

Commentary

Familial risks of breast cancer

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Abstract

A recent analysis by the Collaborative Group on Hormonal Factors in Breast Cancer has provided the most precise quantification to date of the familial risks of breast cancer. The familial relative risks are shown to decrease from more than fivefold in women younger than age 40 years with a first-degree relative aged younger than 40 years at diagnosis, to 1.4-fold in women older than 60 years with a relative diagnosed over age 60 years. These risks increase progressively with the number of affected relatives. The risks associated with an affected mother and an affected sister are similar, and the relative (but not absolute) risks are similar in subgroups defined by other established breast cancer risk factors. These results provide a useful basis for counselling of women with a family history of breast cancer, and they have implications for the genetic basis of the disease.

Keywords: *BRCA1*, *BRCA2*, familial breast cancer, reproductive factors

Introduction

The increased risk of breast cancer among women with a family history of the disease is one of the oldest established facts about the disease. This familial aggregation has been the inspiration for studies to identify breast cancer susceptibility genes that have borne fruit over the past decade, and has been the basis for defining high-risk groups for intervention studies (e.g. with tamoxifen). Yet despite the fact that questions about family history are asked in almost every epidemiological study of breast cancer, some important questions about the quantitative relationship between family history relationship have not been answered with precision. Among these questions are the magnitude of the risk according to the age of the women and the age of their affected relative(s), the precise effect of numbers and types of affected relatives, and the joint effects of family history and other known risk factors.

Since only ~10–15% of women with breast cancer typically report a family history of breast cancer, individual epidemiological studies have not had the power to answer

these questions precisely. The recent analysis by the Collaborative Group on Hormonal Factors in Breast Cancer [1] goes a long way toward resolving some of these uncertainties. This group has brought together data from 52 studies, originally to evaluate the effects of oral contraceptives and hormone replacement therapy. In the current overview, the group examine risks according to family history of breast cancer in a first-degree relative in over 58,000 cases and in nearly 102,000 controls.

Summary of main findings

The main results from the overview [1] are straightforward to summarise. The results of the study are mainly expressed in terms of the risk ratio (or relative risk) of breast cancer associated with a family history; that is, the ratio of the incidence rate of breast cancer in relatives of breast cancer cases to the incidence in the relatives of controls. These risk ratios were estimated from the case-control studies in the usual way, and we refer to them as 'familial relative risks'.

As anticipated, the familial relative risk of breast cancer declines progressively as both the age at diagnosis of the case and the age at diagnosis of the relative increases. The estimated relative risk is thus 5.7-fold when both the case and the relative are younger than age 40 years, but is only 1.4-fold when both are aged older than 60 years. (An anomalous observation here is that the relative risks decline more clearly with age of the case than with age of the relative; for cases older than age 60 years, there was no apparent trend in risk by age of relative. This anomaly might be explicable by inaccuracies in the reporting of a relative's age at diagnosis.)

This pattern of risk was essentially the same whether the affected relative was a mother or a sister. For women aged younger than 50 years, the risk ratio associated with having a relative diagnosed younger than age 50 years was 2.41 (95% confidence interval, 1.86–3.12) for an affected mother and was 3.18 (95% confidence interval, 2.15–4.72) for having an affected sister. For women aged older than 50 years, the risk ratio associated with having a relative diagnosed older than 50 years was 1.60 (95% confidence interval, 1.38–1.84) for an affected mother and was 1.44 (95% confidence interval, 1.19–1.73) for an affected sister.

The second observation was that the risk increased progressively with numbers of affected relatives. The risk ratios were 1.80 with one affected relative, 2.93 with two affected relatives and 3.90 (albeit with wide confidence limits) with three or more affected relatives.

Third, the investigators performed detailed analyses to examine the effects of other known breast cancer risk factors in women with and without a family history, and conversely the effect of family history in women in categories defined by other risk factors. They found that the relative risks associated with other risk factors were essentially identical in women with and without a family history. In women with a family history, risk thus reduced with increasing parity, with earlier age at first child, and with earlier age at menopause to a similar relative extent (but, therefore, a larger absolute extent) as in women without a family history. There was no significant evidence of an association of oral contraceptives or hormone replacement therapy in women with a family history, but the confidence limits for these comparisons were extremely wide and the results were consistent with effects similar to the small increased risks seen in the general population.

Finally, the investigators examined the effect of tumour spread on familial risk, but found that the familial risks were essentially the same whether or not the tumour was localised to the breast at diagnosis.

Limitations of the results

An obvious concern in any studies of familial risk is the accuracy of reporting of cancer diagnoses in relatives. Other studies have indicated that breast cancer is fairly accurately reported, certainly in comparison with other cancer types (for example, [2]), but there is some inaccuracy, and hence potentially some bias in favour of reporting of cancers by cases. However, the investigators found the familial risks from the cohort studies alone (which are not susceptible to this bias) to be very similar.

The main application of these results will be to genetic counselling and identification of high-risk women for screening and intervention studies. There are clearly some important limitations in this respect. Most obviously, the overview did not include data on genotypes at known susceptibility genes (data that would rarely be available in such studies), so these risk estimates would not apply in families where, for example, *BRCA1* or *BRCA2* mutation testing had taken place. At least for the present, however, genetic testing is mostly restricted to women with a strong family history (e.g. three or more affected relatives) so these empirical estimates will still be of value to the large majority of women.

A more subtle problem is that no data on ages of unaffected female relatives were included. Clearly, in practice, the number and ages of unaffected female relatives do affect risk (although to a lesser extent than affected relatives do). Also, the overview had insufficient data to evaluate risks according to whether a daughter was affected, and no data at all on second-degree or more distant relatives (generally poorly recorded in case-control studies [2]). The latter two issues might be answered more reliably through cohort studies of families, such as those based on the Swedish Population Family Register [3].

The overview did not consider risks according to cancers other than breast cancer in relatives. Other studies, however, have indicated that, with exception of a well established but modest risk of ovarian cancer (probably explicable in terms of the association of both cancers with *BRCA1/2* mutations) and an association with childhood sarcoma (perhaps entirely due to *TP53* mutations), there is little or no excess risk of breast cancer associated with a family history of other cancers [4].

Implications of the results for breast cancer genetics

Although the aim of the overview was to present empirical risk estimates, these estimates do raise some interesting issues with regard to the genetics of breast cancer. Two studies have estimated that mutations in the *BRCA1* and *BRCA2* genes only account for approximately 15% of the excess familial risk of the disease [5,6], while the contribution of the other known breast cancer susceptibility genes

(*TP53*, *PTEN*, *CHK2* and *ATM*) is even smaller [7]. The contribution of known genes is higher than this in certain populations where specific *BRCA1* or *BRCA2* mutations have become common as a result of founder effects. These populations include Iceland, Ashkenazi Jewish populations and parts of Poland. In most Western populations, however, the observed familial risks are largely the result either of other genes or of nongenetic familial risk factors. While the possibility of the latter cannot be definitively ruled out, results from twin studies suggest that the majority of the familial risk is in fact genetic in origin [8,9]. (Since adjustment for known reproductive and other breast cancer risk factors had essentially no effect on the familial risks, nongenetic contributors to the familial risk, if there are any, must presumably be unrelated to the known risk factors.)

The absence of substantial difference in risk by type of affected relative (i.e. affected mother versus affected sister) suggests that the important genes are likely to act dominantly or additively on risk, but not to act recessively (recessive susceptibility genes give rise to higher risks in siblings than in parents or offspring). Some studies using a family-based cohort approach have found higher risks in siblings, and these notably include studies of cases diagnosed at a particularly young age [10,11]. These results do not necessarily conflict with the overview, since the risk estimates from the overview are imprecise at young ages. Conversely, it may be that the higher risk to siblings in the cohort studies is due at least in part to cohort effects on background incidence rates, and to the artefactually low rate of breast cancer in mothers who are, by definition, parous.

The pattern of risk by the number of affected relatives is also revealing. The fact that the risk increases progressively with the number of affected relatives suggests the effect of a fairly large number of genetic risk groups, consistent with, for example, a polygenic model as proposed by Antoniou *et al.* [12]. The trend in relative risk with age suggests that (like *BRCA1* and, to a lesser extent, *BRCA2*) some or all of the susceptibility genes involved are likely to confer a higher relative risk at young ages.

Finally, the similarity of the risk ratios for other risk factors in women with and without a family history suggest that these risk factors act to a similar extent in women at any level of genetic susceptibility. Of course, one cannot necessarily assume that this will hold for carriers of particular susceptibility mutations. Studies of *BRCA1* and *BRCA2* mutation carriers have shown that early menopause does have the expected protective effect in these groups [13], but the effects of other risk factors such as parity have not been definitively established [14,15].

What are the implications for genetic counselling? Perhaps the most important is that the absolute risk of breast cancer in women with just one affected relative is

relatively modest, even when the relative is diagnosed at a young age (the authors estimate a cumulative risk of 16% by age 80 years for women with a relative diagnosed younger than age 40 years). The risks associated with having larger numbers of affected relatives are more substantial, and referral to cancer genetics clinics should reflect this. The results of the present study also imply that the effects of reproductive and hormonal risk factors could be usefully incorporated into genetic counselling. Since the effects of family history and these other risk factors on breast cancer risks appear to combine in roughly multiplicative fashion, the absolute effects of risk factors in individuals with a strong family history can be substantial.

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