Precision Medicine Meets Public Health: Population Screening for BRCA1 and BRCA2

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Mutations in BRCA1 and BRCA2 were first discovered in the mid-1990s in families with multiple cases of breast and ovarian cancer and remain the major cause of inherited susceptibility to these malignancies (1). At first, testing for mutations in these genes was limited to women with cancer diagnosis at a young age or with a substantial family history, bilateral breast cancer, or both breast and ovarian cancer (2). Mounting evidence that BRCA1 and BRCA2 mutations account for a substantial proportion of breast and ovarian cancer (3,4), combined with emerging therapies based on BRCA1 or BRCA2 genotype (5), led to expansion of referral criteria to include many women with breast or ovarian cancer upon diagnosis (6).

Among cancer-free women, however, family history has remained the criterion of referral for genetic assessment. The US Preventive Services Task Force (USPSTF) recently reiterated its recommendation against BRCA1 and BRCA2 testing for healthy women in the absence of family history of cancer (7). This recommendation was based on the lack of data on cancer risks among BRCA1 and BRCA2 mutation carriers in the general population, as opposed to mutation carriers in severely affected families (8).

This data gap has now been filled. In a recent population-based demonstration project, we showed that BRCA1 and BRCA2 mutation carriers identified from the general population, regardless of family history of breast or ovarian cancer, have very high risks: by age 80 years, risk for either breast or ovarian cancer was 83% (±7%) for BRCA1 mutation carriers and 76% (±13%) for BRCA2 mutation carriers, and these risks were even higher in more recent birth cohorts (9).

Both these high risks and a second compelling reason invite reconsideration of recommendations for genetic testing of BRCA1 and BRCA2 among healthy women: some 50% of women with BRCA1 or BRCA2 mutations detected at cancer diagnosis do not meet family history criteria for testing. These women are identified as mutation carriers only after they become affected (3,10). Identifying a woman’s high risk of cancer only after she is diagnosed with it is an obvious failure of cancer prevention. Together, these considerations set the stage for population screening of BRCA1 and BRCA2 (11). In this issue of the Journal, Manchanda et al. explore two translational aspects of BRCA population screening: offering testing regardless of family history (12), and a cost-effectiveness analysis of this testing strategy (13).

Our population-based demonstration project (9) and the studies by Manchanda et al. (12,13) were carried out in the Ashkenazi Jewish population (in Israel and in the United Kingdom, respectively) because in this population nearly all BRCA1- and BRCA2-based cancer risk is explained by only three mutations with combined prevalence of one in 40 persons (2.5%) (14). In the Ashkenazi Jewish population, screening for BRCA1 and BRCA2 fulfills World Health Organization criteria (15): Carriers are at high risk regardless of family history (9), and interventions, including risk-reducing salpingo-oophorectomy (RSO) and mastectomy (RRM), have been shown to reduce morbidity and mortality (16,17). Manchanda et al. thus addressed the next step: implementation of a screening program.

All participants in the UK implementation trial (12) were offered traditional pretest genetic counseling, and then were randomly assigned to a population screening arm where all participants were offered genetic testing, or to a family history arm where only those meeting current family history criteria were offered genetic testing. Based on the frequency of mutation carriers in each trial arm and the proportion of mutation carriers who fulfilled family history criteria, the investigators estimated that 56% of carriers would not have been identified if family history criteria had been applied to everyone. Their results are consistent with our observation that 51% of families harboring BRCA1 or BRCA2 mutations had little or no history of breast or ovarian cancer, despite high risks to women carriers in these families (9).

The random assignment design used by Manchanda et al. enables direct comparison of the efficiency and total yield of population vs family history–based testing. Family history–based
testing is obviously more efficient, because it is limited to the small proportion (13%) of individuals most likely to harbor mutations (12). However, the price of this efficiency is that over half of carriers would not be identified and so could not undertake preventive or surveillance measures. Many would go on to develop breast or ovarian cancer.

Would the marginal cost of extending testing to the entire population be offset by reduced morbidity and mortality achieved by identifying many more carriers? Using cost-effectiveness analysis, the investigators show that population screening was highly cost-effective compared with the current family history-based approach (13). The incremental cost-effectiveness ratio (ICER) was $3,500 per quality-adjusted life-year (QALY), well below the NICE effectiveness threshold of $22,000 to $48,000 per QALY. Strengths of this cost-effectiveness analysis include that it incorporated results of the implementation trial (12), that it was based on true costs and health outcomes, and that an extensive sensitivity analysis was performed. Population screening remained cost-effective over a wide range of scenarios, using extreme estimates of cost and other parameters. Population screening also remained effective if women were tested only at age 50 years or older, the ages of the implementation trial participants. These results are encouraging, but will require adjustment for countries with different health systems and cancer screening recommendations (18).

Conclusions from these implementation studies are that population screening enables much more complete identification of carriers, cost effectively and without substantial psychological harm. These results also suggest areas for further research. Cancer prevention will be most successful if mutation carriers are detected in their early 30s, when they should begin surveillance, and certainly before the time for RRSO at age 40 years. Also, genetic counseling strategies should be developed that enable large scale testing. It may be effective to use a variety of pretest counseling approaches (e.g., phone, web, or written material [19,20]), and to reserve traditional post-test counseling for mutation carriers and other women at high risk. Furthermore, wherever screening is implemented, outcome studies will be important to measure program success (15).

Finally, the Ashkenazi Jewish population has served as a model for genetic epidemiology of BRCA1 and BRCA2, based on this population’s high prevalence of three easily tested mutations. It will likely continue to be a model group for population-wide screening. Nonetheless, with the advent of sequencing technologies that enable rapid complete sequencing of both genes, the time has come to consider and test similar approaches in other populations as well (11). The ability to detect inherited cancer predisposition offers unprecedented prospects for cancer prevention. It is time to cast a wider net to provide this opportunity.

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References