ELECTRONIC LETTER

Individual and family characteristics associated with protein truncating *BRCA1* and *BRCA2* mutations in an Ontario population based series from the Cooperative Family Registry for Breast Cancer Studies

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Studies using multicase breast cancer families led to the mapping and eventual cloning of the two susceptibility genes for breast or ovarian cancer or both, *BRCA1*(MIM 113705) and *BRCA2* (MIM 600185).[1][2] In early studies attempting to characterise the clinical impact of mutations in these genes, investigators continued to analyse large multicase families.[3] More recently, groups have focused on patients with breast cancer unselected for strong family cancer history to make their findings more generally applicable.[4-7] With the broadening of study participant ascertainment, there has been a drop in the estimates of lifetime breast cancer penetrance attributable to *BRCA1* and *BRCA2* from greater than 80% initially to values as low as 40%.[3][8]

Attempts to characterise the range and frequency of *BRCA1* and *BRCA2* mutations in breast cancer families have also been complicated by the different molecular techniques used to identify them. Owing to the large size, multiexonic nature, and lack of any universally identified mutational hot spots in the genes, few studies have conducted a thorough investigation of the presence of mutations in both genes. Also, there have been some missense mutations of unknown clinical significance identified (Breast Cancer Information Core). There is also some evidence that the position of the mutation in the *BRCA2* gene may influence the clinical manifestation of cancer risk, which would further complicate the interpretation of findings from studies that use targeted molecular analysis.[9]

Molecular studies of cases ascertained through a population based design more accurately reflect the range and frequency of *BRCA1* and *BRCA2* mutations in a specific population. The Ontario Familial Breast Cancer Registry (OFBCR)[10][11] is one of six sites participating in the international Cooperative Family Registry for Breast Cancer Studies (CFRBCS). The OFBCR is a population based breast cancer registry, the purpose of which is to collect pedigree information, epidemiological data, and biological specimens from patients with incident breast cancer and their families for studies considering familial breast cancer. The OFBCR includes families with a wide range of family history of cancer and provides a large and unique resource for studies of familial cancer.

In this article we describe a preliminary analysis of the characteristics and frequency of carriers of *BRCA1* and *BRCA2* mutations among those OFBCR participants who were diagnosed with invasive breast cancer in a one year ascertainment period and met certain personal and family cancer history criteria. Molecular analysis of the entire coding regions of *BRCA1* and *BRCA2* was undertaken, with the protein truncation test (PTT), to determine the number and range of truncating mutations in our cohort of cases of incident breast cancer. These findings can assist in the pregenetic testing esti-

mation of the likelihood that a person with an incident breast cancer carries a protein truncating *BRCA1* and *BRCA2* mutation. Also, an analysis to determine characteristics that predict the presence of such a mutation was carried out.

Key points

- *BRCA1* and *BRCA2* mutations significantly increase the risk of breast and ovarian cancer. Variability in the estimates of the frequency of these mutations is probably the result of variation in the characteristics of the population studied.
- A population based study of 314 women diagnosed with incident, invasive breast cancer was undertaken in a one year ascertainment period of the Ontario Familial Breast Cancer Registry (OFBCR). The OFBCR is part of the Breast Cooperative Family Registry of the National Cancer Institute.
- We identified 17 (5.4%) *BRCA1* and 14 (4.5%) *BRCA2* mutation carriers. In a multivariable analysis, *BRCA1* mutation was significantly associated with having at least one first degree (p=0.02) or a second or third degree relative (p=0.005) with breast cancer at age 35 or younger or ovarian cancer at age 60 or younger. A diagnosis of breast cancer at age 35 or younger in the proband was also associated with *BRCA1* mutation (p=0.04). Multiple primaries were strongly associated with being a *BRCA2* mutation carrier (p=0.003), and having two second degree relatives with breast or ovarian cancer at any age was also significantly associated (p=0.03). Ashkenazi heritage was the only criterion significantly associated with both *BRCA1* (p=0.03) and *BRCA2* (p=0.04) mutations.
- In a population based group, *BRCA1* mutations were strongly associated with young age of onset in probands and relatives with breast or ovarian cancer. *BRCA2* mutations were particularly associated with probands having multiple primaries. Ashkenazi Jewish background was significantly associated with both *BRCA1* and *BRCA2* mutations.

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Table 1 OFBCR criteria for defining probands (all affected with invasive breast cancer) at possible increased genetic risk of breast cancer

Criteria	Description
1	At least 1 first degree relative with breast or ovarian cancer
2	At least 2 second degree relatives with breast or ovarian cancer
3	Proband diagnosed with breast cancer at age ≤35
4	At least 1 second or 1 third degree relative with breast cancer at age ≤35 or ovarian cancer at age ≤60
5	Proband is male
6	At least 1 second or 1 third degree relative with male breast cancer
7	Proband diagnosed with both breast and ovarian cancer or multiple breast primaries
8	At least 1 second or 1 third degree relative with breast and ovarian cancer
9	At least 1 second or 1 third degree relative with multiple breast cancer primaries
10	Family has at least three relatives in a first degree relationship with any combination of breast, ovarian, colon, prostate, or pancreatic cancer or sarcoma with at least 1 diagnosis ≤50
11	Proband is Ashkenazi Jewish

SUBJECTS AND METHODS

Study population

The OFBCR used a staged approach to the recruitment of all its participants. OFBCR probands were ascertained through the Ontario Cancer Registry, which is a voluntary cancer registry collecting diagnostic and treatment information from about 98% of the province's cases of breast cancer. The initial ascertainment for the OFBCR included those with incident invasive breast cancer, confirmed by pathology report, diagnosed between January 1996 and December 1998. All women between the ages of 20 and 54, and all men between 20 and 79 diagnosed in this period were considered eligible for OFBCR participation. We randomly selected a sample (35%) of the 55 to 69 year old age category to obtain a representative portion of that large group of women. Permission to contact all of these people was sought through a doctor identified on their pathology report as being involved in their care.

Once permission from the doctor to contact the proband was received, a package that included information about the OFBCR, a self administered family history questionnaire, and a consent form was sent to each proband. On return of questionnaires, patients were classified as eligible, regardless of family history, if they were diagnosed under age 36, male, of Ashkenazi Jewish ancestry, or had multiple breast or breast and ovarian primaries. In addition, they were also eligible if they had any of a number of the familial cancer characteristics as described in table 1. The age of diagnosis and the type of cancer were confirmed in all the probands by reviewing the pathology reports. All of these probands were offered genetic counselling and asked to provide a blood sample. Each sample collected underwent *BRCA1* and *BRCA2* analysis and was also banked for future OFBCR research. A signed consent form was sought at each stage.[10][11] In this article we studied OFBCR participants who were diagnosed with invasive breast cancer in a one year ascertainment period between 1 January and 31 December 1996.

Mutational analysis

Nucleic acids, DNA and RNA, were extracted using conventional methods. All probands were analysed for PTT mutations throughout the complete coding sequence of *BRCA1* and *BRCA2* genes as described previously.[12–14] The exception was probands of Ashkenazi Jewish ancestry who were initially tested only for the commonly found Jewish mutations (*BRCA1* 185delAG, 5382insC, and *BRCA2* 6174delT) using heteroduplex analysis.[12][14] Ashkenazi Jewish probands who did not show a common ethnic mutation but fitted any other of the non-ethnic criteria (table 1) were also screened by complete PTT analysis.

Statistical analysis

For each eligibility criterion, the proportion of mutation carriers identified among those meeting the criterion is reported. *BRCA1* and *BRCA2* mutation carriers were examined individually as well as combined as any mutation carrier. To explore the role of age at diagnosis in affected relatives further, we subdivided those with a first degree relative with breast or ovarian cancer (criterion 1) into two groups. These two groups were defined as those with a first degree relative with breast cancer when 35 or younger or ovarian cancer at 60 or younger (criterion 1a) and those with a first degree relative with breast or ovarian cancer in any other age group (criterion 1b). We also examined the presence of ovarian cancer under age 60 in the family using the exact Pearson χ^2 test.

To determine which combination of criteria was the most likely to identify mutation carriers, we combined the criteria in a logistic regression model and carried out backward stepwise elimination until all criteria remaining in the model had a p value ≤0.05. Again, separate models were constructed for *BRCA1* and *BRCA2* mutation carriers.

RESULTS

Assuming that the frequency of mutations is effectively zero in those not meeting any of our genetic risk criteria and accounting for the initial age sampling, we estimate that the prevalence of *BRCA1* carriers in women up to age 69 diagnosed with breast cancer in Ontario would be 1.4%. Similarly, the prevalence of *BRCA2* mutations would be 1.3%. Response rates among those diagnosed in 1996 are described in detail elsewhere.[11] Briefly, only 1.7% of patients were excluded initially because they had died, consent to contact patients was obtained for 92% of cases, and 67% of these provided information on family history. Of these respondents, 36% met inclusion criteria (table 1) and we were able to obtain blood samples from 63% of those eligible. Response was low among male patients, but they made up only 1% of all cases. Response rates also tended to be lower among those who identified themselves as having an ethnic background that was other than white or Ashkenazi Jewish, but only about 5% of those meeting genetic risk criteria were in this group. White participants were represented mostly by those of northern European ancestry (84.6%). Ashkenazi Jewish probands comprised about 12.7% of those tested and the remaining 2.7% were of other origins including Asians, native Indians, and Africans.

The *BRCA1* and *BRCA2* analysis was completed in 314 out of the 370 probands (85%) who had contributed a blood sample in five Ontario diagnostic laboratories (Hamilton, Kingston, London, Ottawa, and Toronto). Analysis was not completed in the remaining probands owing to insufficient specimens. We

Table 2 *BRCA1* and *BRCA2* mutations

Cases	Exon	Nucleotide	Change	Type	BIC	Ethnicity
BRCA1						
1	2	185	insA	Insertion	Yes	White
2	2	185	delAG	Deletion	Yes	AJ
3	2	185	delAG	Deletion	Yes	AJ
4	2	185	delAG	Deletion	Yes	AJ
5	2	185	delAG	Deletion	Yes	AJ
6	8	613	insT	Insertion	Yes	White
7	11	970	ins7	Insertion	No	White
8	11	1292	del40	Deletion	Yes	White
9	11	1806	C-T	Nonsense	Yes	White
10	11	2457	C-T	Nonsense	Yes	White
11	11	3450	DelCAAG	Deletion	Yes	White
12	11	3636	ins154	Insertion	No	White
13	11	3867	G-T	Nonsense	Yes	White
14	14	4603	G-T	Nonsense	Yes	White
15	15	4728	C-T	Nonsense	No	White
16	18	5255	G-A	Nonsense	Yes	White
17	20	5382	insC	Insertion	Yes	White
BRCA2						
18	10	1179	insA	Insertion	Yes	White
19	11	2157	delG	Deletion	Yes	White
20	11	3036	delACAA	Deletion	Yes	White
21	11	3036	delACAA	Deletion	Yes	White
22	11	4304	delC	Deletion	Yes	White
23	11	5117	C-G	Nonsense	Yes	White
24	11	5910	C-G	Nonsense	Yes	White
25	11	6174	delT	Deletion	Yes	AJ
26	11	6174	delT	Deletion	Yes	AJ
27	11	6174	delT	Deletion	Yes	AJ
28	11	6174	delT	Deletion	Yes	AJ
29	11	6503	delTT	Deletion	Yes	White
30	22	9132	delC	Deletion	Yes	White
31	24	9481	insA	Insertion	Yes	White

BIC, Breast Cancer Information Core; AJ, Ashkenazi Jewish descent.

Table 3 Frequency of *BRCA1* and *BRCA2* mutation carriers according to the criteria by which they were ascertained

Criteria*	Total cases† (No)	*BRCA1* No (%)	*BRCA2* No (%)	*BRCA1* or *BRCA2* No (%)
1 One first degree relative	149	9(6.0)	4(2.7)	13(8.7)
1a One younger first degree relative‡	31	4(12.9)	2(6.5)	6(19.4)
1b One older first degree relative§	118	5(4.2)	2(1.7)	7(5.9)
2 Two second degree relatives	41	3(7.3)	4(9.8)	7(17.1)
3 Proband diagnosis at age ≤ 35	53	5(9.4)	2(3.8)	7(13.2)
4 Second or third degree relatives with diagnosis age restriction	46	6(13.0)	3(6.5)	9(19.6)
5 and 6 Male proband or male relative	8	0(0)	0(0)	0(0)
7 Multiple primary tumours	36	2(5.6)	5(13.9)	7(19.4)
8 and 9 Relative with multiple primary tumours	16	1(6.3)	1(6.3)	2(12.5)
10 Three first degree relatives with cancer	69	4(5.8)	3(4.4)	7(10.1)
11 Ashkenazi Jewish background	43	4(9.3)	4(9.3)	8(18.6)

*For details of each inclusion criterion description refer to table 1. †Each proband could be ascertained by more than one criterion, therefore, the categories are not mutually exclusive. ‡ Below age ≤35 for breast and ≤60 for ovarian cancer cases. §Above age 35 for breast and 60 for ovarian cancer cases.

have identified 31 (9.9%) *BRCA1* and *BRCA2* carriers out of 314 probands studied. *BRCA1* and *BRCA2* mutations were detected in 17 and 14 probands, respectively (table 2). Six deletions, five insertions, and six nonsense mutations were identified out of 17 *BRCA1* mutations. Ten deletions, two insertions, and two nonsense mutations were identified out of 14 *BRCA2* mutations. Each of the two Ashkenazi Jewish mutations, 185delAG in *BRCA1* and 6174delT in *BRCA2*, was detected four times. The *BRCA2* mutation 3036delACAA was also detected twice. No other mutation was detected more than once in this study. With the exception of three *BRCA1* mutations (970ins7, 3636ins154, and 4728C-T), all of the *BRCA1* and *BRCA2* mutations have been reported previously in the Breast Cancer Information Core.

Table 3 shows the frequencies of *BRCA1* and *BRCA2* mutation carriers according to the OFBCR inclusion criteria. About half of the probands (149) ascertained had at least one first degree relative with breast or ovarian cancer at any age (criterion 1). The criterion with the highest frequency of *BRCA1* mutation carriers included probands with at least one second or third degree relative with breast cancer at age 35 or younger or ovarian cancer at age 60 or younger (criterion 4). Six out of the 46 (13.0%) who met this criterion carried a *BRCA1* mutation. When probands with affected first degree relatives with breast or ovarian cancer at any age (criterion 1) were divided based on the age of diagnosis of the youngest affected first degree relative, the proportion of carriers of *BRCA1* mutations was also high (12.9%). The criterion with

Table 4 Multivariable models: odd ratios (OR) and 95% confidence intervals (95% CI) of criteria from logistic regression models

Models	Criteria	Criteria	OR	95% CI	p value
BRCA1 model					
	1	First degree relative with diagnosis age restriction*	4.70	1.30 to 17.01	0.02
	3	Proband diagnosed age ≤35	3.41	1.04 to 11.12	0.04
	4	Second or third degree relatives with diagnosis age restriction*	5.19	1.66 to 16.24	0.005
	11	Ashkenazi Jewish background	4.46	1.18 to 16.88	0.03
BRCA2 model					
	2	Second degree relatives	4.08	1.12 to 14.84	0.03
	7	Multiple primary tumours	6.48	1.90 to 22.09	0.003
	11	Ashkenazi Jewish background	3.90	1.07 to 14.16	0.04

*Relatives diagnosed with breast cancer at age ≤35 and ovarian cancer at age ≤60.

Table 5 BRCA1 and BRCA2 mutation carrier status and the presence of ovarian cancer in the family

	Cases No	BRCA1 No (%)	BRCA2 No (%)	BRCA1 or BRCA2 No (%)
Presence of ovarian cancers (total 314):*				
Yes	40	6 (15.0)	2 (5.0)	8 (20.0)
No	274	11 (4.0)	12 (4.4)	23 (8.4)
p value		0.01	1.00	0.03

*Relatives diagnosed with ovarian cancer at age ≤60 in the first, second, or third degree relationship.

the highest frequency of *BRCA2* mutation carriers included probands diagnosed with multiple breast primaries or breast and ovarian cancers (criterion 7). Five out of the 36 patients (13.9%) in this category carried a *BRCA2* mutation. Those with Ashkenazi Jewish descent (criterion 11) were equally likely to carry either a *BRCA1* (9.3%) or *BRCA2* (9.3%) mutation; eight of 43 Ashkenazi patients (18.6%) carried a mutation in either gene. No carriers were found in eight probands who were male or had a male relative with breast cancer.

When all the criteria were combined in a logistic regression model (table 4), those most strongly associated with being a *BRCA1* mutation carrier included probands with at least one first degree relative with breast cancer at age 35 or younger or ovarian cancer at age 60 or younger (criterion 1a), probands with a second or third degree relative with breast cancer at age 35 or younger or ovarian cancer at age 60 or younger (criterion 4), and probands with breast cancer diagnosis at age 35 or younger (criterion 3). Ashkenazi ancestry (criterion 11) was also significantly associated with being a *BRCA1* mutation carrier. Having multiple breast or breast and ovarian primaries (criterion 7) was strongly associated with being a *BRCA2* carrier, but having two second degree relatives with breast or ovarian cancer at any age (criterion 2) was also significantly associated with mutation of *BRCA2*. Ashkenazi heritage (criterion 11) was the only criterion significantly associated with both *BRCA1* and *BRCA2* mutations.

The predictive value of having a relative with ovarian cancer was also examined in a univariate analysis (table 5). The presence of ovarian cancer diagnosed at age 60 or younger in a first, second, or third degree relative was associated with *BRCA1* mutations (p=0.01), but not with *BRCA2* mutations.

DISCUSSION

Several groups have studied the frequencies of *BRCA1* and *BRCA2* mutations in women with breast cancer to evaluate the prevalence of mutations in these genes. Variability in the results of these studies seems to be related to whether the patients were ascertained using a clinic or population based approach. We have studied 314 women and men, all diagnosed in 1996 with invasive breast cancer, who were recruited from the population of Ontario (all women under age 55, 35% aged 55 to 69, and all men aged 20 to 79) and who met the OFBCR

eligibility criteria. These criteria were designed to be broad and inclusive of all who might be at increased genetic risk. A recent investigation of our enrollment method indicates that non-white populations are less likely to respond to our initial contact. However, the presence of genetic risk criteria, as described in table 1, does not influence participation (Mancuso *et al*, in press).

We found that 9.9% of the 314 patients had either a *BRCA1* (5.4%) or a *BRCA2* (4.4%) mutation after a complete analysis of the entire coding regions of both genes with PTT. The sensitivity of the PTT assay was measured previously in a validation study that found complete concordance with a direct sequencing approach in detecting the deleterious truncation mutations. As well as coding region mutations, PTT can also detect protein truncating mutations caused by alterations outside the coding region. These include splice error mutations caused by cryptic site mutations in introns, and large genomic deletions or insertions (BIC). Although, most reported *BRCA1* and *BRCA2* alterations with a functional impact and thus clinical significance are protein truncating mutations, a fraction of missense mutations are also found. However, interpretation of the clinical significance of missense mutations remains difficult because of the lack of a laboratory based functional test for the *BRCA1* and *BRCA2* proteins.

Among the probands studied, about 83% were white, represented mostly by those from the United Kingdom and other northern Europeans, and 13% were Ashkenazi Jewish. As this group was made up largely of white participants, the results can be compared to other population based studies in white populations. In the Anglian Breast Cancer Study of 1435 cases in residents of East Anglia, United Kingdom (age younger than 55 unselected for family history) the frequency of *BRCA1* and *BRCA2* mutations was found to be 2% (0.7% in *BRCA1* and 1.3% in *BRCA2*).[6] Studies of white subjects from Washington State (age less than 35, 203 unselected for family history) found 9.4% mutations in *BRCA1* and *BRCA2* (5.9% in *BRCA1* and 3.4% in *BRCA2*).[7 16] Peto *et al*[4] found that 5.9% of women from the United Kingdom diagnosed with breast cancer at younger than 36 years of age were carriers (3.5% in *BRCA1* and 2.4% in *BRCA2*). The variation in the results of such studies is probably because of differences in the characteristics of the patient population studied, such as the age of diagnosis of the proband and the degree of family history of cancer. Variation

in the sensitivity of the molecular techniques used or completeness of the screening of the genes will also account for differences in the reported results. Additional variability in the results of population based studies may be attributed to the variable contribution of founder mutations in different ethnic populations.[7 18–20]

We found that a younger age at diagnosis of the proband was associated with carrier status for *BRCA1*, but not for *BRCA2*, in the multivariable model. *BRCA1* mutation frequency in the probands diagnosed at age 35 or younger was 9.4% (5/53). These findings are consistent with others suggesting that *BRCA1* mutation is associated with young age of cancer diagnosis of the proband. Fifty-three of the 314 probands were those diagnosed under age 36 and were unselected for family history. Our observed proportion of 9.4% *BRCA1* mutations in this group of patients can be directly compared to proportions of 3.5% and 3.4% identified in other population based studies of similarly aged women.[4 16] As discussed earlier this difference may be because of differences in the ethnicity mixture or the sensitivity of the techniques used.

Family history of breast or ovarian cancer was the characteristic most strongly associated with *BRCA1* mutation, but only if young age at onset was included as part of the definition (tables 3 and 4). It should be noted that along with first degree young relatives, having a young second or third degree relative was also a strong indicator of *BRCA1* mutation carrier status. Of those who qualified for inclusion because of having at least one second or third degree relative with breast cancer at age 35 or younger or ovarian cancer at age 60 or younger, 13% (6/46) carried *BRCA1* mutations. These findings indicate that both family history of breast or ovarian cancer and the age of diagnosis of the relatives are important factors in identifying families with *BRCA1* mutations. Comparing estimates of mutation frequency in probands with a family history in published reports is difficult owing to the variability of the ascertainment criteria used in different studies. In general, there is agreement that family history of breast cancer is an indicator for predicting *BRCA1* mutations. However, there is a stronger consensus that younger age of diagnosis in the relatives is a better predictor of these.[6 17 23 24]

We have also examined, in a univariate analysis only, whether family history of ovarian cancer alone is a good predictor for identifying *BRCA1* mutation carrier families. Relatives with ovarian cancer at age 60 or younger in the first, second, or third generations were considered as positive. We found that ovarian cancer in the family was significantly associated with *BRCA1* carrier status and 15% (6/40) of those with such a history were carriers. *BRCA2* mutations were not associated with the presence of ovarian cancer status in the family. The predictive value of having a relative with ovarian cancer in determining the *BRCA1* mutation status is well supported in several other studies.[3 17 19 22 25 26]

In contrast to *BRCA1* mutations, *BRCA2* mutations in this study did not show any significant association with age of diagnosis of the proband or strong family history, with the exception of having two or more second degree relatives with breast or ovarian cancer at any age. Several studies have indicated that *BRCA2* is less penetrant than *BRCA1*, and that it is not as strongly associated with the age or family history of the proband as is *BRCA1*.[3 17 27 28] The results in this study are consistent with this hypothesis.

Interestingly, *BRCA2* mutations were most strongly associated with the criterion defining probands with either multiple breast primaries or both breast and ovarian cancer. Among probands meeting this criterion, only one proband, a *BRCA2* mutation carrier, had both breast and ovarian cancer, whereas the remainder had multiple breast cancers. Most probands with multiple breast primaries had their second primary in the contralateral breast, although nine were determined to have second ipsilateral primaries. The presence of a second ipsilateral breast cancer was determined to be a primary and

not a recurrence by a review of all the available pathological information. This includes consideration of location, histology, grade, and the presence of ductal carcinoma in situ in both tumours. When tissue from both tumours was available, a full pathology review was done. Most multiple breast tumours in this sample were contralateral. The presence of *BRCA1* and *BRCA2* mutations has been shown to be more common in families where there is a woman with breast cancer and a second non-breast primary when compared to those without a second primary.[29] However, the finding that multiple primaries would be strongly associated with *BRCA2*, but not with *BRCA1*, was unexpected. There are some possible explanations for this finding. The association of multiple primaries with *BRCA2* mutations could be the result of increased survival in carriers of *BRCA2* mutations, who are subsequently diagnosed with a second tumour. It could also indicate that the risk of breast cancer in *BRCA1* mutation carriers decreases with age, as suggested by Verhoog *et al*,[30] whereas the risk in *BRCA2* mutation carriers increases with age. Thus, as they age, *BRCA2* mutation carriers may have an increasing risk of developing a second tumour compared to *BRCA1* mutation carriers. To our knowledge, this finding has not been reported previously and may help to understand the nature of double primary breast or ovarian cancer better. This question should be considered further in future studies. *BRCA2* mutations were not associated with having relatives with multiple primary tumours in this study, probably because of the few cases in this group.

The only criterion that was associated with both *BRCA1* and *BRCA2* mutations was having an Ashkenazi Jewish background. Interestingly, this was the only criterion that was associated equally significantly with both *BRCA1* and *BRCA2* mutations. This may be because of the higher incidence of both mutations in the Ashkenazi Jewish population as has been shown previously.[27 31]

CONCLUSION

In this study we used a population based sample to characterise the clinical impact of *BRCA1* and *BRCA2* mutations in families with breast cancer. Consistent with previous studies, a family history of breast and ovarian cancer with young age at onset is a strong indicator of *BRCA1* mutations. We found that this is true even when breast or ovarian cancers occurred in second or third degree relatives. Regardless of age of diagnosis, family history of breast and ovarian cancer compared to history of breast cancer only is also a strong indicator of *BRCA1* mutations. Ashkenazi Jewish background was significantly associated with both *BRCA1* and *BRCA2* mutations. Of particular interest, we report that *BRCA2* mutations were strongly associated with having multiple primary breast cancers. These associations will help us to identify families for *BRCA1* or *BRCA2* mutational analysis better, providing better clinical management and use of laboratory resources.

APPENDIX

The following members of the Ontario Cancer Genetics Network contributed to this study.
Hamilton: Dr Edmond Chouinard, Ellen Irwin, Laura Hunnisett, Kathleen Bell, Dr Andrea Eisen. Kingston: Cara Rinaldi, Dr Jennifer MacKenzie, Lori VanManen, Dr Harriet Feilotter.

London: Dr Jay Engel, Gayle Sheridan, Dr Jack Jung, Nancy Scanlan. North east: Claire McChesney, Margaux Lachance. North west: Dr Dhali Dhaliwal. Linda Spooner, Cathy Gillies. Ottawa: Dr Judith Allanson, Dr Alasdair Hunter, Cathy Gilpin. Toronto: (Women's College Hospital) Danielle Hanna, Dr Steven A Narod, Alexander Liede; (Mount Sinai Hospital) Dr Pam Goodwin, Velita Contiga, Amy Thompson; (Princess Margaret Hospital High Risk Breast Cancer Clinic) Dr Paul Goss, Chia Chia Sun, Tammy Stothers; (Princess Margaret Hospital Familial Ovarian Cancer Clinic) Dr Barry Rosen, Dr Joan Murphy, Raluca Nedelcu, Susan Randall; (North York General Hospital) Dr Wendy Meschino, Heather Dorman, Joanne Honeyford; (Toronto Sunnybrook Regional Cancer Center) Dr Ellen Warner, Dr Pamela Chart, Tracy Graham, Maureen Seminsky, Lisa Di Prospero; (Credit Valley Hospital) Dr Debbie Terespolsky, Morag Bell, Jodi Campbell. Sault Ste Marie: Lori Russon, H Kwolek. North Bay: Kim MacDonald.

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