Risk of Breast and Ovarian Cancer in Women With Strong Family Histories

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Assessing the risk of breast and ovarian cancer starts with obtaining a complete and accurate family history. This can reveal evidence of inherited cancer risk. The highest risk of cancer is associated with germ-line abnormalities.

The article by Dr. Srivastava and colleagues provides a broad overview of the procedures for assessing the risk of breast and ovarian cancer in women with a family history of these diseases. Below, we make some additional comments that may be useful to practitioners in risk-evaluation clinics.

Founder Mutations

When evaluating patients for possible deleterious BRCA mutations, determining ancestry may be a critical issue. Founder mutations are present in ethnically isolated populations and are responsible for a significant proportion of breast and ovarian cancer cases attributed to an inherited susceptibility. Founder mutations have been identified in Ashkenazi Jews,[1-3] French Canadians,[4] Japanese,[5] Italians,[6] Swedes,[7] Finns,[8] Belgians, and Dutch.[9,10]

In Caucasian individuals, it is estimated that 1 out of 300 individuals carries a mutation in BRCA1 or BRCA2, whereas 1 out of 40 individuals of Ashkenazi Jewish ethnicity harbors such a mutation. Penetrance of BRCA1/2 may be somewhat lower in Ashkenazi Jews than estimates derived from studies of the original families[11]; however, other recent studies show a higher penetrance. Individuals of Dutch ancestry may be advised to pursue a special test that is designed to detect two founder genomic deletions that have been observed in this population.

Genes That Predispose to Breast Cancer

Variants of uncertain significance (VUS) abound in the BRCA genes. Their significance remains uncertain primarily due to the relatively scant knowledge regarding their biological impact. Testing additional family members for the familial VUS can be helpful in establishing, for example, that the VUS was inherited from a noncancer lineage or that the VUS does not appear to track with cancer cases seen in the family.

The BRCA genes are examples of tumor-suppressor genes as defined by Knudson’s two-hit hypothesis. As the authors point out, other tumor-suppressor genes such as p53 (one of the genes responsible for Li-Fraumeni syndrome) also predispose to hereditary breast cancer. Li-Fraumeni syndrome (or SBLA syndrome [sarcomas, breast and brain tumors, leukemia, laryngeal and lung cancer, and adrenocortical carcinoma]) can also be caused by mutations in the newly discovered hCHK2 gene, which confers a predisposition to sarcoma, breast cancer, and brain tumors.[12] It is anticipated that testing for this gene in certain families may be appropriate when such a test becomes clinically available.

The Best Model

When assessing empiric risk for breast cancer, it is best to use the model that shows the fewest limitations for the patient’s personal and family history. In contrast to the authors’ statement, the Claus model does provide estimates of breast cancer risk for women with a family history of ovarian cancer in a first-degree relative.[13] The BRCAPRO model is limited in that it considers BRCA1/2 to be the only possible predisposing genes, with all other high-penetrance breast cancers being scored as sporadic. Some scientific evidence points to other breast cancer susceptibility genes that have yet
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Published on Physicians Practice (http://www.physicianspractice.com)

to be identified, and therefore, BRCAPRO is likely to overestimate the probability of a BRCA mutation in a family. This model also fails to incorporate a previous breast tissue diagnosis that may impact risk.[14] When calculating the risk of finding a BRCA mutation in a family, the uncertainty is even greater.

The Myriad tables should be used with caution, because the informed consents used by many clinics may not allow for the dissemination of family history information to the testing company. All models are meant only as guides for the counselor and patient, setting the stage for a risk-evaluation discussion tailored to the patient’s needs.

Although patients considering risk management options are often referred to practitioners in other disciplines, it is neither time efficient nor cost effective to have onsite multidisciplinary specialists. The model of a risk evaluation clinic run by a genetic counselor or nurse geneticist plus a physician versed in cancer genetics is widely adopted and appears to work quite well.

Treating Women at High Risk for Breast Cancer

The earliest steps in breast carcinogenesis due to BRCA1/2 mutations are not completely understood. More information is needed prior to making any definitive statements on genotype/phenotype correlations. A preponderance of estrogen receptor-negative tumors may apply to BRCA1-related disease, but not cancer associated with BRCA2. Regarding the use of selective estrogen-receptor modulators for chemoprevention, we believe that raloxifene (Evista) is not yet a risk-reduction alternative for high-risk breast cancer patients outside of research protocols.

Breast conservation appears to be a reasonable option for most women who are BRCA carriers. Nevertheless, women who are mutation carriers and require mastectomy to treat a breast cancer diagnosis may wish to discuss the risks and benefits of a possible bilateral prophylactic mastectomy, if they desire reconstruction with autologous tissue after their therapeutic mastectomy, as this type of reconstruction can, in general, only be performed once with present techniques.

With or without reconstruction, prophylactic bilateral mastectomy is an option that many BRCA1/2 carriers wish to discuss. The usefulness of this risk management option is also controversial. A retrospective study by Hartmann et al revealed a 90% reduction in breast cancer risk after prophylactic mastectomy.[15] However, it is not known how many of the women studied actually had a BRCA1/2 mutation. Inclusion criteria for "high-risk" women were broad and included variables that may not be associated with an inherited susceptibility to breast cancer. Therefore, the women in this cohort who underwent prophylactic mastectomy may not have been at "high" enough risk. Furthermore, there are almost no data on any long-term effects, such as quality of life and psychosexual function. These results must be applied with caution to the BRCA carrier population until further genetic information becomes available.

Controlling Breast Cancer Risk

We believe that significant scientific evidence supports certain lifestyle interventions to control breast cancer risk. For example, limiting alcohol to three to five drinks per week,[16] consumption of more than five servings of fruits and vegetables per day,[17] and routine exercise[18,19] have all shown substantial benefits with regard to breast cancer risk. It is reasonable to consider counseling on these measures as part of a patient's breast cancer risk management.

The Health Insurance Portability and Accountability Act is a major step forward in protecting patients from genetic discrimination. However, detailed knowledge of its specific limitations is helpful for certain patients. The protection provided by this law does not extend to life and disability insurance, and we believe these issues should be discussed with patients, especially young patients who may not have life and disability insurance.[20]

Conclusions

In practical terms, there is a pressing need to more fully understand the efficacy of lifestyle changes, as well as chemopreventive and surgical interventions, as they apply to carriers of specific gene
mutations. In particular, appropriate end points and patient satisfaction should be studied, in addition to cancer risk and survival. For example, research outcomes that center on patient desires, satisfaction, and decision-making processes are largely unknown for these high-risk individuals. Integrating this knowledge into a more detailed understanding of hormone action on breast tissue will be needed to design effective and comprehensive cancer risk reduction interventions for women at high risk.

References:


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