Probability of Carrying a Mutation of Breast–Ovarian Cancer Gene BRCA1 Based on Family History

*Donald A. Berry, Giovanni Parmigiani, Juana Sanchez, Joellen Schildkraut, Eric Winer**

Background: **Heritable mutations of the breast cancer gene BRCA1 are rare, occurring in fewer than 1% of women in the general population, and therefore account for a small proportion of cases of breast and ovarian cancers. Nevertheless, the presence of such mutations is highly predictive of the development of these cancers.** ***Purpose:*** **We developed and applied a mathematic model for calculating the probability that a woman with a family history of breast and/or ovarian cancer carries a mutation of BRCA1.** ***Methods and Results:*** **As a basis for the model, we use Mendelian genetics and apply Bayes' theorem to information on the family history of these diseases. Of importance are the exact relationships of all family members, including both affected and unaffected members, and ages at diagnosis of the affected members and current ages of the unaffected members. We used available estimates of BRCA1 mutation frequencies in the general population and age-specific incidence rates of breast and ovarian cancers in carriers and noncarriers of mutations to estimate the probability that a particular member of the family carries a mutation. This probability is based on cancer statuses of all first- and second-degree relatives. We first describe the model by considering single individuals: a woman diagnosed with breast and/or ovarian cancer and also a woman free of cancer. We next considered two artificial and two actual family histories and addressed the sensitivity of our calculations to various assumptions. Particular relationships of family members with and without cancer can have a substantial impact on the probability of carrying a susceptibility gene. Ages at diagnosis of affected family members and their types of cancer are also important. A woman with two primary cancers can have a probability of carrying a mutation in excess of 80%, even with no other information about family history. The number and relationships of unaffected members, along with their current ages or ages at death, are critical determinants of one's carrier probability. An affected woman with several cancers in her family can have a probability of carrying a mutation that ranges from close to 100% to less than 5%.** ***Conclusion:*** **Our model gives informative and specific probabilities that a particular woman carries a mutation.** ***Implications:*** **This model focuses on mutations in BRCA1 and assumes that all other breast cancer is sporadic. With the cloning of BRCA2, we now know that this assumption is incorrect. We have adjusted the model to include BRCA2, but the use of this version must await publication of penetrance data for BRCA2, including those for male breast cancer that are apparently associated with BRCA2 but not with BRCA1. The current model is, nevertheless, appropriate and useful. Of principal importance is its potential and that of improved versions for aiding women and their health care providers in assessing the need for genetic testing. [J Natl Cancer Inst 1997;89:227-37]**

There are approximately 180 000 new cases of breast cancer diagnosed each year in the United States. Approximately 45 000 women die of the disease annually. Although only about 26 000 cases of ovarian cancer are diagnosed each year, proportionately more women (14 000 annually) die of ovarian cancer (*1*). It is estimated that 2% of all breast cancers and 10% of ovarian cancers occur in women who carry a mutation in the BRCA1 susceptibility gene for breast cancer (*2*). The prevalence of mutations at BRCA1 has been estimated to be 0.04%-0.20% in the general population (*3*), but prevalence may vary, depending on racial or ethnic group (*4*). Approximately 85% of female carriers will develop breast cancer and 63% will develop ovarian cancer by the age of 70 years (*2*). Moreover, these two cancers seem to be statistically independent (*2*). In particular, based on these estimates, for female carriers who live to age 70 years, about 95% [or $1 - (1 - 0.85)(1 - 0.63)$] have developed one or the other cancer and about 54% (or 0.85×0.63) have both cancers.

The high penetrances of breast and ovarian cancers among women with BRCA1 mutations mean that family history of these diseases is a strong indicator of whether a mutation is present in the family. This article presents a method for finding the probability that a particular family member carries a mutation at BRCA1 on the basis of her family's history of these two diseases.

Methods and Results

Bayes' Theorem

The fundamental tool for finding the probability of a genotype based on empiric information is Bayes' theorem (*5*,*6*). Let M stand for ''individual carries a mutation,'' N for its complement ''individual does not carry a mutation,'' and H for ''individual's family history.'' Bayes' theorem relates $P(M|H)$, the probability of M conditional on family history H (called posterior probability), with its unconditional or prior probability, $P(M)$. Family history enters through its ''likelihood'' under M and under N: $P(H|M)$ and $P(H|N)$. By Bayes' theorem,

$$P(M|H) = \frac{P(H|M)P(M)}{P(H)}.$$

This is sometimes called the theorem of inverse probabilities because it relates the roles of $P(M|H)$ and $P(H|M)$. According to the law of total probability, $P(H)$

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See ''Notes'' following ''References.''

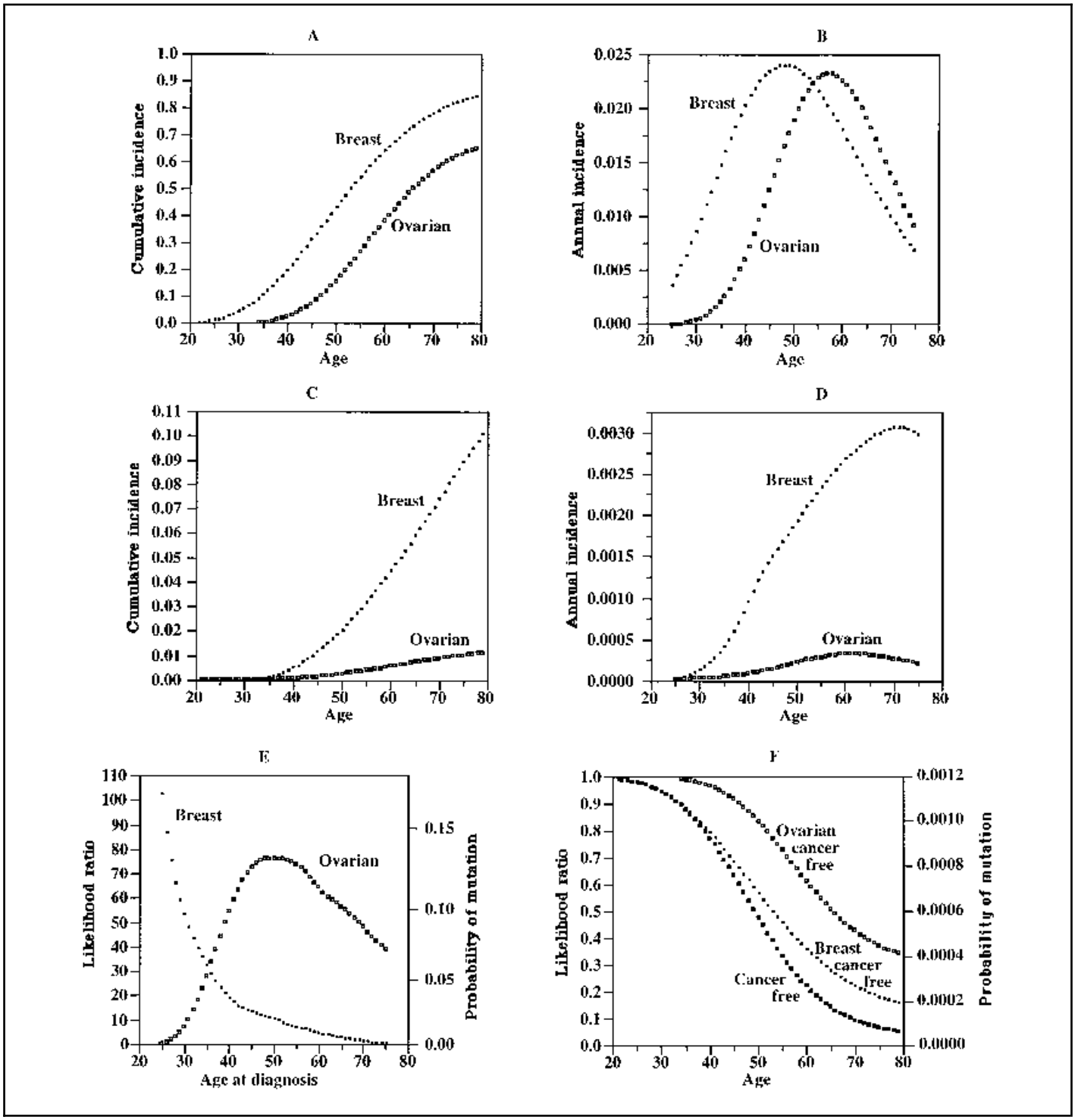

Fig. 1. A) Cumulative risks of breast and ovarian cancers for carriers of mutations at BRCA1. These curves are fit with the use of a three-parameter gamma cumulative function to the estimates of Easton et al. (*2*). In the notation of the ''Methods and Results'' section, these curves are B_M(age) and O_M(age). **B)** Age-specific incidence of breast and ovarian cancers among carriers of mutations at BRCA1. These are derived from the corresponding curves in A by taking differences in values for successive years. In the ''Methods and Results'' section, these curves are b_M(age) and o_M(age). **C)** Cumulative risks of breast and ovarian cancers for noncarriers of mutations at BRCA1. In the notation of the ''Methods and Results'' section, these curves are B_N(age) and O_N(age). **D)** Age-specific incidence of breast and ovarian cancers among noncarriers of mutations at BRCA1. These are derived from the corresponding curves in A. In the ''Methods and Results'' section, these curves are b_N(age) and o_N(age). **E)** The likelihood ratio (LR) and posterior probability of carrying a mutation at BRCA1 based on only the age of diagnosis of a woman's cancer. LR = b_M(age)/b_N(age) for breast cancer only and LR = o_M(age)/o_N(age) for ovarian cancer only. In both cases, probability of mutation = LR/(LR + 832). **F)** The LR and posterior probability of carrying a mutation at BRCA1 based on only the current age of a disease-free woman. LR = (1 − B_M(age))/(1 − B_N(age)) for breast cancer and LR = (1 − O_M(age))/(1 − O_N(age)) for ovarian cancer. The LR for a woman free of both diseases is the product of these two LRs, and is labeled ''cancer free.'' In each case, probability of mutation = LR/(LR + 832).

$= P(H|M)P(M) + P(H|N)P(N)$. Some albegra reveals that $P(H|M)$ and $P(H|N)$ enter Bayes' theorem only through their ratio, called likelihood ratio (LR):

$$\mathrm{LR} = \frac{P(H|M)}{P(H|N)}.$$

We will use the following version of Bayes' theorem:

$$P(M|H) = \frac{\mathrm{LR}}{\mathrm{LR} + P(N)/P(M)},$$

where $P(N)/P(M)$ is the prior odds against being a carrier. Calculating the numerator of the likelihood ratio, $P(H|M)$, means assuming that the individual of interest carries a mutation, and calculating the denominator, $P(H|N)$, means assuming that she is not a carrier; both assume Mendelian genetics.

Posterior probabilities generalize positive and negative predictive values that are standard measures of the usefulness of a laboratory test. They are more general in that there are two types of evidence (positive and negative) for laboratory tests, but many types of family histories must be considered in the analysis described in this article.

The adjectives ''prior'' and ''posterior'' refer to before and after a particular piece of evidence. Both prior and posterior probabilities are based on evidence, but the latter is based on more evidence—in our case, family history. Bayes' theorem applies sequentially to any number of pieces of evidence (and in any order), with the posterior for one piece of evidence serving as the prior for the next. For example, probability $P(M|H)$ is the probability that the individual of interest carries a mutation posterior to observing her family history H, but $P(M|H)$ serves as the prior probability for the result of a genetic test.

The probability prior to family history is $P(M) = 2f - f^2$, where f is the allelic frequency of mutations in the population of interest, that is, the population containing the individual of interest. This frequency is not known precisely; we consider the effect of uncertainty in f on LR and on the posterior probability of being a carrier, but for most of this article, we assume $f = 0.0006$ (*3*). Under this assumption, the proportion of carriers in the population is $P(M) = 0.0012$ and the prior odds against being a carrier equal $P(N)/P(M) = (1 - 0.0012)/0.0012 = 0.9988/0.0012 = 832$. The posterior carrier probability is then

$$P(M|H) = \frac{\mathrm{LR}}{\mathrm{LR} + 832}.$$

If f were equal to 0.005, as is claimed for Ashkenazi Jews (*4*), then the prior odds equal $0.99/0.01 = 99$ and the posterior carrier probability is

$$P(M|H) = \frac{\mathrm{LR}}{\mathrm{LR} + 99}.$$

In finding $P(M|H)$, the information in a family history enters through the LR. The LR compares the probability of the individual's actual family history assuming she carries a mutation with the probability of her family history assuming she does not carry a mutation. Large values of LRs indicate that the first probability is large when compared with the second; $\mathrm{LR} = 1$ is the break-even point at which family history is noninformative as regards *M;* that is, $\mathrm{LR} = 1$ means that the posterior probability of carrying a mutation does not change from the prior probability: $P(M|H) = P(M)$.

Family history used in our model includes the ages at which affected first- and second-degree relatives were diagnosed with breast or ovarian cancer and the current ages or ages at death for unaffected relatives. Extensions to third-degree and more distant relatives are possible, but the calculations are more cumbersome and this information has less value for most families. In addition, information regarding distant relatives is usually less accurate.

The technical development of the method is presented gradually in the following sections. We first address the relatively simple but informative case of a single individual who has been diagnosed with breast or ovarian cancer or both. With the use of the available estimates of BRCA1 mutation frequencies in the general population and the age-specific incidence of breast and ovarian cancers for women with mutations, we calculate the probability that an affected individual carries a mutation at BRCA1 based on her age at diagnosis. We then calculate this probability for a female family member who is disease free, depending on her age. In the Appendix, we describe how the breast and ovarian cancer histories of first- and second-degree relatives are incorporated into the calculations.

Women With Breast Cancer

Consider a very simple family history H: a 30-year-old woman has just been diagnosed with breast cancer. Suppose that her ovarian cancer status is unknown and temporarily ignore the information from other members of her family. The numerator $P(H|M)$ of the LR is the probability that a carrier would be diagnosed with breast cancer at age 30 years. This is the incidence of breast cancer among 30-year-old carriers, which we estimate as follows.

Easton et al. (*2*) give estimates of the cumulative proportion of BRCA1 carriers who have been diagnosed with breast cancer depending on age. A smoothed version is shown in Fig. 1, A. We denote this as $B_M(\mathrm{age})$. The second curve in this figure shows the corresponding proportion with ovarian cancer, $O_M(\mathrm{age})$. (The smoothing method used is described in the figure legend. Neither the curves in Fig. 1, A, nor the eventual conclusions are sensitive to the smoothing method used.) Age-specific incidence, $b_M(\mathrm{age})$, is the increase in the cumulative proportion at that age—the derivative of $B_M(\mathrm{age})$. This is shown in Fig. 1, B, along with the corresponding age-specific incidence for ovarian cancer, $o_M(\mathrm{age})$.

The numerator of LR is then $b_M(30)$, which from Fig. 1, B, is about 0.0088.

The denominator $P(H|N)$ of LR is the probability that a noncarrier would be diagnosed with breast cancer at age 30 years, which is just the incidence of breast cancer among 30-year-old noncarriers. We denote this as $b_N(30)$. This is found in the same way as for carriers. Fig. 1, C, shows the cumulative proportions of breast and ovarian cancers among noncarriers, $B_N(\mathrm{age})$ and $O_N(\mathrm{age})$ (*7,8*). Fig. 1, D, gives the corresponding age-specific incidences for noncarriers, $b_N(\mathrm{age})$ and $o_N(\mathrm{age})$. From this figure, $b_N(30)$ is about 0.00016.

Therefore, the likelihood ratio is

$$\mathrm{LR} = \frac{b_M(30)}{b_N(30)} = \frac{0.0088}{0.00016} = 55.$$

This means that the likelihood of observing breast cancer in a 30-year-old woman is 55 times greater if she is a carrier than if she is not a carrier. (Note of caution: There is a strong tendency in science and the law to confuse such a statement with one about posterior probabilities. The statement does not mean that a 30-year-old woman with breast cancer is 55 times as likely to be a carrier as she is to be a noncarrier. Reversing the conditionals in this fashion requires Bayes' theorem.) Applying Bayes' theorem, where family history H is ''individual diagnosed with breast cancer at age 30'':

$$P(M|H) = \frac{55}{55 + 832} = 6.2\%.$$

The evidence that this woman had breast cancer at a very young age increases the probability that she carries a mutation from $P(M) = 0.12\%$ by about 50-fold.

Fig. 1, E, shows $\mathrm{LR} = b_M(\mathrm{age})/b_N(\mathrm{age})$ and also the posterior probability of carrying a mutation, depending on the individual's age. This is the ratio of the two curves labeled ''Breast'' in Fig. 1, B and D. The functional relationship between the labeling on the left vertical axis and that on the right in Fig. 1, E, is Bayes' theorem: $P(M|H) = \mathrm{LR}/(\mathrm{LR} + 832)$. The dependence on age is dramatic. Since breast cancer is much more common at younger ages among carriers than among noncarriers, the evidence in favor of being a carrier is much stronger if the individual is young. The evidence in favor of being a carrier is slight for an individual who was diagnosed when older. For example, for a 70-year-old individual diagnosed with breast cancer, $\mathrm{LR} = 0.0102/0.0031 = 3.3$, and so the posterior probability that she is a carrier increases to only about 0.4%. While breast cancer at any age is evidence in favor of being a carrier, such evidence is about 15 times as strong for a woman who is aged 30 years (6.2%) than for one who is aged 70 years (0.4%).

Woman Free of Cancer

If an individual is observed not to have breast cancer, the LR is the ratio of the probability of this observation assuming M to the probability of this observation assuming N. These are, respectively, one minus the probability of having breast cancer by the given age assuming M and N—$B_M(\mathrm{age})$ and $B_N(\mathrm{age})$—shown in Fig. 1, A and C:

$$\mathrm{LR} = \frac{1 - B_M(\mathrm{age})}{1 - B_N(\mathrm{age})}.$$

As an example, consider a 70-year-old woman. Only 21.3% ($= 1 - B_M(70) = 1 - 0.787$) of women who are carriers survive to age 70 years without experiencing

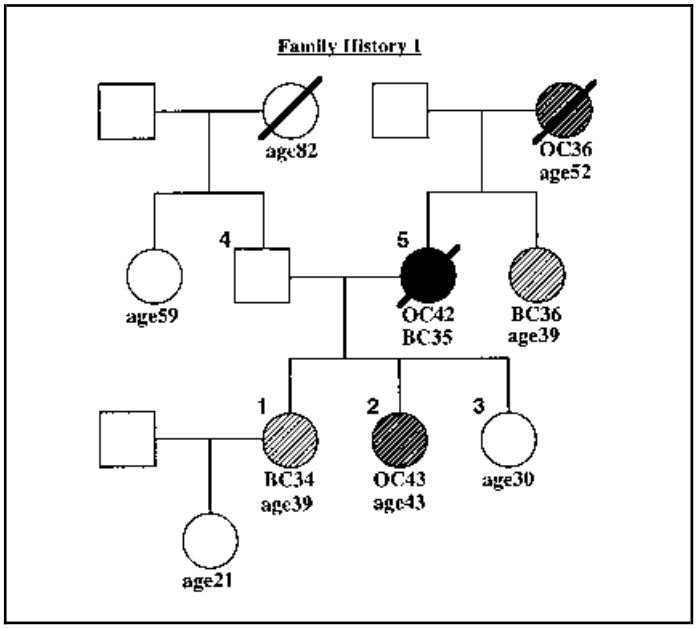

Fig. 2. Family history 1 (H1) of breast and ovarian cancers. Label BC34 indicates that member 1 was diagnosed with breast cancer at age 34 years; label OC43 indicates that her sister, member 2, was diagnosed with ovarian cancer at age 43 years; age is current or at death (the latter shown by a diagonal slash) and indicates that the individual has no cancers other than listed. Member 3 is free of both cancers. There is substantial evidence of a mutation on the maternal side of this family but not on the paternal side.

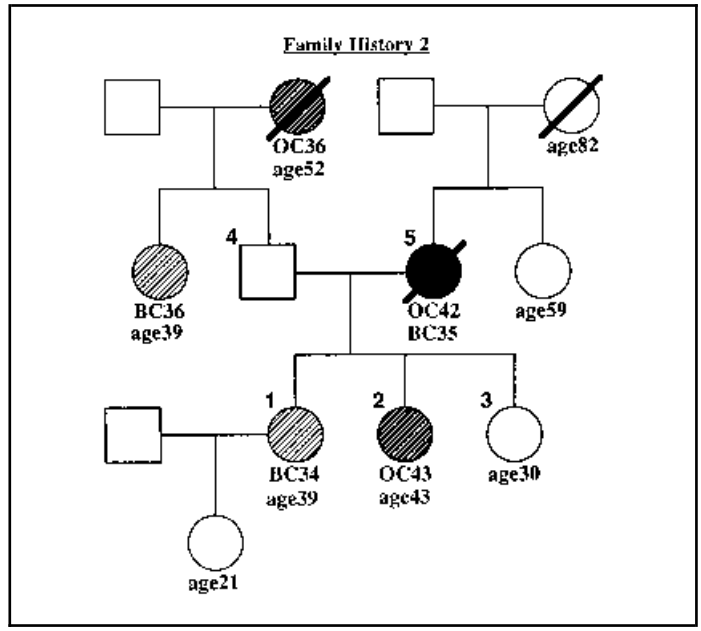

Fig. 3. Family history 2 (H2) is the same as H1 (*see* Fig. 2) but switches paternal and maternal aunts and grandmothers. As opposed to H1, there is evidence of mutations on both maternal and paternal sides of this family.

breast cancer, while 92.5% ($= 1 - B_N(70) = 1 - 0.075$) of noncarriers are free of breast cancer at age 70 years. The LR is

$$\mathrm{LR} = \frac{1 - B_M(70)}{1 - B_N(70)} = \frac{0.213}{0.925} = 0.23.$$

In other words, the evidence that a 70-year-old woman is free of breast cancer is about four times as likely if she is not a carrier than if she is a carrier. For a woman who is free of breast cancer at age 70 years, the probability that she carries a mutation has decreased from $P(M) = 0.0012 = 0.12\%$ at birth to

$$P(M|H) = \frac{\mathrm{LR}}{\mathrm{LR} + 832} = \frac{0.23}{0.23 + 832} = 0.00028 = 0.028\%.$$

Fig. 1, F, shows the effect of age on the LR and also on the posterior probability of being a carrier, assuming that she does not have breast cancer. (These curves apply as well for a woman who died cancer free, where age is that at death.) For a very young woman who is disease free, there is very little evidence about her carrier status—i.e., the LR is close to 1. The evidence against being a carrier gets stronger with age, provided she remains disease free.

Including Both Breast and Ovarian Cancer Statuses

Consider a woman's ovarian cancer status. Ignoring her breast cancer status gives results analogous to those for breast cancer, now using the ovarian cancer curves in Fig. 1, A-D; the LR and posterior carrier probability results are labeled ''Ovarian'' in Fig. 1, E and F. Conditioning on both ovarian and breast cancer statuses requires information about the proportions of carriers who have both diseases and also about noncarriers who have both diseases. The data given by Easton et al. (*2*) suggest that for each age, the proportion of carriers with both cancers is the proportion having breast cancer times the proportion having ovarian cancer, i.e., that these diseases are independent. In this article, we assume independence of the incidence of the two cancers for both carriers and noncarriers. (This does not mean that these two cancers are independent when ignoring carrier status, and, in fact, it implies that they are positively correlated in the general population.)

There are four cases to consider: the woman has both breast and ovarian cancers, only breast cancer, only ovarian cancer, and neither cancer. In each case, the patient LR is the product of the separate LRs, one for breast cancer and the other for ovarian cancer. We provide details for only the first two cases.

Table 1. Likelihood ratios (LRs) and posterior probabilities of having a mutation in BRCA1 gene for members of families 1 and 2

Member	LR1	$P(M\|H1)$	LR2	$P(M\|H2)$
1	31 500	0.974	33 600	0.976
2	42 900	0.981	44 300	0.982
3	807	0.492	997	0.545
4	0.74	0.0009	526	0.387
5	8×10^7	0.99999	3930	0.825
4 or 5*	5×10^7	0.99999	195 000	0.998

*Either or both of these members carries a mutation.

1) In the first case, the woman has both breast and ovarian cancers—breast cancer diagnosed at age_B and ovarian cancer diagnosed at age_O. Where o_M and o_N are the ovarian analogues of incidences b_M and b_N, the LR is

$$\mathrm{LR} = \frac{b_M(\mathrm{age}_B)}{b_N(\mathrm{age}_B)} \frac{o_M(\mathrm{age}_O)}{o_N(\mathrm{age}_O)}.$$

The result is the product of a pair of numbers that can be read off the respective curves in Fig. 1, E. For example, for a woman who was diagnosed at ages 30 and 45 years, respectively, the overall likelihood ratio is

$$\mathrm{LR} = \frac{b_M(30)}{b_N(30)} \frac{o_M(45)}{o_N(45)} = \frac{0.0088}{0.00016} \frac{0.0125}{0.00017} = 55 \times 73 = 4015.$$

The corresponding posterior probability of carrying a mutation is

$$P(M|H) = \frac{\mathrm{LR}}{\mathrm{LR} + 832} = \frac{4015}{4015 + 832} = 0.83 = 83\%.$$

2) Now suppose the woman has breast cancer diagnosed at age_B but does not have ovarian cancer and her current age is age_O. Then the LR is

$$\mathrm{LR} = \frac{b_M(\mathrm{age}_B)}{b_N(\mathrm{age}_B)} \frac{1 - O_M(\mathrm{age}_O)}{1 - O_N(\mathrm{age}_O)},$$

where O_M and O_N are cumulative incidences for ovarian cancer for carriers and noncarriers that are analogous to B_M and B_N for breast cancer. The second factor in this expression is shown in Fig. 1 (which also shows the LR for a woman who is free of both cancers).

As an example, consider a 45-year-old woman who was diagnosed with breast

cancer at age 30 years and assume that she does not have ovarian cancer. The appropriate likelihoods now include both diseases. Therefore, the LR is

$$\mathrm{LR} = \frac{b_M(30)}{b_N(30)} \frac{1 - O_M(45)}{1 - O_N(45)} = 55 \times \frac{1 - 0.079}{1 - 0.0022} = 55 \times 0.92 = 51.$$

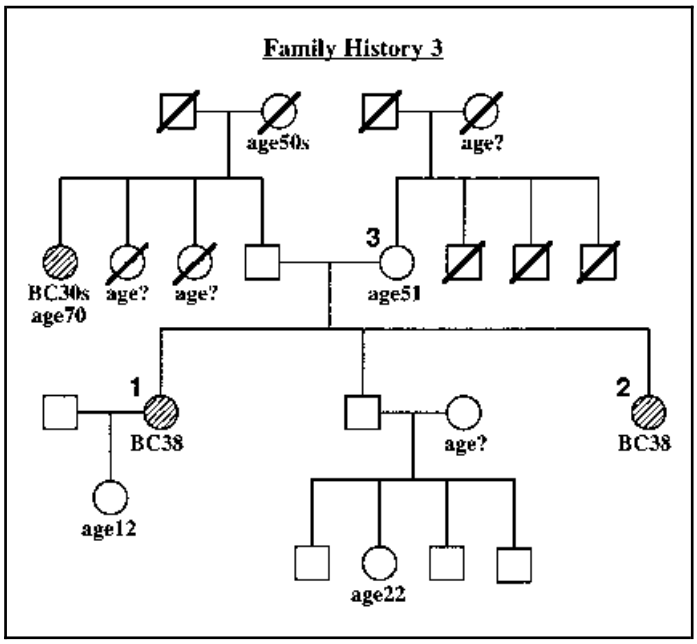

Fig. 4. Family history 3 (H3). Current age or age at death shown for each female family member, when known. With no indication of breast cancer (BC) or ovarian cancer (OC), the member is thought to be free of both breast and ovarian cancers. We took the age of the paternal aunt (BC30s) to be 35 years at diagnosis and the paternal grandmother (50s) to be 55 years at death. We do not know the current ages or the ages at death of members 1 and 2, and so with regard to ovarian cancer, we censored them at the time of their breast cancer; that is, we used the information that they were free of ovarian cancer at age 38 years. We regarded the other three individuals with unknown ages as missing. (Taking all three ages to be 70 years results in a decrease in likelihood ratio by a factor of about 3.) The reason for member 3's relatively young age of 51 years is that she was diagnosed with endometrial cancer at that age and so her current age was not elicited.

The posterior carrier probability is somewhat smaller than when ignoring ovarian cancer status:

$$P(M|H) = \frac{\mathrm{LR}}{\mathrm{LR} + 832} = \frac{51}{51 + 832} = 0.058 = 5.8\%.$$

As another example, reconsider the 70-year-old woman who has just been diagnosed with breast cancer and assume that she does not have ovarian cancer. The LR of carrier to noncarrier for this observation is

$$\mathrm{LR} = \frac{b_M(70)}{b_N(70)} \frac{1 - O_M(70)}{1 - O_N J(70)} = 3.3 \times \frac{1 - 0.57}{1 - 0.0097} = 3.3 \times 0.43 = 1.4.$$

This is only slightly larger than 1 because the evidence that she carries a mutation is rather weak. The posterior probability that she is a carrier is

$$P(M|H) = \frac{\mathrm{LR}}{\mathrm{LR} + 832} = \frac{1.4}{1.4 + 832} = 0.0017 = 0.17\%,$$

which is not much increased from the prior probability of 0.12%.

General Family Histories

The Appendix indicates how Bayes' theorem applies to include history of breast cancer among first-degree relatives. Details of calculations including history of ovarian cancer and unilateral and bilateral breast cancer among first- and second-degree relatives are given separately (*9*).

Family history includes the age at diagnosis of breast cancer, ovarian cancer, or both for each affected family member and the current age or age at death for each unaffected member. Our method considers all affected and unaffected first- and second-degree relatives, including their exact relationships (such as paternal aunt). Missing data do not present a problem for the model, although obviously, accurate information is better than no information. If the status of a family member is unknown, that family member is simply not included in the calculation. However, it may be more likely to be known that a relative has cancer than that she does not have cancer, and so this may create a bias. If a woman was known to be cancer free at a particular age, that age is taken as her current age. If a family member's age at diagnosis is unknown, we recommend using a best guess. However, since a relative's age at diagnosis can have a substantial impact on one's carrier probability, we recommend varying this age over the range of possibilities and providing the resulting interval of probabilities to the woman.

Application to Two Artificial Family Histories

Figs. 2 and 3 show family histories 1 and 2, called H1 and H2. The members of interest are numbered 1-5 and are the same in both families. The only difference in the families is that the sisters and mothers of members 4 and 5 have been exchanged. We assume that the mutation frequency f is 0.0006 (*3*) and, therefore,

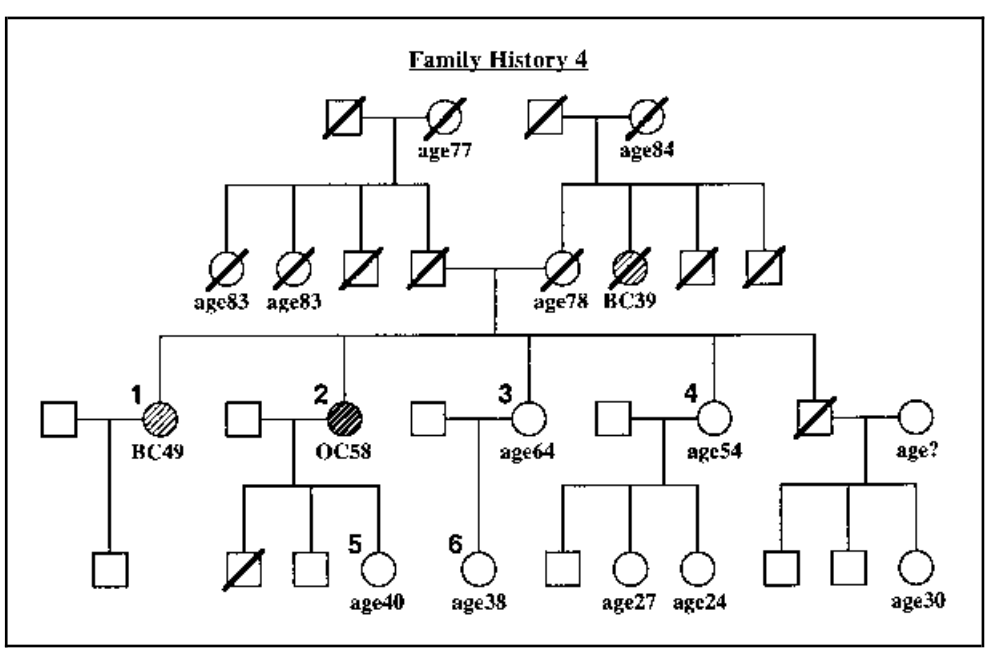

Fig. 5. Family history 4 (H4). Current age or age at death shown for each female family member, when known. If there is no indication of breast cancer (BC) or ovarian cancer (OC), the member is thought to be free of both breast and ovarian cancers. The age of the sister-in-law of member 1-4 is unknown, but it has essentially no effect on the results, because her daughter does not have cancer. We do not know the current ages or the ages at death of the family members with breast or ovarian cancer and so with regard to the other cancer, we censored them at the time of their known cancer. For example, we conditioned on member 1 being free of ovarian cancer at age 49 years.

Table 2. Likelihood ratios (LRs) and posterior probabilities of having a mutation in BRCA1 gene for members of family 3

Member	LR3	$P(M\|H3)$
1, 2	1020	0.550
3	82.9	0.089

Table 3. Likelihood ratios (LRs) and posterior probabilities of having a mutation in BRCA1 gene for members of family 4

Member	LR4	$P(M\|H4)$
1	20.1	0.024
2	21.7	0.025
3	3.16	0.004
4	6.18	0.007
5	9.28	0.011
6	1.92	0.002

that $P(M) = 0.0012$. With the use of our computer program, we calculated the LRs LR1 and LR2 for these families and the corresponding posterior probabilities $P(M|H1)$ and $P(M|H2)$. These are shown in Table 1.

H1 and H2 provide similarly convincing evidence that members 1 and 2 are carriers. Both women have cancer, and each serves to increase the LR of the other. In both families, the mother (member 5) provides a likely source for the mutation of genes in her daughters. In H1, the cancers observed in the two daughters support the hypothesis that their mother carries a mutation; in H2, these cancers support the hypothesis that at least one of the parents carries a mutation. The father (member 4) is a likely source of a mutation in H2 but not in H1. This second possible source in H2 increases the probability that members 1 and 2 carry two mutations, but it has little effect on the strength of the conclusion that they carry at least one. Our program can evaluate the probability that there is at least one or more than one mutation in a subset of family members. For example, the probability that both parents in H2 carry a mutation is 0.214, and the respective probabilities that members 1 and 2 carry two mutations are 0.117 and 0.118. (This probability for member 1 would be only ¼ of 0.214 or about 0.053 without conditioning on her cancer status.)

The conclusions in the two families are somewhat different with regard to member 3. In H1 she has probability of ½ of inheriting her mother's likely mutation. Her cancer-free status means that her carrier probability cannot be greater than ½. (This upper limit applies at birth and can only decrease with age if the woman remains cancer free.) However, the possibility of mutations on both sides of the family in H2 allows the carrier probability to increase beyond ½. With both her mother and her father being possible sources of mutations, the effective upper limit for the probability of a cancer-free woman carrying a mutation is ¾.

Application to Two Actual Family Histories

Figs. 4 and 5 give family histories H3 and H4. Three female members are numbered. Again, assume $f = 0.0006$. The results for H3 are shown in Table 2. The breast cancers of members 1 and 2 enhance each other's probability of carrying a mutation. There is a likely link between these two members and the paternal aunt with breast cancer. However, the possibility of a maternal mutation cannot be ruled out—hence the moderate LR3 for member 3, the mother of members 1 and 2. Although there is no evidence in favor of a maternal mutation, there is not much evidence against it: The only female relative on the mother's side is the maternal grandmother, and even though the mother is free of breast and ovarian cancer, she is relatively young.

The results for H4 are shown in Table 3. For members 1-4 of H4, there is no evidence of a mutation particular to the paternal side of the family. And there is only weak evidence on the maternal side. The maternal aunt with breast cancer (BC39) is evidence in favor of a mutation. (The LR considered separate from the rest of the family is about 22.) However, the mother was free of both breast and ovarian cancers at age 78 years, and this applies for only about 5% of carriers. So, even if the maternal aunt is a carrier, the mother's disease-free status makes it unlikely that she shares her sister's mutation. The mother's disease-free status substantially weakens the possibility of a link between the cancers of the maternal aunt and members 1 and 2. The result is that all six members have moderate LRs. (If the maternal aunt were switched with the two paternal aunts, both of whom died cancer free at age 83 years, then the probabilities that members 1 and 2 carry mutations are greatly increased—to 0.196 and 0.205.)

Discussion

Claus et al. (*10-14*) have developed excellent models for predicting breast cancer incidence based on family history. Their approach includes segregation analysis with the use of population-based, case–control data from the Cancer and Steroid Hormone (CASH) study, in which the liability classes are based on the observed cumulative risk of breast cancer at 10-year age intervals for female relatives. A diallelic major locus model was assumed. An autosomal dominant model provided the best fit to the data.

The approach of Claus et al. is different from ours in several ways. Their models are not tied to any particular breast cancer susceptibility gene but focus on the cumulative probability over age that an unaffected woman will be diagnosed with breast cancer based on her family history. Our model is tied to BRCA1, and we calculate the probability that a woman carries a mutation at this gene. The woman may be affected or unaffected. Our model can be used to find the cumulative probability of breast cancer before a particular age by averaging the cumulative incidence probabilities for carriers and noncarriers, where the weights are those from our model. For example, member 3 of family history 1 is 30 years old. The probability that she carries a mutation at BRCA1 is 49.2%. The probability that she develops breast cancer by age 50 years is $B_M(50) - B_M(30) = 0.437 - 0.049 = 38.8\%$ if she carries a mutation, and it is $B_N(50) - B_N(30) = 0.021 - 0.001 = 2.0\%$ if she does not carry a mutation. So, the unconditional probability that she will develop breast cancer by age 50 years is $0.492 \times 38.8\% + 0.508 \times 2.0\% = 20.1\%$. In addition, our model considers the number, relationship, and ages of unaffected individuals. Having many unaffected family members can substantially lower a carrier probability. Also, our model explicitly considers the ovarian cancer

Table 4. Effect of changing mutation frequency f on likelihood ratios (LRs) and posterior probabilities of having a mutation on BRCA1 gene for members of families 1 and 2

	$f = 0.0002$		$f = 0.0010$	
Member	LR1	$P(M\|H1)$	LR1	$P(M\|H1)$
1	91 800	0.973	19 500	0.975
2	122 000	0.980	27 200	0.982
3	2420	0.492	484	0.492
4	0.74	0.0003	0.73	0.0015
5	8×10^7	0.99997	7×10^7	0.99999
4 or 5*	5×10^7	0.99997	5×10^7	0.99999

	$f = 0.0002$		$f = 0.0010$	
Member	LR2	$P(M\|H2)$	LR2	$P(M\|H2)$
1	73 500	0.967	23 300	0.979
2	90 500	0.973	31 900	0.985
3	2600	0.510	657	0.568
4	1080	0.302	401	0.446
5	8640	0.776	3000	0.857
4 or 5*	153 000	0.992	243 000	0.999

*Either or both of these members carries a mutation.

status of each family member. For BRCA1, the presence or absence of ovarian cancer (including age at diagnosis or current age) is an important consideration. [Claus et al. have recently incorporated age-specific risk estimates of ovarian cancer in mothers and sisters into the genetic risk model for breast cancer (*14*)].

Uncertainty Concerning Prevalence of Mutations in BRCA1

In the ''Methods and Results'' section, the calculations of an individual's probability of carrying a mutation at BRCA1 were based on population mutation frequency $f = 0.0006$. The corresponding prevalence is about 0.0012. The value of f is not known precisely. It has been estimated to be 0.0006, with a 95% confidence interval of from 0.0002 to 0.0010 (*3*). Furthermore, mutation frequency may vary with ethnicity (*4*). One way to handle uncertainty in f (and also that in the age-specific incidence) is to allow the various unknown quantities to have a probability distribution when calculating the posterior probability $P(M|H)$ of carrying a mutation in BRCA1, given an individual's family history (*9*). In the following, we address the effect of uncertainty differently, by letting f take on its upper and lower confidence limits.

If $f = 0.0006$, then, as indicated in the ''Methods and Results'' section,

$$P(M|H) = \frac{\mathrm{LR}}{\mathrm{LR} + 832}.$$

For $f = 0.0002$ or 0.0010, the respective posterior probabilities are

$$P(M|H) = \frac{\mathrm{LR}}{\mathrm{LR} + 2499} \text{ and } P(M|H) = \frac{\mathrm{LR}}{\mathrm{LR} + 499}.$$

(We caution that the calculation of LR itself involves f [*see* Appendix], and so LR is different in these three expressions.)

The prior probability of carrying a mutation is $P(M) = 2f - f^2$, and so it increases approximately proportionally to f when f is small. Suppose the posterior probability $P(M|H)$ is close to 0 for a particular f. Then an increase in f will result in an increase in $P(M|H)$ by approximately the same proportion. But if $P(M|H)$ is close to 1 (or close to ½ for an unaffected individual), then changing f has little impact on the posterior probability.

Consider family histories H1 and H2 (Figs. 2 and 3; Table 1) and consider values of f at the upper and lower 95% confidence intervals mentioned above. The effect on the LR and on the posterior probability $P(M|H)$ is shown in Table 4. The evidence that members 1 and 2 carry mutations is so strong in both H1 and H2 that $P(M|H1)$ and $P(M|H2)$ are close to 1, even for f as small as 0.0002. These posterior probabilities increase only slightly when f increases by fivefold to 0.0010. Similarly, unaffected member 3's $P(M|H3)$ is essentially unchanged when increasing f by a factor of 5, because 0.492 is already about as large as possible in the absence of evidence for multiple mutations in the family. Member 3's posterior probability increases more in H2 when changing f from 0.0002 to 0.0010, because of evidence for two distinct mutations in this family.

Uncertainty Concerning Penetrance and Incidence

We indicated that Claus et al. (*10-14*) used data from the CASH study, which used a defined population in geographic regions of eight population-based tumor registries of the Surveillance, Epidemiology, and End Results[1] (SEER) Program. The families represent a spectrum of cancer families in the population and are not tied to genetic characteristics. On the other hand, Easton et al. (*2*) studied so-called breast cancer families. Families with a high proportion of cancer—highly penetrant—may not be representative of the general population. In particular, they may exaggerate the penetrance of BRCA1. If Easton et al. overestimate penetrance, then our calculation of the probability of being a BRCA1 carrier may be underestimated in some families and overestimated in others.

An example is family 4 (Fig. 5). Suppose that the incidences by age of breast and ovarian cancers are kept proportional to those shown in Fig. 1, B. Reducing penetrance actually increases the carrier probabilities for family members 1 and 2. The reason is that the cancer-free status of their mother would not as definitively break the connection between them and their maternal aunt. With the use of our program, we find that the maximum carrier probability for member 1 is 0.064 (up from 0.024 in Table 3) and for member 2 is 0.070 (up from 0.025 in Table 3). These maxima occur when the penetrance of breast cancer is 48% (down from 85% in Fig. 1, A) and that of ovarian cancer is 36% (down from 63% in Fig. 1, A).

When counseling a woman about testing, a clinician or genetics counselor might incorporate the uncertainty in penetrance, incidence, and prevalence by providing a woman with a range of posterior probabilities. A version of our computer program calculates ranges by considering combinations of upper and lower limits of the penetrance, incidence, and prevalence and giving the smallest and largest posterior probabilities.

Including Bilateral Breast Cancer

We have described calculations for unilateral breast cancer. Carriers of BRCA1 mutations are very likely to have bilateral disease (*2*). Estimates of the incidence of bilateral disease have positive and negative biases. On one hand, the unaffected breast of a woman with unilateral breast cancer is likely to be subjected to more frequent mammographic and clinical examinations. On the other hand, some patients from breast cancer families opt for bilateral mastectomies, and systemic therapies that some women receive for breast cancer may help prevent contralateral disease. These biases have unknown magnitudes, and it is not clear which is more important. The incidence of bilateral disease among BRCA1 carriers reported by Easton et al. (*2*) suggests that cancer occurs independently in the two breasts. Bilateral breast cancers in a family can be input to our computer program; the calculations assume independence of the occurrences of cancers in the left and right breasts and are described elsewhere (*9*).

Role of BRCA2 and Other Breast Cancer Genes

Our model focuses on mutations in BRCA1 and assumes that all other breast cancer is sporadic. In view of the cloning of BRCA2 (*15*), this assumption is incorrect. However, our model can be modified to include multiple genes. We have accomplished this modification in our program, but its use awaits pub-

lication of data concerning the age-specific incidence of breast and ovarian cancers and male breast cancer (apparently associated with BRCA2 but not with BRCA1). Considering both BRCA1 and BRCA2 gives three possibilities for breast cancer: that associated with BRCA1, that associated with BRCA2, and sporadic. Each has a prior probability, and Bayes' theorem applies to give the corresponding posterior probabilities based on family history. Summing the probabilities (whether prior or posterior) for BRCA1 and BRCA2 gives the probability of carrying a mutation at either gene.

Including BRCA2 as well as BRCA1 and considering all other breast cancer as sporadic may well give a different probability—usually smaller—that an individual carries a mutation of BRCA1. It may also give a different probability—usually larger—that an individual carries a mutation at one or more breast cancer genes. The effect of ignoring BRCA2 is as follows: Suppose that the breast cancer penetrance of BRCA2 is the same as BRCA1 but that ovarian cancer penetrance of BRCA2 is relatively small (*3*). For a family with numerous cases of ovarian cancer, the probability of carrying BRCA1 would be approximately that calculated by the use of our current program, and that of carrying BRCA2 would be quite small. For a family with a large number of cases of breast cancer and no ovarian cancer, the probability of carrying BRCA2 would be greater than that of BRCA1. (Since the prevalence of BRCA2 is probably only a fraction of that of BRCA1, the number of cases of breast cancer would have to be rather large for the probability of BRCA2 to dominate over that of BRCA1.) For a family with some male breast cancer, the BRCA1 version of our program would be of little help—except that using it while ignoring cases of male breast cancer in the family gives a lower estimate of the probability that a female member carries a mutation of BRCA2. Finally, for a family with a small number of cases of ovarian cancer (small relative to the number of breast cancers), the program described here approximates the probability of carrying a mutation at either BRCA1 or BRCA2, where f is then the total allelic frequency of mutations at the two genes. In this case, the appropriate allocation of the resulting probability to BRCA1 and BRCA2 depends on the penetrance of ovarian cancer among BRCA2 carriers.

Impact of Genetic Testing

A woman who has a family history of breast and ovarian cancers may consider genetic testing. Such a decision is complicated, as described in Clinical Considerations below.

An important consideration in deciding whether to be tested is the test's specificity (1 − false-positive rate) and sensitivity (1 − false-negative rate). Let a = specificity and b = sensitivity. Bayes' theorem (*5*) applies (just as for any diagnostic procedure) to update the probability of being a carrier. $P(M|H)$ now plays the role of the prior probability and the test result (+/−) is the evidence. The positive predictive value of the test is:

$$P(M|H, +) = \frac{bP(M|H)}{bP(M|H) + (1-a)P(N|H)},$$

and its negative predictive value is

$$P(M|H, -) = \frac{(1-b)P(M|H)}{(1-b)P(M|H) + aP(N|H)}.$$

As an example, consider member 1 of family 4 (Fig. 5) and suppose $a = 95\%$ and $b = 85\%$. On the basis of her family history, her carrier probability is $P(M|H4) = 0.024$. If she is tested, the probability of a positive test is $bP(M|H4) + (1 - a)P(N|H4) = 0.85 \times 0.024 + 0.05 \times 0.976 = 0.069$, and the probability of a negative test is $1 - 0.069 = 0.931$. If her test were positive, then her updated carrier probability would be

$$P(M|H4, +) = \frac{0.85\ (0.024)}{0.069} = 0.295.$$

If she were to test negative, then her updated probability would be

$$P(M|H4, -) = \frac{0.15\ (0.024)}{0.931} = 0.004.$$

As another example, consider member 3 of family 1 (Fig. 2) and suppose $a = 95\%$ and $b = 50\%$, as it might be for a test that examines only a portion of the BRCA1 gene. The carrier probability of this 30-year-old woman is $P(M|H1) = 0.492$. The probability of a positive test is $bP(M|H1) + (1 - a)P(N|H1) = 0.50 \times 0.492 + 0.05 \times 0.508 = 0.271$, and the probability of a negative test is $1 - 0.271 = 0.729$. After a positive test:

$$P(M|H1, +) = \frac{0.50(0.492)}{0.271} = 0.908.$$

After a negative test:

$$P(M|H1, -) = \frac{0.50(0.492)}{0.729} = 0.338.$$

Should this 30-year-old, disease-free woman submit to testing? There are a variety of considerations and these will be discussed below. However, her decision problem is not easy, even restricting consideration to length of life. (We quantify the benefit of genetic testing in terms of quality-adjusted life years as part of an ongoing decision analysis project of the Duke SPORE [Specialized Program of Research Excellence] in breast cancer.) Any benefit of testing depends on the woman's probability of being a carrier based on family history and on the sensitivity and specificity of the testing procedure. It also depends on the effectiveness of available prophylactic interventions, such as mastectomy and oophorectomy. If they are regarded as highly effective, then the woman might choose them, even if her probability of being a carrier is small. In the example with its rather large probability, even for a negative test, she might choose the same intervention, regardless of the test result. In such a case, there is no advantage to testing. But if she would choose one combination of interventions for a positive test result and another for a negative test, then testing has some value. The expected value of testing can be found by averaging expected life years in the two circumstances by their probabilities.

Clinical Considerations

The decision to undergo genetic testing for BRCA1 or other cancer susceptibility genes is complex. Women who have been diagnosed with breast and/or ovarian cancer and who have a family history of these cancers will be among the first to be offered testing. Many unaffected relatives of these women, many of whom already realize they are at increased risk of developing

cancer, will be interested in genetic testing. In view of the potential risks associated with testing (psychological distress; loss or restriction of health, life, and disability insurance; etc.) and uncertain benefits of testing, making a decision about whether to proceed with testing—even one that is fully informed—will not be easy.

For an unaffected woman, the testing decision will be influenced by a wide range of factors, including her fears of and anxieties about developing breast or ovarian cancer (*16*). For women who have already been diagnosed with cancer, the issues are somewhat different, but the decision will still be difficult. Such women may be concerned about the possibility of developing second (and third) primary cancers. They may also have worries and concerns about their unaffected family members. Many women overestimate their chance of having a genetic characteristic that predisposes them to developing breast cancer (*17,18*).

Providing a woman with a probability estimate may allow her to make a more informed decision about testing. It will also assist physicians and genetic counselors in advising women facing decisions about testing. In view of the individual differences in attitudes about testing, one cannot recommend a single probability cutoff so that testing is appropriate above that cutoff and not appropriate below it. Different women will have different probability ranges for which they will consider testing. Physicians and counselors may be able to help women determine what probability of identifying a mutation would lead them to testing and use our model to decide whether a woman's probability of having a mutation falls in this range.

Our model has potential implications for health policy. BRCA1 testing will be costly, with estimates ranging as high as $1500 for the first family member tested. BRCA2 testing will be even more expensive. Given these costs, it is initially important to consider testing in those individuals and families who have at least a moderate chance of carrying a mutation. While the sensitivity and specificity of BRCA1 testing have yet to be determined, its positive predictive value will be lower in individuals who have a low chance of having a mutation. The cost per true positive in low-risk populations will be high because of the number of individuals who have to be screened to identify each true positive. By identifying accurately the women who are unlikely to have mutations, our model has the potential to result in substantial savings.

Appendix: Including Other Family Members

In this Appendix, we extend the development in the ''Methods and Results'' section concerning a woman's carrier probability by including her first-degree relatives. Extending to family members other than the individual of interest entails applying Mendelian principles of inheritance in both the numerator and denominator of the LR (*19*). We assume an autosomal dominant inheritance of mutations, empirically supported by the analysis of Claus et al. (*10*). In the numerator of the LR, we assume that the individual of interest carries a mutation at BRCA1 and calculate the probability of the observed family history under this assumption. We do this by considering the possibilities that she inherited the mutation from her father and her mother and by tracing the mutation's possible passage from and to other family members. In the denominator, we assume that the individual is not a carrier. Any disease among other members of the family is then sporadic or the result of a mutation that is not present in the individual of interest. These two possibilities are weighed accordingly. In the denominator of the LR, we assume that she carries no mutations of BRCA1.

We assume that occurrences of breast cancer in a family are conditionally independent, given the family members' genetic statuses. So when we assume that certain family members carry mutations and others do not, we can multiply the corresponding probabilities of these observations. (Without conditioning on the family members' statuses, occurrences of breast cancer are not independent. In particular, observing breast cancer in one family member makes it more likely to observe breast cancer in another.)

As an example, consider member 1 of family 1 (Fig. 2). For simplicity, consider only breast cancer and consider only family members 1-5. Member 1's breast cancer was diagnosed at age 34 years. Her mother had breast cancer that was diagnosed at age 35 years. Her two sisters' current ages are 43 and 30 years and neither has breast cancer. We seek the probability of *M*: member 1 carries a mutation.

The numerator of LR is the probability of observing this family history (members 1-5) conditioning on *M*. The denominator of the LR is the probability of observing this family history conditioning on *N*. We stress that both conditions involve the carrier status of member 1. Conditioning on member 1's genetic status implies probabilities that other family members are carriers. To find both the numerator and the denominator of the LR, we average over the possible genetic statuses of the various family members conditioning on the respective genetic status of member 1.

Restricting Consideration to the Possibility of a Single Mutation in a Family

Our model allows for the possibility that the individual of interest carries two mutations, even though this is extremely rare. However, for expository purposes, we first make the simplifying assumption that there is, at most, one mutation in the family. This means that, if the family member of interest is a carrier, then one of her alleles is a mutation and her other allele is normal. Also, for the purposes of this section, we assume that if the member of interest is not a carrier, then there are no mutations in the family.

The numerator of the LR is the probability of the various observations of breast cancer (and not) in this family and is the product of five factors, where Factor *i* is the contribution to the numerator of family member *i*:

Factor 1: $b_M(34) = 0.0137$

Factor 2: $\frac{1}{2}(1 - B_M(43)) + \frac{1}{2}(1 - B_N(43)) = \frac{1}{2}(0.730) + \frac{1}{2}(0.990) = 0.860$

Factor 3: $\frac{1}{2}(1 - B_M(30)) + \frac{1}{2}(1 - B_N(30)) = \frac{1}{2}(0.951) + \frac{1}{2}(0.999) = 0.975$

Factor 4: (Member 4 is male and so contributes no information about BRCA1 carrier status.)

Factor 5: $\frac{1}{2}b_M(35) + \frac{1}{2}b_N(35) = \frac{1}{2}(0.0150) + \frac{1}{2}(0.000437) = 0.00770$

Member 1 was diagnosed with breast cancer at age 34 years. The incidence of breast cancer among carriers at this age is thus her contribution to the numerator. With regard to Factor 5, member 1's mutation is either maternal (probability ½) or paternal (probability ½). If it is maternal, then the probability of her mother (member 5) being diagnosed with breast cancer at age 35 years is b_M (35). If it is paternal, then this observation has probability b_N (35). Factor 5 is thus a simple average of these two quantities.

With regard to Factors 2 and 3, both sisters are free of breast cancer. If member 1 carries a mutation, then each sister inherited the same mutation with probability ½, regardless of whether the mutation is paternal or maternal. If a sister inherited the mutation, then the probability that she is free of breast cancer is $1 - B_M$ (sister's age). If she did not inherit the mutation, then this probability is $1 - B_N$(sister's age). Each sister's contribution to the numerator is the average of these quantities.

The numerator of LR is the product of the above five factors: $(0.0137)(0.0077)(0.860)(0.975)(1) = 8.85 \times 10^{-5}$.

Calculating the denominator of LR is straightforward because under the condition that member 1 is not a carrier, we have assumed in this section that there is no mutation in the family. So the denominator is the product of the following five factors:

Factor 1: $b_N(34) = 0.000364$

Factor 2: $1 - B_N(43) = 0.990$

Factor 3: $1 - B_N(30) = 0.999$

Factor 4: 1 (Member 4 is male.)

Factor 5: $b_N(35) = 0.000437$

The product of all five factors equals 1.57×10^{-7}. Therefore, the LR in favor of member 1 carrying a mutation is

$$\mathrm{LR} = \frac{8.85 \times 10^{-5}}{1.57 \times 10^{-7}} = 564.$$

The corresponding posterior probability is

$$P(M|H1) = \frac{\mathrm{LR}}{\mathrm{LR} + 832} = \frac{564}{564 + 832} = 40.4\%.$$

Allowing for Multiple Mutations in a Family

Now consider the possibility of more than one mutation in this family. This possibility is remote, since the probability that a particular individual carries two mutations is on the order of $f^2 \cong 10^{-6}$. Therefore, the assumptions made in the previous section of this Appendix are usually reasonable. In particular, for family 1, allowing for more than one mutation will not change the conclusion much—as shown below. However unlikely it is, any particular family may carry more than one mutation. For some families, there are cases of breast and ovarian cancers on both the paternal and maternal sides. Such families are very likely to present at a genetic counseling clinic, and so they are more important to counselors than their rarity suggests.

We will improve the calculations given above to allow for the possibility of more than one mutation in the same family, and for the possibility that other family members may carry mutations even when the individual of interest does not. Here we assume that there can be no more than two mutations in a family, although our computer program allows for more than two. A woman who carries two mutations may be more likely to experience cancer than does someone who carries only one mutation, but we have no evidence for this. Therefore, we assume the same incidences of breast and ovarian cancer for carriers of two mutations as for carriers of one mutation.

As before, calculations in the numerator of the LR are conditional on the family member of interest being a carrier. Now, there are two possibilities: She carries one mutation, and she carries two mutations. The probability that she is a carrier of either type is $f^2 + 2f(1 - f) = 2f - f^2$. When $f = 0$ (or is very small), the calculations involved in the LR reduce to those in the previous section. The probability that the individual of interest carries two mutations, given that she carries at least one mutation, is the probability of 2 divided by the probability of at least 1. This conditional probability is approximately $f/2$. More precisely, it equals

$$\frac{f^2}{2f - f^2} = \frac{f}{2 - f} = \frac{0.001}{2 - 0.001} \cong 0.0005.$$

The improved numerator of the LR weighs the two possibilities of at least one mutation: exactly 1 and exactly 2. When the individual of interest carries two mutations, her mother must carry at least one. Unlike her mother, her sisters may not share one of her alleles. Each sister shares both alleles with probability ¼, one with probability ½ (total of ¾), and neither allele with probability ¼. When the member of interest carries a single mutation, then the probability that she shares it with her mother is ½. (These probabilities are approximate. Our program makes use of exact probabilities which, for small values of f, are very close to the approximations used here.)

Calculating probabilities of the observed cancer-free statuses of the sisters is more complicated. The numerator of the LR has two principal terms, the first for two mutations and the second for one mutation. Within the second term, there are three possibilities for a second mutation, depending on the genes not inherited from her parents by member 1: (*i*) neither is a mutation (probability $(1 - f)^2$), (*ii*) the same parent who passed a mutation on to member 1 has the other mutation (probability $f(1 - f)$), and (*iii*) the parent opposite from the one who passed a mutation on to member 1 has the other mutation (probability $f(1 - f)$). (We are ignoring the possibility that both of these genes are mutations—an event with probability f^2—because this would total three mutations in the family.) These three possibilities correspond to the three terms within the braces of the second principal term of the numerator of the LR, as follows:

$$\frac{f}{2 - f} b_M(34) b_M(35) \left[\frac{3}{4}(1 - B_M(43)) + \frac{1}{4}(1 - B_N(43))\right]$$

$$\left[\frac{3}{4}(1 - B_M(30)) + \frac{1}{4}(1 - B_N(30))\right] + \frac{2 - 2f}{2 - f} \frac{b_M(34)}{1 - f^2}$$

$$\left\{(1 - f)^2 \left[\frac{1}{2} b_M(35) + \frac{1}{2} b_N(35)\right]\right.$$

$$\left.\left[\frac{1}{2}(1 - B_M(43)) + \frac{1}{2}(1 - B_N(43))\right]\right.$$

$$\left[\frac{1}{2}(1-B_M(30))+\frac{1}{2}(1-B_N(30))\right]$$

$$+f(1-f)\left[\frac{1}{2}b_M(35)+\frac{1}{2}b_N(35)\right]$$

$$(1-B_M(43))(1-B_M(30))+f(1-f)b_M(35)$$

$$\left[\frac{3}{4}(1-B_M(43))+\frac{1}{4}(1-B_N(43))\right]$$

$$\left[\frac{3}{4}(1-B_M(30))+\frac{1}{4}(1-B_N(30))\right]\Bigg\}.$$

Calculations in the denominator of the LR are conditional on the individual of interest being a noncarrier. Her mother may still carry a mutation, and does so with probability *f*. Her sisters may carry mutations, inheriting them from either mother or father. There are three possibilities for the genes not inherited from her parents by member 1: (*i*) neither is a mutation, (*ii*) exactly one is a mutation, and (*iii*) both are mutations. Each corresponds to a term in the denominator of the LR, as follows:

$$b_N(34)\Bigg\{(1-f^2)\,b_N(35)(1-B_N(43))(1-B_N(30))$$

$$+f(1-f)[b_N(35)+b_M(35)]$$

$$\left[\frac{1}{2}(1-B_M(43))+\frac{1}{2}(1-B_N(43))\right]$$

$$\left[\frac{1}{2}(1-B_M(30))+\frac{1}{2}(1-B_N(30))\right]$$

$$+f^2b_M(35)\left[\frac{3}{4}(1-B_M(43))+\frac{1}{4}(1-B_N(43))\right]$$

$$\left[\frac{3}{4}(1-B_M(30))+\frac{1}{4}(1-B_N(30))\right]\Bigg\}.$$

The result for member 1 of family 1 is LR = 564, as before. And the posterior probability is also 40.4%, as before.

Details of calculations in the general case of first- and second-degree relatives and considering ovarian cancer as well as breast cancer (bilateral as well as unilateral) are given separately (*9*).

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Notes

[1]*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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