EDITORIAL

Breast Cancer Prevention in the Era of Precision Medicine

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After the cloning of the second breast cancer gene in 1995 (BRCA2), gene researchers took divergent paths. Some searched for new and rare genes while others sought to explain unusual cancer clusters, but at Cambridge University, a group of genetic epidemiologists devoted their energies to the development of a polygenic model for breast cancer (1). They sought to account for the missing heritability through a model that postulated that there were many genes, each of which contributed in a small way to a woman’s vulnerability. The effort was facilitated through the completion of a genomic map of nucleotide variants (HapMap) and the engineering of a DNA chip that secured many thousands of single nucleotide polymorphisms (SNPs) from across the genome. The first genome-wide association study (GWAS) for breast cancer was published by the Cambridge group in 2007 (2), and there have been many others since.

Doug Easton and his Cambridge colleagues engendered an extraordinary collaborative spirit, which culminates in a landmark paper boasting 218 authors (3) published in this issue of the Journal. The fruits of the enterprise are presented as a genetic risk assessment model that incorporates 77 SNPs. The authors use the model to generate personal risk scores and thereby stratify women according to their lifetime risk. The paper by Mavvadat et al. is important, because it enables us to evaluate the clinical utility of the polygene paradigm—it is unlikely that the model will be improved substantially if we add more SNPs (or different SNPs). For the 77 SNPs, the frequency of the rarer of the two alleles ranged from 0.001% to 48.2% and the corresponding odds ratios range from 0.86 to 1.36. The baseline risk of breast cancer to age 74 years in the UK is 8.2% (4). Based on her personal risk score, a woman in the top one percentile had a three-fold increase in risk relative to the mean (hazard ratio [HR] = 3.36, 95% confidence interval [CI] = 2.95 to 3.83), or roughly 25% lifetime.

If the GWAS studies were the first step towards precision medicine and the development of the model is the second step, then the third step is to show that the personal risk score is useful. Who should be tested and who will pay? There is no reason to assume that scores in the mother and daughter will be correlated, and the effects of family history and the risks score appear to be independent (3), so a family history of breast cancer is not going to help us select women for testing. Rather, all women qualify. The test is unlikely to be paid for by the government in the UK or here in Canada or by a third party payer in the United States, so we can assume it will be paid for by informed and interested consumers. A likely scenario is that the test will be offered direct-to-consumer by a commercial laboratory, possibly in the context of a wider genetic test that includes other cancers and other diseases.

In the event that a woman’s risk score places her in the top percentile, we can offer her more frequent mammography screening, earlier screening (eg, from age 40 years), or more intensive screening (eg, with MRI). It is not universally accepted that mammographic screening is effective (5,6), and the benefits of MRI have been evaluated in terms of downstaging but not mortality (7,8). Even if we assume that mammography does reduce mortality by one-third, we expect the impact of personal risk scoring at a population level to be small. Assume that 1% of women under age 40 years in the UK pay for the test out of pocket and that 1% of these are positive and qualify for mammography at age 40 years instead of age 50 years. For them, the risk of cancer between age 40 and 50 years is now 3% instead of 1%. If the baseline case fatality is 20%, then we expect to prevent one death among every five million women in the country (and 100 000 others will die of breast cancer regardless).

Perhaps tamoxifen is a better option. The recent update of the International Breast Cancer Intervention Study shows a continued decline in the incidence of estrogen receptor (ER)–positive cancer 16 years from randomization, but it still fails to show a decline in breast cancer mortality (9). Despite the fact that there were 99 fewer breast cancer deaths in the tamoxifen arm of the study (251 vs 350), there were six more deaths from breast cancer (31 vs 26). Results of other chemoprevention trials are similar, and hope is fading that we will see a mortality benefit from tamoxifen chemoprevention.

Over the past decade, the incidence of women undergoing contralateral mastectomy for unilateral breast cancer has grown rapidly (10). Bilateral mastectomy is a rational option for women with a BRCA1 or BRCA2 mutation, but most women...
in the United States who have the operation do not carry a mutation. In Ontario, prior to the introduction of genetic testing, we computed the average lifetime risk of breast cancer for women undergoing preventive bilateral mastectomy to be 17%, but the same women estimated their own risk to be 76% (11). In California, the rate of bilateral mastectomy has increased from 2.0% in 1998 to 12.3% in 2011 (an annual increase of 14%) (10). This increase is not the result of more genetic testing or because of personalized risk assessment or because more surgeons are recommending it; rather, it is because of rising levels of anxiety among some patients engendered by media testimonials and incessant awareness campaigns. Despite the fact that bilateral mastectomy has not been shown to reduce mortality (10), women often state that their wish for better survival motivated their decision. Except in extreme cases, the personal risks estimated by the polygenic model will be too low to justify preventive mastectomy, but they are not too low to cause women to worry, and some women will undergo preventive surgery to alleviate their fear.

In conclusion, the polygenic model helps explain the distribution of cancer risk in a population, but it is not a practical approach to breast cancer risk management, and an SNP-based test is not likely to affect mortality. In his State of the Union address of January 20, 2015, President Barack Obama launched a new Precision Medicine Initiative “to give all of us access to the personalized information we need to keep ourselves and our families healthier.” The initiative was endorsed by Drs Francis Collins and Harold Varmus (12). The topic is generating much interest, and the benefits and harms of precision medicine are being debated. Mavaddat et al. (3) provide us with an excellent perspective to help us choose a side in the debate.

Note
The author has no conflicts of interest to disclose.

References