Commentary

More breast cancer genes?

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Abstract

A new gene associated with a high risk of breast cancer, termed BRCAX, may exist on chromosome 13q. Tumours from multicase Nordic breast cancer families, in which mutations in BRCA1 and BRCA2 had been excluded, were analyzed using comparative genomic hybridization in order to identify a region of interest, which was apparently confirmed and refined using linkage analysis on an independent sample. The present commentary discusses this work. It also asks why there should exist genetic variants associated with susceptibility to breast cancer other than mutations in BRCA1 and BRCA2, and what might be their modes of inheritance, allele frequencies and risks. Replication studies will be needed to clarify whether there really is a tumour suppressor gene other than BRCA2 on chromosome 13q.

Keywords: breast cancer, familial aggregation, genes, linkage, replication

Introduction

A study of Nordic families [1] has claimed ‘preliminary evidence’ that a region on chromosome 13q might contain a previously unrecognized tumour-suppressor gene, mutations in which may be associated with an unknown but probable high risk for breast cancer. This potentially exciting finding was achieved using new molecular techniques and ‘a strategy that assumed that somatic genetic changes in cancer tissues may give insights to the nature of the germline predisposing loci’.

Comparative genomic hybridization (CGH) was used to study tumours from multicase breast cancer families. Branching and phylogenetic tree models, and other evidence suggested that loss of 13q was an early genetic event in the development of breast cancers. All five tumours from one particular family showed distinct 13q deletions, which led to identification of a haplotype shared by all five affected members that coincided with the region of loss in the tumours identified by CGH. However, the ‘significance’ of the loss of homozygosity studies, in both the statistical and common language meanings, is difficult to assess, given that the role of chance was not evaluated.

A linkage study, in an independent set of multicase breast cancer families in which BRAC1 and BRCA2 mutations had been excluded, was then targeted on the region of interest in their search for a novel breast cancer predisposition locus that they termed BRCAX [1]. They considered their lod score results promising, although there was no evidence of linkage in an interval that was only 0.5–2.1 cM from the position of their BRCAX. Those investigators were also confident that they could exclude the role of BRCA2, which is not far (recombination fraction 0.25) from where their putative locus lies, even though they did not study extensively markers on both sides of BRCA2. Is there really a BRCAX other than BRCA2 on this chromosome?
What evidence is there that there are more breast cancer genes?

Why would one think there are more genes associated with a high risk for breast cancer other than BRCA1 and BRCA2? The argument proposed in the first line of the abstract of the report by Kainu et al [1] that such genes must exist because there are so-called ‘familial breast cancer families’ in which a BRCA1 or BRCA2 mutation has not been detected is unconvincing. A nontrivial proportion of the multicase breast cancer families studied by Kainu et al will occur by chance alone, as demonstrated by simulation studies [2] that addressed the observation from population-based studies that the majority of hereditary early-onset breast cancer is sporadic. For example, even if the genetic risk of breast cancer (penetrance) is 80% to age 70 years (equivalent to a 20-fold increase in the risk) and is carried by 1 in every 200 women, then approximately 30% of families with three or more cases of breast cancer spread over three generations will not be due to that genetic risk. Use of the expression ‘familial disease’ without precise definition, especially when used as by these authors to refer to ‘hereditary disease’, should be discouraged. Awful family histories can occur through bad luck.

It is well known that having a blood relative who has had breast cancer increases a woman’s risk for the disease. This increased risk is modest, in terms of the individual, being on average approximately twofold and higher if the relative was diagnosed at a young age [3]. It has been estimated that just 16% of this familial aggregation of breast cancer in the UK diagnosed before age 55 years could be attributed to mutations in BRCA1 and BRCA2 [4]. What explains the rest?

What about nongenetic causes of familial clustering of breast cancer?

Familial aggregation does not imply a genetic aetiology; consider infectious diseases such as the common cold, for which clustering of disease within families can occur for nongenetic reasons [5]. It is generally considered that breast cancer is a hormonal disease, as evidenced by the well-established risk factors identified from questionnaire epidemiology (such as age at menarche, age at menopause, parity, number of live births, and even a small effect of oral contraceptive use), and from the change in shape of the incidence curve around menopause. Furthermore, these classic risk factors are themselves ‘familial’, in that sisters, mothers and daughters are moderately or weakly correlated (ie $r < 0.5$).

How much of the familial aggregation of breast cancer is due to the familial correlations in these risk factors? The answer is, on face value, not very much. For example, modelling has shown that five such independent risk factors, each correlated ($r = 0.4$) in first-degree relatives and each associated with a doubling of risk across the interquartile range, would result in an increased risk of disease in relatives of just 1.05-fold [6]. However, it is important to realize that the effect of these familial factors could be substantially greater, given they are imprecisely measured surrogates for the real underlying hormonal determinants of breast cancer. Measurement error will attenuate the estimates of both risk and familial correlation [6]. On the other hand, the reasons why these risk factors aggregate in families could at least partly be due to genetic factors that influence their variation – it is not easy to untangle nature and nurture.

A large proportion of familial aggregation of breast cancer therefore remains unexplained. This is important; even a modest twofold increased risk for disease cannot occur unless there are underlying familial risk factors that, when combined, are an order of magnitude stronger, giving an interquartile risk ratio of 20–100 or more [7–9]. Uncovering all of the sources of familial aggregation of breast cancer will be a major step in understanding the causes of the disease itself.

What about candidate genes?

The ATM locus that is implicated in the rare recessively inherited disease ataxia-telangiectasia (A-T) has attracted attention following the report of a threefold increased risk in heterozygotes from linkage analyses in families containing A-T sufferers [9]. Several studies have since screened A-T cases for protein-truncating and other mutations in the gene (eg [10]) without finding supporting evidence. However, only large, well-conducted population-based studies have the statistical power and credibility to resolve the issue, and those of even several hundred cases and control individuals have little chance of detecting such rare, modest risks [11]. Interest is now shifting to missense mutations [12] – clearly the jury is still out.

Common polymorphisms in other ‘candidate’ genes, chosen for their presumed role in aetiological pathways, have been examined without much success to date [13]. Based on epidemiological evidence, genes that are involved in the metabolism of oestrogen would seem a logical place to start. Initially there was evidence that a T to C variant in the CYP17 gene (allele frequency about 0.4) played a role in serum oestrogen and progesterone levels [14], and was associated with an increased risk of advanced disease [15]. Subsequent case–control and cohort studies [13] failed to support this as a genetic risk factor. Tantalizing new evidence that women with two copies of this allele may have a twofold to fourfold increased risk of early-onset disease [16,17] demands further study.

A common polymorphism in BRCA2 with an allele frequency of about 0.25 may be associated with a 1.4-
1.5-fold recessively inherited risk of the disease [18] (Spurdle AB, et al, unpublished data). The roles of such common polymorphisms are worthy of study because, in terms of attributable risk and explaining familial aggregation on a population basis, they could be more important than the rare high-penetrance mutations in genes such as BRCA1 and BRCA2, or even BRCAX. For example, a twofold risk carried by 20% of the population explains 20 out of 120 (17%) cases, whereas a 20-fold risk carried by 0.5% explains just 9.5 out of 109.5 (9%) cases.

What can we learn from segregation and mutation analyses?

Segregation analyses attempt to estimate from family data the characteristics (in terms of mode of inheritance, allele frequency and risk of disease in carriers) of unmeasured genetic variants that have a major impact on risk of disease. Two recent analyses of population-based families, in which extensive mutation testing for both BRCA1 and BRCA2 had been carried out, have been reported [19,20]. By either removing the families in which mutations are known to be segregating, or by modelling the effects on risk of those identified mutations, these analyses suggest that there may be genes other than BRCA1 and BRCA2 that are involved with a dominantly inherited risk, that there may be genetic loci that are involved with a recessively inherited risk, and that there may also be a ‘polygenic’ background of many genes with small effects. Extensive mutation and linkage analysis in multicase families [21] has also provided evidence to suggest there may be other ‘high risk’ susceptibility genes.

What is the way forward?

There would appear to be considerable evidence to support projects aimed at identifying genes, other than BRCA1 and BRCA2, that are involved in susceptibility to breast cancer. What is evident is that these genes may contain ‘high-risk’ or ‘moderate-risk’ alleles (and even both within the same locus), and that the risk may be dominantly or recessively inherited. Does the approach of the recent report [1] represent the way forward, combining thorough molecular work using tissue material and CGH to help focus gene hunting, and independent verification within the one study? Certainly others are following this lead, using fresh tumour tissue to try to identify groups of genes on the basis of their similarity in expression [22]. This may be the key to overcoming the difficulties in gene discovery due to the genetic heterogeneity of susceptibility to individual cancers.

Conclusion

There is every possibility that are more ‘breast cancer genes’, but whether these include ATM, CYP17, other estrogen metabolism genes and/or the putative BRCAX locus claimed by the Nordic researchers, is at present unresolved.

The bottom line is whether others find supporting evidence; as Kainu et al [1] themselves state, ‘studies to evaluate the significance of this candidate locus in other populations will be critically important’. The answer of course lies with replication.

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