

BRCA1/2 population screening: embracing the benefits

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Whether all adult Ashkenazi women should be offered population screening for recurrent *BRCA1* and *BRCA2* founder mutations is an important question to me both personally as an Ashkenazi Jewish woman and professionally. I was a junior faculty member and a newly certified medical geneticist in 1995 when I participated in the first research study offering 185delAG mutation testing (the other two founders weren't known at the time) to the Ashkenazi Jewish community in Houston¹.

Many colleagues expressed significant concern about the potential risks of that approach. One risk was that the individuals who were negative would have a false sense of security. However, we demonstrated over 2 years of follow-up that mammography behavior didn't change². The concerns expressed for the individuals who tested positive included the fact that no accepted intervention was available, and the risk of cancer associated with *BRCA1* mutations wasn't really known (true enough in 1997). There was also an assumption that identifying mutation carriers based on a positive family history would be easy and that community screening was unnecessary.

By 2003, many, many additional studies had been conducted. One study of note was the New York Breast Cancer Study, which reported that 10% of 1008 unselected Ashkenazi Jewish breast cancer patients carried a *BRCA1/2* founder mutation³. Most important to the argument for population screening, the authors found that, before their diagnosis, 50% of those women would not have undergone genetic testing based on their family history. Requiring a family history before testing missed half the women who would in fact go on to develop breast cancer. Based on those results and the development, in the interim, of effective prophylactic oophorectomy surgery recommendations for *BRCA1/2* carriers, my colleague Ephrat Levy Lahad and I cautiously recommended consideration of population screening for adult women in the Ashkenazi Jewish population⁴.

Despite ongoing research, doubts about population screening continued to be expressed. In 2008, the American College of Medical Genetics declined to include *BRCA1/2* testing in their recommendations for reproductive screening of the Ashkenazi Jewish population, offering doubts similar to those from 1997: "However, the penetrance of these mutations is not fully understood and adequate laboratory and clinical resources for performing the testing and genetic counseling are not currently

available. The possibility of lower cancer risks among unselected patients remained"⁵.

To further address those concerns, Levy-Lahad and colleagues went on to complete a multi-year study of cancer risk in the Israeli Ashkenazi population starting with 8105 unselected Jewish men⁶. Analysis of cancer diagnoses in relatives of the men who tested positive again revealed a very significant risk of breast and ovarian cancer. That work led to the recent development of an Ashkenazi founder mutation population-screening program in Israel. In addition, in 2014, Mary Claire King, Ephrat Levy-Lahad, and Amnon Lahad recommended population screening for both founder and non-founder *BRCA1/2* mutations in the United States⁷. In contrast, the U.S. Preventive Services Task Force gave a grade of "D" to *BRCA1/2* testing in the absence of family history, although it did not provide a specific recommendation on founder mutation screening in Ashkenazi women⁸.

In this issue of *Current Oncology*, Steven Narod and colleagues describe their 7-year experience offering founder mutation screening to more than 7000 Ashkenazi Jewish adults in the Ontario region of Canada (at a cost of \$100 per test)⁹. They provided a more streamlined form of patient education about the test than standard genetic counselling provides. Less-intensive counselling has been found to be effective in other studies¹⁰. Again, a significant portion of the individuals found to be positive during screening did not meet current genetic testing guidelines. Most importantly, the study is one of the first to describe long-term follow-up of a large number of positive individuals offered genetic testing based on their Ashkenazi Jewish status. The investigators report that 100% of the women who tested positive underwent breast magnetic resonance imaging in the subsequent year, and 90% underwent prophylactic oophorectomy within 2 years. Thus, the genetic information provided was rapidly incorporated into health care decisions. Similarly, two recent studies from the United Kingdom also argued that population screening of Ashkenazi individuals was cost-effective, and again, 56% of identified mutation carriers would not have met family history criteria for genetic testing^{11,12}.

Perhaps, 20 years on from the identification of the three Ashkenazi Jewish *BRCA1/2* founder mutations, it is time to embrace the potential benefits of population screening as documented in multiple studies. We should not continue to focus almost exclusively on the potential risks. The

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risks have been well described, but where are the data that describe how the risks outweigh the benefits? The original concern that identifying carriers was not medically helpful has been contradicted. Prophylactic oophorectomy has been demonstrated in multiple studies to lower mortality from cancer (see, for example, Kauff *et al.*¹³). Finally, the concern that the public won't understand this type of testing or the associated cancer risks was not seen in Ontario and has been succinctly contradicted by Angelina Jolie and the public's response to her statements in *The New York Times*^{14,15}.

The remaining obstacles to population screening are those of cost and appropriate staffing or counselling guides. Instituting population screening in the United States without a national health care system (such as in Canada or Israel) will be more challenging. Insurance coverage of genetic testing will likely begin only if a guideline from a professional medical organization recommends population screening. But, there were obstacles when population screening for Tay–Sachs carriers was first recommended in the 1970s, and medical professionals and the Ashkenazi Jewish community found ways to overcome those barriers to effectively perform population screening and drastically reduce births of children with Tay–Sachs disease¹⁶. I hope that, in 2015, professional societies will thoughtfully embrace the potential benefits of adult population screening for Ashkenazi founder mutations in *BRCA1* and *BRCA2*, with the goal of decreasing the untimely death of individuals from breast and ovarian cancer.

CONFLICT OF INTEREST DISCLOSURES

I have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and I declare the following interests: I am an employee of Baylor College of Medicine (BCM). In 2015, BCM and Miraca Holdings, Inc. formed a joint venture with shared ownership and governance of the clinical genetics diagnostic laboratories. I sit on the Scientific Advisory Board of Baylor Miraca Genetics Laboratories.

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