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

K A Metcalfe^{1,2}, A Poll², R Royer², S Nanda², M Llacuachaqui², P Sun² and S A Narod^{*,2,3}

¹Lawrence S Bloomberg Faculty of Nursing, University of Toronto, 155 College Street, Toronto, Ontario M5T 1P8, Canada;

²Women's College Research Institute, 790 Bay Street, 7th floor, Toronto, Ontario M5G 1N8, Canada and ³Dalla Lana School of Public Health, University of Toronto, 155 College St, 6th floor, Toronto, Ontario M5T 3M7, Canada

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; Struewing *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

*Correspondence: Dr SA Narod; E-mail: Steven.narod@wchospital.ca

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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 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)			
<i>BRCA1</i>	10 (45.5%)	25 (36.8%)	0.62
<i>BRCA2</i>	12 (54.6%)	43 (63.2%)	

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	<i>BRCA</i> mutation n (%)	Total number tested	<i>BRCA</i> 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)

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 (Metcalf *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 (Metcalf *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 (Metcalf *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 (Metcalf *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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