovarian cancer, or any close relative diagnosed before age 50. Close relatives of the proband include the mother, sisters, aunts and grandmothers.

There are many ways to measure family history. Desirable characteristics of a measure include its simplicity of calculation and incorporation of the biologic relationships amongst family members, the ages when family members were diagnosed and the rate of disease in the population. Family history measures that are strong in some ways are weak in others and the importance of each characteristic depends upon the intended application. In particular, referral criteria based on family history should be easy to assess. A measure's simplicity might not be so important if family history is used to estimate the probability that someone is a mutation carrier because the calculation of estimates is complicated in any case.

A family history measure might be restricted to information about persons from the same or previous generations because relatives from recent generations will often be younger than the proband and only early-life events will be observed in them. As a result, the inclusion of relatives from generations after the proband's may sensitize a family history measure to early-onset cases of disease. Another consideration is that some measures of family history can be observed directly whereas other measures require a computer to calculate. Moreover, all family history information should be verified by medical records, and the ease of doing so depends on what information is involved. First-degree relatives are more likely to live in the same part of the world as the proband than second-degree relatives and hence medical records might be easier to obtain. In addition, medical records are often destroyed after a person's death, so information might be more difficult to obtain for deceased relatives. Finally, people are more likely to provide accurate information about close family members than distant ones.

The easiest family history measures to assess were FHS and FH. The former was positive if someone's mother or sister had been diagnosed with cancer, and similar definitions have been used to quantify breast and ovarian cancer risk. FHS is simple to assess, but its sensitivity was

the most affected by a person's age and family size. The measure FH was defined by criteria similar to those on which referral to the HCP is based. FH used information about some first-degree and second-degree relatives and only considered multiple diagnoses if they occurred on the same side of the family. FH also distinguished between cases of disease diagnosed before and after age 50. The most appropriate age to define early-onset disease is not clear and will depend on the difference between the age-specific hereditary and sporadic risks, and diagnostic and reporting practices in the population. The most appropriate age to define early-onset disease is also likely to be different for breast cancer and ovarian cancer.

A positive value of FHS implies either the proband's mother or sister has breast/ovarian cancer, but which relative depends on the proband's age and family size. For young people, FHS was most often positive because the mother had cancer. For probands with many sisters, FHS was most often positive because a sister had cancer. The interpretation of FH is more complicated. For probands age 60 with large families, FH was most often positive because they had two close relatives with cancer. For probands age 20 with small families, FH was most often positive because cancer had been diagnosed in a close relative under age 50. The post-test likelihoods for FH and FHS were similar in many instances, but families that have positive values of FHS and FH can be quite different. In families where the proband's mother or sister has cancer, there are not always two affected relatives from one side of the family. Likewise, neither a proband's mother nor a sister is affected in many families where an aunt or grandmother has been diagnosed with cancer before age 50.

This thesis also considered more complicated measures of family history. The family history measures OE and NDX can be generalized to include all kinds of relatives (i.e., not only first-and-second-degree ancestors). OE was difficult to calculate, but might easily be implemented

as a personal computer application that staff could calculate for clinic patients. NDX was created in an attempt to incorporate some advantages of OE while simplifying the calculations. Using a form like that in Figure 4.1, NDX could be determined using a hand calculator. The form could be reproduced in magazines, appear in bus shelters, or used as an office wall chart. Both OE and NDX adjust for population rates of disease, but population phenomena are not always observed in small groups such as families.

The continuous nature of the observed-expected ratio and the family history index was lost when these variables were transformed to OE and NDX. The cutoffs chosen to define positive values of OE and NDX were arbitrary and determine the proportion of probands that will have a positive family history. Low cutoff values will result in more probands having a positive family history regardless of whether they carry a BRCA1 mutation. This will produce higher values of sensitivity and lower values of specificity. High cutoff values will have the opposite effect and intermediate cutoffs can be chosen to produce a desirable tradeoff between the perceived consequences of false positive and false negative predictions. Cutoff values depend on peoples' age and pedigree size because the spectrum of possible values for the observed-expected ratio and family history index depend on these factors. To illustrate, consider a person whose reported family consists only of a mother and whose only possible values of the family history index are 0 and 1 (i.e., the mother has cancer or she does not). For a proband with a large family, the family history index can take many intermediate values and any subset of them can be above or below the cutoff. Finally, the relationship between the family history index and BRCA1, and between the observed-expected ratio and BRCA1, depended on the estimate of hereditary and overall disease risk in the population.

The family history measures in this thesis were generally restricted to the first-degree and second-degree ancestors of the proband. In section 4.6, simulations were considered in which the proband's cousins were included in the family history measure. Predictions made according to the measure FH (which does not incorporate information about the proband's cousins) were compared with predictions made using the measure FHC (which does). Little difference in the sensitivity or specificity of these measures was observed. Other family history measures can be constructed using information about cousins but their ability to predict BRCA1 mutation carrier status is not expected to be any better. Family history measures that include other relatives might also yield better predictions. In particular, measures that include disease information about someone's children and grandchildren might be especially useful in older probands. This thesis did not consider family history measures that incorporate information about bilateral cancer, multiple occurrences of cancer in one individual, cancers other than those of the female breast or ovary, or other forms of disease. The risks of these diseases or disease characteristics in BRCA1 mutation carriers are not well known. It is also difficult in many patients to distinguish between multifocal and metastatic disease, or know whether multiple instances of cancer are independent or related (i.e., recurrent breast or ovarian cancer, or concurrent cancers). In practice, additional details of a person's family history would affect recommendations for genetic testing and the interpretation of genetic test results.

6.3 Sensitivity, specificity and post-test likelihoods

Generally, the sensitivity of family history as a predictor of BRCA1 mutation carrier status was highest for elderly people from large families. The specificity was highest for young people from small families. These results are largely intuitive. Someone with many relatives is more

likely to have a relative with cancer. An older person is likely to have older relatives than a young person, and older relatives are more likely to have cancer. These statements apply to both BRCA1 carriers and non-carriers, so the sensitivity of family history will increase with proband age and family size and the specificity will decrease. Sensitivity was generally higher in populations for which there was a greater risk of hereditary breast/ovarian cancer, but sensitivity only depended on the overall rate of breast/ovarian cancer in the population when family history was measured with OE. The specificity was generally stable with respect to assumptions about both the hereditary and population risks of breast/ovarian cancer.

The behavior of the post-test likelihoods was more erratic than that of sensitivity or specificity with respect to changes in age and family size. The pre-test probability of carrying a BRCA1 mutation (i.e., the proportion of BRCA1 mutation carriers in the BC population) was assumed to be 0.12%. Someone with a family history had at least a 0.88% probability of carrying a mutation, and someone without a family history had at most a 0.05% probability of carrying a BRCA1 mutation. RP increased with both proband age and pedigree size and these effects had a strong interaction; proband age and pedigree size in combination had an effect that exceeded the sum of them individually. PTL- was usually lowest when the estimate of hereditary cancer risk was highest, and PTL+ was usually highest when the population risk was lowest. PTL- did not depend on the hereditary cancer risk and PTL+ did not depend on the disease risk in the population. RP was affected by both risk estimates.

Ideally, the sensitivity and specificity of any family history measure will be near 1 and unaffected by the proband's age and family size, the risk of hereditary disease or the rate of disease in the population. None of the family history measures in this thesis did that. The post-test likelihoods should sharply alter the probabilities of a person carrying a BRCA1 mutation

from the pre-test probability. The behavior of RP demonstrated this is certainly true for 60 year-old probands from large families, but less so for 20 year-old probands from small families. The potential consequences of a false positive result (i.e., observing a positive family history where there is no BRCA1 mutation) are the increased anxiety and stigmatization that might be experienced by the proband. The potential consequences of a false negative result (i.e., a BRCA1 mutation carrier with no family history) are missed opportunities to prevent disease, increase survival and reduce the burden of disease in the population.

The post-test likelihoods associated with a family history measure are estimates of the probability that someone carries a BRCA1 mutation. In section 4.7, the post-test likelihoods were compared to the probability of a carrying a BRCA1 mutation as estimated by the Berry model. There was little difference between the estimates for situations in which there is no family history of cancer. However, in families where there was a history of disease, the current model estimates were up to 30 times greater than the estimates from the Berry model. These results emphasize the differences between the estimation procedures.

The Berry model estimates the probability of a BRCA1 mutation on the disease status of every family member. This can have substantial consequences in a large family. If a proband has 5 sisters, the Berry estimate will be much lower if three sisters are healthy (and two sisters have cancer) compared to a proband having five sisters with cancer. The family history measure FH does not distinguish between these family histories, and the post-test likelihood associated with FH is the same in each. The post-test likelihood associated with a family history measure is akin to Berry's estimate of the probability of a BRCA1 mutation for a minimum configuration of family history. Similarly, the Berry model estimates the probability using the precise age of diagnosis for each case of cancer within a family. A relative diagnosed with breast cancer at

age 35 increases the probability much more than a relative diagnosed at age 49, but these details are not distinguished by the measures FHS or FH.

Perhaps the greatest difference between the Berry estimates and those based on the family history measures is that the former use information about the proband's own disease status. Information as to whether a female proband has breast/ovarian cancer will substantially influence the prediction that she is a BRCA1 mutation carrier, although no information is contributed by a man's personal disease status. The post-test likelihoods associated with the family history measures do not differ for male and female probands because the estimates do not use information about breast or ovarian cancer in the proband.

Some differences between the Berry estimates and those from the simulation study are due to details of the simulation model. The Berry model considers female breast and ovarian cancer as separate diseases, which can be important if a BRCA1 mutation affects the risk of these diseases differently. The simulation model considers breast and ovarian cancer as one disease. Also, the Berry model assumes that a person might carry one or two copies of a germline mutation whereas the simulation model assumes that all carriers have a single copy of the mutation. Little is known about people who carry two copies of a mutation, including whether they exist (i.e., whether a fetus with two copies of a mutation is viable) or their risk of cancer. BRCA1 is generally considered a tumor supressor and a mutation in both copies of a cell is believed to cause cancer. The effect of a germline mutation in both copies of BRCA1 is difficult to imagine.

In general, the simplicity gained by using a family history measure like FHS or FH comes at the expense of accuracy as produced by estimates from a more complex model.

Finally, the probability that someone carries a BRCA1 mutation depends on the frequency of mutations in the population. The post-test likelihoods presented in Chapter 4 assumed the portion of BRCA1 mutation carriers in the population was 0.12% and was based on data from England and Wales (Ford et al 1995). More recently, Peto et al (1999) estimated that 0.11% of the general population in Britain were BRCA1 mutation carriers. Fodor et al (1998) published estimates of their own and several other studies of common BRCA1 mutations in Ashkenazi Jews (i.e., del185AG and 5382insC), and gave a combined estimate that about 1% of the population were mutation carriers. An entire issue of The American Journal of Human Genetics in 1997 examined the population genetics of BRCA1 mutations around the world, and the articles in that collection demonstrated a wide variation in carrier prevalence (Szabo and King 1997). There are no population-based estimates of the proportion of carriers in BC.

6.4 Referral criteria for a BRCA1 testing program

Knowing that a woman has a BRCA1 mutation is useful because there are interventions that might reduce her cancer risk, and some family members can be reassured that they have not inherited a mutation. But a BRCA1 testing program cannot be introduced without the evaluation of its costs. The criteria by which people are referred to the program are a fundamental part of this. The justification for a screening program is based on several factors (Wilson and Jungner 1968) and most of them address either the demand for services or the availability of resources. The editorial (Sutcliffe 1999) accompanying a recent review stated

> "It will be necessary to establish a population-based monitoring system to achieve optimal determination of the highest probability of providing service

to those most likely to benefit (i.e. gene mutation carriers), largely through the ability to obtain accurate, standardized family histories and to provide a coherent, auditable counselling service that triages the most appropriate individuals to genetic testing, while appropriately allaying the anxiety of those tested and those declined for testing."

A model of the need and demand for these services (Elwood 1999c) depended on the number of people who are aware of their increased risk, the number who meet criteria for testing, and the number who carry a detectable genetic abnormality. This thesis addresses only the second of these factors.

The number of patients attending a genetic testing clinic depends on the referral criteria, not the prevalence of BRCA1 mutation carriers in the population. A clinic is likely to see many patients with a family history of cancer and who, upon testing, are found not to carry a BRCA1 mutation. This can occur because of several reasons. Firstly, the son or daughter of a carrier might not inherit his or her parent's mutation. This is typically considered a good scenario because the parent's mutation explains the family history and informs the proband that he or she is not at increased risk of disease. Secondly, someone might test negative because they carry a BRCA1 mutation or form of genetic susceptibility that is not detected by current laboratory methods. A family history might also represent a set of cases with separate and distinct causes, although this is impossible to know for any particular family. Because of these possibilities, a negative BRCA1 test is often considered a non-informative result.

Chapter 5 assumed the average person in BC has a pedigree size of 2 and that 20%, 25%, 35%, 15%, 3% and 2% of people have pedigree sizes of 0 to 5 respectively. The true distribution of

family size and structure in BC is not known. The results are also based on families without instances of consanguinity or multiple births. Both phenomena exist in BC. Family histories at the HCP are largely self-reported. Efforts are made to verify information regarding cancer diagnoses in a family but there are many reasons that family history information might be inaccurate (see section 2.3). This can be especially limiting for immigrants and adopted people. A person might not know all of their relatives or the disease history and vital status of each. An adopted individual might have a large biological family but little knowledge of those relatives. This is also true for immigrants from other parts of Canada and other parts of the world.

There are many factors not considered in Chapter 5 that will affect the sensitivity and PTL+ of referral criteria for a BRCA1 testing program. Most obviously, there is often evidence in addition to family history that a patient seeking referral to the HCP is a BRCA1 mutation carrier. Some patients have been referred to the HCP on the basis of Ashkenazi Jewish ancestry or their own history of breast/ovarian disease, both of which are known to be associated with BRCA1. The probability of this depends on the age and family of the proband. Calculations in Chapter 5 were based on family history as measured by the variable FH. HCP referrals are based on a family history definition that incorporates information about cancer incidence in the proband's children. This is unlikely to provide additional information for young probands, but older probands might indeed have children or grandchildren with cancer. Alternative family history measures will affect the program's performance as well as its cost. Further, genetic testing provides information about the relatives of anyone who has already been tested, so a person's risk estimate will change if someone in their family is tested. The probability that a relative has been tested for BRCA1 is also likely to depend on his or her age and family size, and the risk of hereditary and sporadic cancer in a population. That probability depends on historic referral criteria and the availability of tests. In theory, a person need only be tested for

BRCA1 carrier status once. In reality, standard laboratory methods are unable to identify all genetic alterations and the list of important ones is revised whenever new information becomes available. One-time BRCA1 testing might not be realistic.

Referral criteria for a testing program might include factors that have nothing to do with the probability of someone carrying a BRCA1 mutation, but instead reflect the perceived level of risk and the interventions that are available. For example, a BRCA1 testing program might be restricted to women because cancer risk does not appear to be affected in men. The demand for testing could change even if the availability of it does not. People might discover other explanations for their family history and decide that BRCA1 testing is unnecessary. New information about the role of BRCA1 in the natural history of breast/ovarian cancer might change a person's desire to know their carrier status.

At the HCP, patients had a positive family history in 89% of BRCA1-positive families and a negative family history in 18% of BRCA1-negative families. Those percentages are biased estimates of family history as an indicator of carrier status. As measured here, it is possible that the BRCA1 status of a family does not always correspond to whether there is a germline BRCA1 mutation in the family. This could occur if the index case does not have a germline BRCA1 mutation despite other people in the family being carriers. Conversely, if a parent is a carrier, only 50% of his or her children will inherit the mutation from them. Half the children of a BRCA1-positive parent will not carry a mutation, except in the rare instance where both parents carry a mutation.

There are also reasons why results from the HCP sample might not be representative of HCP patients in general. Genetic testing requires an index case is available, which might depend on a

person's age and family size. In addition, the relationship between family history and BRCA1 might be different in HCP patients compared to the BC population because of geography. The catchment area for the HCP is not known. The program operates clinics in both Vancouver and Victoria but the services are not equally accessible for all areas of the province. Factors affecting the relationship between family history and BRCA1 might be associated with the physical and social environment.

6.5 The family history model

Development of the simulation model was particularly useful in marrying concepts from branches of science that are often studied separately. The model incorporated relationships from genetics, demography and cancer epidemiology, but did not consider every factor that affects cancer incidence. A review of the model's formulation identified several underlying assumptions about the factors and their relationships. Some assumptions were examined formally using stability analyses. Other assumptions were based on available evidence in the form of published data or anecdotal observations.

Step 1 of the model assumes that only one of a carrier's parents has a germline BRCA1 mutation. It is possible that both parents carry a BRCA1 mutation but such an event is unlikely. If p is the probability that someone in the population is a mutation carrier, then p^2 is the probability that two randomly-chosen people are both carriers. In ethnic subpopulations, the highest prevalence of BRCA1 mutation carriers has been observed amongst Ashkenazi Jews. An analysis that combined several studies involving Ashkenazim estimated the prevalence of BRCA1 mutations to be about 1% (Fodor et al 1998). This would imply that both of a person's

parents carry a BRCA1 mutation with a probability of 1 in 10,000. Most of the analyses in this thesis have assumed that the proportion of BRCA1 carriers in the population is 0.12%. This is based on the estimates of Ford et al (1995) and implies the probability that both of a person's parents are BRCA1 carriers is about 1 in 700,000.

The model also assumes a proband's relatives carry the mutation in accordance with the laws of Mendelian genetics. These laws state that the gene BRCA1 is inherited as a single unit, that a person's two copies of BRCA1 segregate to separate gametes during meiosis, and that BRCA1 segregates independently of other genes. The assumptions imply that each person with a germline BRCA1 mutation has a parent with that mutation, each son and daughter of a mutation carrier has a 50% chance of inheriting the mutation, each of the proband's sisters has a 50% chance of carrying the mutation, and each of the proband's aunts and grandparents has a 25% chance of carrying the mutation. The assumptions also imply that one parent and one grandparent from the same side of the family must carry the mutation.

Step 1 also assumes that there are no de novo (i.e., new) mutations of BRCA1 at conception. There is little information about the rate of de novo germline BRCA1 mutations. A person's *fitness* is his or her contribution of offspring to the next generation. For some genes, the de novo rate has been estimated indirectly using the known effects of mutations on fitness. For example, persons with the autosomal dominant condition achondroplasia have an estimated fitness of about 0.2 (Thompson et al 1991, pp.155-6), meaning the genes of only 20% are passed on to the subsequent generation in a population. If the prevalence of achondroplasia has remained constant over generations, the rate of de novo mutations must be sufficient to account for the reduction in prevalence that would be expected because of the lowered fitness. For BRCA1, if mutations have no effect on fitness and the prevalence of BRCA1 mutations hasn't

changed over time, there must be few de novo mutations. There is little evidence in support or defiance of changes in BRCA1 mutation prevalence over time.

The age distribution of BC women at the time of their first full-term pregnancy was obtained from Statistics Canada (Statistics Canada 1995b). The same distribution was used to describe pregnancies in both the parents' and grandparents' generations. It is likely that the average age of women at the time of their first pregnancy has changed over generations, but this age difference is expected to be less than five years and not have a large effect on the results. The typical age distribution of siblings in a BC family is not known, and the model assumed the year in which each sibling was born differed from that of the proband according to a Poisson random variable with mean two years. The Poisson distribution was chosen because it describes phenomena with discrete values. Other distributions could have been used in its place. While the proband in our model can be either male or female, the only siblings considered in this model are sisters. The age distribution in a model that included all siblings (i.e., both brothers and sisters) would be different.

Survival was based on observed rates in BC, but limited such that a person's age could not exceed 100 years. This restriction is assumed to have little effect on family history. The number of persons in BC that live beyond age 100 years is small, as is the number who are diagnosed with breast/ovarian cancer after that age.

The presence of breast/ovarian cancer could affect a woman's number of children. Most obviously, women with breast/ovarian cancer have a lower median survival than do women in general and this could influence the number of children they have and the ages when they give birth. However, no such instances have been found in the literature. Hartge et al (1999) studied

an Ashkenazi population in the Washington DC area and reported family size was similar in mutation carriers and non-carriers. Differences in family size are sometimes associated with ethnicity and socioeconomic status – both of which are associated with cancer risk. Estimates of mothers' ages at childbirth, fathers' ages relative to the mothers', the probability of survival and the probability of developing cancer were assumed to be equal for all family members – regardless of the generation to which they belong. The presence of a germline BRCA1 mutation might also affect the viability of a sperm or egg cell, or the survival of a fetus, although little is known about this. It has been suggested that BRCA1 is involved in DNA repair (reviewed in Kote-Jarai and Eeles 1999) in which case a germline mutation might have consequences beyond increasing the breast/ovarian cancer risk. Such effects would be expected to alter a person's pedigree and the age distribution of siblings within kindred. These effects might further depend on whether the mother or father contributes the BRCA1 mutation to their child, and on whether the child is a boy or girl.

The model assumed that the year in which each sister was born differed from that of the proband according to a Poisson random variable with mean two. The Poisson distribution was chosen because age was modeled as an integer variable. Other distributions could have been used instead. The Poisson mean of two was chosen to generate family structures that are similar to those observed anecdotally, but there is little data on which to evaluate this aspect of the model. The model also assumed that the presence of a germline BRCA1 mutation does not affect a man's or woman's ability to have children, nor the children's survival. This is almost certainly untrue but is expected to have little effect on the simulation results.

The model assumes that all BRCA1 mutations are associated with the risk of breast and ovarian cancer that was estimated by Berry et al (1997). The risk estimate is essentially zero for women

younger than 20 or older than 90, and attains a maximum when a woman is in her late 50's. The risk estimates for mutation carriers were based on a three-parameter gamma function fitted to data collected in England and Wales (Easton et al 1995) and those estimates' veracity in that or any other population is unknown. Alternative estimates of risk have been reported (e.g., Claus et al 1991, Whittemore et al 1997, Hopper et al 1999). The risk of breast/ovarian cancer is probably not the same for all BRCA1 mutations and likely affected by other genes and environmental exposures, implying BRCA1 mutations can be associated with different risks in different populations (Hopper et al 1999) and in different families.

In simulating disease incidence in BRCA1 mutation carriers, the model first uses hereditary risk estimates based on the work of Berry et al (1997), and then adds cases according to risk estimates based on BC population rates. The result is that some of the hereditary disease risk is modeled twice and the number of hereditary cases in a family might be over-estimated. The portion of cancers in the population that are due to BRCA1 is expected to be small. An estimate of sporadic disease risk correcting for the proportion of hereditary disease was considered in section 4.5 and had little effect on the results.

The simulation model assumed there was a causal relationship between germline BRCA1 mutations and breast/ovarian cancer risk. An alternative explanation for the association is that germline mutations in BRCA1 reflect overall genome instability. It also has been suggested that BRCA1 is involved in DNA repair throughout the genome (evidence reviewed in Kote-Jarai and Eeles 1999). Another possible explanation is that a strong family history causes increased susceptibility to disease: if breast/ovarian cancer is caused by an infectious agent, affected family members could increase disease risk in close contacts. Finally, a positive family history

might reflect shared exposures to environmental agents that affect breast/ovarian cancer risk and cause germline BRCA1 mutations.

The best-known model for predicting BRCA1 mutation carrier status is likely that of the computer program BRCAPRO. The model is based on the work of Parmigiani et al (1998) and extends the work of Berry et al (1997) to estimate the probability that someone carries a mutation in either BRCA1 or BRCA2. Age-specific disease risks for BRCA2 were based on unpublished data from D.F. Easton (of the BCLC). Germline mutations in BRCA2 are believed to affect the risk of male breast cancer and BRCAPRO uses information about male relatives when assessing family history. In the simulation model of Chapter 3, male relatives are ignored except for the proband's father, whose age affects the ages of the paternal aunts and grandmother.

In the analyses presented here, data was simulated for over 500,000 families. Parameters in the model were estimated using population statistics whenever possible: survival probabilities, the ages of women at childbirth, the incidence of cancer. Assumptions were necessary when population statistics weren't available. A similar mix of data and assumptions could be used to simulate family history of breast and ovarian cancer in other populations. It is also possible to modify the simulation model to address other types of disease and other forms of genetic susceptibility.

6.6 Other genes associated with breast and ovarian cancer

The OMIM database lists 45 genes for which the title, clinical synopsis or an allelic variant mentioned breast cancer or ovarian cancer (www.ncbi.nlm.nih.gov/omim searched September 20, 2000). To identify those most commonly referred to in the literature, a search was conducted using the PubMed database (www.ncbi.nlm.nih.gov/pubmed searched September 20, 2000). There were more than 70 entries in PubMed for each of BRCA1, BRCA2, TP53, KRAS2, HRAS and AR. A search for each was conducted in the abstracts from this year's meeting of the American Society of Human Genetics (Am J Hum Genet, Vol. 67 No. 4, October 2000) to determine the amount of recent research involving these genes. The annual ASHG meeting is attended by thousands of scientists and this year's program included 2440 abstracts. BRCA2 ("Breast cancer 2, early onset" OMIM 600185) is a gene located on the long arm of chromosome 13 and is associated with male and female breast cancer, ovarian cancer and pancreatic cancer. Twenty-seven (27) abstracts from this year's ASHG meeting were about BRCA2. The genes TP53 ("Tumor protein p53" OMIM 191170) on chromosome 13, HRAS ("Harvey murine sarcoma virus" OMIM 190020) on chromosome 11 and KRAS2 ("Kirsten murine sarcoma virus 2" OMIM 190070) on chromosome 12 are associated with tumors of the breast, lung, bladder, pancreas, esophagus, stomach, colon and rectum. There were nine abstracts at this year's ASHG meeting involving at least one of these genes. Unlike BRCA1, there is little evidence that BRCA2, TP53, KRAS2 or HRAS are associated with ovarian cancer. AR ("Androgen receptor" OMIM 313700) is located on the X chromosome and is associated with prostate cancer and male breast cancer, but also many other conditions affecting the genitalia. Because it is located on the X chromosome and many of the traits associated with it are sex-linked, patterns of familial clustering due to germline AR mutations will be different than patterns associated with other susceptibility genes. There were 10 abstracts from this

year's annual ASHG meeting that concerned AR. All of the aforementioned genes affect the familial clustering of breast and ovarian cancer and could affect the ability of family history to predict mutation carriers.

Entries in PubMed reflect the time since a gene was first identified, the number of diseases and traits that it affects, the allocation of scientific grant funding, the publication interests of editors and the research interests of authors. Abstracts from the ASHG meeting have a similar bias. But it is important to emphasize that the determinants of breast and ovarian cancer risk involve many genes in addition to BRCA1. In the simulations performed here, family histories that occurred in the absence of a BRCA1 mutation were the result of random clustering. In real life, additional positive family histories will result from shared environmental exposures and other types of shared genetic susceptibility in families. Family history is associated with breast cancer risk in women who do not carry BRCA1 mutations (Claus et al 1998, Streuwing 1999) implying there are other causes of familial clustering. Additional positive family histories in BRCA1 mutation carriers will increase the sensitivity. Additional positive family histories in people without germline BRCA1 mutations will decrease the specificity.

6.7 Recommendations for future research

This study examined family history of breast/ovarian cancer as a basis for referring people to a BRCA1 testing program. The simulation model was based on a combination of assumptions and previous observations, and the results from published research. Estimates of breast and ovarian cancer risks in BRCA1 mutation carriers were based on data from a British population (Easton et al 1995). The appropriateness of these estimates in other populations is not known,

and the estimates' symmetric relationship with age has not been considered in detail. It would be useful to study the prevalence and spectrum of BRCA1 mutations in BC and the risk of breast/ovarian cancer that is associated with them. Similarly, the distributions of family size parameters in BC are unknown. The simulation model assumed that familial clustering occurred as the result of inherited BRCA1 mutations or as the result of chance. There are likely other environmental and genetic factors that cause familial clustering of cancer. A population-based study of BRCA1 and family history of cancer in BC is warranted.

It also would be useful to simulate family history of breast and ovarian cancer using both genetic and environmental variables. Such research would require knowledge or assumptions about the interaction of genes and factors that are known or suspected to affect breast and ovarian cancer risk. Studies that have examined these factors separately cannot consider their interactions, and combining risk estimates from separate studies is almost certain to produce incorrect results. For example, risks associated with a family history of early-onset disease and a woman's menopausal status are likely to be related. Simulation studies force a critical examination of model assumptions and might generate new hypotheses that can be tested with observations.

Appendix

This appendix contains the S-Plus (Mathsoft, Inc. 1997) computer program ("sim") to simulate family history of breast and ovarian cancer. A description of the model is provided in Chapter 3 and Bajdik et al (2001). Following the program are S-Plus instructions to invoke the simulation model and perform the analyses in the example of section 3.5.

```
# Program sim

# The code creates a series of pedigrees according to the input
# specifications, determines who in the family carries a BRCA1
# mutation, determines each family member's age, and then simulates the
# incidence of hereditary (i.e., BRCA1-related) and cancer.
# Every proband in these families has a BRCA1 mutation.  The family
# history of probands without mutations can be determined by ignoring
# the hereditary cancer cases in their pedigree.  The families include
# only the proband's parents, grandparents, aunts and sisters.
# Pedigrees do not include male relatives other than the father and
# grandfathers - and this is only to determine BRCA1 inheritance and
# the ages of their offspring and siblings.

# Program parameters
#
#   sites is the number of cancers under consideration
#   pica is an array of the age-and-sex-specific hereditary
#     cancer incidence probability for each site
#   psca is an array of the age-and-sex-specific cancer
#     incidence probability for each site
#   lifetm is an array of lifetable probabilities for males
#   lifetf is an array of lifetable probabilities for females

# Input parameters
#
#   reps is the number of pedigrees to generate
#   agepro is the age of the proband
#   nsis is the proband's number of sisters
#   nmaunt is the proband's number of maternal aunts
#   npaunt is the proband's number of paternal aunts

#########################################################################
#
#                              PARAMETERS
#
#########################################################################

sites_2
sexes_2

psca_array(0,c(sites,sexes,100))
psca[1,1,]_BC174f9397
psca[2,1,]_BC183f9397

pica_array(0,c(sites,sexes,100))
pica[1,1,]_CB174x
pica[2,1,]_CB183x

lifetf_BC1990f
lifetm_BC1990m

#########################################################################
#  Determine carrier status of parents and grandparents
#########################################################################

# Variables
#
#   gmo, gfa, gmgrm, gmgrf, gpgrm and gpgrf are arrays describing 2
```

```
#     copies of BRCA1 for the proband's mother, father, maternal
#     grandmother, maternal grandfather, paternal grandmother and
#     paternal grandfather

# initialize BRCA1 gene arrays

gmo_array(0,c(2,reps))
gfa_array(0,c(2,reps))
gmgrm_array(0,c(2,reps))
gmgrf_array(0,c(2,reps))
gpgrm_array(0,c(2,reps))
gpgrf_array(0,c(2,reps))

# if the proband is a mutation carrier, either their mother or father
#    must have a mutation (assume only 1 parent and only 1 copy)

for (j in 1:reps) {
   mut_rep(0,4)
   mut[sample(4,1,replace=F)]_1
   gmo[1,j]_mut[1]
   gmo[2,j]_mut[2]
   gfa[1,j]_mut[3]
   gfa[2,j]_mut[4]
}

# if the mother has a mutation, either her mother or father must have
#    it (again assume 1 parent and 1 copy)

for (j in 1:reps)
   if (gmo[1,j]==1 || gmo[2,j]==1) {
      mut_rep(0,4)
      mut[sample(4,1,replace=F)]_1
      gmgrm[1,j]_mut[1]
      gmgrm[2,j]_mut[2]
      gmgrf[1,j]_mut[3]
      gmgrf[2,j]_mut[4]
   }

# if the father has a mutation, either his mother or father must have
#    it (again assume 1 parent and 1 copy)

for (j in 1:reps)
   if (gfa[1,j]==1 || gfa[2,j]==1) {
      mut_rep(0,4)
      mut[sample(4,1,replace=F)]_1
      gpgrm[1,j]_mut[1]
      gpgrm[2,j]_mut[2]
      gpgrf[1,j]_mut[3]
      gpgrf[2,j]_mut[4]
   }



#########################################################################
#  Determine carrier status of sisters and aunts
#########################################################################

# Variables
#
```

```
#   gsis, gmaunt and gpaunt are arrays describing 2 copies of BRCA1 for
#     each of the proband's sisters, maternal aunts and paternal aunts

# initialize BRCA1 gene arrays

if (nsis>0) gsis_array(0,c(2,nsis,reps))
if (nmaunt>0) gmaunt_array(0,c(2,nmaunt,reps))
if (npaunt>0) gpaunt_array(0,c(2,npaunt,reps))

# sisters (aunts) inherit 1 copy of BRCA1 from each parent (grandparent)

for (j in 1:reps) {
      if (nmaunt>0)
         for (i in 1:nmaunt) {
            gmaunt[1,i,j]_gmgrm[sample(2,1,replace=F),j]
            gmaunt[2,i,j]_gmgrf[sample(2,1,replace=F),j]
         }
      if (npaunt>0)
         for (i in 1:npaunt) {
            gpaunt[1,i,j]_gpgrm[sample(2,1,replace=F),j]
            gpaunt[2,i,j]_gpgrf[sample(2,1,replace=F),j]
         }
      if (nsis>0)
         for (i in 1:nsis) {
            gsis[1,i,j]_gmo[sample(2,1,replace=F),j]
            gsis[2,i,j]_gfa[sample(2,1,replace=F),j]
         }
   }

#########################################################################
#  Determine relatives' minimum and maximum (i.e., potential) ages
#########################################################################

# Variables
#
#   agesismax, agemauntmax and agepauntmax are the potential ages of
#     the proband's sisters, maternal aunts and paternal aunts
#   agemomin, agemgrmmin and agepgrmmin are the minimum possible ages
#     attained by the mother, maternal grandmother and paternal
#     grandfather based on the ages of their children
#   agefamin, agemgrfmin and agepgrfmin are the minimum possible ages
#     attained by the father, maternal grandfather and paternal
#     grandfather based on their wives' minimum ages
#   agemomax, agefamax, agemgrmmax, agemgrfmax, agepgrmmax and
#     agepgrfmax are the potential ages of the mother, father, maternal
#     grandmother, maternal grandfather, paternal grandmother and
#     paternal grandfather

# function MAXAGE returns a person's age and ensures the ages
# of siblings are unique

maxage_function(...) {
   ages_c(...)
   plusminus_(-1)**(runif(1,0,1)<.5)
   x_ages[1]+(plusminus*rpois(1,2))
   z_max(ages==x)
   if (z==1) x_maxage(ages) else x
}
```

```
# initialize variables

if (nsis>0) agesismax_matrix(0,nsis,reps)
agemomin_rep(0,reps)
agemomax_rep(0,reps)
if (nmaunt>0) agemauntmax_matrix(0,nmaunt,reps)
agefamin_rep(0,reps)
agefamax_rep(0,reps)
if (npaunt>0) agepauntmax_matrix(0,npaunt,reps)
agemgrmmin_rep(0,reps)
agemgrmmax_rep(0,reps)
agepgrmmin_rep(0,reps)
agepgrmmax_rep(0,reps)
agemax_0
agemin_0
agediff_rep(0,reps)

for (j in 1:reps) {

# sisters ...

   if (nsis>0)
      for (i in 1:nsis) agesismax[i,j]_maxage(agepro,agesismax[,j])

# mother ...

   if (nsis>0) {
      agemax_max(agepro,agesismax[,j])
      agemin_min(agepro,agesismax[,j])
   }
   if (nsis==0) {
      agemax_agepro
      agemin_agepro
   }
   plusminus_(-1)**(runif(1,0,1)<.5)
   shift_plusminus*rpois(1,3)
   agemomin[j]_23+shift+(agemax-agemin)
   agemomax[j]_23+shift+agemax

# father ...

   agediff[j]_rpois(1,2)
   agefamin[j]_agemomin[j]+ agediff[j]
   agefamax[j]_agemomax[j]+ agediff[j]

# maternal aunts ...

   if (nmaunt>0)
      for (i in 1:nmaunt)
         agemauntmax[i,j]_maxage(agemomax[j],agemauntmax[,j])

# paternal aunts ...

   if (npaunt>0)
      for (i in 1:npaunt)
         agepauntmax[i,j]_maxage(agefamax[j],agepauntmax[,j])

# maternal grandmother ...
```

```
   if (nmaunt>0) {
      agemax_max(agemomax[j],agemauntmax[,j])
      agemin_min(agemomax[j],agemauntmax[,j])
   }
   if (nmaunt==0) {
      agemax_agemomax[j]
      agemin_agemomax[j]
   }
   plusminus_(-1)**(runif(1,0,1)<.5)
   shift_plusminus*rpois(1,3)
   agemgrmmin[j]_23+shift+(agemax-agemin)
   agemgrmmax[j]_23+shift+agemax

# paternal grandmother ...

   if (npaunt>0) {
      agemax_max(agefamax[j],agepauntmax[,j])
      agemin_min(agefamax[j],agepauntmax[,j])
   }
   if (npaunt==0) {
      agemax_agefamax[j]
      agemin_agefamax[j]
   }
   plusminus_(-1)**(runif(1,0,1)<.5)
   shift_plusminus*rpois(1,3)
   agepgrmmin[j]_23+shift+(agemax-agemin)
   agepgrmmax[j]_23+shift+agemax

}

#############################################################################
#  Determine relatives' real ages
#############################################################################

# Variables
#
#   agesis, agemaunt and agepaunt are the ages (if still living) or
#     ages-at-death (if dead) of sisters, maternal aunts and paternal
#     aunts
#   agemo, agefa, agemgrm, agemgrf, agepgrm and agepgrf are the ages
#    (if still living) or ages-at-death (if dead) of the mother,
#     father, maternal grandmother, maternal grandfather, paternal
#     grandmother and paternal grandfather

# function REALAGE returns a person's current age (if they're still
# alive) or age-at-death (if they've died)

# Variables
#   mn is the person's minimum  age
#   mx is the person's maximun (i.e., potential) age
#   lifet is a vector of age-specific annual survival probabilities

realage_function(mn,mx,lifet) {
   dead_rep(NA,100)
   maxx_min(mx,100)
   dead[maxx]_maxx
   for (i in (mn+1):mx) if (runif(1,0,1)>lifet[i]) dead[i]_i-1
   min(dead,na.rm=T)
}
```

```
# intialize vectors

if (nsis>0) agesis_matrix(0,nsis,reps)
agemo_rep(0,reps)
if (nmaunt>0) agemaunt_matrix(0,nmaunt,reps)
agefa_rep(0,reps)
if (npaunt>0) agepaunt_matrix(0,npaunt,reps)
agemgrm_rep(0,reps)
agepgrm_rep(0,reps)

for (j in 1:reps) {

# assign ages ...

   if (nsis>0)
      for (i in 1:nsis) agesis[i,j]_realage(0,agesismax[i,j],lifetf)
   if (nmaunt>0)
      for (i in 1:nmaunt)
          agemaunt[i,j]_realage(0,agemauntmax[i,j],lifetf)
   if (npaunt>0)
      for (i in 1:npaunt)
          agepaunt[i,j]_realage(0,agepauntmax[i,j],lifetf)
   agemo[j]_realage(agemomin[j],agemomax[j],lifetf)
   agefa[j]_realage(agefamin[j],agefamax[j],lifetm)
   agemgrm[j]_realage(agemgrmmin[j],agemgrmmax[j],lifetf)
   agepgrm[j]_realage(agepgrmmin[j],agepgrmmax[j],lifetf)

}

#########################################################################
#  Determine hereditary cancer cases
#########################################################################

# function CA determines the age at which a person is diagnosed with
# a cancer

ca_function(mx,pcancer) {
   maxx_min(mx,100)
   dxage_rep(NA,100)
   if (maxx>0)
     for (i in 1:maxx) if (pcancer[i]>=runif(1,0,1)) dxage[i]_i-1
   min(dxage,na.rm=T)
}

# Variables
#
#   icsis, icmaunt and icpaunt are the ages at which hereditary cancer
#     occurs in the proband's sisters, maternal aunts and paternal
#     aunts
#   icmo, icmgrm, and icpgrm are the ages at which hereditary cancer
#     occurs in the proband's mother, maternal grandmother and paternal
#     grandmother

# initialize arrays

if (nsis>0) icsis_array(NA,c(nsis,reps,sites))
icmo_matrix(NA,reps,sites)
if (nmaunt>0) icmaunt_array(NA,c(nmaunt,reps,sites))
```

```
if (npaunt>0) icpaunt_array(NA,c(npaunt,reps,sites))
icmgrm_matrix(NA,reps,sites)
icpgrm_matrix(NA,reps,sites)

# determine hereditary cancer cases and ages at diagnosis

for (j in 1:reps)
  for (s in 1:sites) {
    if (nsis>0) for (i in 1:nsis)
       if (gsis[1,i,j]==1 or gsis[2,i,j]==1)
          icsis[i,j,s]_ca(agesis[i,j],pica[s,1,])
    if (gmo[1,j]==1 or gmo[2,j]==1) icmo[j,s]_ca(agemo[j],pica[s,1,])
    if (nmaunt>0) for (i in 1:nmaunt)
       if (gmaunt[1,i,j]==1 or gmaunt[2,i,j]==1)
          icmaunt[i,j,s]_ca(agemaunt[i,j],pica[s,1,])
    if (npaunt>0) for (i in 1:npaunt)
       if (gpaunt[1,i,j]==1 or gpaunt[2,i,j]==1)
          icpaunt[i,j,s]_ca(agepaunt[i,j],pica[s,1,])
    if (gmgrm[1,j]==1 or gmgrm[2,j]==1)
       icmgrm[j,s]_ca(agemgrm[j],pica[s,1,])
    if (gpgrm[1,j]==1 or gpgrm[2,j]==1)
       icpgrm[j,s]_ca(agepgrm[j],pica[s,1,])
  }

#########################################################################
#  Determine other cancer cases
#########################################################################

# Variables
#
#   scsis, scmaunt and scpaunt are ages at which other cancer occurs
#     in the proband's sister, maternal aunts and paternal aunts
#   scmo, scmgrm and are the ages at which other cancer occurs in
#     the proband's mother, maternal grandmother and paternal
#     grandmother

# For each member of the pedigree, except the proband, determine if
# they developed cancer and their age at the time of diagnosis.

# initialize arrays

if (nsis>0) scsis_array(NA,c(nsis,reps,sites))
scmo_matrix(NA,reps,sites)
if (nmaunt>0) scmaunt_array(NA,c(nmaunt,reps,sites))
if (npaunt>0) scpaunt_array(NA,c(npaunt,reps,sites))
scmgrm_matrix(NA,reps,sites)
scpgrm_matrix(NA,reps,sites)

# determine other cancer cases and ages at diagnosis

for (j in 1:reps)
  for (s in 1:sites) {
    if (nsis>0) for (i in 1:nsis)
        scsis[i,j,s]_ca(agesis[i,j],psca[s,1,])
    scmo[j,s]_ca(agemo[j],psca[s,1,])
    if (nmaunt>0)
      for (i in 1:nmaunt) scmaunt[i,j,s]_ca(agemaunt[i,j],psca[s,1,])
    if (npaunt>0)
      for (i in 1:npaunt) scpaunt[i,j,s]_ca(agepaunt[i,j],psca[s,1,])
```

```
    scmgrm[j,s]_ca(agemgrm[j],psca[s,1,])
    scpgrm[j,s]_ca(agepgrm[j],psca[s,1,])
  }

# done!
```

```
# Program that provides survival probabilities and risk estimates
# and uses the simulation model (stored as the file "sim") to
# generate 1000 families in which the proband is 40 years old
# and has 2 sisters, 2 maternal aunts and 2 paternal aunts.

reps_1000

agepro_40
nsis_2
nmaunt_2
npaunt_2

# lifetable pr(survival) values from BC pop 1990-92;  values for
# ages 85-99 are constant

BC1990m_c(99213,99951,99961,99968,99976,99982,99985,99987,99989,99989,
          99987,99986,99978,99965,99948,99929,99910,99896,99885,99876,
          99869,99863,99859,99857,99858,99860,99861,99860,99856,99850,
          99843,99836,99830,99825,99820,99816,99811,99805,99800,99795,
          99790,99781,99769,99753,99734,99712,99687,99660,99632,99602,
          99570,99533,99492,99447,99400,99348,99286,99211,99120,99017,
          98904,98784,98660,98539,98420,98292,98142,97961,97750,97517,
          97258,96968,96644,96294,95921,95512,95052,94529,93941,93299,
          92602,91850,91042,90179,89261,rep(88288,15))/100000

BC1990f_c(99439,99969,99973,99974,99985,99989,99989,99988,99988,99987,
          99985,99986,99981,99977,99972,99967,99962,99959,99957,99956,
          99956,99956,99956,99955,99955,99955,99954,99953,99953,99953,
          99952,99951,99947,99941,99933,99923,99914,99907,99903,99902,
          99902,99898,99890,99876,99857,99836,99814,99792,99771,99751,
          99729,99706,99680,99650,99618,99583,99547,99510,99474,99441,
          99404,99357,99296,99219,99129,99029,98920,98804,98687,98569,
          98440,98289,98107,97902,97680,97430,97140,96800,96423,96016,
          95559,95034,94421,93733,92983,rep(92152,15))/100000

# female breast and ovarian cancer rates values obtained from BC pop
# 1993-97

BC174f9397_c(rep(    0.0,5),rep(    0.0,5),rep(    0.0,5),
             rep(0.03415,5),rep(0.03083,5),rep(0.44575,5),
             rep(1.65010,5),rep(4.38363,5),rep(10.9130,5),
             rep(20.4326,5),rep(33.6582,5),rep(53.4728,5),
             rep(57.3520,5),rep(61.9991,5),rep(70.2776,5),
             rep(91.2456,5),rep(116.309,5),rep(118.838,5),
             rep(118.838,5),rep(118.838,5))/100000

BC183f9397_c(rep(    0.0,5),rep(    0.0,5),rep(0.09971,5),
             rep(0.37570,5),rep(0.64734,5),rep(0.80793,5),
             rep(1.30531,5),rep(2.02134,5),rep(1.93833,5),
             rep(4.04426,5),rep(5.26651,5),rep(6.25642,5),
             rep(7.42574,5),rep(8.97992,5),rep(11.6283,5),
             rep(11.1849,5),rep(10.0321,5),rep(8.18230,5),
             rep(8.18230,5),rep(8.18230,5))/100000

# BRCA1-carrier rates of breast and ovarian cancer estimated from
# figures in Berry et al (1997)

CB174x_c(rep(0.00000,5),rep(0.00000,5),rep(0.00000,5),rep(0.00000,5),
         0.0006,0.0012,0.0018,0.0024,0.0030,0.0040,0.0050,0.0060,
```

```
          0.0070,0.0080,0.0094,0.0108,0.0122,0.0136,0.0150,0.0160,
          0.0170,0.0180,0.0190,0.0200,0.0206,0.0212,0.0216,0.0224,
          0.0227,0.0231,0.0232,0.0234,0.0235,0.0234,0.0233,0.0230,
          0.0226,0.0223,0.0220,0.0214,0.0208,0.0202,0.0196,0.0190,
          0.0180,0.0170,0.0160,0.0150,0.0140,0.0132,0.0124,0.0116,
          0.0108,0.0100,0.0093,0.0086,0.0079,0.0072,0.0065,0.0058,
          0.0053,0.0045,0.0035,0.0030,0.0024,0.0018,0.0012,0.0006,
          rep(0,16))

CB183x_c(rep(0.00000,30),
          0.00030,0.00060,0.00090,0.00120,0.00175,
          0.00200,0.00250,0.00300,0.00350,0.00450,
          0.00550,0.00700,0.00850,0.01000,0.01150,
          0.01235,0.01320,0.01405,0.01490,0.01575,
          0.01675,0.01775,0.01875,0.01975,0.02025,
          0.02120,0.02165,0.02210,0.02255,0.02300,
          0.02260,0.02220,0.02180,0.02140,0.02100,
          0.02015,0.01930,0.01845,0.01760,0.01625,
          0.01570,0.01465,0.01360,0.01255,0.01150,
          0.01060,0.00970,0.00880,0.00790,0.00700,
          0.00630,0.00560,0.00490,0.00420,0.00350,
          0.00280,0.00210,0.00140,0.00070,0.00000,
          rep(0,10))

#

source("sim")

#################################################################
# calculate sensitivity                                         #
#################################################################

# count relatives with hereditary or sporadic cancer

ncasis_rep(0,reps)
camo_rep(0,reps)
ncamaunt_rep(0,reps)
ncapaunt_rep(0,reps)
camgrm_rep(0,reps)
capgrm_rep(0,reps)

for (j in 1:reps) {
   if (nsis>0) ncasis[j]_sum(!is.na(dxsis[,j,]))
   camo[j]_sum(!is.na(dxmo[j,]))
   if (nmaunt>0) ncamaunt[j]_sum(!is.na(dxmaunt[,j,]))
   if (npaunt>0) ncapaunt[j]_sum(!is.na(dxpaunt[,j,]))
   camgrm[j]_sum(!is.na(dxmgrm[j,]))
   capgrm[j]_sum(!is.na(dxpgrm[j,]))
}

# define FH

crit1_rep(0,reps)
crit2_rep(0,reps)

#   first criterion = any 2 close relatives from the same
#   side of the family with ca
```

```
crit1_(ncamaunt+camgrm)>1
for (j in 1:reps) if (crit1[j]==0)
    crit1[j]_(ncasis[j]+ncapaunt[j]+capgrm[j])>1

#   second criterion = any close relative with cancer
#   prior to age 50

for (j in 1:reps) {
   if (is.na(dxmo[j]!=1) crit2[j]_dxmo[j]<50
   if (crit2[j]!=1 && ncasis[j]>0)
      crit2[j]_(min(dxsis[,j,],na.rm=T)<50)
   if (crit2[j]!=1 && ncamaunt[j]>0)
      crit2[j]_(min(dxmaunt[,j,],na.rm=T)<50)
   if (crit2[j]!=1 && ncapaunt[j]>0)
      crit2[j]_(min(dxpaunt[,j,],na.rm=T)<50)
   if (crit2[j]!=1 && camgrm[j]>0)
      crit2[j]_(min(dxmgrm[j,],na.rm=T)<50)
   if (crit2[j]!=1 && capgrm[j]>0)
      crit2[j]_(min(dxpgrm[j,],na.rm=T)<50)
}

#

FH_rep(NA,reps)
FH_(crit1+crit2)>0

a_rep(0,reps)
c_rep(0,reps)
a_FH==1
c_FH==0

sens_sum(a)/(sum(a)+sum(c))

################################################################
# calculate specificity                                        #
################################################################

# count relatives with non-hereditary cancer

ncasis_rep(0,reps)
camo_rep(0,reps)
ncamaunt_rep(0,reps)
ncapaunt_rep(0,reps)
camgrm_rep(0,reps)
capgrm_rep(0,reps)

for (j in 1:reps) {
   if (nsis>0) ncasis[j]_sum(!is.na(scsis[,j,]))
   camo[j]_sum(!is.na(scmo[j,]))
   if (nmaunt>0) ncamaunt[j]_sum(!is.na(scmaunt[,j,]))
   if (npaunt>0) ncapaunt[j]_sum(!is.na(scpaunt[,j,]))
   camgrm[j]_sum(!is.na(scmgrm[j,]))
   capgrm[j]_sum(!is.na(scpgrm[j,]))
}

# re-define FH

crit1_rep(0,reps)
crit2_rep(0,reps)
```

```
#   first criterion

crit1_(ncasis+ncamaunt+camgrm)>1
for (j in 1:reps) if (crit2[j]==0)
   crit1[j]_(ncasis[j]+ncapaunt[j]+capgrm[j])>1

#   second criterion

for (j in 1:reps) {
   if (is.na(scmo[j]!=1) crit2[j]_scmo[j]<50
   if (crit2[j]!=1 && ncasis[j]>0)
      crit2[j]_(min(scsis[,j,],na.rm=T)<50)
   if (crit2[j]!=1 && ncamaunt[j]>0)
      crit2[j]_(min(scmaunt[,j,],na.rm=T)<50)
   if (crit2[j]!=1 && ncapaunt[j]>0)
      crit2[j]_(min(scpaunt[,j,],na.rm=T)<50)
   if (crit2[j]!=1 && camgrm[j]>0)
      crit2[j]_(min(scmgrm[j,],na.rm=T)<50)
   if (crit2[j]!=1 && capgrm[j]>0)
      crit2[j]_(min(scpgrm[j,],na.rm=T)<50)
}

#

FH_rep(NA,reps)
FH_(crit1+crit2)>0

b_rep(0,reps)
d_rep(0,reps)
b_FH==1
d_FH==0

spec_sum(d)/(sum(b)+sum(d))
```

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