

Variation in rates of uptake of preventive options by Canadian women carrying the *BRCA1* or *BRCA2* genetic mutation

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ABSTRACT

Background: Women with a *BRCA1* or *BRCA2* genetic mutation have several options for cancer prevention, including prophylactic surgery, chemoprevention and screening. In this study we report on preventive practices used by women with and without breast cancer and examine differences in their selection of preventive practices according to geographic area in Canada.

Methods: Canadian women with a *BRCA1* or *BRCA2* mutation were followed after genetic testing and questioned about their preventive practices. Women reported on uptake of prophylactic mastectomy, prophylactic oophorectomy, tamoxifen or raloxifene usage and screening practices. We analyzed the uptake of each preventive option and completed a subanalysis according to the geographic area in Canada where genetic testing was provided.

Results: The study included 672 women. Follow-up questionnaires were completed after a mean of 4.0 years (range 1.6–9.1 years). Of the 342 women without breast cancer, 72 (21%) had had a prophylactic bilateral mastectomy. Three hundred and sixty-three women (54%) had had a bilateral prophylactic oophorectomy. Seventeen (6%) of the 270 women without breast cancer who had not had a prophylactic mastectomy took tamoxifen, and 12 (4%) reported taking raloxifene. Of the 342 women without breast cancer, 157 (46%) had not undertaken any cancer prevention option (mastectomy, oophorectomy or treatment with tamoxifen or raloxifene). Sixty-five (39%) of the 167 women from Ontario, 19 (34%) of the 56 women from Western Canada and 73 (62%) of the 119 women from Quebec had not undertaken any preventive procedure.

Conclusion: Significant differences in the uptake of preventive options by women with a *BRCA1* or *BRCA2* mutation were observed across 3 regions of Canada. Future research is needed to explain why these differences exist.

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WOMEN WITH A *BRCA1* OR *BRCA2* GENETIC mutation have a lifetime risk of breast cancer of between 45% and 87%.^{1,2} By identifying women at high risk of cancer and by adopting appropriate intervention strategies, it is anticipated that cases of cancer will be prevented. Ultimately, the value of genetic testing for the *BRCA1* and *BRCA2* mutations depends on the uptake of effective cancer prevention options. The preventive options that are available have varying levels of effectiveness.

Prophylactic mastectomy offers the greatest reduction in breast cancer risk (approximately 95%).³ Prophylactic oophorectomy before 40 years of age in women with a *BRCA1* or *BRCA2* mutation is associated with a 50% reduction in the risk of breast cancer.⁴ Tamoxifen usage has been shown to reduce breast cancer risk by 50% in women at high risk of the disease.⁵ The evidence in favour of tamoxifen usage for primary prevention in carriers of the *BRCA1* and *BRCA2* mutations is based on the prevention of contralateral breast cancer.⁶

Some women prefer screening over preventive surgery or chemoprevention. Screening does not prevent breast cancer; the goal is to detect cancer at an early, treatable stage. The superiority of magnetic resonance imaging (MRI) over mammography in detecting small breast cancers in *BRCA1* and *BRCA2* mutation carriers is becoming evident.⁷⁻⁹

There has been limited previous research examining uptake rates of various preventive options among *BRCA1* and *BRCA2* carriers. However, there are suggestions that the uptake of preventive procedures differs significantly according to country.¹⁰⁻¹⁴ Such differences are likely due to many factors, including patient preferences, physician preferences and access to care. In this study we present data on a Canadian cohort of *BRCA1* and *BRCA2* carriers who were followed systematically from the time at which they underwent genetic testing. We report on the preventive practices of women with and without breast cancer and examine differences in uptake rates according to geographic area within Canada.

Methods

Study population. Eligible subjects were drawn from a database of carriers of deleterious mutations in either the *BRCA1* or the *BRCA2* gene. These women had been assessed for genetic risk at 12 Canadian centres between 1995 and 2003. All study subjects provided written informed consent for genetic testing. The study

was approved by the ethics committees of all participating centres. In most cases, testing was initially offered to women who had either breast or ovarian cancer. When a mutation in either the *BRCA1* or *BRCA2* gene was found in a proband or in one of her relatives, testing was offered to other at-risk women in her family. However, in some cases (fewer than 10% of the total) a woman with breast cancer in the family was not available for study and a woman who had not had the disease was the first member of the family to be tested. Mutation detection was performed using a range of techniques, but in every case nucleotide sequences were confirmed with direct sequencing of genomic DNA. A woman was eligible for the study when the molecular analysis established that she was a mutation carrier. We studied both women who had had breast cancer and those who had not.

Women were eligible for this study if they were a resident of Canada and had received their genetic testing at a Canadian genetics centre, were known to be a *BRCA1* or *BRCA2* mutation carrier, were between 25 and 80 years old, and had no previous history of cancer other than breast cancer. Women who were diagnosed with breast cancer during the follow-up period were excluded from the study. In addition, to be included, the women had to have had at least 18 months of follow-up after genetic testing and had to be alive at the date of follow-up.

Women were grouped according to geographic area. Women who received genetic testing in Vancouver (n = 67), Edmonton (n = 20), Saskatoon (n = 8) and Winnipeg (n = 15) were classified as being from Western Canada. Women from Ontario received genetic testing and counselling at 3 centres in Toronto (n = 229), at a centre in London (n = 56) or at a centre in Hamilton (n = 30). Women from Quebec received genetic testing and counseling at 2 centres (n = 247).

Procedures. All subjects completed a baseline questionnaire at the time of genetic testing that assessed cancer history and past use of cancer prevention options and screening tests. Follow-up questionnaires were administered by telephone or by mail. Questions assessed uptake of cancer prevention options, including prophylactic surgery (mastectomy or oophorectomy), chemoprevention (usage of tamoxifen or raloxifene) and MRI of the breast.

Statistical analysis. Chi-square testing was used to compare frequencies of categorical variables, such as different preventive options among regions, and ANOVA was used to compare mean values of continuous variables among regions. All statistical tests were conducted using SAS version 9.1.3 (SAS Institute, Inc., Cary, NC).

Results

We identified 1051 women with a *BRCA1* or *BRCA2* mutation for this study. Of these, 328 women were ineligible (12 women were less than 25 years of age, 10 women were over 80 years of age, 105 women were deceased at follow-up, 111 women had ovarian cancer, 15 women were followed for less than 18 months, 52 women were diagnosed with breast cancer during the follow-up period and 23 women lived outside of Canada), 29 women refused to complete the follow-up questionnaire and 22 women were lost to follow-up. A total of 672 women were included in the study. Follow-up questionnaires were completed a mean of 4.0 years after genetic testing (range 1.6–9.0 years). Genetic testing and counselling was received by 110 women in Western Canada (from 4 centres), 315 women in Ontario (from 5 centres) and 247 women in Quebec (from 2 centres). Three hundred and thirty women (49%) had had a previous diagnosis of breast cancer and 342 (51%) women had not. Characteristics of the study participants are presented in Table 1. There were no statistical differences in mean ages at the time of genetic testing according to geographic area ($p = 0.39$).

Prophylactic mastectomy. Of the 342 women without breast cancer, 72 (21%) had had a prophylactic bilateral mastectomy (Table 2). Fifty-three of these women (74%) had their surgery after receiving their genetic test result. The other 19 women (26%) had a prophylactic mastectomy before genetic testing, on the basis of their family history alone. All 72 prophylactic mastectomies were performed in women under age 60 (range 26–58 years). Table 3 presents uptake by geographic area.

Prophylactic oophorectomy. Three hundred and sixty-three women (54%) had bilateral prophylactic

oophorectomy; of these, 215 (59%) had the surgery after receiving their genetic test result (Table 4). We were not able to distinguish between oophorectomies that were done for cancer prophylaxis and those done for other reasons. More women with a history of breast cancer had had a prophylactic oophorectomy (60%) than women without breast cancer (48%) ($p = 0.002$). Table 3 presents uptake by geographic area.

Tamoxifen and raloxifene usage. Usage of tamoxifen and raloxifene was examined for women without breast cancer but with both breasts intact (i.e., no prophylactic mastectomy). Seventeen women (6%) took tamoxifen and 12 women (4%) reported having taken raloxifene (Table 5). It is unknown if any of the women took tamoxifen or raloxifene as part of a clinical trial. Table 3 presents uptake by geographic region.

No preventive option. Of the study participants without breast cancer, 157 (46%) had chosen no cancer prevention option (mastectomy, oophorectomy or treatment with tamoxifen or raloxifene). Thirty-nine percent of the women from Ontario (65 of 167), 34% of those from Western Canada (19 of 56), and 62% of those from Quebec (73 of 119) had not undertaken any preventive procedure.

MRI and mammography. Data on uptake of MRI were available for 241 of the 270 women without breast cancer who had not had a prophylactic bilateral mastectomy. One hundred and four women (43%) had been screened for breast cancer with MRI. One hundred of these women (96%) were less than 60 years old. Table 3 presents uptake by geographic area.

In contrast, the majority of women without breast cancer had undergone mammography (96%, 328 of 342). Most of these women (86%, 282 of 328) began mammography screening before genetic testing;

Table 1: Characteristics of study participants by region

Characteristic	Ontario (n = 315)	Quebec (n = 247)	Western Canada (n = 110)	All (n = 672)	p value [*]
Mutation, no. (%)					
<i>BRCA1</i>	190 (60.3)	132 (53.4)	70 (63.6)	392 (58.3)	0.12
<i>BRCA2</i>	123 (39.1)	110 (44.5)	40 (36.4)	273 (40.6)	
<i>BRCA1+2</i>	2 (0.6)	5 (2.0)	0 (0.0)	7 (1.0)	
Mean age at genetic testing, yr (range)	47.0 (25–79)	47.3 (25–77)	45.6 (25–76)	46.9 (25–79)	0.39
Breast cancer diagnosis, no. (%)	148 (47.0)	128 (51.8)	54 (49.1)	330 (49.0)	0.52
Mean age at diagnosis, yr (range)	42.4 (24–70)	42.3 (27–75)	42.3 (24–70)	42.41 (24–75)	1.00
Date of genetic testing, year (range)	1999.7 (1995.5–2003.9)	1998.8 (1994.9–2003.7)	2000.0 (1995.3–2002.5)	1999.4 (1994.9–2003.9)	< 0.001
Mean follow-up, yr (range)	3.84 (1.59–8.95)	4.20 (1.70–8.03)	3.88 (1.57–8.86)	3.98 (1.57–8.95)	0.06

^{*}ANOVA was used to analyze differences in mean values between the 3 regions; chi-square testing was used to analyze differences in the frequency distributions of the 3 regions.

Table 2: Prophylactic mastectomy for women without breast cancer

Age (yr)	Women without breast cancer, n (%)	Women without breast cancer who had a prophylactic mastectomy, n (%)	Prophylactic mastectomy timing, n (%)	
			Before genetic testing	After genetic testing
25–35	66 (19.3)	16 (24.2)	3 (4.6)	13 (19.7)
36–60	245 (71.6)	56 (22.9)	16 (6.5)	40 (16.3)
61–70	18 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
> 70	13 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Total	342 (100.0)	72 (21.1)	19 (5.6)	53 (15.5)

Table 3: Uptake of preventive options by geographic area

Option	All regions	Western Canada	Ontario	Quebec	p value
Prophylactic mastectomy,* n (%)	342	26 (46.4)	36 (21.6)	10 (8.4)	< 0.001
Prophylactic oophorectomy,† n (%)	672	74 (67.3)	193 (61.3)	96 (38.9)	< 0.001
Tamoxifen or raloxifene therapy,‡ n (%)	270	4 (13.3)	21 (16.0)	4 (3.7)	0.008
MRI,‡ n (%)	270				< 0.001¶
No	–	22 (73.3)	32 (24.4)	81 (74.3)	–
Yes	–	8 (26.7)	81 (61.8)	15 (13.8)	–
Data missing	–	0 (0.0)	18 (13.7)	13 (11.9)	–

*Data are for women without breast cancer.

†Data are for all women in the three regions.

‡Data are for women without breast cancer who had not had a prophylactic mastectomy.

¶Missing data not included in the test.

Table 4: Prophylactic oophorectomy by breast cancer status

Age (yr)	All women, n (%)	Women who had had a prophylactic oophorectomy, n (%)	Prophylactic oophorectomy timing, n (%)	
			Before genetic testing	After genetic testing
All women				
25–35	82 (12.2)	18 (22.0)	2 (2.4)	16 (19.5)
36–40	127 (18.9)	57 (44.9)	12 (9.5)	45 (35.4)
41–60	375 (55.8)	240 (64.0)	95 (25.3)	145 (38.7)
61–70	56 (8.3)	33 (58.9)	26 (46.4)	7 (12.5)
> 70	32 (4.8)	15 (46.9)	13 (40.6)	2 (6.3)
Total	672 (100.0)	363 (54.0)	148 (22.0)	215 (32.0)
Women without breast cancer				
25–35	66 (19.7)	13 (19.7)	2 (3.0)	11 (16.7)
36–40	80 (23.4)	33 (41.3)	6 (7.5)	27 (33.8)
41–60	165 (48.3)	103 (62.4)	40 (24.2)	63 (38.2)
61–70	18 (5.3)	13 (72.2)	10 (55.6)	3 (16.7)
> 70	13 (3.8)	3 (23.1)	2 (15.4)	1 (7.7)
Total	342 (100.0)	165 (48.3)	60 (17.5)	105 (30.1)
Women with breast cancer				
25–35	16 (4.9)	5 (31.3)	0 (0.0)	5 (31.5)
36–40	47 (14.2)	24 (51.1)	6 (12.8)	18 (38.3)
41–60	210 (63.6)	137 (65.2)	55 (26.2)	82 (39.1)
61–70	38 (11.5)	20 (52.6)	16 (42.1)	4 (10.5)
> 70	19 (5.8)	12 (63.2)	11 (57.9)	1 (5.3)
Total	330 (100.0)	198 (60.0)	88 (26.7)	110 (33.3)

Table 5: Tamoxifen and raloxifene usage by women without breast cancer who had not had a prophylactic mastectomy

Age (yr)	All women, n (%)	Women who used tamoxifen, n (%)	Women who used raloxifene, n (%)	Women who used either tamoxifen or raloxifene, n (%)
25–35	50 (18.5)	0 (0.0)	0 (0.0)	0 (0.0)
36–60	189 (70.0)	14 (7.4)	10 (5.3)	24 (12.7)
61–70	18 (6.7)	3 (16.7)	2 (11.1)	5 (27.8)
> 70	13 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Total	270 (100.0)	17 (6.3)	12 (4.4)	29 (10.7)

however, 14% of the women had had their first mammogram after receiving their genetic test result. Uptake rates were similar across the 3 geographic areas: 99% of the women from Ontario (165 of 167), 93% of the women from Western Canada (52 of 56) and 93% of the women from Quebec (11 of 119) reported undergoing mammography.

Interpretation

We have reported on the rates of uptake of various cancer prevention options among Canadian women with a *BRCA1* or *BRCA2* mutation. Approximately two-thirds of women from Quebec had not taken up any preventive option, compared with approximately one-third of women from Western Canada and Ontario. The greatest differences in uptake rates were observed with prophylactic mastectomy. Women from Western Canada had the highest uptake of prophylactic mastectomy (46%), followed by women from Ontario (22%), and Quebec (8%). We also observed pronounced differences in rates of uptake of prophylactic oophorectomy. Sixty-seven percent of women from Western Canada and 61% of women from Ontario had undergone preventive oophorectomy. Again, fewer women from Quebec elected to have this preventive surgery (39%). Overall, the uptake rates of various preventive modalities were similar to those reported in other countries.^[11,12,14–18] The surprising result was the great difference in uptake of preventive options depending on where a woman received her genetic counselling and testing.

Our results, and those of others, suggest that there are wide variations in the uptake of preventive options among *BRCA1* and *BRCA2* mutation carriers. The differences in uptake could be due to a number of factors, including health care professionals' acceptance and recommendation of the procedures, cultural differences that influence patient preferences, and access (including cost and availability).

Health care professionals' acceptance and recommendations clearly influence uptake. There is

evidence that physicians have differing opinions on the various preventive options available to women with a *BRCA1* or *BRCA2* mutation. In the United States, a greater proportion of plastic surgeons (84.6%) than general surgeons (47.0%) or gynecologists (38.3%) in Maryland agreed that bilateral prophylactic mastectomy has a role in the care of women at high risk of developing breast cancer.¹⁹ In France, only 11% of physicians found it acceptable to propose prophylactic mastectomy to women with a *BRCA* mutation.²⁰ Peshkin and colleagues surveyed physicians regarding recommendations for tamoxifen for primary breast cancer prevention and reported that physicians were more likely to recommend tamoxifen to *BRCA2* carriers (73%) than to *BRCA1* carriers (57%) ($p < 0.0001$).²¹ They concluded that physicians were not convinced of the benefits of tamoxifen in *BRCA1* and *BRCA2* mutation carriers. Although this research did not examine women's uptake of preventive options with respect to their physician's preference, it is expected that physicians would influence their patients' choices.

Cultural influences may also be responsible for some of the discrepancies that we observed. Other authors have examined the differences in uptake of preventive options in various countries. Bouchard and colleagues surveyed women from Canada (Quebec), France and Great Britain about their medical decisions related to *BRCA1* and *BRCA2* mutation testing and found differences in the uptake of preventive procedures in the 3 countries, which they attributed to cultural differences.²² Previous single-country follow-up studies of *BRCA1* and *BRCA2* mutation carriers have reported various rates of uptake of all of the preventive options.^{11,12,14–18} When the single-country uptake rates are compared across countries, noticeable differences in uptake are observed. This suggests that variations between countries could be due to cultural influences.

Access to services may also contribute to the observed differences, particularly in the case of uptake of MRI screening. To date, screening MRI is offered on a research basis and is not widely available as a clinical

service. Women with access to research studies are more likely to have MRI for screening. The differences in tamoxifen uptake may also be due to access issues, including cost. Currently, tamoxifen costs approximately \$25 per month. Some women may not have drug coverage and therefore may not be able to afford this drug. The differences in surgical uptake that we observed are probably not due to differences in access across the country. Canadian women have coverage for prophylactic surgeries, including breast reconstruction, without cost. This would not be the case in the United States, where differences in uptake of preventive procedures have been attributed to financial constraints. For example, Schwartz and colleagues attributed the low rate of prophylactic oophorectomy they observed to the constrained financial resources of their study subjects.²³

Study limitations. The study participants were women who had been found to carry a *BRCA1* or *BRCA2* mutation at one of 12 specialized genetic counseling centres in Canada between 1995 and 2003. Although ours is a relatively large sample (672 women), it may not be representative of all women who have received a positive genetic test result in Canada. Canadian women may have undergone genetic testing in centres other than the ones included here and we do not have any information on their uptake of cancer prevention options. Patterns of practice have evolved since 1999, the average time at which our study subjects received their genetic testing. We believe that genetic services are now better integrated with surgical care and that physician attitudes may have changed with regard to specific preventive measures. It is our intention to repeat this survey in 5 years to evaluate trends in clinical practice.

We have described the significant differences in uptake of preventive options by women with a *BRCA1* or *BRCA2* mutation who have received genetic testing in different areas of one country. The differences cannot be explained by differing health care systems because Canada has a universal health care system: all of the women in this study had similar access to health care (with the exception of MRI), and therefore no woman would be denied any of the preventive procedures because of lack of health insurance. We have speculated that the differences exist because of health care professionals' acceptance and recommendation of the preventive procedures; cultural differences across Canada; and access (including cost and availability). In this study we could not ascertain the specific reason for the discrepancies across Canada, but future research will address this important question.

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