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E7. The search for new breast cancer susceptibility genes

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Approximately 13% of all breast cancer patients have one or more first-degree relatives with breast cancer [1]. The overall Relative Risk for a first-degree relative to develop breast cancer herself (also termed excess familial risk) is approximately 1.80. How much of this risk is determined by genetic factors? A large Scandinavian twin study has indicated that 27% of the variance in susceptibility was attributable to heritable factors. Peto and Mack [2] observed that patients with breast cancer are at a very high risk of developing another cancer in the other breast and that this risk does not change with the age of the first cancer, being approximately 0.7% per year. They argue that most of this high-risk is genetic because a similar pattern is seen in monozygotic twins, where the risk is approximately twice the contralateral breast cancer risk of any individual, which is consistent given that in the latter case only one breast is at risk. The inference of their model is that the first cancer (i.e., breast cancers in the population as a whole) occurs in a minority of women who are susceptible for it. A more conventional model of inherited breast cancer susceptibility is that disease risks are affected by mutations in a small number of genes causing a high-risk of the disease, and a larger number of lower risk gene variants probably interacting together [3]. Model-based linkage analysis in multiple-case families followed by positional cloning led to the identification of several high-risk breast cancer susceptibility genes. *BRCA1* and *BRCA2* are the most well known of these, and the cancer risks conferred by mutations in these genes are now well established. It has been estimated that mutations in *BRCA1* and *BRCA2* can explain only approximately 25% of the overall excess familial risk. Families with at least four cases of breast cancer and at least one case of ovarian cancer can be attributed largely to *BRCA1*. Multiple-case families with at least one case of male breast cancer are mainly due to *BRCA2*. However, most families with four or five cases of female breast cancer diagnosed before the age of 60 years are not due to *BRCA1* or *BRCA2* [4]. This has been taken as evidence that one or more moderate- to high-risk breast cancer susceptibility genes still remain to be identified. There have indeed been several linkage claims since *BRCA1* and *BRCA2* were identified, but none of these have been replicated in other, often larger studies. However, most studies are heavily underpowered to detect a new breast cancer locus by linkage in the presence of substantial genetic heterogeneity. If *BRCA3* causes familial breast cancer in only 25% of such families, over 300 families would be required to detect it by conventional linkage analysis. The Breast Cancer Linkage Consortium is currently compiling genome-wide linkage data on approximately 200 families in which the role of *BRCA1* or *BRCA2* has been excluded with >90% certainty. This comprises the largest linkage search effort in the world to date. These families are characterised by the presence of at least three cases of breast cancer diagnosed before the age of 60 years, no cases of ovarian or male breast cancer.

A model in which several common, low penetrance genes with multiplicative effects on risk could also account for the residual non-*BRCA1*/*BRCA2* familial aggregation [5]. The biggest immediate challenge now is to identify such genetic factors. Parametric linkage analysis in families is not feasible, and here one generally relies on some form of genetic association study. As genome-wide searches for associations between genetic variation and disease susceptibility are presently still too costly, the study design most often opted for is one in which a functional variant in a candidate gene is selected, and its prevalence assayed

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in a population of cases and controls. The present state of this research area is characterised by many conflicting results. Whereas everybody agrees that genes involved in oestrogen biosynthesis and metabolism, DNA repair, apoptosis, and cell cycle control are all good candidates for breast cancer risk factors, it is very often not clear what the functional relevance of genetic variation in these genes is. In addition, hidden population stratification may give rise to false-positive or false-negative results, and many association studies have in fact been conducted on too small populations. Finally, there is a debate raging in the literature between proponents of a model which assumes that most disease susceptibility variants are common in the population (frequency > 1%) versus those that assume that late-onset diseases are due to large numbers of rare variants at many loci [6,7]. Under the first model, common susceptibility alleles are potentially detectable in large-scale patient-control association studies, but under the last model, such a strategy would fail and the contribution of most individual variants would be too small to further our understanding of disease.

If all of the susceptibility factors could be identified, it would, in principle, be possible to identify women as susceptible for breast cancer by their genotypic profile, opening up avenues for targeted breast cancer prevention [8]. However, population-based gene testing for breast cancer will never become acceptable in the absence of a cost-effective, non-invasive preventive intervention.

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