Population-Based BRCA1/2 Testing in Ashkenazi Jews: Ready for Prime Time

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Deleterious mutations in the BRCA1 and BRCA2 genes are associated with a markedly elevated risk of early-onset breast and ovarian cancer. Mutation carriers have up to a 70% risk of breast cancer and an 11% to 40% risk of ovarian cancer by age 70 years.1–3 Germline testing for these genes provides an opportunity to reduce morbidity and mortality by allowing for appropriate integration of risk reduction and screening options. Studies evaluating the efficacy of these prophylactic strategies in patients with BRCA1/2 mutation have confirmed that risk-reducing bilateral salpingo-oophorectomy (RRSO) is associated not only with a reduction in cancer risk but, most importantly, with a significant reduction in cancer-specific and all-cause mortality. Compared with women who did not undergo RRSO, those who had the surgery had lower all-cause mortality (10% vs 3%; hazard ratio [HR], 0.40; 95% CI, 0.26–0.61), breast cancer–specific mortality (6% vs 2%; HR, 0.44; 95% CI, 0.26–0.76), and ovarian cancer–specific mortality (3% vs 0.4%; HR, 0.21; 95% CI, 0.06–0.8).4 Markov modeling suggests that a healthy 30-year-old woman with the mutation would gain 0.2 to 1.8 years in life expectancy with RRSO and 0.6 to 2.1 years from risk-reducing mastectomies.5,6

Additionally, risk-reducing surgeries have been shown to be the most cost-effective measures. Using costs, life-years (LY), and quality-adjusted life-years (QALY) as outcomes, a study that compared preventive surgery, chemoprevention, MRI, and mammography showed that prophylactic surgeries were associated with the lowest overall cost and the longest survival in LYs, dominating all other strategies.5 Thus, testing for BRCA1/2 mutations meets the ultimate goal of a screening test: it saves lives.

Unfortunately, many mutation carriers are only identified after their first cancer diagnosis. This is often because they have few female relatives or because their family history was not striking enough to warrant testing. However, it is clear that for genetic testing to have its greatest impact, it should occur before a carrier develops cancer. This argument forms the basis for considering population-based genetic testing.7 Concerns about this approach have focused on an expected increase in the rate of identification of variants of unknown significance (VUS) causing anxiety and uncertainty; a lack of clarity regarding the cancer risks in carriers without a strong family history of cancer; the accuracy of interpretation of negative results; the ability of the current model of genetic counseling practices to deal with the increase in patient volume; and the cost-effectiveness of such an approach.8,9

One way of minimizing the identification of VUS, the impact of false-negatives, and financial concerns is to focus population-based testing on groups with known founder mutations, such as individuals of Ashkenazi Jewish (AJ), Icelandic, or French-Canadian descent.10–13 The advantage of such an approach is that, in these populations, the founder mutations often account for the majority of mutations identified. Additionally, this more narrowed testing reduces cost and decreases the likelihood of detecting a VUS. For example, in Ashkenazi Jews, 2 BRCA1 mutations (185delAG and 5382insC) and 1 BRCA2 mutation (6174delT) have been found in approximately 1 in 40 individuals (2.5%). Importantly, these account for 90% of the mutations identified in this ethnic group.14–18

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Population-Based Testing: Cancer Risks and Detection Rate

The data regarding cancer risks in women with BRCA1/2 mutations have primarily been derived from studies performed in individuals with a very strong family history of malignancy. Thus, questions have arisen as to whether carriers identified through population testing rather than because of family history would harbor similarly elevated risks for cancer.

A recent study involving 8,195 men from Israel with AJ heritage unselected for family history attempted to address this issue. In this study, men were tested to avoid bias related to previous diagnosis of cancer, thus enabling female carriers to be identified based on their relationship and not family or personal history of cancer. For each of the 175 men identified as having a BRCA1/2 mutation, genetic testing was offered to all of their female relatives. Among the 431 female relatives tested, 211 were found to harbor deleterious mutations. The cumulative risks of developing either breast or ovarian cancer by age 60 and 80 years, respectively, were 0.60 (±0.07) and 0.83 (±0.07) for BRCA1 carriers and 0.33 (±0.09) and 0.76 (±0.13) for BRCA2 carriers, rates very similar to those quoted in the literature. Of note, half of the families found to carry a deleterious mutation did not have a clinical history that would otherwise meet criteria for referral for genetic testing.

Other studies have confirmed that substantial numbers of carriers would have been missed if population-based testing was not performed. In a randomized trial comparing family history and population-based approaches for BRCA1/2 testing, individuals from the AJ British population were offered standard pretest genetic counseling and then randomized either to undergo genetic testing only if they met clinical criteria based on family history or to a population-based testing arm in which all participants were offered genetic testing. Of 1,017 individuals eligible for analysis, 13 with the mutation were identified in the population-screening arm and 9 in the family history–based testing arm. The overall BRCA1/2 prevalence detected was 2.45% (95% CI, 1.31–4.16). In this study, 56% of those positive for mutation would not have been detected based on conventional family history approach. Additionally, population-based testing saved 0.09 more LY compared with family history–based testing, resulting in an overall reduction in treatment costs estimated at 3.7 million British pounds (approximately 5.5 million US dollars).

In a similar study performed in Ontario, Canada, 2,080 (Ashkenazi or Sephardic) Jewish women unselected for personal or family history of cancer were recruited through an article in a national newspaper. Twenty-two women were identified as having one of the founder mutations. Significantly, only 10 (45%) of these women would have qualified for genetic testing based on the guidelines for testing in the province of Ontario. Testing was then offered to these women’s first-degree relatives, and 3 were found to be obligate carriers and an additional 8 were found to carry a deleterious mutation.

All 3 of these trials suggest that approximately half of the people with mutations in this population would not have been identified if only standard criteria for testing had been used.

Impact and Feasibility of Population-Based BRCA1/2 Testing

Studies performed in high-risk clinics have shown that genetic testing does not adversely impact the psychological status of individuals found to carry a BRCA1/2 mutation, but whether these findings apply to individuals identified through population
testing is unclear. The population-based British study assessed the psychological impact of BRCA1/2 testing,20 and found no statistically significant differences between the carriers identified in the family history–based arm and the population screening arm in terms of anxiety, depression, health anxiety, distress, uncertainty, and quality of life, evaluated at 7 days and at 3 months.

Additionally, in the population-based study performed in Ontario,21 a streamlined approach to genetic testing was provided. In this study, women did not undergo standard in-person pretest counseling but rather received a brochure that outlined basic information about the genetics of BRCA1 and BRCA2, implications of testing, and management options for mutation carriers. Negative test results in women without significant family history were sent by mail. In women with negative test results but a significant family history, the result was communicated over the phone by a genetic counselor and followed by a letter summarizing cancer risks and surveillance recommendations. In the event of a positive test result, the result was disclosed by phone, but a follow-up in-person session was promptly scheduled. As expected, cancer-related distress increased in women identified as carrying the mutation, but diminished only slightly in those without a mutation. More than 92% of women were satisfied with the testing process.26 Additionally, uptake of appropriate surveillance and prevention options was seen among women with a positive test result. Within 1 year of receiving their test result, 100% underwent an MRI, and within 2 years, 11% had undergone prophylactic mastectomy and 90% underwent RRSO.27

Conclusions

The work described in this commentary clearly shows both the feasibility and the impact of population-based testing in individuals of AJ descent. Individuals of AJ descent who are identified through population-based screening have been demonstrated to have the same cancer risks as those identified based on the strength of their personal or family history, and those with mutations have a high uptake of cancer screening and risk-reducing options. Additionally, population-based testing has been shown to be feasible, and such testing importantly results in a doubling of the numbers of carriers identified. Based on all of these factors, we believe that the time has come to offer population-based testing to individuals of AJ descent. Mechanisms must exist to provide appropriate pretest and posttest genetic counseling. Further efforts are needed to validate alternatives to traditional genetic counseling and to address the potential insurance and other barriers to testing.

References