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Risk Assessment for Sporadic Breast Cancer: The Need for a Molecular Profile

*David N Danforth**

Department of Surgery, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, USA

Abstract

Breast cancer is the most common malignancy in women. Many women are at risk for breast cancer, and the assessment of this risk is important in their care and management. Several models are available to determine risk for breast cancer, however these models may not apply to many women, or may have limitations for selection of women who may or may not benefit from prevention therapy. Molecular profiling is now standard practice in the care of women with breast cancer, raising the possibility that a molecular profile of normal breast tissue, from which breast cancer develops, may be feasible and of value for risk assessment. Such a profile might be valuable for women who do not have identifiable risk factors, or may compliment existing risk assessment models in several ways. Normal breast tissue is known to contain a range of gene expression and other genomic abnormalities, and is also accessible for analysis. Several factors must be considered in the development of such a profile, including endpoints, genomic character of the profile, and the normal at-risk tissues to be studied. Together these observations support the feasibility and encourage efforts to develop a molecular profile of normal breast tissue for breast cancer risk assessment in women.

Keywords: Breast cancer; Breast cancer risk; Sporadic breast cancer risk assessment; Molecular profile; Normal breast tissue; Risk assessment profile

Introduction

The assessment of risk for breast cancer is important in the care and management of many women. Several models are available for the assessment of risk, and these evaluate information primarily regarding age, hormonal and reproductive factors and family history; however these models have limitations and may not apply to all women. Breast cancer develops through the accumulation of molecular changes in normal breast tissue, and molecular profiling of breast cancer is now standard practice in the care of women with early stage breast cancer. This raises the possibility that a molecular profile of gene expression or other changes in normal breast tissue may contribute to the assessment of risk for breast cancer, and compliment existing risk assessment models. To address this possibility, the rationale encouraging the development of a molecular profile of normal at-risk breast tissue for use in the risk assessment of breast cancer is discussed, including factors which must be considered in the development of this risk assessment profile.

Background and Discussion

Breast cancer is the most common malignancy in women, with over 3,16,000 cases annually in the United States, of which 20.1% are in situ and 79.9% are invasive carcinoma [1]. The incidence of breast cancer has remained relatively stable over the past decade, with the lifetime incidence among women approximately 1 in 8, or 12.4%. This indicates there are not only a significant number of women with breast cancer in the US, but also a large population of women who are at risk for developing breast cancer in the future. The majority of breast cancers (85% to 90%) are considered to be sporadic in nature (not associated with heritable mutations).Multiple demographic factors are known to increase the risk for sporadic breast cancer including older age, family history, reproductive and hormonal factors, and breast tissue abnormalities such as atypical hyperplasia and lobular carcinoma in situ. An understanding of the risk an individual woman has for breast cancer is important for several reasons: 1) to promote awareness of personal risk. 2) To identify risk factors that may be modified and potentially lower the risk for breast cancer, such as exercise, correction of postmenopausal obesity, and cessation of hormone replacement therapy. 3) To determine the type and schedule of breast imaging to recommend for women at normal risk *vs.* high risk for

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Correspondence:
David N Danforth, Department of Surgery, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA,
E-mail: david danforth@nih.gov

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breast cancer. 4) To determine if antiestrogen therapy is indicated for prevention of breast cancer. 5) To determine the need for genetic counseling and genetic testing.

There are several models available for the assessment of risk for sporadic breast cancer, including the Gail, IBIS, and CLAUS models. The Gail and IBS models use demographic information including age, hormonal and reproductive factors, personal history of breast disease, and family history of breast cancer to determine the risk for breast cancer. The most commonly used model is the Gail which includes age, age of menarche and first live birth, number of first degree relatives with breast cancer, breast biopsy history, and the presence of atypical hyperplasia. A five-year risk of breast cancer >1.66% is considered high risk for breast cancer [2]. The most inclusive model may be the IBIS (Tyrer-Cuzick) model which includes the above demographic information as well as the presence and age of breast cancer in first, second and third degree maternal and paternal relatives, a history of ovarian carcinoma, and Ashkenazi heritage. Other models are focused primarily on either family history (Claus), on the probability of carrying a BRCA mutation (BRCAPro), or mutational probability in individuals with a family history (BOADICEA) [3,4]. Together, these models provide useful information for breast cancer risk assessment for many women. However, it is important to recognize that 50% to 70% of women who develop breast cancer have no identifiable risk factors for breast cancer [5,6] and thus the above models would likely underestimate their risk for breast cancer, and not provide any information which would make them candidates for breast cancer prevention therapy despite their increased risk for breast cancer. The anti-estrogen tamoxifen has been shown to be effective for the prevention of breast cancer in women at high risk. For example, the NSABP P-1 trial compared tamoxifen to placebo in high risk women and found tamoxifen reduced the incidence of breast cancer at a median 7 years from 4.25% in the placebo arm to 2.48% in the tamoxifen arm, with the majority of the developing breast cancers being estrogen receptor (ER) negative [7]. Most of the women in the placebo arm, however, did not develop breast cancer within this time frame. Tamoxifen therapy was also accompanied by a moderate incidence of serious toxicity (endometrial cancer, thromboembolic disease, and stroke). Additional means are needed to identify women at high risk who may not benefit from, or may not require, tamoxifen, as well as a means to identify women who are more prone to develop ER negative breast cancer. The risk assessment models discussed above, while their inclusion of demographic factors may be comprehensive, do not contain any molecular features of the respective normal breast tissue in their evaluation. Molecular profiling of breast cancer has been an important contribution to the evaluation of women with breast cancer and has allowed further characterization according to risk of recurrence and benefit from adjuvant chemotherapy. Several multigene prognostic tests have been developed, including Oncotype Dx, Prosigna, Breast Cancer Index, and Endopredict [8,9]. These assays assess expression of a panel of genes (different for each assay) in the primary breast cancer. According to the Guidelines by the American Society of Clinical Oncology, Oncotype Dx and Endopredict have been approved for management of breast cancers which are ER+/PR+, Her-2/neu negative, and lymph node negative to guide decisions in respective patients about adjuvant chemotherapy [10]. These assays identify women who are at risk for recurrence and who will, or will not, need adjuvant chemotherapy. This supports the utility of molecular profiling in the management of these women. In addition, among all the assays, genes representing a wide range of cellular functions have been used, providing information about different signaling pathways in the breast cancers and indicating the diversity of the assays. Together these findings indicate that gene expression profiling may be used to characterize tissues as complex as breast cancer and play an important role in the management of women with these tumors.

The usefulness of molecular profiling in the management of patients with breast cancer encourages the evaluation of molecular patterns in normal breast tissue for the risk assessment for sporadic breast cancer. A recent literature review has demonstrated that a wide range of genomic changes are present in normal breast tissue at high risk for breast cancer [11]. Several studies, in particular, have used gene expression profiling to compare tissues at high risk (such as normal tissue adjacent to breast cancer) with those at normal risk (such as reduction mammoplasty), [11] and have identified multiple differentially expressed genes between these two groups. For example, Tripathi et al. [12] identified 105 genes differentially expressed, most commonly in immediate early genes, genes of MAPK signaling cascade, G-protein coupled and chemokine receptor activity, and transcription factors. A total of 32 genes (31%) were previously implicated in breast carcinogenesis. Graham et al. [13] found that the gene expression profile from normal tissue adjacent to breast cancer was similar to that from prophylactic mastectomy specimens, indicating that this profile may mark increased risk. Further, they noted that if future studies confirm these findings, then evaluation of gene expression in normal epithelium could improve risk assessment. A similar finding was reported by Radovich et al. [14] using RNA-seq, who identified 933 genes differentially expressed between high risk normal adjacent and normal risk breast tissue. A direct application of molecular profiling to risk assessment was provided by Chen et al. [15]. They identified a malignant-risk signature in high risk normal adjacent breast tissue, for which pathway analysis showed a remarkable over expression of proliferative function genes, with the majority of the malignant-risk genes classified as being associated with DNA replication and mitosis. They concluded that these results suggest a predictive role for the malignancy risk signature in normal breast tissue. Lastly, a recent study analyzed normal adjacent tissues from samples in The Cancer Genome Atlas [16]. This identified two mRNA/microRNA expression phenotypes in normal adjacent breast tissue which correlated with significantly worse 10-year survival among Estrogen Receptor (ER) positive cases of the associated breast cancer. There were no significant associations between copy numbers, DNA sequence, or methylation genetic defects in the normal breast tissue and survival, supporting the application of the gene expression profile [16]. Together these findings indicate that gene expression abnormalities may be present in normal breast tissue at high risk for breast cancer which can distinguish these tissues from breast tissues at normal risk. In addition, these findings suggest molecular profiling of normal breast tissue may contribute to and complement risk assessment models in several ways; 1). It could provide a risk indicator which directly reflects genomic changes in normal breast tissue. 2). It could provide a comprehensive risk indicator which potentially reflects the genomic changes from multiple demographic factors. 3). It would represent a risk indicator which is quantifiable and potentially more so than reproductive factors such as age of menarche or age of 1st pregnancy. 4). It would represent a risk indicator which provides information about biology and altered signaling pathways in breast tissue. 5). It would be potentially applicable to women with no identifiable risk factors. 6). If the molecular profile is developed from

very high risk normal tissue (such as normal tissue adjacent to cancer) as was done in the studies above, [12,15-17] then intuitively it would also contain genomic changes from earlier risk states(through progressive field cancerization) and potentially be applicable to a range of risk states. These observations encourage efforts to develop a molecular profile for risk assessment from normal breast tissue of women. Important considerations may include the following: 1). The endpoints of the study. Risk of development of breast cancer would be the most definitive endpoint and at the same time compliment existing risk assessment models. Alternatively, correlation of a normal tissue molecular profile with quantitative risk estimates for that individual determined from risk assessment models. Selection of the best risk assessment models for correlation, differences in risk estimates for a given subject between different models, and selection of appropriate risk factors will be important considerations. 2). The source of tissue and subject population for study. Several sources might be considered: A). analysis of normal breast tissue from women known to develop breast cancer in the future (cases), compared with tissue from women without future breast cancer (controls) would be informative. Demographic information including risk factors would allow further characterization of these tissues, as well as information about characteristics of the developing breast cancer. These tissues would also be available in commercial and University repositories. B). Analysis of normal breast tissue adjacent to cancer might also be appropriate for several reasons: i) it is associated with a defined breast cancer. In the study by Tripathi, et al. [12] it was been noted that 25% of cancer-adjacent samples had moderate-to-high levels of tumor-like somatic mutations, and on average, about half of a tumor's somatically mutated loci were expressed in matched cancer-adjacent normal tissue [16]. ii) Its association with breast cancer would also provide an opportunity to characterize the normal breast tissue for precursor changes according to receptor subtype and other characteristics of an associated breast cancer. [17]. iii) It has been shown in several studies to have multiple differentially expressed genes compared with breast tissue at normal risk for breast cancer (such as reduction mammoplasty) [12-14]. iv). It is at very high risk for developing breast cancer 12.0 to 15.0 fold increased risk as determined from recurrence rates in breast segmentectomy trials without whole breast radiation, [18] and thus would likely contain relevant and informative genomic changes. v). Breast cancer specimens with adjacent normal tissue, and control reduction mammoplasty specimens, would be readily available in existing repositories. Validation studies for prediction of breast cancer could be conducted on normal tissue from women who developed future breast cancer *vs.* those who did not (cases *vs.* controls as described above). 3.) The molecular profile to be used. Several molecular parameters in normal breast tissue have been associated with risk for breast cancer, including loss of heterozygosity, [19] DNA methylation, [20] gene expression profiling, [15] and individual markers [21]. Whole genome studies are preferred, however, to allow a comprehensive assessment of genomic changes. Several gene expression profiling studies, cited above, have demonstrated multiple differentially expressed genes between normal adjacent tissue and normal risk (reduction mammoplasty) tissue. Gene expression profiling also has the advantage of a proven track record for providing prognostic and clinically useful information with the analysis of breast cancer [8,10], and can be performed on small quantities of material. Gene expression profiling has also been recognized by Tripathi et al. [12] who proposed that if differential expression of these genes can be detected in women without evident breast cancer, and associated with future disease, then they may be pertinent to risk assessment. 4). Bioinformatics. An essential part of the study which will be influenced by the nature of the molecular profile selected, by variability of genomic changes (gene expression or other parameters studied) within and between subjects, and by the endpoints selected, and which must be incorporated from the outset in the study.

Summary and Conclusion

In summary, risk assessment is a very important part of the management of women at risk for breast cancer. Risk assessment models evaluating hormonal and reproductive factors, personal history of breast disease, and family history of breast and/or ovarian cancer can provide useful estimates of risk for breast cancer. Many women at increased risk for breast cancer, however, will not have any identifiable risk factors for breast cancer, and thus not benefit from these models. Additional risk assessment tools are needed. Breast cancer develops through the accumulation of genomic abnormalities in normal breast tissue, and many of these abnormalities are reflected in gene expression changes. Supported by the successful application of gene expression profiling in breast cancer, the application of gene expression profiling to normal at-risk breast tissue may hold promise to compliment and expand risk assessment evaluation for sporadic breast cancer for many women, and encourages efforts to study its potential application.

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