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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}

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.¹⁹ 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.²⁰ 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.²¹ 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,^{22–25} 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

1. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family: a combined analysis of 22 studies. *Am J Hum Genet.* 2003; 72:1117–1130. [PubMed: 12677558]
2. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol.* 2007; 25:1329–1333. [PubMed: 17416853]
3. Mavaddat N, Peock S, Frost D, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. *J Natl Cancer Inst.* 2013; 105:812–822. [PubMed: 23628597]
4. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA.* 2010; 304:967. [PubMed: 20810374]
5. Grann VR, Patel PR, Jacobson JS, et al. Comparative effectiveness of screening and prevention strategies among BRCA1/2 affected mutation carriers. *Breast Cancer Res Treat.* 2011; 125:837–847. [PubMed: 20644999]
6. Schrag D, Kuntz KM, Garber JE, et al. Life expectancy gains from cancer prevention strategies for women with breast cancer and BRCA1 and 2 mutations. *JAMA.* 2000; 283:617–624. [PubMed: 10665701]
7. King MC, Levy-Lahad E, Lahal A. Population-based screening for BRCA1 and BRCA2: 2014 Lasker Award. *JAMA.* 2014; 312:1091–1092. [PubMed: 25198398]
8. Yurgelan MB, Hiller E, Garber J. Population-wide screening for germline BRCA1 and BRCA2 mutations: too much of a good thing? *J Clin Oncol.* 2015; 33:3092–3095. [PubMed: 26282646]
9. Long EF, Ganz PA. Cost-effectiveness of universal BRCA1/2 screening: evidence-based decision making. *JAMA Oncol.* 2015; 1:1217–1218. [PubMed: 26335890]
10. Szabo CI, King MC. Population genetics of BRCA1 and BRCA2. *Am J Hum Genet.* 1997; 60:1013. [PubMed: 9150148]
11. Ferla R, Calò V, Cascio S, et al. Founder mutations in BRCA1 and BRCA2 genes. *Ann Oncol.* 2007; 18(Suppl 6):vi93. [PubMed: 17591843]
12. Ghadirian P, Robidoux A, Zhang P, et al. The contribution of founder mutations to early-onset breast cancer in French-Canadian women. *Clin Genet.* 2009; 76:421–426. [PubMed: 19863560]
13. Thorlacius S, Sigurdsson S, Bjarnadottir H, et al. Study of a single BRCA2 mutation with high carrier frequency in a small population. *Am J Hum Genet.* 1997; 60:1079–1084. [PubMed: 9150155]
14. Roa BB, Boyd AA, Volcik K, Richards CS. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nat Genet.* 1996; 14:185–187. [PubMed: 8841191]
15. Kauff ND, Perez-Segura P, Robson ME, et al. Incidence of non-founder *BRCA1* and *BRCA2* mutations in high risk Ashkenazi breast and ovarian cancer families. *J Med Genet.* 2002; 39:611–614. [PubMed: 12161607]
16. Phelan CM, Kwan E, Jack E, et al. A low frequency of non-founder BRCA1 mutations in Ashkenazi Jewish breast-ovarian cancer families. *Hum Mutat.* 2002; 20:352–357. [PubMed: 12402332]
17. Frank TS, Deffenbaugh AM, Reid JE, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. *J Clin Oncol.* 2002; 20:1480–1490. [PubMed: 11896095]
18. Rosenthal E, Moyes K, Arnell C, et al. Incidence of BRCA1 and BRCA2 non-founder mutations in patients of Ashkenazi Jewish ancestry. *Breast Cancer Res Treat.* 2015; 149:223–227. [PubMed: 25476495]

19. Gabai-Kapara E, Lahad A, Kaufman B, et al. Population-based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. *Proc Natl Acad Sci USA*. 2014; 111:14205–14210. [PubMed: 25192939]
20. Manchanda R, Loggenberg K, Sanderson S, et al. Population testing for cancer predisposing BRCA1/BRCA2 mutations in the Ashkenazi-Jewish community: a randomized controlled trial. *J Natl Cancer Inst*. 2014; 107:379. [PubMed: 25435541]
21. Metcalfe KA, Poll A, Royer R, et al. Screening for founder mutations in BRCA1 and BRCA2 in unselected Jewish women. *J Clin Oncol*. 2010; 28:387–391. [PubMed: 20008623]
22. Christie J, Quinn GP, Malo T, et al. The cognitive and psychological impact of BRCA genetic counseling in before and after definitive surgery breast cancer patients. *Ann Surg Oncol*. 2012; 19:4003–4011. [PubMed: 22766984]
23. Butow PN, Lobb EA, Meiser B, et al. Psychological outcomes and risk perception after genetic testing and counselling in breast cancer: a systematic review. *Med J Australia*. 2003; 178:77–81. [PubMed: 12526728]
24. Schlich-Bakker KJ, ten Kroode HF, Ausems M. A literature review of the psychological impact of genetic testing on breast cancer patients. *Patient Educ Couns*. 2006; 62:13–20. [PubMed: 16242293]
25. Schwartz MD, Peshkin BN, Hughes C, et al. Impact of *BRCA1/2* mutation testing on psychologic distress in a clinic-based sample. *J Clin Oncol*. 2002; 20:514–520. [PubMed: 11786581]
26. Metcalfe KA, Poll A, Llacuachaqui M, et al. Patient satisfaction and cancer-related distress among unselected Jewish women undergoing genetic testing for BRCA1 and BRCA2. *Clin Genet*. 2010; 78:411–417. [PubMed: 20653694]
27. Metcalfe KA, Mian N, Enmore M, et al. Long-term follow-up of Jewish women with a BRCA1 and BRCA2 mutation who underwent population genetic screening. *Breast Cancer Res Treat*. 2012; 133:735–740. [PubMed: 22240989]

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