Most Genes Associated With Increased Risk of BC Remain Poorly Characterized

Written by Lynne Lederman

Mutations in the high-penetrant genes BRCA1 and BRCA2, large tumor suppressor autosomal genes involved in DNA repair, are associated with about 85% of hereditary breast cancer (BC). However, hereditary BC accounts for only 5% to 10% of BCs [Schwartz GF et al. *Breast J.* 2009]. Another 15% to 20% of BCs are familial, occurring primarily in postmenopausal women, and are currently not associated with specific mutations [Turnbull C, Rahman N. *Annu Rev Genom Human Genet*. 2008]. According to Banu Arun, MD, University of Texas MD Anderson Cancer Center, Houston, Texas, USA, who discussed risk management of hereditary BC, the remaining 70% to 80% of BCs now characterized as sporadic are probably due to low-penetrance genes and high-frequency risk alleles.

Estimates of the cumulative risk of BC due to BRCA mutations vary from study to study because of differences in the populations studied. In addition to being associated with an increased risk of BC in women, BRCA1 and BRCA2 are associated with an increased risk of ovarian cancer [Chen S, Parmigiani G. *J Clin Oncol.* 2007]; BRCA2 is also associated with increased risk of male BC, prostate cancer, pancreatic cancer and other gastrointestinal cancers, and melanoma [Ginsburg OM et al. *Fam Cancer.* 2010; Ferrone CR et al. *J Clin Oncol*. 2009; Levy-Lahad E, Friedman E. *Br J Cancer*. 2007; Tai YC et al. *J Natl Cancer Inst*. 2007].

Peer-Reviewed Highlights From the

San Antonio Breast Cancer Symposium

December 9–13, 2014
San Antonio, TX, USA

The National Comprehensive Cancer Network (NCCN) 2014 guidelines for breast and ovarian genetic/familial high-risk assessment [NCCN Panel. Version 2.2014] suggest referral for genetics evaluation for patients with BC if invasive and aged ≤50 years, or aged ≤60 years if triple negative, even in the absence of family history, with ductal carcinoma in situ; with ovarian, fallopian tube, or primary peritoneal cancer, multiple primary cancers in a single individual including 2 breast primaries, breast and ovarian, fallopian tube, peritoneal primary, or 2 or more primary cancers in close relative(s) from the same side of the family; Ashkenazi Jewish ancestry with breast or ovarian cancer at any age; members of a family with a known BRCA mutation; and men with BC.

Before testing, possible genetic test outcomes that should be discussed with patients include

1) positive (deleterious or pathogenic) mutation, or true negative mutation (there is a known mutation in the family, and the tested individual does not have it);
2) inconclusive negative result (includes families who have many individuals with early-onset BC where a mutation cannot be identified); and
3) variants of uncertain clinical significance.

In the case of a deleterious BRCA mutation, the NCCN 2014 guidelines state that breast awareness should start at age 18 years, clinical breast examination every 6 to 12 months starting at age 25 years, annual magnetic resonance imaging (MRI) at age 25 to 29 years, and annual mammogram plus MRI at age 30 to 75 years; at age >75 years, management should be on an individual basis.

Preventive bilateral mastectomy reduces BC risk by >90% in prospective studies [Rebbeck TR et al. *J Clin Oncol*. 2004; Meijers-Heijboer H et al. *N Engl J Med.* 2001]. Preventive bilateral salpingo-oophorectomy reduces BC risk by 50%, and also reduces ovarian cancer risk by >95% [Domcheck SM et al. *JAMA*. 2010; Rebbeck TR et al. *J Natl Cancer Inst.* 2009]; it is recommended between ages 35 and 40 years. Preventive oophorectomy is associated with a 77% reduction in all-cause mortality [Finch APM et al. *J Clin Oncol*. 2014].

There are no prospective chemoprevention studies in carriers of BRCA mutations. One retrospective analysis found no benefit from tamoxifen in BRCA1 carriers but looked at only 8 patients in a cohort of over 13 000 participants [King MC et al. *JAMA*. 2001]. Because so many BRCA-associated BCs are estrogen receptor-negative or triple negative, tamoxifen may not be of benefit as a preventive, although in patients with BC, it might be beneficial for contralateral BC prevention.

When a mutation of uncertain significance is found, it is frustrating for patients and health care providers alike. Options are to use standard risk-assessment models that take family history into account. Chemoprevention and preventive surgery are individual patient decisions in this situation.

Next-generation sequencing panels will allow simultaneous analysis of many genes at a cost similar to that of current single-gene tests. Several well-established clinical genetic-testing laboratories are now offering hereditary cancer-specific panel tests geared to a particular cancer type or focused on high-penetrant genes only; others may test for any possible known cancer-associated mutation. High- and moderate-penetrance genes associated with BC in addition to BRCA include TP53, PTEN, CHEK2, and PALB2 (partner and localizer of BRCA2).

Currently, the panels do not have clinical utility and do not contribute to improved patient outcomes, and there are no prospective trials in individuals with any of the low-penetrance genes that are now being offered in panel testing. Going forward, studies of single nucleotide polymorphisms (SNPs) and risk modifier genes may help with risk assessment. Dr Arun recommends enrolling patients into the many registries and screening and prevention trials that are now recruiting.

Antonis C. Antoniou, PhD, University of Cambridge, Cambridge, United Kingdom, discussed characterizing cancer risks for carriers of various mutations, including PALB2. In a recently published study [Antoniou AC et al. *N Engl J Med*. 2014], the risk of BC in families (362 members of 154 families) with germline loss-of-function mutations in PALB2 was estimated. Among female carriers, the risk was 14% by age 50 years and 35% by age 70 years, which is between 5 and 9 times the risk of the general population, depending on carrier age. Like BRCA2, PALB2 is also associated with an increased risk of ovarian, male breast, and pancreatic cancers. At this time, the lifetime risk of BC in individuals with these truncating, splice, or deletion mutations in PALB2 is unknown.

Prof Antoniou observed that ideal studies would compare patients with and without mutations, but because, as Dr Arun noted, many of these mutations are rare and large sample sizes are required for accurate risk assessment. Most studies are cohort studies where mutations are identified in selected patients who have BC or family history of BC. Phenotype and genotype information is collected, and family members are considered a prospective cohort and are used to estimate cancer risk, but this method is subject to bias. Genome-wide association studies are ongoing in women with BC mutations, and these will one day contribute to a more complete risk assessment model.

MD CONFERENCE EXPRESS®

The editors would like to thank the many members of the San Antonio Breast Cancer Symposium presenting faculty who generously gave their time to ensure the accuracy and quality of the articles in this publication.