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Genetic Counselling Referral Rates and Uptake of *BRCA1* and *BRCA2* Testing among Women Diagnosed with Serous Ovarian Cancer in a Tertiary Care Cancer Centre

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Abstract

Rationale: In Ontario, all women diagnosed with serous ovarian, fallopian tube or primary peritoneal cancers are universally eligible for *BRCA* genetic testing (GT). We aim to document referral patterns and factors predictive of referral at the Juravinski Cancer Centre (JCC), Hamilton, ON.

Methods: Retrospective chart review of all patients with a diagnosis of serous ovarian, fallopian tube and primary peritoneal cancers seen at the JCC from January 2009 to December 2011 was completed. The percentage of these patients referred to the JCC genetics clinic was calculated. Potential factors prognostic for referral (age and stage at diagnosis, grade, existence of biological children, family history, provider, discussion of genetics referral) were analyzed by logistic regression.

Results: 226 eligible patients were identified; 73 (32%) were referred and 61 (84%) consented to testing. 11 (18%) were found to carry a *BRCA1* or *BRCA2* mutation. In univariable models, stage (p=0.013), genetics discussion within the first three visits (p<0.001), and family history of breast and/or ovarian cancer (p=0.002) were significant predictors of referral. Stage (p=0.017) and early discussion (<0.001) remained significant in multivariable model.

Conclusions: The referral rate of women with serous ovarian, fallopian tube and primary peritoneal cancers to our genetics program is currently suboptimal. Stage at diagnosis and early discussion of GT were significant prognostic factors for referral. This information will be used to explore alternative delivery models of *BRCA* testing services to optimize uptake of GT within this eligible population, and ultimately improve care.

Keywords: *BRCA* genetic testing; Cancer genetics

Introduction

Germline *BRCA1* and *BRCA2* mutations are identified in approximately 10-25% of unselected patients with invasive ovarian cancer [1-5] and 30% of women with fallopian tube cancer [6]. Family history is one of the most critical pieces of information related to likelihood of a *BRCA1* or *BRCA2* mutation, but it is not always consistently recorded or used by clinicians to determine appropriateness of a genetics referral [1,5-7]. There are a variety of additional factors that are associated with an increased likelihood of a patient harbouring a deleterious *BRCA1* or *BRCA2* mutation including serous high grade histology, family history [4] and ethnicity [8], however, no one factor is sufficient for comprehensively identifying *BRCA1* or *BRCA2* mutation carriers [9]. It has therefore been recommended that genetic testing be considered in all women with a diagnosis of serous ovarian cancer, fallopian tube cancer or primary peritoneal cancer regardless of family history or other risk factors [3-5].

In Ontario, access to genetic counselling and genetic testing is primarily obtained through physician referral to a familial cancer clinic. Ideally, *BRCA1* and *BRCA2* genetic testing occurs using a blood sample obtained from a family member who was diagnosed with breast or ovarian cancer. Since 2001, all women with a diagnosis of serous ovarian cancer, fallopian tube cancer or primary peritoneal cancer have been eligible for germline *BRCA1* and *BRCA2* genetic testing under the criteria defined and funded by the Ministry of Health in Ontario, Canada. Despite this, referral rates for these women are less than expected at sites across North America [9-12].

The purpose of this study was to determine the rate of referral within a large, tertiary care centre for genetic testing among patients diagnosed with serous ovarian cancer, primary peritoneal cancer or fallopian tube cancer over a 3 year period, and to identify factors which might be associated with referral patterns. Secondary aims of this review were to determine the percentage of patients who attended a genetic counselling appointment following referral, the uptake *BRCA1/2* testing among these patients and the proportion of *BRCA1* or *BRCA2* mutations carriers within the tested population.

Methods

Research ethics board approval was obtained to review records on all women with histologically confirmed serous ovarian cancer, primary peritoneal cancer or fallopian tube cancer seen at the Juravinski Cancer Centre between January 1, 2009 and December 31, 2011. All other

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histology types, including non-epithelial ovarian cancer, were excluded from this analysis. A retrospective chart review was undertaken to obtain primary oncology provider, patient age at diagnosis, grade and stage of cancer, documentation of a genetics discussion within the first three visits, family history of breast and/or ovarian cancer, and whether the patient was identified as having living biological children. A referral was said to occur if the patient was entered into the genetics referral database.

Descriptive statistics were used to summarize the patient characteristics. Logistic regression was used to investigate which characteristics were prognostic for patients having a referral to the genetics clinic. Each covariate was investigated univariately and then a multivariable model was constructed using a forward selection process. All tests were two-sided and a p-value of 0.05 or less was considered statistically significant. Similar methods were used to investigate whether genetic testing occurred amongst those who were referred.

Results

Table 1 shows the characteristics of this patient population. There were 226 patients identified, and they had a mean (standard deviation) age of 63.9 (12.2) and 67 (19.6%) had a family history of breast and/or ovarian cancer. Seventy-three (32.3%) were referred to the genetics clinic. Of these 73 patients, the mean age was 62, compared with a mean age of 64.8 amongst those not referred. Over half of patients with stage 1-2 disease (18 of 33 or 54.6%) were referred, compared with only 29.2% (52 of 178) for those with stage 3-4 disease.

As one physician (#7) treated only one patient, data from this patient were excluded from the logistic regression analyses. Table 2 shows the results of the logistic regression analysis. In the univariable analysis, stage (p=0.013), a genetics discussion in the first 3 visits (p<0.001) and family history (p=0.002) were all statistically significant prognostic factors for a referral. Provider (p=0.074), having children (p=0.083) and age (p=0.11) all approached, but did not attain, statistical

		All	Referred	Not Referred
N		226	73 (32.3%)	153 (67.8%)
Age	Mean (std dev)	63.9 (12.2)	62.0 (12.0)	64.8 (12.2)
N (%) Stage	1-2 3-4 Unknown	33 (14.6) 178 (78.8) 15 (6.6)	18 (54.6) 52 (29.2) 3 (20.0)	15 (45.5) 126 (70.8) 12 (80.0)
N (%) Provider	1 2 3 4 5 6 7	65 (28.8) 35 (15.5) 11 (4.9) 44 (19.5) 38 (16.8) 32 (14.2) 1 (0.4)	28 (43.1) 7 (20.0) 2 (18.2) 10 (22.7) 16 (42.1) 10 (31.3) 0 (0.0)	37 (56.9) 28 (80.0) 9 (81.8) 34 (77.3) 22 (57.9) 22 (68.8) 1 (100.0)
N (%) with Children	Yes No	194 (85.8) 32 (14.2)	67 (34.5) 6 (18.8)	127 (65.5) 26 (81.3)
N (%) Genetics Discussion in 1st 3 visits (n=225)	Yes No	44 (19.6) 181 (80.4)	35 (79.6) 38 (21.0)	9 (20.5) 143 (79.0)
N (%) with Family History	Yes No	67 (29.7) 159 (70.4)	32 (47.8) 41 (25.8)	35 (52.2) 118 (74.2)
N (%) Grade	Low/Intermediate High Unavailable	24 (10.6) 154 (68.1) 48 (21.2)	5 (20.8) 52 (33.8) 16 (33.3)	19 (79.2) 102 (66.2) 32 (66.7)

Table 1: Baseline characteristics of study population.

Factor	Definitio	Odds Ratio (95% CI)	p-value
Univariable Models			
Age	/ decade	0.83 (0.66-1.04)	0.11
Stage	1-2 3-4 Unknown	4.80 (1.14-20.24) 1.65 (0.45-6.09) Reference	0.013
Provider	1 2 3 4 5 6	Reference 0.33 (0.13-0.87) 0.29 (0.06-1.47) 0.39 (0.17-0.92) 0.96 (0.43-2.16) 0.60 (0.25-1.47)	0.074
Children	Yes vs No	2.29 (0.90-5.83)	0.083
Discussion in 1st 3 visits	Yes vs No	14.63 (6.48-33.07)	<0.001
Family History	Yes vs No	2.63 (1.45-4.78)	0.002
Grade	Low/Intermediate High Unknown	0.53 (0.17-1.67) 1.02 (0.51-2.03) Reference	0.46
Multivariable Model			
Discussion in 1st 3 visits	Yes vs No	17.93 (7.69-41.82)	<0.001
Stage	1-2 3-4 Unknown	6.55 (1.27-33.82) 1.44 (0.32-6.52) Reference	0.017

Table 2: Logistic regression analyses of factors associated with referral.

significance. In the multivariable model, having a genetics discussion in the first 3 visits (p<0.001) and disease stage (p=0.017) entered the model. Having a genetics discussion in the first 3 visits increased the odds of referral by 17.93 times (95% confidence interval [CI]: 7.69-41.82), while patients with stage 1-2 cancers had a 6.55 times increased odds (95% CI: 1.27 to 33.82) of a referral compared with those with unknown stage.

61/73 (86.3%) of patients who were offered a referral attended a genetic counselling appointment. 11 patients declined the consultation and 1 patient died prior to her appointment. 61/61 (100%) of patients who attended a genetic counselling appointment consented to *BRCA1* and *BRCA2* genetic testing.

Table 3 shows the characteristics of patients who were referred, while Table 4 shows the results of the logistic regression analyses looking at factors prognostic for testing amongst those patients who were referred. Both patients referred by provider #3 and all 3 patients with unknown disease stage who were referred had genetics testing performed; thus, these data were excluded from the regression analysis of factors prognostic for testing. No variable was statistically significant as a prognostic factor for having genetic testing performed, once the patient was referred. The reduced statistical power due to the relatively small sample size may be a contributing factor as only 12 patients in this sample did not have genetic testing performed.

Discussion

Approximately 32% of our patient population was referred for genetic counselling, with referrals by provider varying between 18 and 42%. The reasons for non-referral of this population are likely multifactorial. The results of our study indicate that a discussion of genetics soon after a diagnosis is made significantly improves likelihood of a referral to genetic counselling and that referrals are more likely to be made in patients with stage 1 or 2 disease. It is possible that the missed opportunity for referrals in patients with later stage disease reflects the complexity or acuity of disease taking necessary priority over consideration of genetic testing. A referral remains appropriate for these patients. The family should be made aware of the importance of obtaining a blood sample from an affected family member. This can help to prevent the challenging situation which arises when women are seen due to a family history of ovarian cancer, but whose affected relatives

		All	Not Tested	Tested
N		73 (32.3%)	12 (16.4)	61 (83.6)
Age	Mean (std dev)	62.0 (12.0)	66.2 (12.5)	61.2 (11.8)
N (%) Stage	1-2 3-4 Unknown	18 (24.7) 52 (71.2) 3 (4.1)	1 (5.6) 11 (21.2) 0 (0.0)	17 (94.4) 41 (78.9) 3 (100.0)
N (%) Provider	1 2 3 4 5 6	28 (38.4) 7 (9.6) 2 (2.7) 10 (13.7) 16 (21.9) 10 (13.7)	6 (21.4) 1 (14.3) 0 (0.0) 2 (20.0) 2 (12.5) 1 (10.0)	22 (78.6) 6 (85.7) 2 (100.0) 8 (80.0) 14 (87.5) 9 (90.0)
N (%) with Children	Yes No	67 (91.8) 6 (8.2)	11 (16.4) 1 (16.7)	56 (83.6) 5 (83.3)
N (%) Genetics Discussion in 1st 3 visits	Yes No	35 (48.0) 38 (52.0)	6 (17.1) 6 (15.8)	29 (82.9) 32 (84.2)
N (%) with Family History	Yes No	32 (43.8) 41 (56.2)	5 (15.6) 7 (17.1)	27 (84.4) 34 (82.9)
N (%) Grade	Low/Intermediate High Unavailable	5 (6.9) 52 (71.2) 16 (21.9)	1 (20.0) 7 (13.5) 4 (25.0)	4 (80.0) 45 (86.5) 12 (75.0)
N (%) Result of Genetic Testing	Uninformative BRCA1 + BRCA2 +	50 (82.0) 6 (9.8) 5 (8.2)	-	-

Table 3: Baseline characteristics of patients referred for genetic counseling.

Factor	Definitio	Odds Ratio (95% CI)	p-value
Univariable Models			
Age	/ decade	0.68 (0.38-1.21)	0.19
Stage	1-2 3-4	4.56 (0.55-38.14) Reference	0.16
Provider	1 2 3 4 5 6	Reference 1.64 (0.16-16.35) Not Calculated 1.09 (0.18-6.56) 1.91 (0.34-10.82) 2.46 (0.26-23.40)	0.90
Children	Yes vs No	1.02 (0.11-9.59)	0.99
Discussion in 1st 3 visits	Yes vs No	0.91 (0.26-3.13)	0.87
Family History	Yes vs No	1.11 (0.32-3.90)	0.87
Grade	Low/Intermediate High Unknown	1.33 (0.13-15.70) 2.14 (0.54-8.55) Reference	0.55

Table 4: Logistic regression analyses of factors associated with genetic testing.

did not have genetic testing prior to their death. For these unaffected female relatives, they would not qualify for *BRCA1* and *BRCA2* genetic testing unless they have a family history which is otherwise strongly suggestive of hereditary breast and ovarian cancer. When *BRCA1* and *BRCA2* genetic testing is offered, it is often uninformative in the absence of a result from an affected family member.

This study has limitations in that the data account for referral and testing patterns from a single cancer centre, and may not reflect the experience of other institutions. In addition, a retrospective review of medical notes may not accurately reflect the discussions between patients and their physicians about genetic testing. The reasons for low referral rates likely include patient factors that cannot be measured by this type of analysis. It is possible that a larger number of women actually declined the offer of a referral. In our patient population, 11 of the 73 women referred declined the appointment. If a referral is not generated and the discussion is not captured in their chart notes, this would lead to an underestimate of the referral rates. This type of review also cannot capture the reasons that women may chose to decline a referral, including concerns about potential psychological harms associated with genetic testing, family communication and confidentiality issues, and insurance discrimination.

The literature suggests a high level of interest in genetic testing in this population, particularly if it would affect their treatment and/or benefit their family members [9,13]. In our study population, 11 new carriers, representing 18% of patients who underwent genetic testing, were identified as carrying a deleterious *BRCA1* or *BRCA2* mutation. The majority of carriers had high grade disease and a positive family history of breast and/or ovarian cancer, as expected. Two of the 11 (18%) patients with a *BRCA* mutation did not report a positive family history, highlighting the importance of offering testing universally to these women. Additionally, by extrapolating these results to the entire study population, potentially 30 patients with a deleterious *BRCA1* or *BRCA2* mutation were seen at the JCC but not tested representing a missed opportunity.

Optimizing referrals in this population has important clinical implications. It is becoming increasingly evident that *BRCA1* and *BRCA2* related ovarian cancers may be associated with improved survival [14,15]. Although an ovarian cancer diagnosis is likely to represent the most significant risk in terms of mortality for these women, an overall trend towards improved survival in this population will be relevant in the ongoing care of patients with *BRCA1* or *BRCA2* mutations who are in clinical remission from their ovarian cancer, but remain at significantly increased risk to develop primary breast cancer [16]. Further, knowledge of *BRCA* mutation status may become integral to the delivery of personalized treatment as emerging data suggests these patients have a unique chemosensitivity profile and may additionally benefit from the use of novel targeted therapies such as PARP inhibitors [17]. Beyond the patient, the significance of this information to family members is considerable as the identification of a familial *BRCA1* or *BRCA2* mutation allows for highly accurate predictive genetic testing for at-risk family members.

We propose that cancer treatment centres should consider a mechanism that results in an automatic referral of these patients for discussion of *BRCA1* and *BRCA2* testing soon after a diagnosis is made. Rapid access for genetic counselling and *BRCA1* and *BRCA2* testing has been evaluated in the women with newly diagnosed breast cancer, and is associated with a high level of uptake of genetic testing [18]. This would be of significant benefit to women with ovarian cancer, particularly if they had a guarded prognosis, and/or if this information was important for treatment planning. Furthermore, it would be reasonable to consider an abbreviated genetic counselling process to the extent that a detailed three generation family history is not immediately needed in order to determine eligibility for *BRCA1* and *BRCA2* testing. Family history information should ultimately be obtained in order to rule out the possibility of other cancer genetics syndromes that can predispose women to ovarian cancer, such as Lynch syndrome. The process by which improving referral rates could be achieved might include the inclusion of testing eligibility on pathology reports [9] and/or embedding a genetic counsellor within the multidisciplinary oncology team for these patients.

Determining the most appropriate models of service delivery for this patient population will require further study, however, novel approaches should be considered given the significant hereditary component of ovarian cancer and the importance of this information to these patients and their family members.

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