Am. J. Hum. Genet. 56:265–271, 1995

Breast and Ovarian Cancer Incidence in BRCA1-Mutation Carriers

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Summary

Dominant predisposition to early-onset breast cancer and/or ovarian cancer in many families is known to be the result of germ-line mutations in a gene on chromosome 17q, known as BRCA1. In this paper we use data from families with evidence of linkage to BRCA1 to estimate the age-specific risks of breast and ovarian cancer in BRCA1-mutation carriers and to examine the variation in risk between and within families. Under the assumption of no heterogeneity of risk between families, BRCA1 is estimated to confer a breast cancer risk of 54% by age 60 years (95% confidence interval [CI] 27%–71%) and an ovarian cancer risk of 30% by age 60 years (95% CI 8%–47%). Similar lifetime-risk estimates are obtained by examining the risks of contralateral breast cancer and of ovarian cancer, in breast cancer cases in linked families. However, there is significant evidence of heterogeneity of risk between families; a much better fit to the data is obtained by assuming two BRCA1 alleles, one conferring a breast cancer risk of 62% and an ovarian cancer risk of 11% by age 60 years, the other conferring a breast cancer risk of 39% and an ovarian cancer risk of 42%, with the first allele representing 71% of all mutations (95% CI 55%–87%). There is no evidence of clustering of breast and ovarian cancer cases within families.

Received December 22, 1993; accepted for publication September 27, 1994.

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0002-9297/95/5601-0034$02.00

Introduction

Genetic linkage studies have demonstrated that many families with dominant predisposition to early-onset breast cancer and/or ovarian cancer are the result of a gene located on chromosome 17q21, known as BRCA1 (Hall et al. 1990; Narod et al. 1991). In an analysis of 214 breast and breast-ovarian cancer families, Easton et al. (1993) showed that BRCA1 was responsible for almost all families with multiple cases of both breast and ovarian cancer, and approximately half the families with breast cancer only. By maximizing the LOD score over different penetrance functions, Easton et al. (1993) estimated that the penetrance of the BRCA1 gene is 59% by age 50 years and 83% by age 70 years.

The purpose of the present study is to provide estimates of the cumulative risks of breast and ovarian cancer by age in BRCA1 carriers. These have been estimated both indirectly, by maximizing the LOD score over different penetrance functions, and directly, by examining the incidence of second breast and ovarian cancers. The possibilities of variation in cancer risk between families, suggesting allelic heterogeneity, and of variation in risk within families, suggesting the presence of modifying factors, have also been examined.

Methods

Families

Families were eligible for inclusion in this study if they contained at least four cases in total either of ovarian cancer diagnosed at any age or of breast cancer diagnosed under the age of 60 years, together with evidence that the family was linked to BRCA1, as described below. Thirty-three eligible families were contributed by 11 collaborating groups. The data provided on these families include the dates (or ages) of occurrence of all breast and ovarian cancers, including second primaries, together with the date or age at last observation. The data set also contains information on the incidence of other cancers, which was reported elsewhere (Ford et al. 1994).

All families were typed with the polymorphic marker D17S579 (Hall et al. 1992), which lies ~2 cM distal to BRCA1 (Chamberlain et al. 1993). Most families were also

typed for the markers D17S250 (Weber et al. 1990), THRA1 (Bowcock et al. 1993), D17S588 (Goldgar et al. 1993), and, in some cases, other markers in the region. These latter markers were used to define whether the families met the criteria for inclusion in the study and to resolve some inconsistencies but were not used in the main penetrance analysis.

The linkage evidence required for inclusion was a LOD score of ≥ 0.4 for families with one or more ovarian cancer cases, and a LOD score ≥ 1.0 for families with breast cancer only. These LOD scores were computed on the basis of a multipoint analysis of D17S579, D17S250, and the disease, except in a few families where one of the markers was not sufficiently informative. In these families information from D17S588 or THRA1 was also used. These LOD-score criteria were chosen so as to give a posterior probability of ~90%, assuming a prior probability of linkage to BRCA1 of 45% for breast-cancer-only families and 79% for breast-ovarian families. The former figure is the best estimate of the proportion of linked breast cancer families, obtained by Easton et al (1993). The latter figure is somewhat arbitrary; Easton et al (1993) estimated 100% of breast-ovarian families to be linked. However, it has become clear subsequently that some breast-ovarian families collected since the consortium analysis and a few families included in the original analysis but for whom more definitive marker typing is now available are not linked to BRCA1 (Narod et al. 1994; in this issue). For this reason the lower 95% confidence limit from the consortium data set, of 79% has been chosen.

Statistical Analysis

The basic method used for estimating the overall penetrance of BRCA1 was to maximize the LOD score with respect to different penetrance functions, by using a modification of the ILINK program (Lathrop et al. 1984). This is equivalent to maximizing the likelihood of the marker data conditional on all the disease phenotype data and allows the penetrance to be estimated free of bias due to ascertainment of families on the basis of multiple affected individuals (Risch 1984). In order to minimize the computation required, two-point LOD scores based on D17S579 and the disease were used. The penetrance was estimated by assuming a separate incidence rate for each of the age groups 20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, and >80 years and maximizing over these seven parameters.

Strictly, restricting the data set to families with a certain LOD score violates the requirement of the maximum LOD score that families not be selected on the basis of linkage data. Such a restriction was necessary to exclude families not due to BRCA1, but in principle this could lead to biased penetrance estimates, since certain linked families—for example, families with old unaffected carriers—would give lower LOD scores and tend to be excluded, whereas they would have been included with a lower threshold. However, this is unlikely to be a serious problem, since most of the information on penetrance comes from relatively large families who would have been included on any criterion. Furthermore, the overall estimated penetrance from this analysis is close to that previously estimated by Easton et al. (1993) in an analysis both including all families regardless of linkage evidence and allowing for heterogeneity.

Estimates of the risks of breast and ovarian cancer were obtained by multiplying the estimated overall incidence rate in each age group by the numbers of first breast and ovarian cancers, respectively, in that age group, as a proportion of the total number of cancers of both types. The basic assumption here is that the ascertainment of each family is made on the basis of the numbers of breast and ovarian cancers and ages at diagnosis but not on the basis of the type of each tumor. This is not strictly true, in that some families were undoubtedly ascertained initially on the basis of multiple early-onset breast cancers and others on the basis of both breast and ovarian cancer. Unfortunately, it is not possible to allow formally for this ascertainment; most of the families have, however, been extended well beyond their initial ascertainment, and it seems unlikely that the proportions of breast and ovarian cancers are materially biased in either direction.

Inspection of the families suggested that the ratios of breast to ovarian cancers differed substantially between families, and we therefore carried out a further analysis allowing for allelic heterogeneity. In this analysis, two different susceptibility BRCA1 alleles were assumed, conferring different breast and ovarian cancer risks. For simplicity, the age-specific incidence rates for breast and ovarian cancer due to the second susceptibility allele were assumed to be constant multiples of the corresponding disease-specific rates due to the first allele.

This analysis involved maximizing a log-likelihood of the form

$$l = \sum \log[\alpha L(\lambda_1; \theta) + (1 - \alpha)L(\lambda_2; \theta)] - \log[\alpha L(\lambda_1; \tfrac{1}{2}) + (1 - \alpha)L(\lambda_2; \tfrac{1}{2})],$$

where the sum is over families. $L(\lambda; \theta)$ represents the likelihood for a family, under homogeneity, given penetrance function λ and recombination fraction θ. α represents the proportion of alleles in the population of type 1, and λ_1 and λ_2 are the penetrance functions for type 1 and type 2 families. The hypothesis of no allelic heterogeneity was tested using a likelihood ratio test, comparing twice the difference in the log-likelihoods under the heterogeneity and homogeneity models to a χ^2 distribution on 3 df. (Strictly speaking, the log-ratio statistic does not follow a

χ^2 distribution in this case, since the parameter space is degenerate at the null hypothesis; in fact, the tests should be conservative.) A similar likelihood-ratio test (on 1 df) was performed to test the hypothesis that the breast cancer risk was the same for both alleles, and a further test was performed (on 7 df, since there were seven age groups) to test the hypothesis that one of the alleles conferred no ovarian cancer risk.

The risks of second breast and ovarian cancers, in breast cancer cases diagnosed before age 60 years, were computed using standard cohort analysis. For the analysis of ovarian cancer risks, follow-up was assumed to start at the date of the first breast cancer or January 1, 1945, if later, and to cease at the date of diagnosis of ovarian cancer, the date of death, or January 1, 1993. The analysis of contralateral breast cancer risks was similar, except that the first 3 years after the diagnosis of the first breast cancer were ignored. In the analysis of contralateral breast cancers there were 1,006 woman-years of follow-up between ages 30 and 70 years, during which 26 second breast cancers occurred; in the analysis of second ovarian cancers there were 1,451 woman-years of follow-up, during which 23 cancers occurred.

Analysis of Modifying Genetic Effects

If the risks of breast and/or ovarian cancer in BRCA1-mutation carriers were substantially influenced by other "modifying" genes unlinked to BRCA1, then the risks of either cancer should be greater in gene carriers who are close relatives of affected individuals than in carriers who are more distant relatives. It is not possible to examine the overall risk of breast and ovarian cancer in relatives, because of ascertainment biases. However, we have examined the risk of ovarian cancer as a proportion of the risk of either cancer, by degree of relationship, to address the possibility that the site-specific risks may be determined by "modifying" genes.

To test formally for familial clustering of breast/ovarian cancers, we use the test derived by Easton (1992), which is based on the statistic

$$X = \sum_{i=1}^{N} \sum_{j \neq k} (O_{ij} - E_{ij})^{\mathrm{T}} R_{ijk} (O_{ik} - E_{ik}) .$$

Here, O_{ij} is the observed data for affected individual j in family i, that is *1* for ovarian cancer and 0 for breast cancer; E_{ij} is the "expected" value for O_{ij}; and R_{ijk} is twice the kinship coefficient between individuals j and k in family i. E_{ij} is based on the total number of breast and ovarian cancers in the age group to which individual j belongs, categorized as <40 years, 40–59 years, and ≥60 years. A permutation test based on X can be derived by permuting the breast and ovarian cancers within each family.

Table 1

Estimated Cumulative Risks of Breast and Ovarian Cancer in BRCA1-Gene Carriers

	Cumulative Risk of		
Age (years)	Breast Cancer	Ovarian Cancer	Either Cancer
30	.032	.0017	.034
40	.191	.0061	.195
50	.508	.227	.619
60	.542	.298	.678
70	.850	.633	.945

Results

Penetrance Estimates, under the Assumption of Homogeneity

Table 1 shows the estimated risks of breast and ovarian cancer in BRCA1-mutation carriers by using the maximum LOD score method, assuming no heterogeneity between families. The estimated cumulative risk for breast cancer rises to 54% by age 60 years (95% confidence limits 27%–71%). The corresponding estimated cumulative risk of ovarian cancer is 30% (95% confidence limits 8%–47%).

Risks of Second Cancers

Table 2 gives the risks of a second breast cancer or of an ovarian cancer in putative gene carriers already affected with one breast cancer. The cumulative risk of a second breast cancer is estimated to be 60% by age 60 years (95% confidence limits 41%–73%). However, allowing for the fact that such women only have one breast at risk, the corresponding penetrance estimate would be 83% by age 60 years, with 95% confidence limits 63%–92%. The corresponding estimate for ovarian cancer is 38% by age 60, with 95% confidence interval 22%–50%.

Overall, the estimated age-specific penetrances derived from the second cancer data are somewhat higher than those derived from the maximum LOD score method; in particular, the cumulative risks by age 60 years (though not by age 70 years) based on the second cancer data are significantly higher for both cancers than are those based on the maximum LOD score method. The difference is most marked below age 40 years.

Relative Risks

We also computed relative risks for breast and ovarian cancer in BRCA1 carriers, as compared with general population risks (for convenience, based on the incidence rates for England and Wales 1978–82; Muir et al. 1987). The relative risk for breast cancer based on the contralateral breast cancer data declines significantly with age, from >200-fold below age 40 years to 15-fold in the 60–69 years

Table 2

Estimated Cumulative Risks of Breast and Ovarian Cancer in BRCA1-Gene Carriers, on the Basis of the Incidence of Second Cancers

	Breast Cancer				Ovarian Cancer		
Age Group (years)	Observed	Incidence Rate	Cumulative Risk	Estimated Penetrance[a]	Observed	Incidence Rate	Estimated Penetrance
30–39	7	.040	.33	.55	4	.014	.10
40–49	9	.028	.50	.73	12	.024	.29
50–59	7	.023	.60	.83	5	.013	.38
60–69	3	.015	.65	.87	2	.010	.44

[a] Estimated penetrance for a first breast cancer, computed by doubling the incidence rates for contralateral breast cancer, to allow for only one breast being at risk.

age group ($P_{trend} < .0001$). Some decline in the relative risk is also apparent from the maximum LOD score method. The relative risk for ovarian cancer, based on the second cancer data, also declines significantly ($P_{trend} < .001$), though the decline is not so dramatic as for breast cancer. There is no obvious trend in the relative risk for ovarian cancer, based on the maximum LOD score method.

Penetrance Estimates, under the Assumption of Heterogeneity

To allow for the possibility of allelic heterogeneity, we fitted a model with two susceptibility alleles conferring different breast and ovarian cancer risks, as described in Methods. The cumulative risks of breast and ovarian cancer conferred by the two alleles under the best-fitting model are illustrated in figure 1. Allele 1 is estimated to confer a breast cancer risk of 62% by age 60 years and an ovarian cancer risk of 11%, while allele 2 confers a breast cancer risk of 38% and an ovarian cancer risk of 42%. Under this model α, the population frequency of allele 2 as a proportion of all susceptibility alleles, is estimated to be .29 (95% confidence limits 13%–45%). The ratios of the breast and ovarian cancer incidence rates due to allele 2 and to allele 1 are 0.51 and 4.8, respectively. This model is a highly significantly better fit than is the homogeneity model ($\chi^2_3 = 54.56$). The major difference between the two alleles is in the estimated ovarian cancer risk; the model is not a significant improvement over a model in which the breast cancer risks are assumed to be the same for both alleles ($\chi^2_1 = 3.35$). Under this latter model, the cumulative breast cancer risk is estimated to be 48% by age 60 years, and the cumulative ovarian cancer risk is 9% and 45%, respectively, for alleles 1 and 2, with α being 0.11. We also fitted a model under which allele 1 conferred no excess ovarian cancer risk over that in the general population; however, this model fitted poorly in comparison with the model in which both alleles confer an increased ovarian cancer risk ($\chi^2_7 = 33.31$; $P < .0001$).

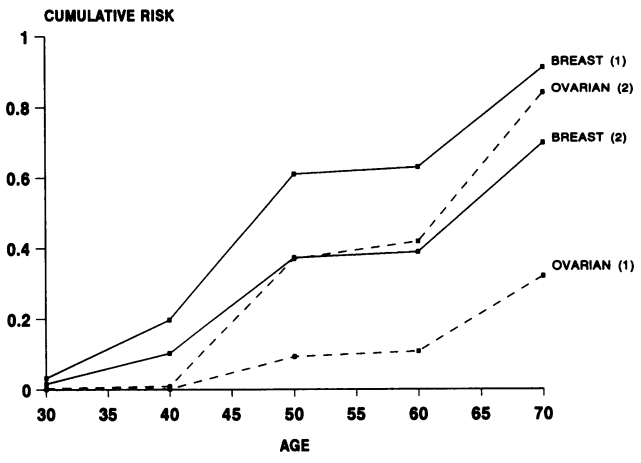

Figure 1 Cumulative risks of breast and ovarian cancer in BRCA1 gene carriers, allowing for allelic heterogeneity with two susceptibility alleles (1) and (2).

On the basis of the assumed heterogeneity model, most of the families can be assigned to either allele 1 or allele 2, on the basis of their posterior probabilities. Of the 33 families, 11 have a posterior probability of ≥95% of carrying the type 2 allele, and 9 have posterior probabilities of >99%; 16 have posterior probabilities of <5% of carrying a type 2 allele, and 10 have posterior probabilities of <1%; only 6 families have posterior probabilities of 5%–95%. It is interesting to note that, in the 16 families with a posterior probability of ≥95% of carrying the type 2 allele, the ratio of the number of breast cancers to ovarian cancers is ≤1.33, whereas the 11 families with a posterior probability of ≥95% of being type 1 all contain at least four breast cancers for every ovarian cancer.

One prediction from the heterogeneity analysis of the previous section would be that the risk of ovarian cancer in a patient with a previous breast cancer should be higher in families carrying allele 2. There is some evidence for

Table 3

Numbers of Ovarian Cancers in Relatives of Breast and Ovarian Cancer Patients, as a Proportion of All Breast and Ovarian Cancers, by Degree of Relationship

	Degree of Relationship			
Relatives of	1st	2d	3d	4th
Breast cancer patients:				
Type 1 families	30/226 (13%)	33/231 (14%)	31/195 (16%)	46/288 (16%)
Type 2 families	35/57 (61%)	65/99 (66%)	78/114 (68%)	272/550 (49%)
UTAH 2082	4/6 (67%)	10/20 (50%)	18/34 (53%)	208/420 (50%)
IARC 1816	5/15 (33%)	17/29 (59%)	23/29 (79%)	45/107 (42%)
Ovarian cancer patients:				
Type 1 families	0/30 (0%)	2/33 (6%)	4/33 (12%)	4/46 (9%)
Type 2 families	104/139 (75%)	108/173 (62%)	82/160 (52%)	228/500 (46%)
UTAH 2082	14/18 (78%)	10/20 (50%)	10/28 (36%)	176/384 (46%)
IARC 1816	14/19 (74%)	14/31 (45%)	16/39 (41%)	28/73 (38%)

such a difference, although the difference is less marked than would be predicted from the heterogeneity analysis. Among the 13 families with a >50% posterior probability of carrying the type 2 allele, the estimated cumulative second ovarian cancer risk was 58%, based on 10 cases, whereas in the 20 families with a posterior probability of <50%, the estimated risk was 35%, based on 13 cases. This difference is not quite statistically significant ($\chi^2_1 = 3.19$; $P = .07$). The relative risk for a second ovarian cancer in type 2 families, compared with the type 1 families was 2.1 (95% confidence limits 0.91–4.8).

Clustering of Breast and Ovarian Cancers

Table 3 shows the numbers of breast and ovarian cancers in the relatives of breast and ovarian cancer patients, by degree of relationship. The results have been subdivided into families probably carrying the type 1 allele and those probably carrying the type 2 allele, to avoid confounding with allelic heterogeneity. The results are also shown separately for the two largest families. There is some suggestion that the proportion of ovarian cancers is higher among first-degree relatives of ovarian cancer patients than among more distant relatives, though there is no suggestion of a corresponding effect for breast cancer. Using the statistical test described in Methods, there is no significant evidence of clustering within families ($\chi^2_1 = 0.63$).

Discussion

This study provides age-specific cumulative risk estimates for breast and ovarian cancer in BRCA1-mutation carriers, which should be valuable for counseling women in breast-ovarian cancer families linked to BRCA1. Estimates have been derived by two methods using essentially independent data sources, namely, maximizing the LOD score over possible penetrance functions and using the incidence of second cancers following a breast cancer, Both methods confirm that the overall lifetime penetrance is close to 100%, the estimated risk of either cancer by age 70 years being 95%, using the maximum LOD score method, and 93%, using the second cancer method. At younger ages, the second-cancer data give somewhat higher estimated risks.

One important observation from this study is that the absolute lifetime risk of ovarian cancer in BRCA1 carriers is high, at least in some families, which could have important management implications. It could be argued that this high ovarian cancer risk is an artifact of ascertainment of families for the consortium. This seems unlikely, since the consortium was originally established to examine linkage in breast cancer (rather than ovarian cancer) families, and it seems unlikely that families were included on the basis of a large number of ovarian cancers, as opposed to a corresponding number of breast cancers. However, to further address this issue, we have also examined the numbers of breast and ovarian cancers that have occurred in these families over the period 1991–1993, i.e., since the families were originally reported to the consortium. These cases should not be susceptible to any ascertainment bias. Over this period, two ovarian cancer cases have occurred in previously unaffected women, and one case has occurred in a woman with breast cancer. Over the same period one first primary breast cancer and three second primary breast cancers have occurred. In addition, five breast cancers and one ovarian cancer have occurred in branches not included in the initial pedigree. Thus, the ratio of breast:ovarian cancers over this prospective period is 4:3, or 8:4 including new branches. These prospective cases, though few in number, are consistent with the ratio of the overall breast and ovarian cancer incidence rates estimated in this study,

which is about twofold between ages 30 and 70 years (see table 2).

Further evidence for the high lifetime risk estimates of ovarian cancer and breast cancer in BRCA1 carriers was obtained by Goldgar et al. (1994) using a life-table analysis in a single large breast-ovarian cancer kindred containing 30 breast cancers and 20 ovarian cancers. In this family the estimated cumulative risk, of either cancer, by age 70 years was 90%, and the risks of ovarian and breast cancer by age 70 years were 65% and 73%, respectively (D. E. Goldgar and C. M. Lewis, personal communication).

This study confirms that the age-specific incidence of breast cancer in gene carriers follows a markedly different pattern from that in the general population; the relative risk for breast cancer declines by an order of magnitude over the age range 30–70 years. This dramatic decline suggests that there may be important mechanistic differences between sporadic breast cancers and those caused by BRCA1 (it is a much faster decline, for example, than would be predicted under a simple Knudson-type model in which a germ-line BRCA1 mutation was the first event (Knudson 1971). The results for ovarian cancer are somewhat more ambiguous; the relative risk based on the second-cancer data does decline significantly with age, though not as dramatically as for breast cancer, but there is no clear pattern in the relative risks from the maximum-LOD-score method.

This study also provides evidence that the ovarian cancer risk conferred by different BRCA1 mutations is likely to differ substantially. This heterogeneity is to some extent apparent simply by inspection of breast-ovarian cancer families reported here and elsewhere; for example, the seven families originally reported by Hall et al. (1990) to be linked contained 43 cases of breast cancer in patients <60 years and just 2 ovarian cancer cases (both in the same family), whereas other large families, such as those reported by Feunteun et al. (1993) and Goldgar et al. (1993), contain similar numbers of breast and ovarian cancers. One extreme example has recently been reported by Steichen-Gersdorf et al. (1994), in which a linked family contains six ovarian cancer cases and no breast cancers. It seems unlikely that these differences could be entirely explained as an artifact of ascertainment. One could argue that the differences in ovarian cancer risks between families might be due to either the effect of other genes unlinked to BRCA1 or shared environmental factors modifying the risk. If this were true, the ovarian cancer cases should tend to cluster together in families, since the effect of any modifying genes would diminish with degree of relationship. In fact, there is little evidence for such clustering of cases.

Under the best-fitting model in this analysis, 29% of the BRCA1 mutations would confer a high risk of ovarian cancer (estimated to be 84% by age 70 years), while the remaining 71% would confer a more moderate risk (32% by age 70 years). Some independent evidence for this allelic heterogeneity was found by considering the risks of ovarian cancer in individuals already affected with breast cancer, according to whether cancer in the family was probably due to the type 1 or type 2 allele. The risk of ovarian cancer in women with a previous breast cancer is higher in the type 2 families, although the difference is only 2-fold, as compared with the 10-fold difference predicted by the heterogeneity analysis. This suggests that the difference in ovarian cancer risk, between high- and low-risk families, may have been exaggerated by the heterogeneity analysis. In any event, the proposed heterogeneity model can be at best an approximation of the true situation; there may, for example, be a larger number of alleles conferring a spectrum of risks. Moreover, the proportion of high-risk alleles is very imprecise; under the model in which both alleles confer the same breast cancer risk (which fits the data almost equally well), only 11% of mutations confer a high ovarian cancer risk.

Now that BRCA1 has been identified (Miki et al., 1994), it may ultimately be possible to resolve this issue by correlating the type of mutation with the observed disease phenotypes in the families, although this will obviously depend on the complexity of the spectrum of mutations.

It is interesting to note that, under heterogeneity, the average ovarian cancer risk to BRCA1 carriers would be much lower than that estimated by the homogeneity analysis (47% compared with 63%). This is because the high risk mutations are overrepresented in the large BRCA1 families used in this analysis. If this allelic heterogeneity is confirmed, it could have an important bearing on clinical management of BRCA1 families, since, clearly, women who are given a lifetime ovarian cancer risk of >80% are more likely to opt for prophylactic oophorectomy than are women with a risk of 26%.

It is interesting to compare the breast and ovarian cancer risks with those obtained from previous segregation analyses. The estimated cumulative risk of breast cancer in BRCA1 carriers was 85% by age 70 years, using the maximum-LOD-score method, and 87%, using the contralateral breast cancer data. These estimates are somewhat higher, though not significantly so, than are the cumulative risks to carriers of the breast cancer–susceptibility gene in the segregation analysis of Claus et al. (1991), which gave a risk of 67% by age 70 years. Under the assumption of no allelic heterogeneity, the estimated risk of ovarian cancer in gene carriers was 30% by age 60 years, using the maximum-LOD-score method and 38% by age 60 years, using the second-cancer data. These estimates are much higher than the estimated risk of 10% by age 60 years, given by Claus et al. (1993) for the carriers of the breast cancer–susceptibility allele in the Cancer and Steroid Hormone study data set. There are two obvious reasons for this dis-

crepancy. First, not all early-onset breast cancer families are linked to BRCA1, and from our previous analysis it would appear that the risk of ovarian cancer is largely restricted to those families linked to BRCA1. Second, if there is substantial heterogeneity in the ovarian cancer risk, as is suggested by the heterogeneity analyses presented here, the multiple case families analyzed here will contain a much higher proportion of high ovarian cancer–risk alleles than are present in general population.

Acknowledgments

The analysis of this study was supported by the Cancer Research Campaign. Meetings of the Breast Cancer Linkage Consortium have been supported by an E.C. Biomedical and Health Research Concerted Action. Collection and analysis of families at the University of Michigan have been supported by grants CA57601 and HG00209 from the NIH.

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