Short communication

Assessing risk for breast cancer

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Published: 18 December 2008
This article is online at http://breast-cancer-research.com/content/10/S4/S13

Breast Cancer Research 2008, **10(Suppl 4):**S13 (doi:10.1186/bcr2173)

Risk factors for breast cancer can be allocated to one of four major groups: family history/genetic, reproductive/hormonal, proliferative benign breast disease and mammographic density. These four factors have now been thoroughly studied, and accurate quantitative estimates for the risk are now available for many of them. The most useful summary comes from the Oxford collaboration, which has now produced a series of papers estimating the risk associated with individual factors [1-3]. In terms of family history, compared with a woman with no affected relatives, a single affected first-degree relative roughly doubles the risk; two such individuals triple the risk, and three or more quadruple the risk. The age at which cancer occurs in a mother or sister also affects risk, with young age at onset leading to higher risk; risk is approximately threefold for onset under age 40 years, twofold for age 40 to 50 years and 1.5-fold for age 50 to 65 years, and there is little increase for older ages unless there are multiple affected cases. This is further complicated by the fact that the relative risk is greatest when the woman herself is young, especially if the family member had early onset cancer, and diminishes as the women ages and does not develop cancer. A relative with bilateral breast cancer can be treated as having two affected relatives for the purposes of these calculations.

Reproductive factors are also well established risk factors, with age at first childbirth being the most well known. Nulliparous women have similar risk to that in women whose first child was born when they were aged 30 years, with a later first birth giving rise to a higher risk (especially within 5 years after delivery) and women giving birth when they were young at lower risk. The relative risk decreases by about 3% for every year younger (maternal age) that childbirth occurs, so that a woman whose first child was born when she was aged 20 years has about a 30% lower relative risk than a woman whose first child was born when she was aged 30 years. Because the absolute lifetime risk for breast cancer is about 10%, this translates into a 3% lower absolute risk. Subsequent births reduce relative risk by about 7% per birth, but these also have a similar but weaker link to age at first childbirth.

Breast feeding is protective, but substantial periods of breast feeding are needed to have a material impact, and the relative risk is estimated to decrease by 4.3% per cumulative year of breast feeding, so several cumulative years are needed before this factor becomes appreciable.

An early age at beginning of menstruation increases risk (4% per year), as does late age at menopause (3% per year). Hence, increased duration of ovulation is a risk factor, and this unifies the above factors because single pregnancy and lactation suppress ovulation while they occur. Use of hormone replacement therapy, especially combined oestrogen and progesterone preparations, also increase risk by up to 5% per year of use, but only in current users, and the risk returns to baseline levels within a year of stopping use [4]. Certain types of benign breast disease increase risk as well. Ductal carcinoma *in situ* (DCIS) is considered to be a precursor lesion to cancer and not benign, and the risk for invasive disease is very high. In contrast, lobular carcinoma *in situ* is considered benign and indicative of a field change, so that subsequent cancers can arise anywhere in either breast, as opposed to DCIS, in which subsequent cancer more frequently occurs in the same quadrant as the DCIS. In any case, lobular carcinoma *in situ* confers an approximately 10-fold relative risk. Atypical ductal or lobular hyperplasia confers a relative risk of about 4 to 5, whereas proliferative hyperplasia or other benign lesions without atypia (for instance, intraductal papillomatosis) roughly double the risk. Non-proliferative lesions, including a sizeable portion of fibroadenomas and cysts, do not increase risk.

Being obese increases risk in postmenopausal women, whereas being tall and drinking alcohol increases risk at all ages. Obesity is well known to be related to increased

DCIS = ductal carcinoma *in situ*.

oestrogen levels in postmenopausal women. The other two factors (alcohol and height) undoubtedly are also related to hormones or growth factors, but the mechanisms are not well understood.

Mammographic density is probably the single most important factor in terms of population attributable risk. Almost 5% of the population has more than 75% of the breast covered by density on a mammogram, and they have about a fivefold increased risk compared with women with less than 10% density [5]. Women with 50% to 75% of the mammogram covered by opaque tissue also have about a twofold to threefold increase in risk and comprise about 14% of the population. Mammographic density can be rapidly and reliably estimated visually from a mammogram, as indicated by the large Breast Cancer Consultation study of 81,777 women [6], in which simple Breast Imaging Reporting and Data Systems (BIRADS) categories yielded risk prediction accuracy similar to that of the Gail model. The challenge is to combine these factors effectively.

Computer-assisted approaches appear to yield slightly more accurate and reproducible readings, but they are currently rather time consuming. This will undoubtedly change, however, when digital mammography becomes more widespread, so that digitization of films will not be necessary.

Less is known about the possible interactions between these factors, and virtually nothing is known about how different factors influence the risks for different types of breast cancer (for example, oestrogen receptor positive versus negative tumours). However, risk factors appear to be largely independent, and this facilitates the building of a model to predict risk in individuals. Previous models have focused on either nongenetic factors [7], in which important factors relating to genetic risk are not considered, or strictly familial factors [8], in which the modifying effect of other factors is not included.

Our own model [9] incorporates the best features of both of these models and was found to be a more accurate predictor of risk in a genetic counselling clinic [10].

Mammographic density has not been included in any of these models, although it is currently the one risk factor with the largest population attributable risk [5]. There is an urgent need to learn how best to combine this information with other factors and to learn how best to counsel women about their risk and the need for preventative actions.

Even with all of these factors, our ability to determine who will develop breast cancer and who will not is limited, and improving risk determination is important in targeting prevention activities and screening. It remains to be seen how much further prediction can be derived from identifying rare and low-risk genetic polymorphisms. In my view, the greatest likelihood of improved prediction will come from phenotypic markers based on hormone profiles, methylation status (both in serum and breast biopsies) and possibly further refinement of mammographic features.

Competing interests

The author declares that they have no competing interests.

Acknowledgement

This article has been published as part of *Breast Cancer Research* Volume 10 Supplement 4, 2008: Controversies in Breast Cancer 2008. The full contents of the supplement are available online at http://breast-cancer-research.com/supplements/10/S4

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