

VIEWPOINT

Population-Based Screening for *BRCA1* and *BRCA2* 2014 Lasker Award

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The 2014 Lasker-Koshland Special Achievement Award in Medical Science has been presented to Dr Mary-Claire King to recognize and honor her "for bold and imaginative contributions to medical science and society – exemplified by her discovery of a single gene BRCA1 that causes a ... form of hereditary breast cancer ..." This Viewpoint describes the application of that discovery, and suggests that population-based screening of women for BRCA1 and BRCA2 should become a routine part of clinical practice.

Inherited mutations in *BRCA1* and *BRCA2* predispose to extremely high risks of breast and ovarian cancer. But these risks are not immutable. Among women who carry mutations in *BRCA1* or *BRCA2*, surgical intervention, in particular risk-reducing salpingo-oophorectomy, reduces risk of both ovarian and breast cancer and reduces overall mortality.¹ However, many women with mutations in these genes are identified as carriers only after their first cancer diagnosis because their family history of cancer was not sufficient to suggest genetic testing.² To identify a woman as a carrier only *after* she develops cancer is a failure of cancer prevention.

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to every woman, at about age 30, in the course of routine medical care. Women with cancer-predisposing mutations in *BRCA1* and *BRCA2* are a high-risk group in whom special screening and counseling can be focused.

World Health Organization criteria for population screening for genetic predisposition to disease are that the disease is an important public health burden in the target population; that the risk of disease due to mutations in the screened genes is known; and that effective interventions exist to reduce morbidity and mortality among genetically susceptible individuals.⁴ At present, the US Preventive Services Task Force (USPSTF) supports *BRCA1* and *BRCA2* testing based on family history and ancestry, but not for the entire female population, given the lack of data on risks for mutation carriers ascertained from the general population, rather than through a personal or family history of cancer.⁵ This position was correct based

on the data then available. However, a just-completed study now provides evidence that supports offering *BRCA1* and *BRCA2* sequencing to all women.

To determine cancer risks to *BRCA1* and *BRCA2* mutation carriers identified from the general population, we conducted a study of population-based screening in the Ashkenazi Jewish population of Israel.⁶ This population was selected because its limited number of cancer-predisposing *BRCA1* and *BRCA2* mutations made the study feasible before next-generation sequencing platforms were in place. Families were identified by recruiting more than 8000 healthy Ashkenazi Jewish men. Each male index participant was screened for 3 loss-of-function mutations that collectively account for the great majority of inherited cancer risk due to *BRCA1* and *BRCA2* in this population. *BRCA1* and *BRCA2* mutations are equally common in women and men and are inherited equally from mothers and from fathers. Men were tested as a gateway to families because men were unaffected by breast cancer themselves, thus enabling female mutation carriers to be identified only by relationship to a healthy male relative, not based on their personal or family history of cancer. By multiple criteria, the index men were representative of their population with respect to mutation prevalence and family history. For each of the 175 men identified as a carrier of a mutation in *BRCA1* or *BRCA2*, genetic testing was offered to all female relatives.

Women ascertained in this way, and found to carry a mutation in *BRCA1* or *BRCA2*, had very high cancer risks. For *BRCA1* mutation carriers, the combined risk of developing either breast or ovarian cancer was 60% ($\pm 7\%$) by age 60 and 83% ($\pm 7\%$) by age 80. For *BRCA2* mutation carriers, risk was 33% ($\pm 9\%$) by age 60 and 76% ($\pm 13\%$) by age 80. Furthermore, these risks were significantly higher, at every age, among women born more recently than among women born earlier, a birth cohort effect also seen in prior studies. This trend likely reflects increasing prevalence of nongenetic risk factors for breast cancer, including earlier age of menarche and later ages of childbearing, factors related to improved nutrition and education for women in modern society. Notably, 50% of families found to harbor *BRCA1* or *BRCA2* mutations had no history of breast or ovarian cancer that would have triggered clinical attention. Female mutation carriers from these low-cancer-incidence families had similar cancer risks to female carriers from families with high cancer incidence. Low-cancer-incidence families were simply smaller, with fewer females who inherited *BRCA1* or *BRCA2* mutations, and hence fewer females

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who developed breast or ovarian cancer. Absent population-wide screening, women with *BRCA1* or *BRCA2* mutations from such families would not have been identified until they developed cancer.

The population-based study in Israel has implications for public health and prevention strategies in the United States. Large-scale population screening for *BRCA1* and *BRCA2* mutations was feasible, and cancer risks for women with mutations were high, with greater risks for mutation carriers in more recent birth cohorts. Nonetheless, major questions arise in generalizing from the results of the study in Israel to population-based screening in the United States or any other country. An obvious difference is the vast number of cancer-predisposing mutations in *BRCA1* and *BRCA2* in the US population. Thousands of *BRCA1* and *BRCA2* mutations with unambiguously severe effects on cancer risk have been identified, nearly all of which truncate or delete their host gene.³ In addition, a dozen or so amino acid substitutions have been proven experimentally to lead to loss of function of either *BRCA1* or *BRCA2* and to predispose to breast and ovarian cancer, whereas the great majority of amino acid substitutions in both genes are benign.

Testing for *BRCA1* and *BRCA2* should focus solely on unambiguously loss-of-function mutations with definitive effect on cancer risk. With modern genomics tools, it is possible to identify all variants in any gene. The challenge is not identification, but interpretation, of making sense of what is identified. Thus far, cancer genetic testing has responded poorly to this challenge, specifically in reporting large numbers of VUS (variants of unknown significance). A VUS can increase confusion and compromise clinical management; for population-based screening, these variants should not be reported. Multi-institution collaborative efforts are under way to evaluate and catalog the clinical significance of all possible variation in *BRCA1* and *BRCA2*. If any VUS ultimately proves causal for breast or ovarian cancer, it should be integrated into future testing. Meanwhile, waiting for a perfect test denies women excellent resources that are now available.

This view reflects that of the American College of Medical Genetics, which recommends that for persons undergoing exome sequencing for any condition, including for conditions other than cancer, laboratories report all unambiguous loss-of-function mutations in *BRCA1* and *BRCA2* that are identified by chance (ie, incidental findings), because these mutations are medically actionable.⁷

In addition to *BRCA1* and *BRCA2*, other genes involved in DNA repair by homologous recombination harbor mutations that in-

crease risk of breast and ovarian cancer. For some of these genes, such as *PALB2*, the spectrum and risks associated with loss-of-function mutations are well characterized.⁸ Furthermore, genomic technology enables simultaneous screening for many genes as easily as for 2. Nonetheless, because there is 2 decades more experience with *BRCA1* and *BRCA2* than with most other breast cancer genes, we suggest that population-based screening begin with *BRCA1* and *BRCA2*, with the important understanding that women from severely affected families be tested for all known breast and ovarian cancer genes.⁹ As population-based screening for *BRCA1* and *BRCA2* among adult women becomes a routine part of clinical practice, other genes are expected to be phased into the process.

Population-based screening enables mutation carriers to be identified independent of physician referral or family involvement. This is important, because at present, there is marked variability in practice in following USPSTF guidelines. A recent survey revealed that only 19% of US primary care physicians accurately assessed family history for *BRCA1/BRCA2* testing.¹⁰ In our study in Israel, only 35% of families with high incidence of breast or ovarian cancer had been previously referred for genetic counseling, despite common knowledge of the increased risk due to *BRCA1* and *BRCA2* in the Ashkenazi Jewish population and the availability of free testing and counseling in the Israeli health system. Population-based screening circumvents these barriers.

Both the number and frequency of *BRCA1* and *BRCA2* mutations vary among populations, and many mutations are private, found in only one or a few families. In the United States as a whole, the number of carriers of actionable mutations in *BRCA1* and *BRCA2* carriers is estimated to be between 1 in 300 and 1 in 500 women,⁶ or between 250 000 and 415 000 adult women for whom breast and ovarian cancer is both highly likely and potentially preventable. With modern genomics tools, all actionable mutations can be readily identified. Intensive monitoring and early intervention protocols reduce risk in carriers. Sufficient knowledge is available to allow women to make informed decisions.

Population-wide screening will require significant efforts to educate the public and to develop new counseling strategies, but this investment will both save women's lives and provide a model for other public health programs in genomic medicine. Women do not benefit by practices that "protect" them from information regarding their own health. They should have the choice to learn if they carry an actionable mutation in *BRCA1* or *BRCA2*.

ARTICLE INFORMATION

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