

Short communication

Identification of personal risk of breast cancer: genetics

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Background

Family history has long been recognized to be a potent risk factor for breast cancer [1]. Family histories often comprise only one or two affected relatives, who frequently were not particularly young at onset. Occasionally, a family contains a striking constellation of young-onset breast (and often other) cancers apparently transmitted as a dominant genetic trait. Over a century ago, the much referenced French neurologist Paul Broca wrote about the family of his wife, in which the occurrence of many cancers, particularly of the breast, strongly suggested the presence of a genetic predisposition [1]. It was to be more than a hundred years before the discovery of the structure of DNA and rapid advances in molecular technology would allow the first major breast cancer susceptibility gene, *BRCA1*, to be mapped to chromosome 17q [2]. In families linked to the *BRCA1* locus, a much younger age at onset than average and the frequent occurrence of ovarian cancers were noted to be typical. At about the same time, the cause of a rare but devastating familial cancer syndrome was identified; mutations in the *TP53* gene had also been found to account for the very rare Li Fraumeni syndrome associated with very young onset breast cancers and childhood malignancy, particularly soft tissue sarcomas [3,4].

A second major breast cancer susceptibility gene, *BRCA2*, was mapped to chromosome 13q in 1994 shortly before the sequence of the *BRCA1* gene was clarified and family-specific disease-causing mutations started to be reported [5,6]. The full *BRCA2* gene sequence was reported in 1995 [7]. Families with mutations in the *BRCA2* gene were noted to be more likely to contain a male breast cancer case than might be expected by chance (and more than had been seen in families due to *BRCA1* mutations); ovarian and fallopian tube cancers still occurred with increased frequency but overall not as frequently as in *BRCA1*-associated families. With the discovery of the correct gene sequences for *BRCA1* and *BRCA2* it became possible to offer predictive genetic testing to members of families in which the causative gene mutation had been identified. Predictive testing for breast cancer susceptibility was introduced as a clinical

service from the mid-1990s in some centres in the UK [8]. Families in which mutations were identified through research studies were the first to be informed [9]. Many of these families had been identified because of their high incidence of cancer, and so inevitably the estimated lifetime chance that a carrier of one of these genes would develop cancer was high [10,11].

The *BRCA1* and *BRCA2* genes are very large, and mutation testing was either very expensive (in the USA) or very slow (in European countries) when it first became available. It soon became clear that mutations in these genes accounted for a relatively small proportion of all families with breast cancer clusters. Families with four or more cancer cases developing at young age, particularly those families in which ovarian cancers occurred, were more likely to yield pathogenic mutations when DNA from a cancer-affected family member was screened for mutations. Smaller clusters of later onset cancers, although clearly familial, were noted to have a much lower probability of harbouring a *BRCA1* or *BRCA2* mutation [12].

In the presence of a *BRCA1* or *BRCA2* mutation, the lifetime risk for developing breast cancer may be as high as 80% to 90%, although other genes and lifestyle factors may reduce the lifetime risk to levels as low as 26%. Ovarian cancer risk in *BRCA1* gene carriers is estimated at about 50%, but again this risk is likely to be modified by both genetic and other risk factors. For *BRCA2*, ovarian cancer risk is about 15%, but all these average risks are likely to be modified by context [13].

Other breast cancer susceptibility genes

During the past decade, no other highly penetrant breast cancer susceptibility genes like *BRCA1* and *BRCA2* have emerged, despite huge efforts using linkage-based studies in large breast cancer familial clusters. A variety of candidate genes were investigated and evidence presented of their involvement in breast cancer susceptibility but with much lower associated risks than for *BRCA1* and *BRCA2* [14-17]. It was realized that it was likely that there were no more high penetrance genes to be discovered, and that much of the

remaining familial risk would be due to common variants in multiple genes, each conferring only very small increases in lifetime breast cancer risk [18]. As techniques for genotyping common variants (polymorphisms) across the entire genome became more economically viable, large cohorts of breast cancer patients (cases) and unaffected individuals (controls) were evaluated in genome-wide association studies [19]. Recently, these led to the discovery of several genetic variants, common in the general population, that confer an increase in lifetime breast cancer risk with odds ratios (compared with the population average) of the order of 1.3 [20-22].

Risk assessment using these genetic variants with much lower penetrance presents an interesting challenge for the future. Incorporating the seven main risk alleles of the low penetrance type discovered through genome-wide association studies, it is clear that not only would it be a very rare occurrence to carry all seven high risk alleles, but also the lifetime risks conferred are modest at best even in the presence of all seven alleles [23]. Incorporation of the effect of these common variants into risk prediction algorithms that take other known epidemiological risk factors into account does not result in a major improvement in risk prediction (at least hypothetically) [24]. The nature of the case-control cohorts thus far studied inevitably leads to findings that are more likely to apply to oestrogen receptor positive breast cancers, because these are the more frequent type of breast cancer overall. This may mean that a group identified as being at risk on the basis of today's single nucleotide polymorphisms could benefit more from intervention with a chemopreventive option such as tamoxifen [25]. However, variants that alter the rate of metabolism of tamoxifen could prevent any benefit in a proportion of the population [26].

Where risks conferred by a single gene mutation (penetrance) is high and inheritance is clear (usually autosomal dominant), the use of genetic testing in risk prediction and risk management are relatively straightforward. This is the case for *BRCA1* and *BRCA2* gene mutations, although risks are still clearly affected by low penetrance genetic variants as well as lifestyle factors [27-29].

In conclusion, testing of multiple single nucleotide polymorphisms to predict lifetime risk of breast cancer is not clinically valuable for an individual at present. However, over the coming decade, as most breast cancer risk associated genetic variants are identified and a clearer picture of gene-gene and gene-environment interactions emerges, it is likely that genetic profiles may help to guide selection of women for earlier mammographic screening and for targeted risk-reducing strategies, potentially including chemoprevention or lifestyle changes (for example, weight control, earlier child-bearing and longer breast feeding). Whether enough women will be prepared to change their lifestyle radically and from a young age in order to ameliorate predicted breast cancer risk remains to be seen.

Competing interests

The author declares that they have no competing interests.

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