



ORIGINAL CONTRIBUTIONS

The Kin-Cohort Study for Estimating Penetrance

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A cross-sectional study may be more feasible than a cohort or case-control study for examining the effect of a genetic mutation on cancer penetrance outside of cancer families. The kin-cohort design uses volunteer probands selected from a population with a relatively high frequency of the mutations of interest. By considering the cancer risk in first-degree relatives of mutation-positive and -negative probands as a weighted average of the risk in carriers and noncarriers, with weights calculated assuming a known mode of inheritance, one can infer the penetrance of the mutations. The estimates of penetrance by age 70 years for three specific mutations in the *BRCA1* and *BRCA2* genes common among Ashkenazi Jews for the first occurrence of breast or ovary cancer is 63%. The kin-cohort design can be a useful tool for quickly estimating penetrance from volunteers in a setting in which the mutation prevalence is relatively high. *Am J Epidemiol* 1998;148:623-30.

biometry; breast neoplasms; colon neoplasms; epidemiologic methods; genetics; Jews; ovarian neoplasms

Cohort and case-control designs are seldom feasible for estimating the penetrance of a rare mutation in a cancer gene, such as *BRCA1* or *BRCA2*. To launch either a cohort study or a case-control study with adequate numbers of carriers who develop cancer poses daunting feasibility, economic, and ethical issues. Direct estimates of risk from studies of cancer-prone families, which often will have already been collected for linkage analysis and gene cloning, are likely to be too high. Modeling genotype conditional on phenotype (1) can estimate penetrance without ascertainment bias from high-risk families (1, 2), but if the risk is higher in cancer families because of other genetic or environmental factors, the estimates may be too high for carriers in families with less cancer. In

this paper, we propose the kin-cohort design, an alternative, cross-sectional approach that we used with volunteers to study effects of specific mutations in the *BRCA1* and *BRCA2* genes on cancer risk. We present further penetrance estimates from our kin-cohort study as an example (3).

The key measure of the effect of a mutation in a cancer gene is penetrance, or absolute risk of cancer in carriers. Cumulative risk of either breast or ovarian cancer near 95 percent by age 70 has been estimated from families with multiple cases, often at young ages, known to be segregating for a mutation (2). However, penetrance of a mutation in an individual with a less extreme family history cannot always be generalized from carriers in families with several early-onset cases across generations—exactly the ones used to find and clone the gene. The apparent high risk may be at least partially due to chance or to shared environmental risk factors or other genes (4). We therefore expected the lifetime penetrance of *BRCA1* mutations to be lower in carriers outside cancer-prone families than the 85 percent for all mutations combined estimated from family studies, but we did not know how much lower. While

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over 200 *BRCA1* and *BRCA2* mutations have been identified, specific ones are quite rare, so identification of carriers outside of cancer-prone families is difficult. Ashkenazi Jews, the descendants of Jews who lived in Western and Central Europe during the Middle Ages and mostly in Germany and Eastern Europe during recent centuries, however, have an estimated prevalence of 2.5 percent for three specific *BRCA1* and *BRCA2* mutations (5-7). A population in which a small number of mutations are relatively common, a setting where volunteering was likely, and a disease that close family members are likely to learn about and remember provided us with an opportunity to initiate a study that could estimate penetrance.

We developed the kin-cohort approach to obtain estimates of penetrance from a study of volunteers. The relatives of the volunteers form a retrospective cohort who are "followed" from birth to development of cancer or to censoring at time of interview or death; relatives of cases and controls have been used to form retrospective cohorts to estimate the distribution of age at cancer diagnosis (8) and the effect of family history on cancer risk (9). While members of this cohort of the kin of volunteers are not genotyped, we have some information about their mutation status from a relative who is genotyped. We show below how to infer cancer incidence rates for carriers and for noncarriers by using the available information.

We have already reported penetrance estimates using this method for breast, ovary, and prostate cancers separately (3). In this paper, we report on the estimates for penetrance using the earlier of breast and ovary cancers in women and of colorectal cancer in men and women.

MATERIALS AND METHODS

The Washington Ashkenazi Study

We launched a volunteer study among Jews in the Washington, DC, area (3). Approximately 2-3 percent of the population of the United States is Jewish, predominantly Ashkenazi; the proportion of Jews in the study area is slightly higher. We chose volunteers because of the difficulty and expense in obtaining a random sample of Jews. Random digit dialing would be too expensive, even if we were able to exclude neighborhoods with very low concentrations of Jews. We rejected sampling from a roster of Jews that might be available from Jewish organizations because it would oversample those involved in community activities, with unknown effects on genetic composition. Further, regardless of how a "random sample" would be selected, we would still face a possible bias from nonparticipation.

Every one of the approximately 150,000 adults age 21 years or over who resided in the metropolitan Washington, DC, area and identified himself or herself as Jewish was eligible. Participants received a finger stick to obtain drops of blood spotted on a modified Guthrie card for genotyping by polymerase chain reaction and completed a 20-minute questionnaire. Questions focused on breast cancer risk factors in the subjects, religious and geographic origins of parents and grandparents, and the vital status and history of cancer at several sites in the volunteers' first- and second-degree relatives, specifically parents, children, full and half-siblings, grandparents, and siblings of the volunteers' parents.

Analytic approach

Family units. On the consent form, we asked for each volunteer's name as well as the name and relationship of each blood relative who had participated or was likely to participate in the study. From this information, we reconstructed family relationships before destroying the personal identifiers. To avoid counting one person related to two participants twice in the cumulative risk calculations, we defined the family's carrier status and history with respect to an index volunteer according to an algorithm that tended to maximize informative person-years at risk of the selected cancer. If there were two or more siblings and only one was a carrier, the index family member was the carrier. If all were carriers or noncarriers, we chose a male over any female as the index volunteer for estimating breast, ovarian, or colorectal cancer risks; we chose a female in preference to a male for our previously reported prostate cancer analysis (3). The allele frequencies of the mutation were calculated as approximately half the carrier frequency in the index family members.

Basis of penetrance estimate. We can directly estimate the cumulative risk of disease in two distinct subsets of the cohort of relatives of volunteers. We refer to the set of those with at least one first-degree relative among the volunteers who is a carrier as the *carrier* kin and to the set of those whose relatives among the volunteers are all noncarriers as the *non-carrier* kin. The cumulative risks in both the carrier and the noncarrier kin are weighted averages of the risks in carriers and noncarriers (conditional on other risk factors), with, of course, more weight to the risks in carriers for the carrier kin. The kin-cohort approach provides an estimate of the age-specific penetrance of a mutation by decomposing these weighted averages into their component parts. The weights depend on the known mode of inheritance of the susceptibility and the prevalence of the mutation in the population. It is

shown in appendix 1 that assuming at all ages a frequency of p for an autosomal dominant mutant allele in the study population and, therefore, a carrier rate of almost $2p$ if p is small or homozygosity for the mutation is rare, a member of the carrier kin has a probability of carrying the mutation approximately equal to $(p/2) + (1/2)$. By contrast, a member of the noncarrier kin has approximate carrier probability p . Let R_+ and R_- , respectively, be the proportions of individuals who develop disease before age t in the carrier and noncarrier kin. Then R_+ and R_- are both weighted averages of S_+ and S_- , the cumulative risks of individuals developing the disease before age t in carriers and noncarriers. These approximate equations

$$R_- = pS_+ + (1 - p)S_- \quad (1)$$

$$R_+ = \left(\frac{p}{2} + \frac{1}{2}\right)S_+ + \left(\frac{1}{2} - \frac{p}{2}\right)S_- \quad (2)$$

can be used to estimate S_- and S_+ , by solving two equations in two unknowns:

$$S_- = \frac{1 + p}{1 - p}R_- - 2\frac{p}{1 - p}R_+ \quad (3)$$

$$S_+ = 2R_+ - R_- \quad (4)$$

Thus, we can infer the age-specific penetrance S_+ without knowing p ; S_- requires that p be known or estimable from the data. Remarkably, if p is low, the extra probability of disease conferred by the mutation, $S_+ - S_-$, can be approximated by a simple relation:

$$S_+ - S_- = 2\frac{(R_+ - R_-)}{1 - p} \quad (5)$$

$$\approx 2(R_+ - R_-) \quad (6)$$

Analysis. Because R_+ and R_- are estimated using Kaplan-Meier methods, there are jumps at the ages of diagnosis of cancer in cohort members. Therefore, estimates of S_- and S_+ , which are weighted differences between R_+ and R_- , may be nonmonotonic; for example, if there is an event in the carrier kin but none in the noncarrier kin at age t , R_+ will be unchanged while R_- will increase, resulting in a decline in S_+ , by equation 4.

Because of dependence in cancer risk among first-degree relatives of a single volunteer or related volunteers due to shared genetic and environmental factors, we report bootstrap confidence intervals of estimates of S_- , S_+ , and $S_+ - S_-$, where the units in the bootstrap resampling are the families of the volunteers.

Underlying assumptions

Several assumptions underlie our approach.

Known mode of inheritance of susceptibility. Susceptibility to breast and ovary cancers from *BRCA1* and *BRCA2* mutations is inherited in an autosomal dominant fashion. A similar analysis could be used for other modes of inheritance by altering the weights in equations 1 and 2 to reflect the risk of a relative of the genotyped individual.

Constancy of frequency of mutant allele. In equations 1, 2, 3, and 5, p refers to the frequency of the mutation allele at birth. If the mutation has a strong effect on total mortality, the age-specific mutation frequency will become smaller for older persons. We found carrier frequencies for any of the three mutations in our unaffected female volunteers of 2.7, 2.0, and 0.7 percent at ages 20–39, 40–59, and 60 or more years, respectively. The frequency in males appears to be less affected by mortality associated with the mutations (2.3, 2.2, and 1.5 percent carriers in the three age groups, respectively), so the use of both men and women will tend to buffer age-related changes in p .

Homogeneity of risk. Equations 1–4 do not account for any heterogeneity in risk associated with other genes or with environmental factors. For breast and ovary cancers, the excess risk associated with these mutations may overwhelm the effect of any of the other known risk factors. Probability-of-exposure models, like those of Satten and Kupper (10), could be used to incorporate individual risk factors among relatives, such as parity or age at menarche, if available. Of course, the pathways of disease for carriers may be different from those with sporadic disease.

Volunteer effects. Probably the major concern in a kin-cohort study is the reliance on volunteers. A strictly valid estimate of penetrance requires that volunteers have the same distribution of family history of disease as the population to which we infer. If those with a family history of cancer are more likely to participate, as might be expected, estimates of mutation prevalence and of R_+ and R_- will tend to be too high. While knowledge of the pattern of volunteering as a function of family history is required to ascertain the volunteer effect on estimates of S_+ and S_- , it seems likely that the estimate of penetrance S_+ , in particular, is likely to be biased upward.

For the specific purpose of comparing family history in carriers and noncarriers, we believe that participants in the Washington Ashkenazi Study constitute a reasonable approximation to a random sample of the Jewish population of the area. Family history of breast cancer was reported somewhat more often than in Jewish subjects in previous case-control studies (11, 12). The effect of family history on volunteering was

probably small because of the broad community concern demonstrated by the high participation rate: From nearly 150,000 Jewish people in the area, over 5,300 adults consented to give blood during a 9-week period.

Use of volunteers who do not know their mutation status ought not to affect comparisons of the penetrance of mutations at different genes or of different alleles in the same gene, nor does the size and age structure of the volunteer's family, unlike the evaluation of the effect of family history in most case-control studies (9).

Data quality. This design relies on information from volunteers about their family medical history. While the well-educated Jewish population in our study is probably knowledgeable, participants in other settings may not know, remember, or report accurately their parents', childrens', or siblings' cancer history, especially for tumors of the reproductive organs or of other sites likely to be confused by lay people (13), and the problem is undoubtedly worse for second-degree relatives. More-accurate information, potentially, could be obtained through the family "historian" or by direct contact with the relatives (perhaps even yielding data about individual risk factors). The credibility of using the volunteer as a proxy in this context needs to be explored, especially for phenotypes that are less likely than cancer to be known or remembered by a relative.

RESULTS

Figure 1 shows the estimated cumulative risk of the first of breast or ovary cancer in the subcohorts, of first-degree relatives of study volunteers; R_- is the

risk in the noncarrier kin, and R_+ is the risk in the carrier kin. Figure 2 shows the estimated cumulative incidence in carriers of any of the three mutations and in noncarriers (S_+ and S_- , respectively). Figure 3 presents the mutation-specific estimates of penetrance S_+ for the three alterations we studied.

Figure 4 displays the Kaplan-Meier curves for colorectal cancer in the noncarrier and the carrier kin. Figure 5 displays the estimates of penetrance derived from our method. There were only nine first-degree relatives of carriers with a history of colorectal cancer, so the estimate of S_+ is unstable. There is clearly no evidence that *BRCA1* or *BRCA2* carriers have increased risk of colorectal cancer.

DISCUSSION

Reliance on volunteers is the major weakness of the kin-cohort approach for two opposing reasons. First, eligible participants with greater family history may be more likely to volunteer, and consequently, estimates of penetrance will probably be too high (3). Indeed, our estimate of risk in noncarriers is higher than national rates (based predominantly on noncarriers), even allowing for slightly higher risk in Jews. We find a greater percentage of our volunteers with a family history of breast or ovary cancer than do case-control studies (3), although some of the difference might be explained by underreporting of family history in case-control studies conducted by telephone. On the other hand, if the volunteers underreport cancer in relatives, our penetrance estimates would probably be too low. However, the well-educated Jewish population we studied can be expected to provide high-quality infor-

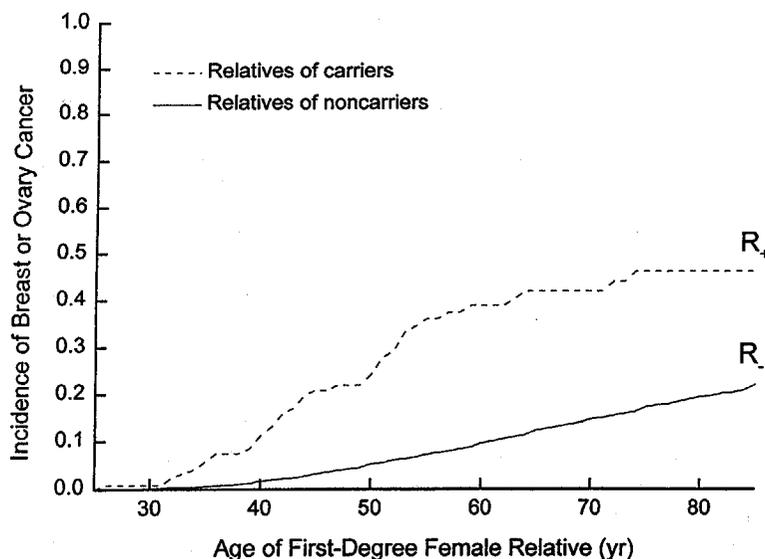


FIGURE 1. Estimates of cumulative risk of first occurrence of breast or ovary cancer in first-degree relatives of carriers of any of three mutations and in first-degree relatives of noncarriers among Ashkenazi Jewish volunteers in the Washington, DC, area, 1996.

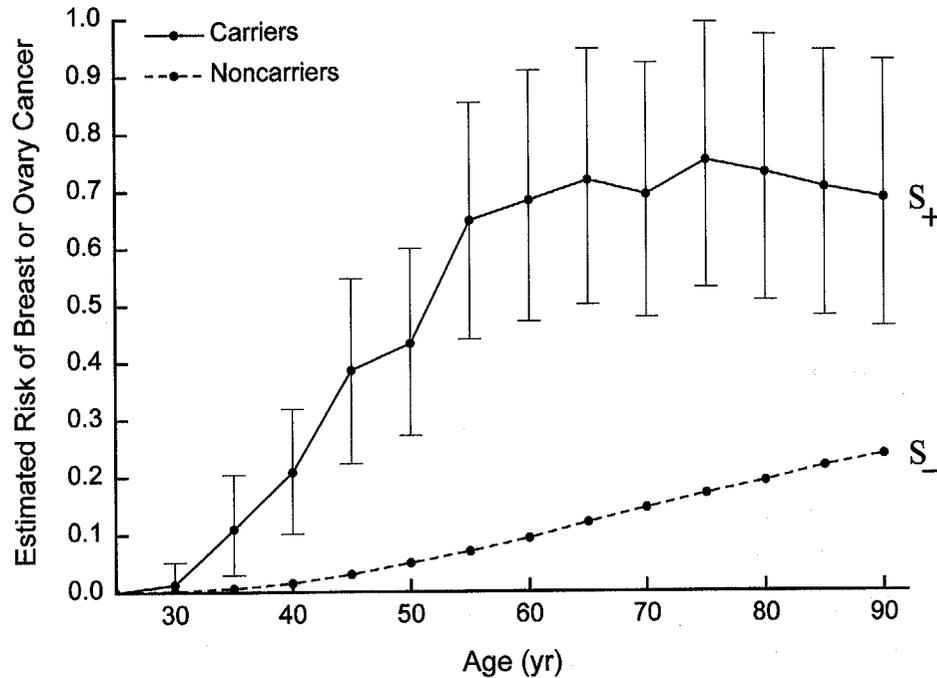


FIGURE 2. Estimates of cumulative risk of first occurrence of breast or ovary cancer in carriers of any of three mutations and in noncarriers.

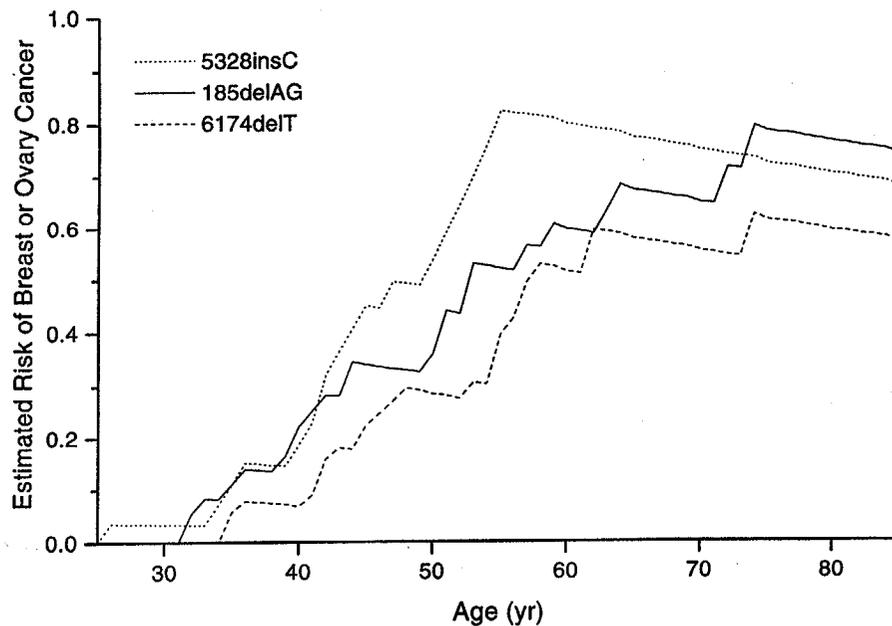


FIGURE 3. Estimates of cumulative risk of first occurrence of breast or ovary cancer in carriers of each of three mutations.

mation about the cancer history and vital status of their first-degree relatives. On balance, overestimation seems more likely.

Our estimates of the risk of either breast or ovary cancer are still substantially lower than those reported by Easton et al. (2) from the Breast Cancer Linkage Consortium. They estimate cumulative risk of 94 percent at age 70 years, while we estimate 63 percent.

They estimate 3, 20, 62, and 68 percent at ages 30, 40, 50, and 60 years, respectively, compared with 1, 15, 37, and 61 percent from our data. Explanations worthy of consideration include competing risk and dependent censoring, use of members of high-risk families versus more population-based volunteers, heterogeneity of penetrance from familial aggregation of genetic or environmental risk factors, and differences in the spe-

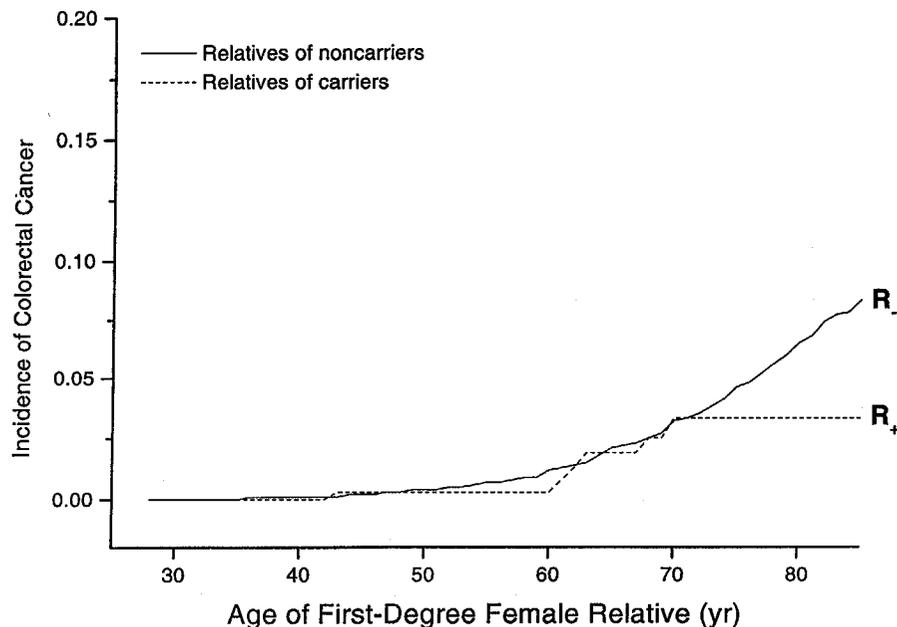


FIGURE 4. Estimates of cumulative risk of colorectal cancer in first-degree relatives of carriers of any of three mutations and in first-degree relatives of noncarriers among Ashkenazi Jewish volunteers in the Washington, DC, area.

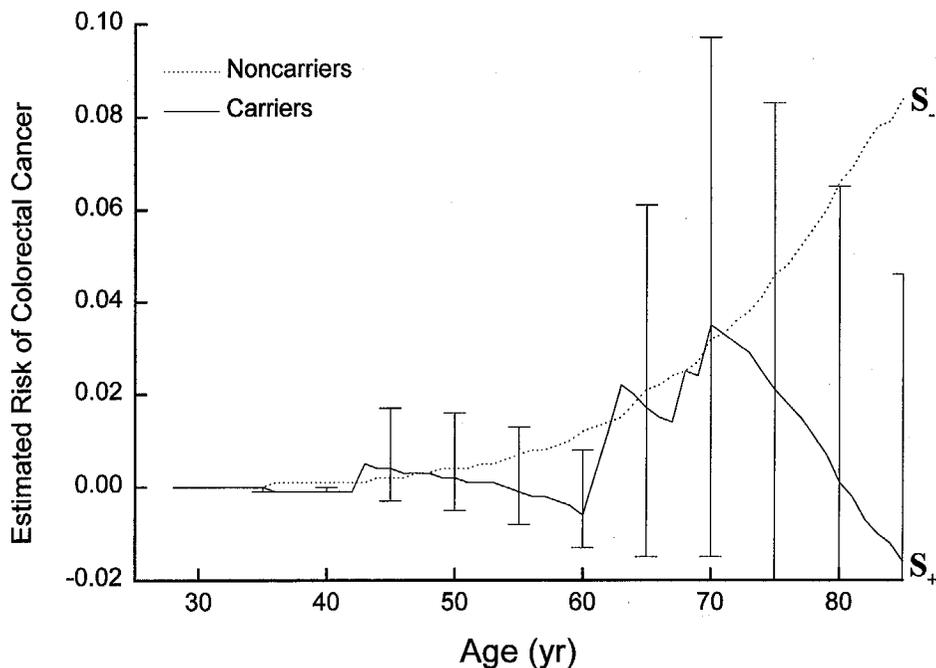


FIGURE 5. Estimates of cumulative risk of colorectal cancer in carriers of any of three mutations and in noncarriers.

cific mutations commonly found in the carriers in the two studies.

Competing risks and dependent censoring. Our equations are expressed as cumulative risk rather than incidence, allowing us to use the allele frequency at birth as p in our equations. That is, variation in the age-specific gene frequency does not affect our equa-

tions. By using Kaplan-Meier estimates of R_- and R_+ with censoring at the relatives' times of death or current age, our estimates are free of bias from competing risks. In studies of breast and ovary cancers separately, we do need to make the usual assumption of independent censoring, i.e., that those who die from other causes were at the same risk for the cause of

death of interest in the intervals after death, had they survived. The fact that the differences between our estimates and those of the Consortium persist when the outcome is the earlier of breast or ovary cancer also argues against competing risks or dependent censoring as explanations.

High-risk families versus population-based volunteers. The kin-cohort penetrance estimates from the Washington Ashkenazi Study fall well below those from the Consortium but closely resemble those from a report by Whittemore et al. (14), which was based on the reported family history of 922 cases and 922 controls from three American case-control studies of ovarian cancer, and from a smaller series in Israel (15). The low estimates from the population-based studies argue against the suggestion by Easton (16) that chance explains the difference in penetrance estimates between the Washington Ashkenazi Study and the Consortium data.

Heterogeneity of penetrance. Another potential explanation is epistasis, or heterogeneity of penetrance due to another genetic or environmental factor that aggregates in families. If there is heterogeneity, the cancer families identified for linkage studies are likely to show higher risk than are families of lower-risk carriers who would not be included in the studies at the centers in the Consortium. The mixture of lower- and higher-risk carriers in our study reflects the totality of carrier families better than do individuals from high-risk families only; if so, the Consortium estimates will apply more to members of the highest-risk carrier families, while ours will be closer to an average across all families of carriers. Comparison of risk estimates derived from noncarriers in cancer families using the conditional method (1, 2) with risks in standard populations may clarify these issues.

Low-penetrance mutations. Another explanation for the discrepancy in estimates is that risks from different mutations are not the same. The three mutations common in Ashkenazim, while they have similar penetrances, may each have a lower penetrance than do other mutations in the *BRCA1* and *BRCA2* genes found in non-Jewish populations.

Variations of the design

Flexibility in choosing a study population. This approach offers great flexibility in choosing the source of subjects for genotyping. One option, a random sample of the population from a source such as the National Health and Nutrition Examination Survey, would give the added advantage of yielding a direct estimate of the allele frequency p . A series of cases with tissue available for genotyping may be more convenient if information about the medical history of their relatives

is easy to obtain. There are more likely to be mutations in a case series than in individuals without disease, but the penetrance estimates may be high because of overrepresentation of high-risk families.

The volunteers themselves do not need to be at risk of the disease. For example, we used men as volunteers, even though we were most interested in the risk of female breast and ovarian cancers.

Incorporation of higher-degree relatives. Information from relatives more distant than first degree can also be used in estimating S_+ and S_- . The cancer history of each second-degree relative conveys less information on genetic risk, but there are more of them, on average. Indeed, the total information from second-degree relatives may be greater than that from first-degree relatives. On the other hand, cancer history will be less reliably recalled and reported for more distant relatives. It is possible to consider a regression model that extends equations 3 and 4 by expressing risk of disease in first- and higher-degree relatives as dependent on the weighted average of unknown genotype-specific risk.

Summary

The kin-cohort design is a new cross-sectional approach that provides several advantages over cohort and case-control designs. It offers an opportunity for a relatively quick assessment of the effect of a mutation. In our study, we completed recruitment of over 5,000 volunteers in just over 2 months, with the help of an extensive publicity effort in a committed population. More generally, the requirement is a series of representative probands who consent to genotyping and give a complete and accurate family history of disease. From this, the rates in those with and those without the mutation and the allele frequency of the mutation all can be approximated. There is considerable flexibility in choosing subjects for genotyping to maximize the yield of carriers of the rare mutation, provided carriers and noncarriers with extensive family history are not overrepresented.

In many circumstances, the kin-cohort design will not be appropriate. For many diseases other than cancer, including perhaps mild birth defects or mental illness, volunteers will not always be aware of their relatives' histories. For many diseases, it could also be very difficult to recruit participants who do not have a family member with the disease, resulting in an overestimate of risk due to volunteer effects.

The kin-cohort approach adds to the design options for studying penetrance of a cancer gene, despite its potential limitations in studying other diseases. When the mutation-positive volunteers report substantially more family histories of cancer than do those without

the mutation, bias is unlikely to be the complete explanation. Then, if more robust quantitative estimates of effects of mutation are desired, a more rigorous, time-consuming, and expensive effort will be required. If no major difference in cancer history emerges, the problem may not warrant further expensive investigation. In either case, we believe that this relatively simple design provides less-biased estimates of risk in carriers without extensive family history than are obtained from cancer families. It offers an intermediate option between estimates from high-risk families and estimates from standard population-based designs.

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APPENDIX 1

Assume that the mother is known to carry a specific mutation, denoted by A^* , on one allele and the wild type A^w on the others, and that the father's genotype is unknown. We can denote the genotype of the mother by A^*A^w and that of the father by $A^{a_1}A^{a_2}$. A child's genotype will be $A^*A^{a_1}$, $A^*A^{a_2}$, $A^wA^{a_1}$, or $A^wA^{a_2}$, each with probability $1/4$. For autosomal dominant inheritance, the probabilities of being a carrier equal $1/2$, $1/2$, p , or p , respectively, where p is the allele frequency of the mutation. Thus, conditionally on the mother being a carrier, the offspring has probability $(1 + p/2)$ of being a carrier. If the mother carries the wild type on both alleles, denoted as A^wA^w and the father's status is still unknown, the child's genotype can be denoted as $A^wA^{a_1}$ or $A^wA^{a_2}$, each with probability of $(1/2)$, and each implying carrier probability equal to p from the single, unknown allele. Given the offspring's carrier status, the probabilities of a parent being a carrier can be calculated easily by using Bayes theorem, assuming allele frequencies across generations are unchanged. The computation for siblings is trickier, but the results are approximately the same for low p .

As a simple example, assume a (heterozygote) carrier mother and a father of unknown genotype in a population in which the frequency of the allele of interest is $p = 0.01$. The probability that the offspring will inherit the mutant allele from the mother is 0.50, and the probability that the allele descending from the father is mutant is $p = 0.01$. Thus, by Mendelian reasoning, the offspring has probability $0.50 + 0.01 - 0.50 \times 0.01 = 0.505 = (1 + p/2)$ of being a carrier.