A comparison of the detection of BRCA mutation carriers through the provision of Jewish population-based genetic testing compared with clinic-based genetic testing

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Background: Guidelines for genetic testing for BRCA1 or BRCA2 stipulate that a personal or family history of cancer is necessary to be eligible for testing. Approximately 2% of Ashkenazi Jewish women carry a mutation, but to date population-based testing has not been advocated. Little is known about the relative yield of a conventional genetic testing programme versus a programme of widespread testing in a population with common founder mutations.

Methods: We provided both referral-based and Jewish population-based testing between 2008 and 2012. We compared the numbers of BRCA mutation carriers identified through the two streams and estimated the number of genetic counselling hours devoted to each programme.

Results: From 2008 to 2012, 38 female carriers were identified through 487 referrals to our genetics centre (29 unaffected with cancer). During the same time, 6179 Jewish women were tested through our population-based programme and 93 mutation carriers were identified (92 unaffected with cancer). Fewer counsellor hours were devoted to the population-based than to the clinical referral-based testing programme.

Conclusion: Genetic testing of all Jewish women above the age of 25 years will greatly expand the number of BRCA mutation carriers identified without a commensurate increase in the number of hours required for counselling.

Genetic testing for BRCA1 and BRCA2 has been available for over 15 years. Since 1995, the eligibility criteria for genetic testing have been evolving. Presently, eligibility for genetic testing relies on personal and/or family history of breast or ovarian cancer. In some cases, a woman who is ineligible for testing will become eligible after she develops cancer. In contrast, population-based genetic testing does not restrict testing to women at an elevated risk and offers a greater opportunity to identify women at a high risk of developing cancer before diagnosis.

Two founder mutations in BRCA1 and one in BRCA2 are present in 1.2–2.5% of all Ashkenazi Jewish individuals (Roa et al., 1996; Struwing et al., 1997) and comprise the majority of deleterious BRCA mutations in the Jewish population (Kauff et al., 2002; Phelan et al., 2002). Genetic testing for the founder panel is technically straightforward and is much less expensive than conducting a full mutation screen. We have recently proposed, based on a study of over 2000 women, that population-wide genetic testing for all Jewish women is warranted (Metcalfe et al., 2010a). The approach has not been adopted and is not promoted in any of the current testing guidelines. It is not known yet to what extent the yield of population-based genetic testing compares with the yield of traditional clinical referral
genetic testing. From 2008 to 2012, we offered genetic testing through both clinical streams at the Women’s College Hospital, Toronto, and we are now in the unique position to compare the yield of the two approaches.

METHODS

All women who presented for evaluation for genetic testing for 
BRCA1 and BRCA2 at Women’s College Hospital, Toronto  
between 1 May 2008 and 1 May 2012 were included in the study.  
Patients were either tested through the regular clinical referral-
based programme or the Jewish population-based study. Ethics  
approval was obtained from the Women’s College Hospital.

Clinical referral sample. All women who were referred to  
the Women’s College Hospital for genetic counselling and possible  
testing were identified. These women met the Guidelines of the  
Ontario Ministry of Health for the provision of genetic testing for 
BRCA1 or BRCA2. The family history of cancer was assessed and  
included the evaluation of the number and types of cancer and ages  
of cancer. All women received standard pre- and post-test  
counselling (regardless of genetic test result). Genetic testing  
involved complete sequencing of both BRCA1 and BRCA2 and  
detection of large rearrangements by multiplex ligation-dependent  
probe amplification. If a BRCA mutation was identified, relatives  
were also offered genetic testing. These subjects are included in  
this group as well; that is, some patients were the first in the family to  
have a mutation detected (proband) and some were tested on the  
basis of a known family mutation (secondary case).

Ashkenazi Jewish sample. During the study period, 6108  
unselected Jewish women presented for population-based genetic  
testing (three mutations) in the context of a research study  
(Metcalf et al., 2012). Pretest counselling was in the context of an  
information brochure. In the event when a mutation was detected,  
the woman was offered full genetic counselling and all first-degree  
female relatives over the age of 18 were offered genetic testing.

RESULTS

A total of 6421 women were tested for BRCA1 and BRCA2  
mutations: 242 women were tested through the clinical genetics  
service (192 probands and 50 relatives) and 6179 women were  
tested in the Jewish population-based genetic testing study (6108  
probands and 71 relatives).

Referral-based sample. Of the 437 female probands referred to  
the clinical cancer genetics programme, 192 (44%) met the  
provincial criteria for the genetic testing for BRCA1 and BRCA2  
and underwent a genetic test (Table 1). Twenty-two women  
(11.5%) were identified as having a mutation (10 in BRCA1 and 12  
in BRCA2). The mean age of the women with a BRCA mutation  
was 46 years (range 28–71 years). Nine women (41%) had a  
previous diagnosis of cancer (8 breast cancers and 1 ovarian cancer).  
A total of 50 female relatives were tested, of whom 16 (32%) were positive. In summary, 487 women were referred to  
our clinic genetics service (including probands and relatives), of  
whom 242 women underwent genetic testing and 38 women  
(15.7%) were identified with a BRCA mutation.

Population-based Jewish sample. Sixty-eight of 6108 probands  
(1.1%) were found to have a BRCA mutation (25 in BRCA1 and 43  
in BRCA2). The mean age of these women was 44.2 years (range  
24–68 years). None had a previous diagnosis of breast cancer or  
ovarian cancer. On the basis of the Ontario Ministry of Health  
Guidelines for BRCA genetic testing, 26 of these women (38.2%)  
would have qualified for genetic testing. Seventy-one female  
relatives presented for testing. Of these 71 female relatives, 25  
(35.2%) were found to have a BRCA mutation. In summary, as a  
result of Jewish population genetic testing, 6179 women received  
genetic testing for the three common Jewish founder mutations  
(including probands and relatives), and 93 women (1.5%) were  
identified as having a BRCA mutation. Of those, 92 women  
(98.9%) were unaffected (Table 2). Pretest genetic counselling was  
not offered; however, if the woman was identified with a mutation,  
a 90-min post-test genetic counselling session was provided. This  
resulted in a 102 h of genetic counselling. All the 71 relatives were  
provided with a 1 h each of pre- and post-genetic testing  
counselling sessions, resulting in 142 h of counselling. The total  
amount of time provided by genetic counsellors for Jewish  

Table 1. Genetic test results in women who presented at the women’s  
college hospital from 2008 to 2001

|                      | Clinical referral genetic testing | Jewish population genetic testing |
|----------------------|----------------------------------|----------------------------------|
|                      | Total number tested | BRCA mutation n (%) | Total number tested | BRCA mutation n (%) |
| Probands             | 192                        | 22 (11.5)            | 6108                | 68 (1.1)            |
| Relatives            | 50                         | 16 (32.0)            | 71                  | 25 (35.0)           |
| Total                | 242                        | 38 (15.7)            | 6179                | 93 (1.5)            |

Table 2. Comparison of characteristics of BRCA-positive patients in  
clinical stream and population-based stream

|                          | Clinical referral genetic testing (n = 22) | Jewish population genetic testing (n = 68) | Univariate P |
|--------------------------|-------------------------------------------|------------------------------------------|--------------|
| Mean age (years)         | 46.1 (28–71)                              | 44.2 (24–68)                             | 0.51         |
| Personal history of cancer |                                           |                                          |              |
| Any                      | 9 (23.6%)                                 | 0 (0.0%)                                 | <0.0001      |
| Ovary                    |                                            |                                          |              |
| Breast                   |                                            |                                          |              |
| None                     |                                            |                                          |              |
| Ethnic group             |                                           |                                          |              |
| Jewish                   | 3                                         | 68                                       | <0.0001      |
| Other white              | 18                                        | 0                                        |              |
| Asian                    | 0                                         | 0                                        |              |
| Black                    | 1                                         | 0                                        |              |
| Other                    | 0                                         | 0                                        |              |
| First-degree relative with ovarian cancer | 6 of 22 (27.2%) | 3 of 68 (4.4%) | 0.006 |
| First-degree relative with breast cancer | 13 of 22 (59.1%) | 8 of 68 (11.8%) | <0.0001 |
| Proband met Ontario genetic testing criteria | 22 of 22 (100%) | 26 of 68 (38.2%) | <0.0001 |
| Mutation (proband)       |                                           |                                          |              |
| BRCA1                    | 10 (45.5%)                                | 25 (36.8%)                               | 0.62         |
| BRCA2                    | 12 (54.6%)                                | 43 (63.2%)                               |              |
population genetic testing was 244 h (2.6 h per BRCA-positive result) compared with 484 h of genetic counselling in order to identify 38 carriers in the regular clinical stream (12.7 h per positive BRCA result).

DISCUSSION

Our results provide further justification that genetic testing for BRCA1 and BRCA2 mutations should be offered to all Jewish women, regardless of personal or family history of cancer. Over a 4-year period, we identified far more unaffected women with a BRCA1 or BRCA2 mutation \( (n = 92) \) through a genetic testing programme that targeted all Jewish women than we did through a conventional, referral-based programme \( (n = 29) \), despite the fact that the population-based approach was less resource intensive. The Ontario genetic testing criteria were established under the assumption that a woman should have a risk of 10% or greater for carrying a BRCA mutation for testing to be warranted. However, not all women with a mutation meet this standard and many carriers will be missed. The US National Comprehensive Cancer Network (NCCN, 2012) has guidelines for genetic testing for hereditary breast and/or ovarian cancer. In Jewish individuals without breast or ovarian cancer, the guidelines specify that a close family member must have breast or ovarian cancer. In our study, only 38% of the Jewish BRCA mutation carriers qualified for genetic testing (Metcalfe et al, 2010b). Many women who are at high risk of developing breast and ovarian cancer are not being identified because of our historical reliance on personal and family history of cancer. Moreover, many women who do meet the criteria for testing are not identified as such by their health-care providers (Metcalfe et al, 2009). In the current study, 38% of the women identified as having a BRCA mutation would have qualified for genetic testing, but they were either unaware of the recommendation or had not been referred by their health-care provider.

Our goal of population-based Jewish genetic testing is to identify unaffected women at risk of developing cancer, so they may pursue risk reduction options and intensive cancer screening. However, with traditional genetic testing for BRCA1 and BRCA2, we rely on the diagnosis of cancer in order to identify a high-risk individual or family. In the clinical sample, 41% of the probands identified with a BRCA mutation had a previous diagnosis of cancer compared with none of the women in the population-based Jewish sample with a BRCA1 or BRCA2 mutation. We are in a better position to reduce the numbers of new cancers in carriers identified by population genetic testing in the Jewish population than through conventional clinical genetic testing. We have previously reported that women who are identified with a BRCA mutation through the provision of population genetic testing elect for cancer risk reduction options at similar levels to that of women identified in a clinical population (Metcalfe et al, 2012). Within 2 years of receiving a positive BRCA result through the unselected Jewish study, 11.1% of women underwent prophylactic mastectomy, and 89.5% underwent a prophylactic salpingo-oophorectomy. We have also reported that Jewish population genetic testing does not cause long-term psychosocial distress (Metcalfe et al, 2012). Bosch et al (2012) suggest that we should aim to ‘demystify’ the presumed negative effect on psychosocial functioning in order to increase the number of individuals who elect for genetic testing. In conclusion, the data in this paper further support the position for offering genetic testing to all Jewish women. It is hoped that in the future, the cost of genetic testing will be sufficiently low and that such testing might be extended to non-Jewish women as well.

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