CURRENT ONCOLOGY COMMENTARY

Is it time to offer *BRCA1* and *BRCA2* testing to all Jewish women?

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It was 2007 when Women's College Hospital first began to test for *BRCA1* and *BRCA2* mutations among all Jewish women in Ontario. On a research basis, testing was performed regardless of personal or family history of cancer for three recurrent Jewish founder *BRCA* mutations[1]. To date, more than 7000 women have been tested, and the program remains active. Recently, two studies have supported the conclusion that population-based testing is a rational approach to identifying *BRCA* mutation carriers. In an Israeli study of 8105 unselected Jewish men[2] and a British study of 1034 unselected Jewish men and women[3], more than one half of the identified mutation carriers failed to qualify for genetic testing based on family history. Much in the news, Mary-Claire King has highlighted the results of the Israeli study to support the position that genetic testing for *BRCA1* and *BRCA2* should be offered to all women, and not just to Jews[4]. Her recommendation is based on the finding that the cancer risks associated with a *BRCA* mutation are high even in the absence of a family history of cancer[2]. Critics of population-based testing say that more research has to be done before that recommendation can be entertained.

Over the course of the past 10 years, our group has tried to accumulate evidence to answer the relevant questions. Dr. Robert Nuttall, assistant director of cancer control policy at the Canadian Cancer Society, told *The Canadian Jewish News* that "while genetic screening can identify women at high risk for cancer, there are still questions that need to be addressed before genetic screening is made available to the Ashkenazi Jewish population." Here, we address his questions.

Who Constitutes the Appropriate Target Population?

Considered together, two mutations in *BRCA1* and one mutation in *BRCA2* are present in up to 2.5% of Ashkenazi Jewish women[5,6]. Those three mutations represent a preponderance of the deleterious mutations in the Jewish population[7,8]. Genetic testing for the "founder" panel is relatively straightforward and inexpensive. In our study of more than 6000 unselected Jewish women, only 38% of the women who were found to have a *BRCA* mutation would have qualified for genetic testing based on current genetic testing guidelines[7]. That finding was recently confirmed in Israel and Britain[2,8]. Most women with mutations are not being identified because of a historical reliance on personal and family history of cancer—a policy that goes back to the 1990s and that fails to take into account advances in molecular techniques.

Our experience is Ontario-based, but should be relevant for Jewish populations elsewhere. The utility of testing will depend to a large degree on the cost of the test provided and of the regional health care system. We do not argue that costs must be covered by a third-party payer (for example, the Canadian public health care system); it could be that the most efficient delivery of services will be based on direct-to-consumer testing offered by a private laboratory. Various scenarios should be explored.

Other ethnic populations in Ontario and elsewhere could also potentially benefit from testing (Bahamian, Polish, Icelandic groups, for example); however, it is not our goal to deal with those groups here. (French-Canadians, who are also characterized by a small number of founder mutations, are also of particular interest, and in fact, eligible individuals in Quebec can receive genetic testing for those mutations.) It may be that, in the future, other groups in Ontario (and elsewhere in Canada) will qualify for testing, but that expectation does not imply that Jewish women should not be tested until complete knowledge of the ethnic distribution of mutations in the country is available. It might also prove to be efficacious to offer testing to Jewish men, but the evidence is, at present, insufficient to consider that particular case.

What Is the Appropriate Age for Testing?

We are guided by a policy stating that any adult woman (18 years and older in Ontario) should be able to access testing on her own initiative. That is, we do not think it ethically justifiable to restrict testing based on age alone. However, in current practice, we generally do not promote testing to women less than 25 years of age.

To prevent cancer, predisposed individuals have to be identified before cancer develops. In our dataset of *BRCA* mutation carriers, fewer than 1% of breast cancers are found to develop before age 25, and 7% develop before age 30. We estimate the risk of breast cancer for *BRCA1* carriers to be 0.7% by age 25 and 3.5% by age 30 (Narod SA. Personal communication). Between the ages of 25 and 30, the annual risk for breast cancer in a *BRCA1* carrier is 0.7%. Those risk levels justify the policy of making testing available to woman more than 25 years of age. In Ontario, magnetic resonance imaging (MRI) breast screening programs for high-risk individuals begin at age 30.

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At What Point Should Individuals Be Offered Genetic Counselling?

It is impractical to offer intensive genetic counselling to 100 women having no family history with the expectation that only 2 will be positive. We propose that Jewish women without a significant family history who are contemplating genetic testing for *BRCA1/2* should have access to accurate information about the risks and benefits of testing. Intensive counselling should be limited to those with cancer, those with a family history of cancer, or those with a known mutation in the family. Once a mutation is identified, the family will be counselled using the same protocols in place in the recently expanded network of cancer genetics clinics throughout Ontario. Nevertheless, it is prudent to offer relevant information to, and to respond to questions from, any woman undergoing a *BRCA* test. Various models have been proposed, including telephone counselling, group counselling, and Internet portals.

We evaluated a model of genetic counselling in our study of population-based testing[9]. The counselling consists of providing a detailed brochure on *BRCA1* and *BRCA2,* which includes information about options available to reduce the cancer risk if a mutation is detected. If a woman is negative for the three Jewish *BRCA* mutations and if she has no significant family history of breast or ovarian cancer, she receives her negative genetic test result by mail. If a woman is negative for the genetic tests, but has a moderate or strong family history of breast or ovarian cancer, the result is given by telephone by a genetic counsellor, and a follow-up letter is sent. The letter summarizes the individual's breast cancer risk and provides recommendations for surveillance. If a woman has a positive genetic test, the result is disclosed by telephone by the genetic counsellor, and the woman is invited to a full genetic counselling session within 3 days of receiving her result. Notably, all women in the latter category returned for an in-person counselling session. More than 90% of the women, those with and without a *BRCA* mutation alike, were satisfied with the genetic testing process[9]. If population-based genetic testing for *BRCA1* and *BRCA2* is proposed to be offered, it will be critical to consider nontraditional modes of genetic counselling.

How Significant and Important Are the Psychosocial Effects of Screening?

The provision of Jewish population–based *BRCA* testing leads to 98% of women receiving a negative test result, and there is no compelling reason to suppose, or empirical evidence to suggest, that those women will suffer adverse psychological consequences—as we observed in our study[9]. Our concern resides with those testing positive for a mutation.

In clinic-based studies, genetic testing has not been shown to negatively affect the psychosocial functioning of women who are found to have a *BRCA1* or *BRCA2* mutation[10–13]. Most women who present for clinical genetic testing already have significant family or personal histories of breast or ovarian cancer, and receipt of a positive genetic test result is not unexpected. However, women participating in a population-based genetic testing program often have no family history of cancer, and a positive genetic test will come as a surprise. In unselected Jewish women who present for population-based genetic testing, cancer-related distress is low before testing and increases significantly by 1 year after receipt of positive genetic test results[9]. Distress levels decrease significantly by 2 years after genetic testing[14]. For women who elect to undergo preventive surgery, distress levels decline to near baseline values. Those findings suggest that the psychosocial implications associated with receipt of positive genetic test results through population screening are relevant but transient.

Are Current Cancer Risk Management Strategies Appropriate for Expanded Population-Based Screening?

For women with an identified *BRCA* mutation, options include screening with annual MRI and mammography, and preventive surgeries to reduce the risks of breast and ovarian cancer. Gabai-Kapara and colleagues[2] suggest that the cancer risk for women with a *BRCA1* or *BRCA2* mutation is similar whether the woman was identified by population-based screening or by family history. With respect to the Jewish population, penetrance estimates for the three specific mutations are required. Of principal interest is the penetrance of the 6174delT mutation, which appears to be lower than that of other *BRCA2* mutations[15]. Antoniou *et al.*[15] estimate the penetrance of this mutation to be 43% to age 70; Finkelman *et al.*[16] estimate it to be 55%. Further, the risk of cancer in the mutation carriers varies according to family history, in particular for *BRCA2* carriers, but the extent of the increase in risk with each affected relative is not yet clear[17]. Although no specific risk estimates have been generated for the penetrance of 6174delT in women with a mutation but no family history of breast cancer, we estimate the risk to be between 30% and 40% based on the three foregoing studies. At present, the information is insufficient to offer management strategies that differ by family history. The hope is that future studies will help to refine the risk estimates for carriers with no family history.

An assessment of whether women elect to undergo cancer risk screening and reduction strategies after receipt of positive *BRCA* results through population testing is also important. We evaluated the uptake of screening and prevention options in women with a *BRCA* mutation identified through Jewish population genetic testing[14]. Before genetic testing, none of those women had undergone breast MRI screening or any type of cancer risk reduction surgery. By 1 year after testing, 100% of the women had undergone MRI screening examination. Within 2 years of receiving a positive genetic test result, 11.1% had undergone prophylactic mastectomy, and 90%, a prophylactic oophorectomy. Within the cohort of women with an identified *BRCA* mutation, the provision of population genetic testing reduced the risk of breast cancer to 21% from 37% and the risk of ovarian cancer to 7% from 25%. Those cancer risk reductions are significant and will lead to a lower cancer-related mortality burden in this group of women, a conclusion that is supported by a separate larger study of *BRCA* mutation carriers in which we reported that, compared with women who do not undergo prophylactic salpingo-oophorectomy, those who have the surgery reduce their all-cause mortality by more than 70%[18]. That result further highlights the importance of identifying high-risk women before the development of cancer.

Is There a Sense of What the Overall Impact on Cancer Incidence and Mortality Rates Would Be with Population-Wide Screening?

To measure the impact of a genetic screening program at the population level, it is vital to know the proportion of cancers being caused in that population by the mutations being sought, the uptake of genetic testing by carriers, and the compliance with (and effectiveness of) preventive strategies. Given that only a small proportion of breast and ovarian cancers occur in Jewish women in Ontario and that among Jews only 12% of breast cancers and 40% of ovarian cancers are attributable to those mutations, the case for genetic testing of Jewish women cannot be made based on the global cancer incidence and mortality rates in Ontario. However, given the relatively low cost of testing ($100 in our research laboratory) and the prevalence of mutations (1%–2.5%), we can expect to identify 1–2 carriers for every $10,000 expended on laboratory costs. Notably, if intensive counselling were to be included on a routine basis, the cost per carrier identified would more than double. Over a 4-year period at our hospital, a genetic testing program that targeted all Jewish women in the province identified far more unaffected women with a *BRCA1* or *BRCA2* mutation (n = 92) than did a conventional referral-based program that relied on the criteria set out by the Ontario Ministry of Health and Long-Term Care for genetic testing (n = 29), despite the fact that the population-based approach was less resource-intensive[7].

Is There a Sense of What the Overall Harm of Population-Based Screening Would Be?

We have not identified any substantial harms of population-based screening. Satisfaction with population genetic testing for *BRCA1/2* mutations in the Jewish population is extremely high. The paradigm of screening in specific populations (including Ashkenazi Jews) for rare genetic disorders is the standard of care in the prenatal setting and is also well accepted.

What About Genetic Testing in the Non-Jewish Population?

The focus on testing Jewish women is advanced here only because such testing was the topic of a commentary by Nuttall. It might be premature to offer *BRCA* testing to the entire female population given these premises:

- The frequency of mutations is much lower in the general population (1 in 500) than in the Jewish population (1 in 100), and the prior probability of a positive test is much lower.
- In the non-Jewish population, non-founder mutations predominate, and the cost associated with full gene sequencing is a much higher than it is when testing only for the three common founder mutations in the Jewish population.
- In non-Jewish women, variants of unknown significance will be highly prevalent when performing full gene testing, complicating interpretation of the results.

If we assume that 1 in 500 women in the general population has a mutation, but that 10% carry a variant of unknown significance, we can predict that there will be 51 variants to interpret for every mutation, making genetic counselling burdensome. As a result, we do not currently support population-based *BRCA* testing for all women.

SUMMARY

Given that the prevalence of *BRCA1* and *BRCA2* mutations in unselected Jewish women is 1%–2%; that most women with a *BRCA* mutation identified through population screening would not qualify for testing based on current testing criteria; that population-based genetic testing results in the identification of more unaffected *BRCA* mutation carriers than does clinical testing (which relies on personal or family history of cancer) and is less expensive; that women identified with a *BRCA* mutation through population screening opt for intensive breast screening and preventive surgeries; that preventive oophorectomy and mastectomy reduce cancer deaths dramatically; that cancer-related distress is transient; and that almost all tested women are satisfied with testing, we consider genetic testing of the general population of Jewish women to be justified.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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