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Referral Rate for, and Uptake of Genetic Testing in Women Diagnosed with Breast Cancer ≤ 35 and Triple Negative Breast Cancer (TNBC) ≤ 50

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Abstract

Background: With the advent of novel treatment options for women with known *BRCA* status and breast cancer, it is important to understand the process and efficiency of referral to a genetics program.

Objectives: To understand the referral rate to the Cancer Risk Assessment Clinic for women under and including age 35 with newly diagnosed breast cancer and women under and including age 50 with newly diagnosed triple negative breast cancer at the Juravinski Cancer Centre (JCC) from January 1, 2012 until December 31, 2015 with attention to the time between referral and first genetic counseling appointment, referral and uptake of *BRCA*1/2 testing, uptake and lab report, and time to disclosure of *BRCA*1/2 test results to the patient.

Methods: All patients meeting the inclusion criteria were identified and reviewed through the decision support database at JCC. Descriptive statistics were used to summarize patient characteristics, cancer parameters and treatment information. Logistic regression analysis was used to investigate factors which are potentially associated for receipt of a referral to the Cancer Risk Assessment Clinic. Factors including: Patient age, disease stage, pathology, physician specialty, family history, having a discussion around genetics at intake, time from first cancer centre appointment and time from surgery to diagnosis were investigated. Univariate and then a multivariable model was constructed using a forward stepwise selection process from these factors. Analyses were performed in SAS (v 9.2 SAS Institute, Cary, NC) and R (v 3.2.2, www.r-project.org). Regression analyses were two-tailed and statistical significance was defined as a p-value of 0.05 or less.

Results: Five hundred and fifty-six women with breast cancer who were seen as new patients at JCC from January 2012 to December 2015 were identified. Of this number, 50 women were included in this study. Of these 50 patients, 60% were referred to the Cancer Risk Assessment Clinic for genetic counselling. Of the 60% of women referred to genetics, 8 (16%) had stage 1 disease, 26 (52%) has stage 2 disease, 13 (26%) had stage 3 disease, and just 1 (2%) had stage 4 disease. One person (2%) included in this study had an unknown disease stage, and one other person (2%) had ductal carcinoma *in situ*. Just over half (58%) of the study participants were referred to the Cancer Risk Assessment Clinic within their first three visits to the JCC. All women referred to the Cancer Risk Assessment Clinic attended their genetic counselling appointment and consented to genetic testing. Time from referral to their first genetic counselling appointment was on average 3 weeks (0, 30.1). The numbers in brackets represent the minimum and maximum amount of time waited (days, weeks, or months). The time from drawing the blood sample to revelation of the test result was a mean of 3.6 days (1, 16.1). The time from the lab result to disclosure to the patient was a mean of 1.8 days (0.1, 9.3). Factors that predicted referral by univariate analysis were patient age (p = 0.001), the physician (p = 0.013), and whether a discussion of genetics was done at intake. Only age and pathology disease grade were predictive by multivariate analysis.

Conclusion: The current rate of referral of patients in the presented study is 60%. In an ideal world, this number would be sitting at or near 100%. This study was conducted as an internal quality control measure for the Juravinski Cancer Centre. We conclude that the system at JCC has a number of limitations in optimizing patient referrals in a timely fashion.

Introduction

Breast cancer is a potentially fatal malignancy. This form of cancer is the most common among Western women [1]. Breast cancer is a heterogeneous disease. Clinically, one can classify it based on biomarker expression (e.g. estrogen receptors, progesterone receptors,

and HER-2 expression). Triple negative breast cancer is a unique type where the tumors are negative for estrogen receptors, progesterone receptors, and HER-2 expression which results in a more aggressive biology and treatment approach [2]. Despite recent declines in the mortality rate of breast cancer in the province of Ontario, nearly 10,000 women are expected to be diagnosed with the disease in the new year [3] and it is estimated that 17% of breast cancers occur in women under the age of 50 [4].

In the 1990's *BRCA*1 and *BRCA*2 tumor suppressor genes were discovered [5]. These genes can be genetically mutated causing uncontrolled cell growth or an inability to regulate cell death [6]. These mutations increase the risk of developing certain cancers, such as breast cancer. Ontario has the largest proportion of breast cancer cases in Canada (39%) [4]. Since 2001, women diagnosed with breast cancer before the age of 50 are eligible for a referral for germline *BRCA*1 *and BRCA*2 genetic counseling or testing under the criteria established by the Ontario Ministry of Health and Long Term Care (MOHLTC) [6]. Individuals in Ontario who are interested in pursing genetic testing must be assessed by a genetic counselor and meet at least one of the MOHLTC criteria prior to being offered genetic testing [6]. The MOHLTC criteria include: Having multiple cases of breast cancer on the maternal and or paternal side of the family, being diagnosed with breast cancer at or under 35 years of age, having a family member diagnosed with both breast and ovarian cancer, the presence of breast and/or ovarian cancer in a family of Jewish ancestry, having a family member with breast cancer in both breasts, having a family member with serous ovarian, fallopian tube, or primary peritoneal cancer, having a male family member with breast cancer, having a family member with a *BRCA*1/2 mutation, or having a familial history suggesting any other type of hereditary cancer [7]. In a small number of cases, a genetic counselor may relied on a number of validated risk calculation tools to determine the presence of a 10%, or greater, a priori risk of having hereditary breast or ovarian cancer syndrome [6]. One often used to quantify an individual's risk is the BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) [8]. If the risk is 10% or more, the individual is eligible for genetic analysis. There is an emphasis on genetic consultation in Ontario because the benefits are two-fold. If a mutation in found in the *BRCA*1 or *BRCA*2 genes of an affected patient, genetic consultation allows for a discussion around novel treatment options such as the newly discovered Poly-ADP-Ribose Polymerase (PARP) inhibitors [9]. It also allows for the testing family members where the the discovery of a *BRCA*1 or *BRCA*2 mutation may lead to preventative measures including prophylactic mastectomy and/or preventative tubo-ovar-

ian surgery, which can be associated with a survival benefit [9]. Genetic testing of the *BRCA*1 *and BRCA*2 genes involves the drawing of a blood sample from the at-risk patient. The financial burden of the test is covered by the MOHLTC when the risk is present [6]. It is estimated that approximately 10% of women with breast cancer will have a genetic mutation in the *BRCA*1/2 gene [6]. A woman with a *BRCA*1 mutation has a 57% chance of developing breast cancer in her lifetime whereas a woman with a *BRCA*2 mutation has a 49% lifetime risk [5]. Additional risks arise in women who are carriers for *BRCA*1/2 mutations including that they are at an increased risk of developing a second breast cancer in the contralateral breast [5]. Therefore, early detection and intervention of *BRCA*1/2 positive and cancer affected individuals have the potential to improve survival rates, course of treatment, and quality of life, subsequently reducing the burden of disease and costs of treatment.

The Hamilton-Niagara-Brant Haldimand-Wentworth-Local Health Integrated Network (HNBW LHIN) is one of 14 LHINs in Ontario Canada. It is home to 1.4 million people. The LHIN is a mechanism to plan, integrate and fund health care for the region. There are two cancer centres in the LHIN (Juravinski Cancer Centre (JCC), Hamilton and Walker Family Cancer Centre, St. Catharines). JCC is a component of the Hamilton Health Sciences Centre (HHSC). The only Cancer Risk Assessment unit for cancer genetic counselling and testing for this LHIN located at the JCC. Any physician can refer a patient to the Cancer Risk Assessment Unit. However, genetic testing can only be ordered by genetic counselors as per guidelines from the MOHLTC which is covered within the health care budget. For breast cancers, all women diagnosed with breast cancer who are aged 35 and under and all women diagnosed with triple negative breast cancer who are aged 50 and under are eligible for germline *BRCA1* and *BRCA2* genetic testing. Other criteria for genetic testing exist and typically include family history of breast and/or ovarian cancers as previously mentioned.

Currently, wait times for a genetic counselling appointment in the Cancer Risk Assessment Clinic at JCC are between 4 and 6 months and the turn-around time

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for *BRCA1/2* testing is approximately 16 weeks. The primary purpose of this study is to determine what proportion of women eligible for genetic testing are referred and tested, and to determine wait times of the referral, testing, and result disclosure processes. The secondary aim is to investigate the factors that might be associated with referral and uptake of genetic testing.

Methods

This study was approved by the Hamilton Integrated Research Ethics Board. All women with breast cancer who were seen as new patients at the Hamilton Health Sciences Centre (HHC) from January 1, 2012 until December 31, 2015 were identified through a hospital based pathology database. This is a computerized information system that allows users to analyze and collect patient pathology reports. Included in this study were women with a diagnosis of breast cancer (who were aged 35 and under) and women with a diagnosis of triple negative breast cancer (who were aged 50 and under). Excluded were patients with papilloma, papillary lesions, usual ductal hyperplasia, fibroadenomas, fibrocystic changes, and women over 50 years of age.

For the included population, a retrospective chart review was conducted capturing information on patient characteristics (like age at breast cancer diagnosis, presence of living biological children, family or personal history of cancer), disease parameters (like breast cancer diagnosis and stage of disease), and treatment information (like date of first surgery for breast cancer, primary oncology provider). Using a data manual, this information was abstracted into Excel.

The source population was then identified in PROGENY (a genetics database) (Delray Beach, FL) for family history information and attendance to the JCC Cancer Risk Assessment Clinic. Of interest, were process parameters like the wait time from first cancer centre appointment to referral, time from referral to Cancer Risk Assessment consult, time from consult to testing, and time from testing to disclosure.

The primary objective of this analysis was to describe patient referral patterns to genetics, thus, descriptive statistics were used to summarize both patient characteristics and referral patterns. Logistic regression analyses were used to investigate if any patient characteristic was prognostic for a patient referral to genetics. Each factor (age, pathology, physician specialty, having a family history taken or discussion of genetics at intake, time from 1st cancer centre appointment and time from surgery to diagnosis) was investigated univariate and then a multivariable model was constructed using a forward selection process from these factors. Analyses were performed in SAS (v 9.2, SAS Institute, Cary, NC) and R (v 3.2.2, www.r-project.org), and regression analyses were two-tailed.

Results

Out of a possible five hundred and fifty-six women with breast cancer during the timeframe January 2012 to December 2015, 50 women were included in this study based on inclusion criteria. Of these 50 women, 60% had triple negative invasive ductal carcinoma, 8% had Infiltrating ductal carcinoma, and 32% had another type of breast can-

Table 1: Demographic Information.

Invasive ductal ca in the third column of the Table below is short form for invasive ductal carcinoma. Infiltrating ductal ca is short form for infiltrating ductal carcinoma. Note, in the "Current Diagnosis" row, second column, invasive ductal ca, triple negative is one category and corresponds to the first set of numbers in the corresponding results section. Infiltrating ductal ca, triple negative is the second category and corresponds to the second set of numbers in the corresponding results section, and so on. DCIS stands for ductal carcinoma *in situ*.

Characteristic	Statistics	Number (N) of Participants	Result
Age at Surgery	Mean (std. dev.)	50	39.2 (7.5)
Age at Diagnosis	Mean (std. dev.)	50	39.2 (7.5)
Current Diagnosis	Invasive ductal ca, triple negative	50	20 (40.0%)
	Infiltrating ductal ca, triple negative		10 (20.0%)
	Infiltrating ductal ca		4 (8.0%)
	Other		16 (32.0%)
Clinical Disease Stage	N (%) DCIS	50	1 (2.0%)
	1		8 (16.0%)
	2		26 (52.0%)
	3		13 (26.0%)
	4		1 (2.0%)
	Unknown		1 (2.0%)
Pathologic Grade	N (%) 1	50	1 (2.0%)
	2		8 (16.0%)
	3		40 (80.0%)
	Missing		1 (2.0%)
Living Children	N (%) Yes	50	34 (68.0%)
Prior Diagnosis of Cancer	N (%) Yes	50	1 (2.0%)

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cer (Table 1). The mean age of this population of women at the time of their diagnosis was 39 years of age and 68% of them had living children (Table 1). Out of that sample (50 women), 60% were referred to the Cancer Risk Assessment Clinic for genetic counselling (Table 2). Disease stage at the time of referral was as follows: Stage 1 (16% of women), stage 2 (52% of women), stage 3 (26% of women), stage 4 (2% of women) (Table 1). The grade of breast cancer based on the pathology report was as follows: Grade 1 (2% of women), grade 2 (16% of women), grade 3 (80% of women) (Table 1). A family history was taken by clinicians in the cancer centre and reported from all patients (100%) (Table 3). Results revealed that 8% of women had a family history of ovarian cancer, 38% of women had a family history of breast cancer, 6% of women had a family history of both ovarian and breast cancer, and 46% of women did not have a family history of either types of cancer (Table 3). The degree of relatedness was not always reported. Study participants were referred to the Cancer Risk Assessment Clinic within their first three visits to the JCC in 58% of women (Table 3). The time between the first cancer center appointment and the first genetic consult was about 1 month (Table 2). In terms of physician discipline, surgical oncologists referred patients to genetics 34% of the time and medical oncologists referred patients 28% of the time (Table 2). All women referred to the Cancer Risk Assessment Clinic attended their genetic counselling appointment, 93% consented to genetic testing, and 89% of women provided a blood sample on the same day as their first genetic consult (Table 4). Time from referral to their first genetic counselling appointment was on average 3 weeks (0, 30.1) (Table 2). The time from drawing the blood sample to revelation of the test result was a mean of 3.6 weeks (1, 16.1) (Table 4). The time from the lab result to disclosure to the patient was a mean of 1.8 days

Table 2: Genetics Referral Information.

In the Table below CC is short form for cancer centre. The data range may be negative in the results section if the patient had a referral to genetics, a genetic counselling appointment, or surgery before their first Juravinski Cancer Centre consult note. The numbers that represent a range in brackets indicate the minimum and maximum amount of time waited in weeks or months as indicated in the characteristics column.

Characteristic	Statistics	Number (N) of Participants	Result
Had a Referral to Genetic Counselling Session	N (%) Yes	50	30 (60.0%)
Referred by	Surgeon	30	12 (40.0%)
	Other		18 (60.0%)
1st CC Appointment to Referral (months)	Median (range)	30	0 (-27.2, 5.7)
Surgery to Referral (months)	Median (range)	30	12 (-854, 185)
1st CC Appt. to Genetic Consult (months)	Median (range)	30	0.8 (-23.5, 12.5)
Referral to Genetic Consult (weeks)	Median (range)	30	3 (0, 30.1)

Table 3: Patient Encounter Information.

In the Table below OC/BC stands for ovarian cancer or breast cancer. CC is short form for cancer centre. Data range may be negative in the results section if the patient had surgery prior to visiting the Juravinski Cancer Centre (CC). The numbers that represent a range in brackets indicate the minimum and maximum amount of time waited in days as indicated in the characteristics column.

Characteristic	Statistics	Number (N) of Participants	Result
JCC Physician	Surgeon	50	34 (68.0%)
	Other		16 (32.0%)
JCC Physician Discipline	Medical Oncologist	50	14 (28.0%)
	Surgeon		34 (68.0%)
	Genetic Counsellor		1 (2.0%)
	Radiation Oncologist		1 (2.0%)
Family history taken at intake	N (%) Yes	50	50 (100%)
Discussion of genetics at intake	N (%) Yes	50	29 (58.0%)
Positive history of OC/BC	N (%) Ovarian	50	4 (8.0%)
	Breast		19 (38.0%)
	Both		3 (6.0%)
	Neither		23 (46.0%)
	Unknown		1 (2.0%)
Family History	1st Degree Relative	50	6 (12.0%)
	2nd Degree Relative		16 (32.0%)
	3rd Degree Relative		3 (6.0%)
	NA		23 (46.0%)
	Unknown		2 (4.0%)
Days, 1st CC Appointment to Surgery	Median (range)	50	3.5 (-349, 618)
Days, Surgery to Diagnosis	Median (range)	50	8.5 (2, 393)

Table 4: Details relating to the Genetic Test Result.

In the Table below *BRCA2* VUS is short form for a *BRCA2* variant of unknown clinical significance. The numbers that represent a range in brackets indicate the minimum and maximum amount of time waited in days or weeks as indicated in the characteristics column.

Characteristic	Statistics	Number (N) of Participants	Result
Consented to Genetic Testing, of N referred	N (%) Yes	30	28 (93.3)
Genetic Test Result	N (%) BRCA1+	28	9 (32.1)
	BRCA2+		2 (7.10)
	BRCA 1/2 Negative		16 (57.1)
	BRCA2 VUS		1 (3.6)
Genetic Consult to Testing (weeks)	Median (range)	28	0 (0, 39.4)
Testing on Same Day as Consult	N (%)	28	25 (89.3%)
Testing to Disclosure (days)	Median (range)	28	6.1 (2.6, 24.1)
Testing to Lab Date (weeks)	Median (range)	28	3.6 (1, 16.1)
Lab Date to Disclosure (days)	Median (range)	28	1.8 (0.1, 9.3)
Genetic Consult to Disclosure (weeks)	Median (range)	28	6.1 (2.6, 57.1)

Table 5: Factors influencing a referral to the cancer risk assessment centre by univariate analysis. A p-value less than 0.05 are considered statistically significant (predictive of a referral to genetics).

Characteristic	Comparison	Odds Ratio (95% CI)	p-value
Age at Diagnosis	/year	0.81 (0.71, 0.92)	0.001
Physician	Surgeon vs. Other	0.13 (0.03, 0.65)	0.013
Surgery to Diagnosis	Days	0.99 (0.97, 1.02)	0.44
Genetics Discussion at Intake	Yes vs. No	266 (22, > 1000)	< 0.001
Positive History of OC/BC	Yes vs. No	3.21 (0.98, 10.45)	0.053
1st Degree Relative	Yes vs. No	3.80 (0.41, 35.28)	0.24
Living Children	Yes vs. No	0.58 (0.16, 2.02)	0.39
Clinical Stage	3-4 vs. DCIS-2	0.89 (0.25, 3.12)	0.85
Pathology Grade	3 vs. 1-2	0.68 (0.15, 3.10)	0.61

Table 6: Factors influencing a referral to the cancer risk assessment centre by multivariable analysis.

Characteristic	Comparison	Odds Ratio (95% CI)	p-value
Age	/year	0.70 (0.56, 0.87)	0.002
Pathology Grade	3 vs. 1-2	20.68 (1.23, 348.7)	0.036

(0.1, 9.3) (Table 4). The time from the first genetic consult to disclosure of the test result was 6 weeks (2.6-57.1) (Table 4). Of the 50 women included in the study, 32% tested *BRCA1* positive, 7% tested *BRCA2* positive, 3.6% tested *BRCA2* positive with a variant of uncertain significance, and 57% tested *BRCA1* and *BRCA2* negative (Table 4). Factors that predicted referral by univariate analysis were patient age (p = 0.001), physician (p = 0.013), and whether a discussion of genetics was done at intake (Table 5). Only age and histology were predictive of a referral to genetics by multivariate analysis (Table 6).

Discussion

All 50 of the women with breast cancer included in this study were eligible for *BRCA* testing regardless of family history. Despite this fact, only 60% of these patients were actually referred to the Cancer Risk Assessment Clinic. Since genetic counselling is considered standard of care for patients under the age of 50 with breast cancer, this analysis suggests room for improvement in both the rate of referral and time to results of genetic testing at JCC. To our knowledge, an internal quality control study assessing the genetics referral pattern of patients with breast cancer has not been performed in comparable institutions.

The rate of referral to the Genetic Risk Assessment Clinic varies by physician discipline and the reasons for this are not entirely clear. The study revealed that patient age, histology, physician discipline, and whether or not a discussion of genetics was done at intake were the factors predicting a referral for genetic analysis. More patients with grade 3 breast cancer were referred for an assessment. This would be expected in the patient population studied (triple negative breast cancer). Patients with a *BRCA* mutation may benefit from the use of PARP inhibitors, a novel therapy option that is currently under study. Genetic counselling is considered a standard of care for all patients meeting eligibility criteria in this study. Based on our findings, referral rates and uptake of genetic testing for all eligible women should be improved at our centre. Genetic counselling and analysis of the *BRCA1/2* genes can play a role in breast cancer prevention in the province of Ontario. If all patients with breast cancer aged 35 and under and all patients aged 50 and under with TNBC were referred for genetic counselling and analysis of the *BRCA1/2* genes, agreed to testing, and

tested positive for a mutation, their immediate family members would qualify for a genetic risk assessment funded by MOHLTC. Genetic counselling would allow affected cancer patient's female family members to explore cancer prevention options such as chemoprevention and prophylactic surgeries. In this study 40% of women with cancer were not referred for genetic risk assessment which deprives not only the patient, but also their family members of access to counselling and possible testing. While breast cancer rates have remained relatively Stable since the 1980's, breast cancer continues to be one of the most commonly diagnosed cancers in women. 38.5% of women in Ontario alone were newly diagnosed with breast cancer in 2016 [5]. With increased referral and uptake of genetic testing, this number could be greatly minimized with the cancer prevention options available to high-risk, *BRCA1/2* mutation carriers.

One possible solution to increase the rate of referral to genetic counselling and analysis of the *BRCA1/2* genes is to implement a two-stage approach to genetic risk assessment in primary care, as proposed by Atienza, et al. [8]. In this particular model, the first stage is intended to collect a limited amount of information from the patient. This information is then analyzed using a simplified version of a risk assessment tool such as the *BRCA*PRO [8]. If the initial assessment risk is relatively high, then more detailed information is collected and a more extensive tool is used. Atienza, et al. discovered that a two-stage approach allowed for the identification of a number of *BRCA1/2* carriers without the need to collect and evaluate an entire family history [8]. If JCC were to implement a similar two stage approach to genetic risk assessment of using their own risk assessment tools in primary care, large-scale genetic risk assessment could take place, potentially minimize the burden of genetic counselling on counsellors and freeing up time and resources in the Cancer Risk Assessment Clinic for new patient referrals. The implementation of such a model could ultimately minimize wait times and turnaround times in genetics, ultimately benefiting all patients.

This study is limited in that it is a retrospective review of patient charts which may not adequately capture all details discussed at the time of consultation and follow-up. As a result, it is possible that we may be missing important information that might have been considered regarding genetic testing during these encounters which could artificially decrease the referral rate as it may have been offered and declined. Additionally, the source population in this cohort of patients was taken from the pathology data base. There is the potential of lost cases due to missed coding of diagnosis, which would decrease the denominator of the potential cases. This is also the first quality control study done using breast cancer patients when assessing referral rate to genetics so we cannot compare this study to a previous quality control study performed with the same disease population

because one does not exist. The strengths of this study include clear inclusion and exclusion criteria, a standardized manner of drawing cases, and available data from electronic health records both in the cancer centre and the cancer risk assessment centre.

Conclusion

The rate of referral for women with breast cancer included in this study (only women breast cancer 35 years of age and under and women with triple negative breast cancer 50 years of age and under) to the Cancer Risk Assessment Clinic at JCC is 60%. This information can be used as an internal quality control measure for referring clinicians that will be disseminated to the breast oncology disease site team at JCC to improve referral rate of these patients in the future. This information may lead to increased awareness and access to genetic counseling services, the benefits of which can include access to genetic testing, accurate risk assessment and the provision of personalized recommendations for early detection and prevention of *BRCA*-related cancers. Ultimately, knowledge of *BRCA* status in women diagnosed with breast cancer can inform care and provide access to novel therapies through clinical trials targeting *BRCA*-associated breast cancers.

Acknowledgement

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