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Genetic Counseling Referrals and Genetic Profiles of Male and Young Female Breast Cancer Populations

Ji-Sun Kim
Sarah Lawrence College

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By

Ji-Sun Kim

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Department of Human Genetics
Sarah Lawrence College

Abstract

Genetic counselling and genetic testing of breast cancer patients can be helpful in estimating recurrence risks and guiding clinical management. Genetic testing results are useful for family members and their medical decisions as well. However, not all breast cancer patients are eligible for genetic counselling, but must meet eligibility criteria in Ontario to be referred. We studied two groups of patients – male breast cancer patients and young female patients aged 35 or under – who make up of a small subset of overall breast cancer patients. These groups should be offered genetic testing irrespective of family history. They could also potentially represent unique genetic profiles, different from the majority of breast cancer patients. Our study showed that the genetic testing uptake rates were 44% for male patients and 60% for young female patients, respectively. Pathogenic mutation rates were 4% for male patients and 25% for young patients, respectively. Our study demonstrated that 1) genetic referral rates and testing rates are low, and 2) pathogenic mutation rates are different from the general breast cancer population.

Introduction

Breast cancer is one of the most common cancers occurring in Canadians, with approximately 1 in 8 Canadian women affected during her lifetime (Canadian Cancer Stats, 2012). The majority of breast cancer is diagnosed in women over 50 years of age while 7% of breast cancer is diagnosed among women age 40 years and younger (Brenner et al., 2016). While uncommon, breast cancer can also occur in males. It is estimated that <1% of breast cancer occurs in men (Rizzolo et al., 2013). Not surprisingly, research most often focuses on older female populations, and breast cancer in males and young females is not routinely examined due to smaller sample sizes (Brenner et al., 2016; Rizzolo et al., 2013). Currently, treatment strategies for these individuals are extrapolated from older female patients, which may result in suboptimal outcomes.

Clinical outcomes such as risks of contralateral breast cancer, local and distant recurrence, and subsequent mortality are worse among young women with breast cancer than older women (Brenner et al., 2016). Routine breast screening begins at age 50 in Ontario, contributing to delayed discovery and more advanced stage of cancer in women affected prior to this age. In terms of tumor pathology, distinct subtypes are more prevalent in younger patients than among

older women, including triple-negative breast cancer (TNBC), TP53-positive, and HER-2 over-expressing tumors (Brenner et al., 2016). All these factors lead to worse outcomes for the patients. Despite these known differences in breast cancer outcomes and tumor subtypes, there is a limited understanding of genetic etiology, epidemiology, and optimal therapeutic strategies for breast cancer in young women.

Similarly, clinical outcomes of male breast cancer (MBC) tend to be poor due to lack of breast screening guidelines in men; because of this, tumors tend to be at more advanced stages once discovered. There have been some efforts to study MBC; however, due to their rarity, little is known. MBC accounts for less than 1% of all breast cancers and less than 1% of all cancers in men (Rizzolo et al., 2013). Histologically, the majority of MBCs are invasive ductal carcinomas (Fentiman, 2018) and can be classified as luminal A (ER+, PR+, HER2-) (60-98%) (Deb et al., 2014; Johansson, Killander, Linderholm, & Hedenfalk, 2014). Fewer basal-like (TNBC) (0-2% vs. 16%) and HER2-enriched (0% vs. 6%) MBC tumors have been reported compared to female breast cancer (Johansson et al., 2014). These data further suggest that men and women diagnosed with breast cancer of similar immunohistochemical (IHC)-based subtype do not have similar outcomes, demonstrating different responses to standard therapies. Taken together, this indicates the need for identification of additional biomarkers to more accurately classify all cases of MBC and inform more effective treatment strategies (Johansson et al., 2014).

While a relatively small population of young females are diagnosed with breast cancer, they tend to be diagnosed with more advanced stages of cancer, which contributes to a disproportionately high rate of mortality. Screening with mammogram and breast MRI annually starts at age 30 for those who are considered at high risk for breast cancer based on risk assessment at a genetics clinic, rather than starting at age 50 for the general population. Women are included in the high-risk group if they are known carriers of pathogenic variant, have first degree relatives with pathogenic variant, have been assessed to be at a greater than 25% lifetime risk using an established risk assessment tool at a genetics clinic, or have received chest radiation treatment before age 30 and at least 8 years previously.

Majority of breast cancers occur sporadically, but approximately 10% are hereditary. Being a carrier of a pathogenic variant of certain genes, such as *BRCA1/2, PALB2, PTEN, STK11, TP53, ATM, BARD1, CHEK2, NF1, RAD50, RAD51C, RAD51D* among others, increase one's risk of developing breast cancer significantly.

Studies have shown that breast cancer in younger women has as distinctive profile in terms of risk factors, clinical outcomes, and tumor biology (Rizzolo et al., 2013). There is a lack of understanding about the genetic profiles of young females with breast cancer, suggesting that the existing literature does not reflect the insights afforded by genetic testing. Similarly, breast cancer in males is also regarded to have a unique disease profile compared to that of older female patients. Breast cancer risk for male carrier of mutations in *BRCA1/2* appears to be lower compared to female carriers (Canadian Cancer Stats). Pathogenic variant carriers of *BRCA2* are considered to be at an increased risk (5-10%) of developing breast cancer in males (Tai, Domchek, Parmigiani, & Chen, 2007). As with the young female population, there is a general shortage of current understanding of male breast cancer genetics. With the limited understanding of the cancer biology as well as their genetic status, the affected individuals face challenge in receiving appropriately tailored treatment and testing plans. A better understanding of the genetic and pathologic profiles of breast cancer in these populations would likely improve the quality of care and improve outcomes.

Current guidelines for referral to genetic counselling state that any women diagnosed with breast cancer at age 35 or under or a male diagnosed with breast cancer at any age should be referred, regardless of personal or family history of breast and/or ovarian cancer. Similar guidelines are in place for ovarian cancer diagnoses, yet 55% of women who are diagnosed are unaware of the availability of genetic testing (reference). A previous study by Demsky et al. (year) looked at the referral rates of ovarian cancer cases to genetic counselling, and whether having a family history of breast/ovarian cancer influenced the referral (Armel et al., 2013). Only 23% of women with invasive serous cancer in Ontario attended genetic counselling services (Armel et al., 2013); of those, 99% of women pursued genetic testing. Of women wound to carry a pathogenic mutation, 16% had no previous family history (Armel et al., 2013). These data suggest that among some cancer patients, it is lack of awareness of the availability of testing – rather than lack of interest

in genetic testing – that may act as a significant barrier to genetic counseling. Even with demonstrated need for public awareness, education initiatives will be ineffective if physicians caring for women with breast cancer are unaware of recommended referral practices. It is critical for physicians to be aware of referral guidelines so that they assist patients who are eligible for genetic counseling. Presence of family history is a component; however, this should not the only criteria alarms a physician. Cases of rarer cancer occurrence like male breast cancer, ovarian cancer, or breast cancer in young patients should all lead to genetic counseling services. In a study examining referrals for women with ovarian cancer who had a strong family history of cancer, it was noted that women were significantly more likely to be referred for genetic counselling (Meyer et al., 2010).

The provision of genetic counseling and genetic testing to patients with breast cancer has many benefits, foremost among these the potential for the prevention of future cancers in both the patient and their biological relatives. High-risk cancer screening protocols and risk-reducing strategies for BRCA1 and BRCA2 mutation carriers are well established (Clinical, Guidelines, & Guidelines, 2018; Meyer LA, Anderson Me, Lacou Ra, Suri A, Daniels Ms, Urbauer DL, Nogueras-Gonzalez GM, Schmeler KM, Gershenson DM, 2010). It has been demonstrated that identifying mutation carriers and their families with hereditary predisposition is cost-effective in preventing future cancers (Warner, 2018). In addition to prevention, genetic testing results can impact treatment course, including platinum chemotherapy and Poly (ADP)-ribose polymerase (PARP) inhibitors, which have shown to have high response rates in patients with recurrent disease (Warner, 2018). Given these benefits, guidelines have been published to help physicians determine who refer for genetic counseling (Clinical et al., 2018). In 2001, the province of Ontario expanded its BRCA1 and BRCA2 genetic testing eligibility criteria to include all men diagnosed with breast cancer, irrespective of age or family history, as well as women under age 35, irrespective of family history. The Familial Breast and Ovarian Cancer Clinic (FBOCC) at Princess Margaret Hospital (PMH) is a specialized cancer genetics clinic within one of the largest oncology programs in Canada. Evaluating men and young women diagnosed with breast cancer at PMH, the number who had clinical genetic counseling at FBOCC, and the number who underwent testing through Mount Sinai Hospital (MSH) pathology lab provides an estimate of the proportion of male and young female patients who are offered genetic testing. By studying

trends at this centre, we can characterize referral practices and identify potential barriers to genetic counseling in these populations.

Methods

Study Population

The study protocol received research ethics board approval from University Health Network in Toronto. Females aged 35 or younger or males diagnosed with breast cancer (invasive ductal carcinoma, adenocarcinoma, carcinoma NOS, invasive mammary, DCIS NOS, ductal carcinoma, ductal micropapillary carcinoma, invasive duct and lobular carcinoma, invasive lobular carcinoma, intraductal carcinoma, intraductal micropapillary carcinoma, LCIS NOS, lobular carcinoma, medullary carcinoma NOS, metaplastic carcinoma NOS, micropapillary carcinoma NOS, mucinous adenocarcinoma, papillary carcinoma, and tubular carcinoma) between 2000 and end of 2015 at Princess Margaret Hospital (PMH) were identified through the PMH Cancer registry. All patients were either diagnosed at PMH, and/or completed their initial treatment at PMH. Patients who were seen for consultation only and patients diagnosed with low grade malignant potential breast tumours were excluded. All those who presented for genetic counselling, the date of their first appointment, and any genetic testing results were identified from the Familial Breast and Ovarian Cancer Centre (FBOCC). Family history of cancer was extracted from the three-generation pedigree contained in the FBOCC chart.

Statistical analysis

Descriptive statistics were used to summarize patient demographics. Chi-Square tests and univariate analysis were used to examine association between the year of diagnosis and time between diagnosis and first visit to the FBOCC. The probability of having genetic counseling after a diagnosis of breast cancer was estimated using multivariable logistic regression with age and year of diagnosis as explanatory variables. Mutation rates and family history among patients who pursued genetic testing were also examined.

Results

Genetic Testing

Genetic testing included analysis of the *BRCA1* and *BRCA2*, *TP53* genes between 2000 and 2014, and thereafter a panel of 20 genes (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, TP53, XRCC2*). DNA was isolated from patients' peripheral blood lymphocytes and testing was performed using different technology, including protein truncation test (PTT), denaturing high performance liquid chromatography (DHPLC), sequencing and multiplex ligation-dependent probe amplification (MPLA).

Male breast cancer population

A total of 101 eligible patients were identified from the PMH cancer registry; 28 received genetic counseling at FBOCC and 16 received genetic counseling elsewhere; 44 were tested through Mount Sinai Pathology Lab (Fig 1). Mean age at the time of diagnosis was 63.4 years (range); there was not a statistically significant difference in mean age among those who had genetic counseling (60.5 years, range 53-85) and those who did not have genetic counseling (65.6 years, range 39-88) (p=0.195) (Table 6). Of men seen for genetic counseling, 14/26 (54%) reported a positive family history of breast cancer and 18/26 (69%) reported family history of any cance. Family history information could not be obtained for the 16 patients who were not seen for genetic counseling at FBOCC. In total, 26 of 28 (89.3%) men who had genetic counseling at FBOCC pursued genetic testing. Two of the 44 (4.5%) men who underwent genetic testing were found to have a BRCA1 or BRCA2 mutation (Table 1). The patient with BRCA1 pathogenic mutation did not have a family history of breast or ovarian cancer, though there was family history of another cancer (type not specified). Family history information on the patient with BRCA2 mutation was not available as he was seen elsewhere for genetic counselling.

Univariate analysis results showed that the number of men seen for genetic counseling did not increase over time (Table 4, Fig5b), and age at diagnosis was not a significant predictor of attendance at genetic counseling or testing (p=0.195) (Table 3, Fig 4). Not a significant trend was noted between the year of diagnosis and the likelihood of genetic counseling (p= 0.196) (Fig 5a, Fib 5b). The time between diagnosis and the first visit to genetic counseling decreased over the years (Fig 7). A trend was noted, but it was not statistically significant, likely due to the few number of patients seen over the years.

Young female breast cancer population

A total of 521 eligible patients were identified from the PMH cancer registry, and eight were excluded based on their diagnoses, making initial number of patients 529. Excluded pathology included angiosarcoma, lymphoma, hemangiosarcoma, peripheral nerve sheath tumour, and phyllodes tumour. 169 received genetic counseling at FBOCC and 146 were seen at a different genetic counseling clinic; 313 (60%) patients were tested through Mount Sinai Hospital Pathology Lab (Table 9, Table 10). Demographic information for those individuals counselled at FBOCC is included in Table 10. Six patients out of 169 (3.55%) who attended genetic counseling at FBOCC declined genetic testing. Age at diagnosis ranged from 16 to 35, with the mean age being 31.5. There was a correlation between age and likelihood of genetic testing ($p=0.017$) (Table 14). However, there was no a correlation between pathogenic variant finding and a family history of breast ($p=0.071$) (Table 15). Family history information could not be obtained for patients who were not seen for genetic counseling at FBOCC. In total, 163 of 169 (96.4%) patients who had genetic counseling at FBOCC pursued genetic testing, 39 of 163 (25%) patients had a BRCA1 or BRCA2 pathogenic mutation; three additional patients were identified to have pathogenic mutations in other genes (PALB2, TP53 or STK11) (Table 14, Fig 11). Most mutation carriers had a family history of cancer, not necessarily breast or ovarian. One patient with STK11 mutation had no family history of cancer.

Univariate analysis showed the proportion of women opting for genetic testing increasing with older ages at diagnosis such that age at diagnosis was a significant predictor of attending genetic counseling or having genetic testing ($p = 0.017$) (Table 16). Results from linear regression analysis showed that for each year increase in date of diagnosis, there was an increase in the number of genetic testing, with a positive correlation of 1.52 (Table 13, $p=4.57E-06$). There was a positive trend between the year of diagnosis and the time to genetic counseling for young female patients (Fig 9, Table 13, $p=4.57E-06$).

Discussion

Current guidelines for referral to genetic counselling state that any women diagnosed with breast cancer at age 35 or under or any male breast cancer diagnosed at any age should be initiated, regardless of family history of breast and/or ovarian cancer, as these groups are eligible for

genetic testing. Mutation status for the young patients is helpful in determining clinical management. Risk of second breast cancer or other primary cancer might be of concern. Cascade testing for family members could also be offered to identify other relatives at risk, which could then facilitate increased screening or prevention for those family members. Despite clear guidelines for genetic counseling and genetic testing among these patient groups, uptake of genetic testing is lagging. In male breast cancer patients, only 44% pursued genetic testing. Among young female breast cancer patients, a greater proportion (60%) opted for genetic testing (Fig 8), yet there remain many members of both groups who might benefit from genetic testing but were not seen for genetic counseling (56% of male breast cancer patients and 60% of young female breast cancer patients) and subsequently were not offered genetic testing. This suggests barriers and/or resistance to the access to genetic counseling. Identifying these barriers and developing strategies to ameliorate them are the next step in increasing identification of those individuals and families at high risk to develop cancer.

One potential reason for low numbers of patients seen for genetic counseling is a lack of patient awareness for genetic counseling or testing. 96.4% of female patients who attended genetic counseling proceeded with genetic testing; this indicates that there is a high interest among those who are aware of genetic testing as an option. Thus, it suggests that the low numbers of genetic testing do not appear to be due to low patient interest as such a high proportion of those who have counseling pursued testing. Perhaps it is more likely that low numbers of genetic testing are due to lack of awareness about or interest in genetic counseling.

Additionally, studies have shown that patients are more likely proceed with genetic testing if it could influence their treatment or benefit their family members (Lacour et al., 2008; Meiser et al., 2018), both topics which would likely be reviewed during a genetic counseling session. With a high interest in testing following proper education during genetic counseling, it seems likely that patients are unaware of the availability of genetic counseling and testing. Increasing awareness among eligible patients should therefore be promoted and prioritized by the providers.

Physicians caring for men or young women with breast cancer should be aware of the recommended referral practices. While studies have indicated that pathogenic mutation rate

among breast cancer patients is between 10-15%, this incidence rate is likely higher among in women in younger age at diagnosis, as indicated in the findings of the present study. National Comprehensive Cancer Network (NCCN) guideline recommend that any female diagnosed with breast cancer at age 50 or younger be offered genetic counseling. In Ontario, the age at diagnosis threshold is lower at age 35. Our study demonstrates that the positive mutation rate was relatively high at 25% (Figure 11). This confirms usefulness of the current criteria and suggests Ontario Ministry of Health (MOH) could consider increasing this lower age limit for genetic testing eligibility to capture more patients who might be pathogenic mutation carriers.

Another factor in reduced genetic test uptake rate, especially for male breast cancer patients, might be social stigma surrounding a diagnosis of a cancer type typically found in females. A study by Li et al. (2018) has shown that breast cancer diagnosis in male patients negatively impacts self-efficacy, as well as the relationship between physician and patient (Li et al., 2018). Another study by France et al. (2000) demonstrated that psychological and social factors play significant roles in male breast cancer patients, delaying their care and management (France et al., 2000). Similar factors might be influencing reduced referral for genetic counseling and testing in our male patient population.

In addition to age at diagnosis, year of diagnosis also was shown to be a significant predictor of referral to genetic counseling for both men and women. This correlation is likely due to increasing physician awareness of the availability of genetic testing. In support of this is our observation that patients with a more recent diagnosis of breast cancer had a significant shorter period of time between diagnosis and genetic counseling. From this, we can further conclude that there has been an increase in the number of patients seen at genetic counseling clinics, and for those who are seen at genetics, they are being referred earlier in their cancer journey.

Of the female patients who were referred to genetic counseling, 59% reported a family history of breast cancer; 50% of male patients reported a positive family history of breast cancer. Studies have shown that only 13-16% of all women with breast cancer have a positive family history (Cancer, 2001). This suggests that there may be a tendency for physicians to only refer patients to genetic counseling when there is also a family history of cancer, even though characteristics of

the personal diagnosis may be sufficient to meet eligibility criteria for a referral. Another possible explanation is the greater incidence of hereditary predisposition among young women with breast cancer (25% of our study population).

A limitation to this study is incomplete patient records available for review. It was assumed that patients diagnosed or treated at PMH would be seen for genetic counseling at the FBOCC. However, some chose to pursue genetic counseling at another hospital, yet testing was performed through MSH pathology lab. For those who had genetic counseling elsewhere, we were unable to access information such as family history, ethnicity, referral history or wait time. Additionally, there was missing information on patients who pursued genetic counseling elsewhere but declined testing. While we set out to investigate the pathology information on both male and female patients, we were unable to obtain complete set of data on this aspect of the study. If they received care elsewhere, we were unable to access detailed pathology information including tumour receptor status.

In conclusion, despite the Ministry of Health guidelines that women diagnosed with breast cancer at age 35 or younger, or any men diagnosed with breast cancer at any age should be referred for genetic counseling irrespective of family history, this practice is not occurring at optimal rates at our centre. As the result, the number and proportion of men or young women with breast cancer seen for genetic counseling is lower than expected and does not allow for maximal identification of individuals who might benefit from genetic testing. Additionally there is evidence that those without any family history of cancer might be disproportionally affected by the low rate of referral for genetic counseling. A significant proportion of men and women with breast cancer who are eligible for genetic testing are missing the opportunity to have testing, the results of which might impact their management and ultimate outcomes, as well as the health and wellbeing of family members. Given the current understanding of the benefits of testing, it is important that efforts to improve referral rates are established and enacted. Educational initiatives for both physicians and patients should be implemented, and the referral rates should be continually monitored to ensure improvement, and additional research should be done to identify and address other barriers. Additionally, we recommend that practice guidelines review

evidence of mutation rates in young breast cancer patients and consider increasing the age at diagnosis for eligibility for genetic counseling and testing, irrespective of family history.

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Male breast cancer data

Table 1

total number of patients	101
genetic testing provided	44
no genetic testing	57
negative result	36
BRCA1 positive	1
BRCA2 positive	1
BRCA1 vus	3
BRCA2 vus	2
ATM vus	1

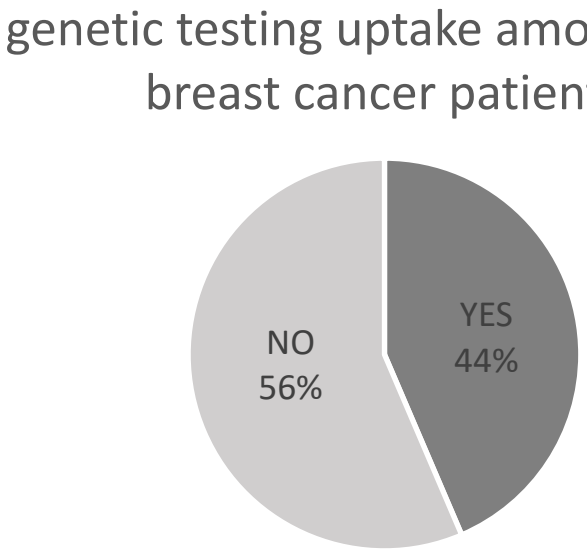

Figure 1. Despite the genetic testing eligibility guidelines established by the Ministry of Health, only 44% of male breast cancer patients received genetic testing between 2000-2016.

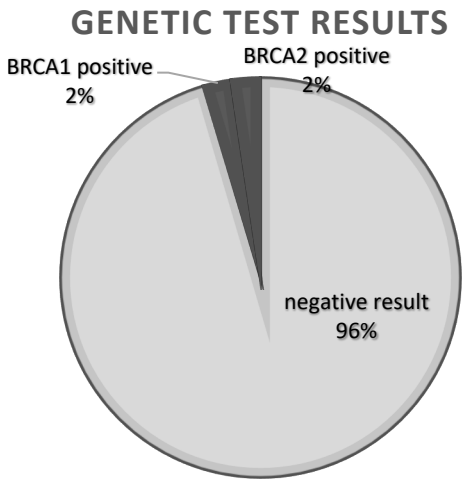

Figure 2. Pathogenic mutation rate in male breast cancer patients is low. N=101

Table 2

Age Group	Number of patients
≤40	1
41-50	10
51-60	32
61-70	28
71-80	24
>80	6

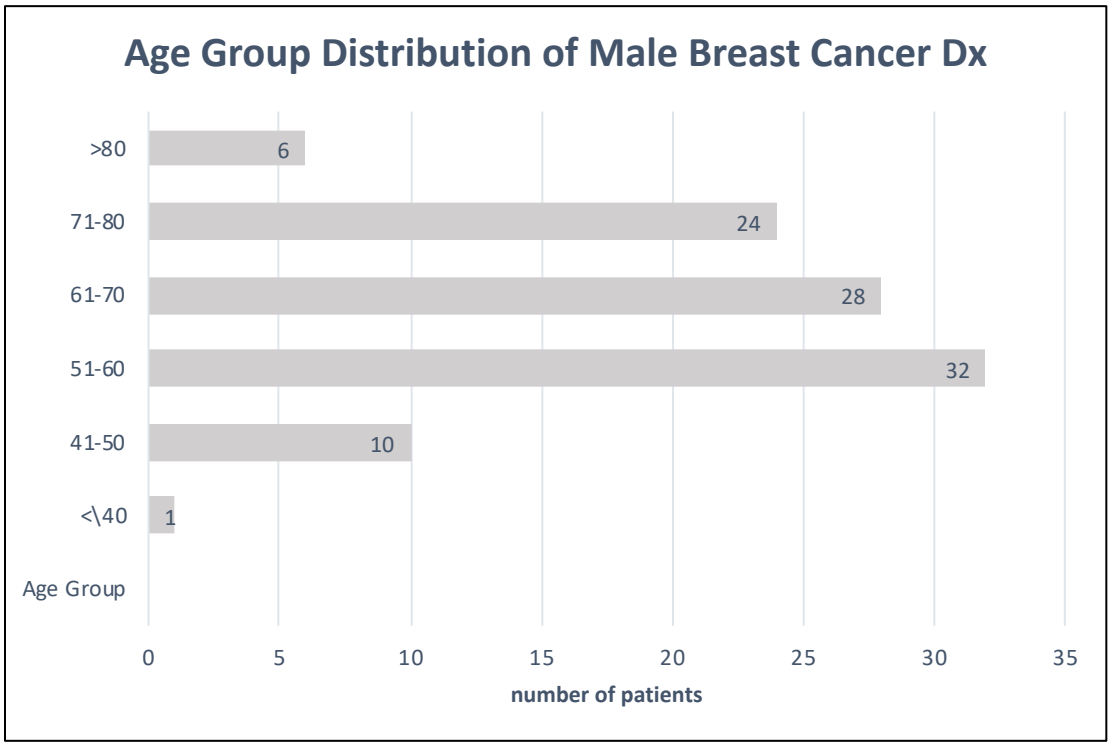

Figure 3. Age distribution of male breast cancer diagnosis, N for each age group is indicated at the right end of each bar. N=101

Table 3

Age Group	Number of patients	% genetic testing uptake
≤40	1	0
41-50	10	50
51-60	32	59.375
61-70	28	42.85714286
71-80	24	20.83333333
>80	6	50

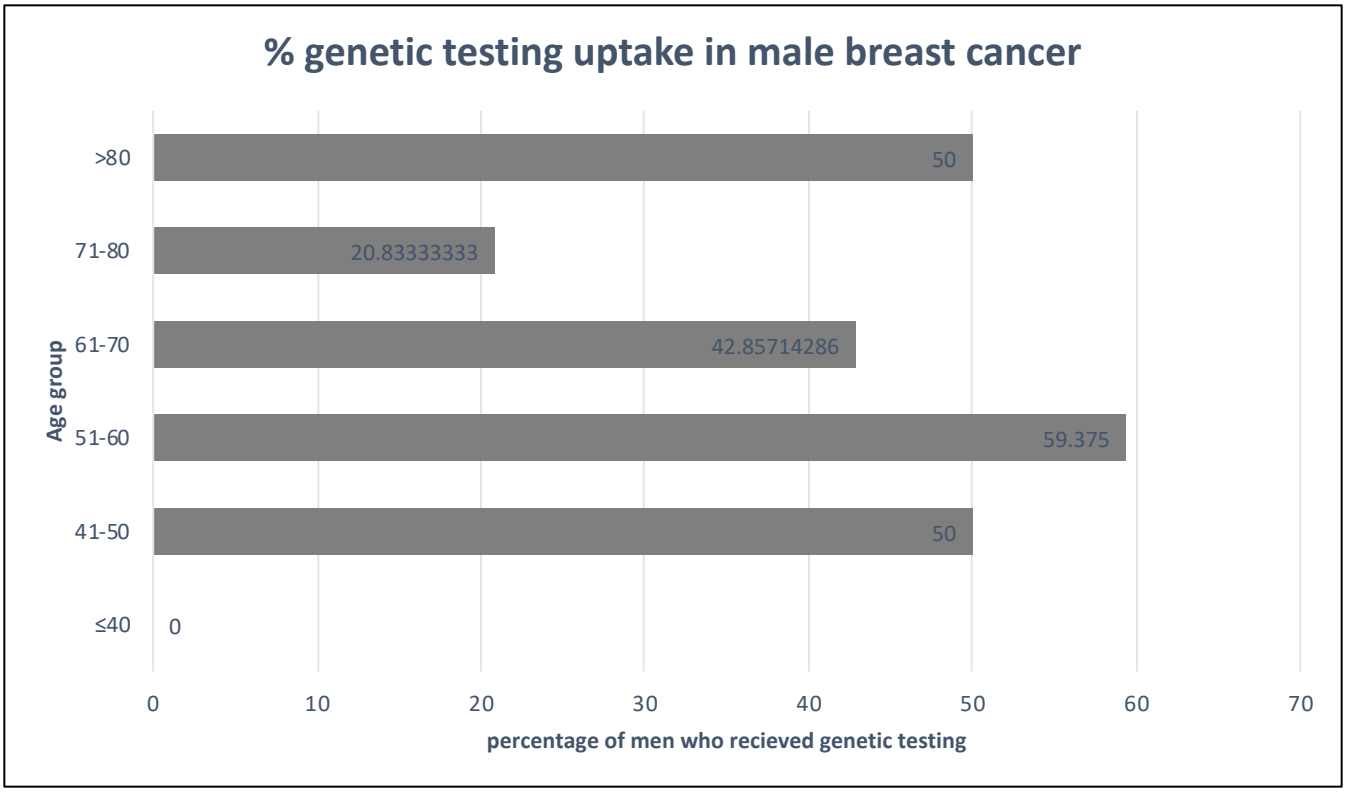

Figure 4. percentage of male patients receiving genetic testing by age at the time of breast cancer diagnosis. N=101

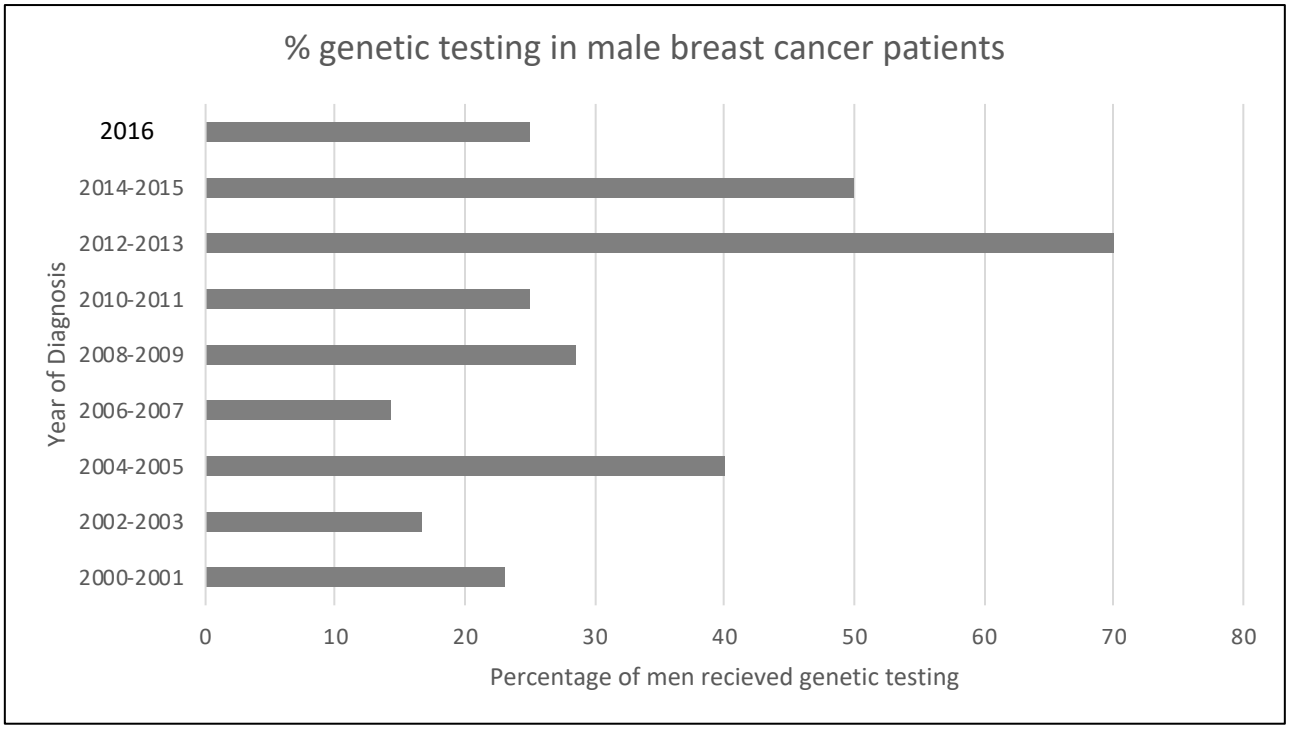

Figure 5a. percentage of male patients who had genetic testing by year of diagnosis. N=101

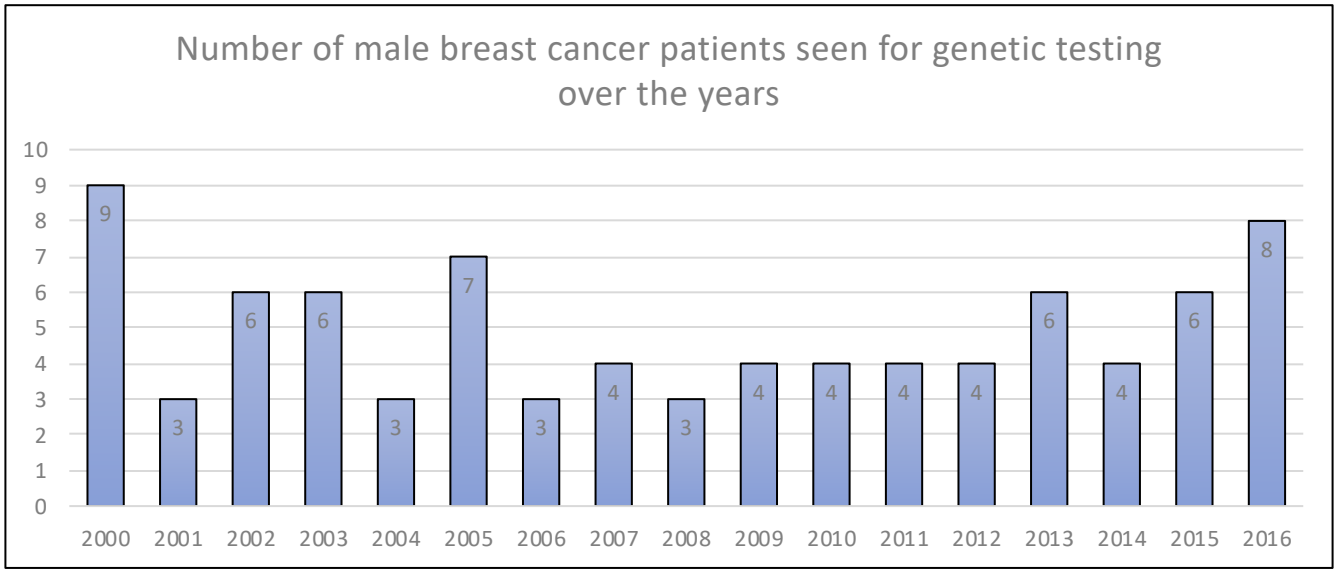

Figure 5b. There is no correlation between the number of male breast cancer seen for genetic testing over the years. P= 0.196.

Table 4

Year of Diagnosis	N (tested)
2000	9
2001	3
2002	6
2003	6
2004	3
2005	7
2006	3
2007	4
2008	3
2009	4
2010	4
2011	4
2012	4
2013	6
2014	4
2015	6
2016	8

Case Processing Summary

		N	Marginal Percentage
genetic test	no	52	51.5%
	yes	49	48.5%
year of dx	1999	2	2.0%
	2000	7	6.9%
	2001	3	3.0%
	2002	6	5.9%
	2003	5	5.0%
	2004	6	5.9%
	2005	7	6.9%
	2006	3	3.0%
	2007	4	4.0%
	2008	7	6.9%
	2009	5	5.0%
	2010	5	5.0%
	2011	5	5.0%
	2012	5	5.0%
	2013	5	5.0%
	2014	9	8.9%
	2015	7	6.9%
	2016	10	9.9%
Valid		101	100.0%
Missing		2	
Total		103	
Subpopulation		18[a]	

Pseudo R-Square

Cox and Snell	.194
Nagelkerke	.258
McFadden	.155

p= 0.196, not significant

Likelihood Ratio Tests

Effect	Model Fitting Criteria			Likelihood Ratio Tests		
	AIC of Reduced Model	BIC of Reduced Model	-2 Log Likelihood of Reduced Model	Chi-Square	df	Sig.
Intercept	70.095	117.168	34.095[a]	.000	0	.
year	57.816	60.431	55.816	21.721	17	.196

The chi-square statistic is the difference in -2 log-likelihoods between the final model and a reduced model. The reduced model is formed by omitting an effect from the final model. The null hypothesis is that all parameters of that effect are 0.

a. This reduced model is equivalent to the final model because omitting the effect does not increase the degrees of freedom.

Table 5

Total number of male patients tested	44
AJ	4
Caucasian	20
Asian	2
Middle Eastern	1
West Indies	1
Unknown	16

28 seen at FBOCC

Table 6

mean age at dx	63.38613861	
mean age, tested group	60.5	53-85 (age range)
mean age, not tested	65.6	39-88 (age range)

P=0.195, not significant

Likelihood Ratio Tests

Effect	Model Fitting Criteria: AIC of Reduced Model	BIC of Reduced Model	-2 Log Likelihood of Reduced Model	Likelihood Ratio Tests: Chi-Square	df	Sig.
Intercept	113.545	215.534	35.545[a]	.000	0	.
age	82.814	85.429	80.814	45.269	38	.195

The chi-square statistic is the difference in -2 log-likelihoods between the final model and a reduced model. The reduced model is formed by omitting an effect from the final model. The null hypothesis is that all parameters of that effect are 0.

a. This reduced model is equivalent to the final model because omitting the effect does not increase the degrees of freedom.

Table 7. Most male breast cancer cases in our cohort is luminal A type, ER+ PR+ Her2-.

Total number of cases	28 identified through progeny
Ductal Carcinoma	7/28
Invasive Ductal Carcinoma	17/28
Papillary Carcinoma	1/28
Unknown	3/28
Receptor – ER+, PR+, HER2-	22/28
Receptor unknown	6/28

Case Processing Summary

		N	Marginal Percentage
genetic test	no	52	51.5%
	yes	49	48.5%
age	39	1	1.0%
	41	1	1.0%
	42	1	1.0%
	43	1	1.0%
	46	3	3.0%
	47	1	1.0%
	50	3	3.0%
	51	4	4.0%
	52	3	3.0%
	53	3	3.0%
	54	4	4.0%
	55	4	4.0%
	56	1	1.0%
	57	4	4.0%
	58	4	4.0%
	59	3	3.0%
	60	2	2.0%
	61	7	6.9%
	62	4	4.0%
	63	3	3.0%
	64	2	2.0%
	65	2	2.0%
	66	1	1.0%
	67	1	1.0%
	68	1	1.0%
	69	4	4.0%
	70	3	3.0%
	72	5	5.0%
	73	3	3.0%
	75	2	2.0%
	76	4	4.0%
	77	5	5.0%
	78	1	1.0%
	79	2	2.0%
	80	2	2.0%
	83	2	2.0%
	84	1	1.0%
	85	1	1.0%
	88	2	2.0%
Valid		101	100.0%
Missing		2	

Table 8

year	2000	2002	2004	2005	2006	2008	2009	2010	2011	2012	2013	2014	2015
number of months	164	88	125	110	38	4	6	8	15	33	5	0.27	4
						34		11		7	19	7	11
						6		3		44	10	1	0.4
						8							
						36							

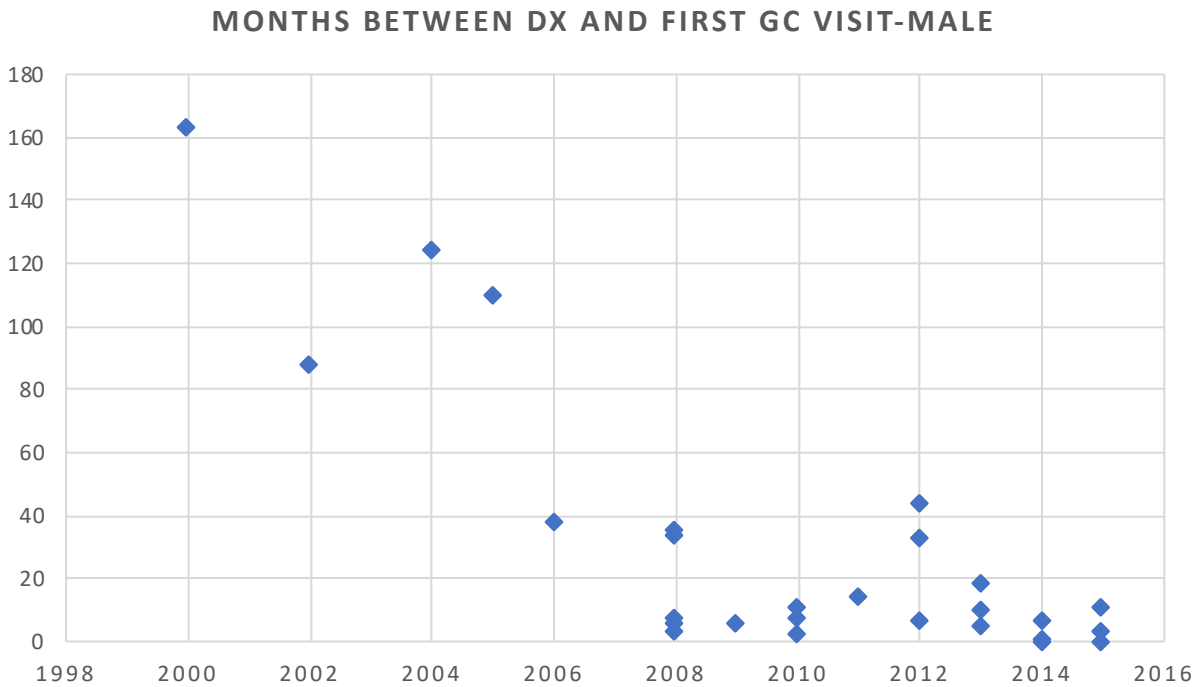

Figure 6. Scatter plot demonstrating time in months between diagnosis of breast cancer and first genetic counseling visit by the year of diagnosis. N =27.

Number of months between diagnosis and genetic counseling

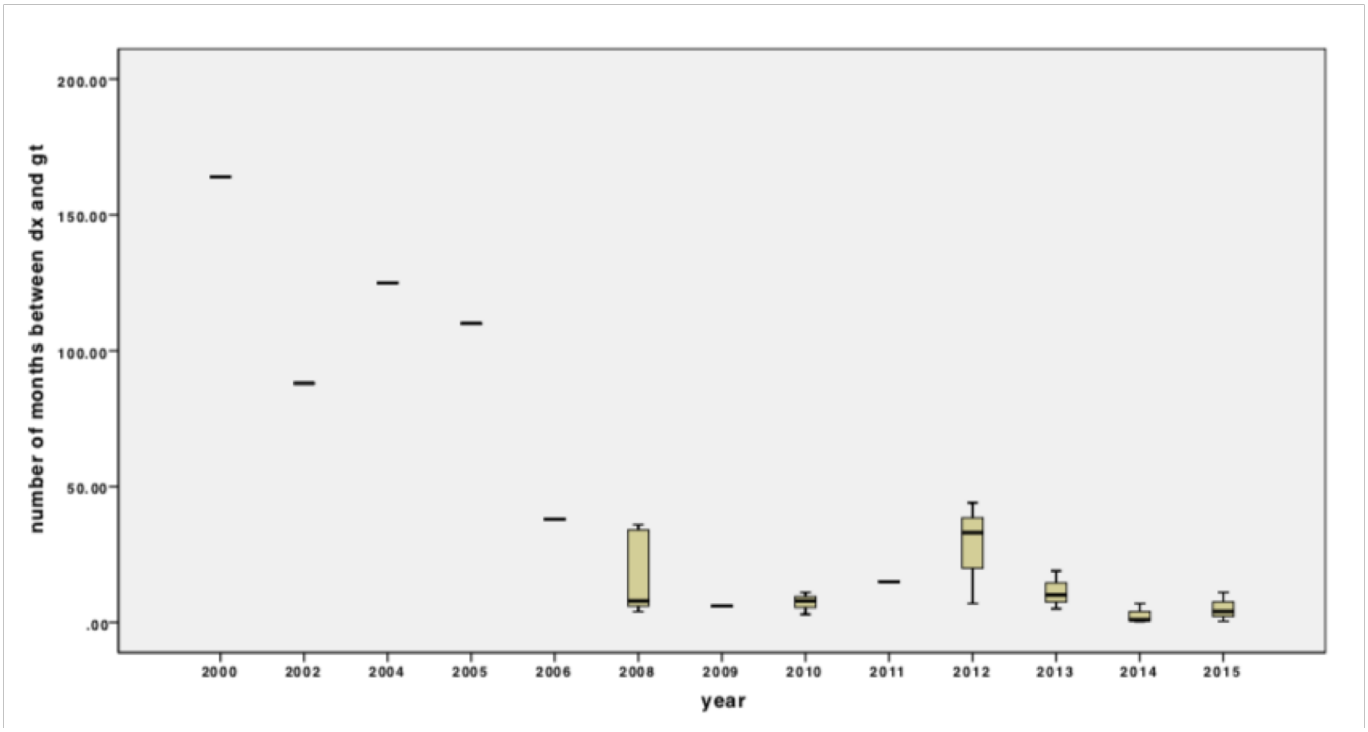

Figure 7. Modified boxplot demonstrating time in months between diagnosis of ovarian cancer and first genetic counseling visit by the year of diagnosis. N =27. Median values are indicated as thick horizontal lines and the interquartile ranges as the upper and lower edges.

Young Female data

Table 9.

Yes to Genetic Testing	313
No to Genetic testing	208
total	521

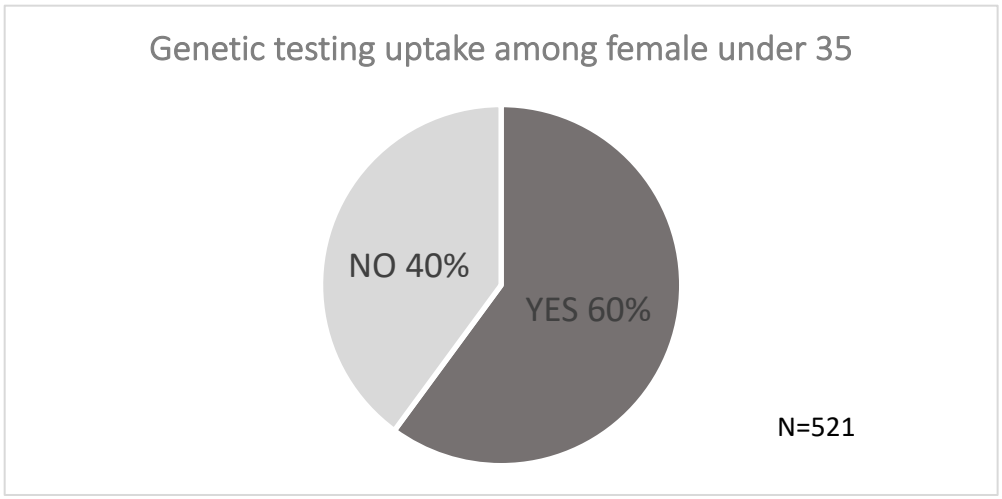

Figure 8. Ministry of Ontario's genetic testing eligibility criteria encourages all women diagnosed with breast cancer at age 35 or younger get tested. Yet genetic testing uptake rate between 2000—2016 is only about 60%.

Table 10.

progeny data			progeny +MSH	tested through MSH - 146
African	3		African	3
AJ	14		AJ	14
Asian	29		Asian	29
Caucasian	78		Caucasian	78
East Indian	11		East Indian	11
Hispanic	3		Hispanic	3
Middle Eastern	8		Middle Eastern	8
West Indies	6		West Indies	6
Mixed	15		Mixed	15
Unknown	2		Unknown	146
total	169		total	315

Table 11

Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
number of months between dx and gc	156	84	6	115	84	60	12	6	3	15	3	1	1	7	1	5	2
	156	39	120	15	58	19	146	98	36	4	0	9	0	4	4	22	3
	136	13			158	108	8	114	19	42	1	2	2	1	2	2	1
	29	12			35	14	10	22	2	4	2	3	3	5	2	2	1
						14	37	12	27		14	2	66	2	6	4	2
						140	6	13	47		7	10	1	6	2	1	4
						75		18	65		36	2	0	1	3	3	2
						130		9	0		6	36	3	0	2	0	5
						4		3	3		4	1	7	0	1	3	2
								8	2		1	58	1	1	13	3	1
									2		1	4	8	1	8	1	2
									9		2	4	1		1	4	1
											1		3		1	9	5
											8				1	4	2
											3					1	

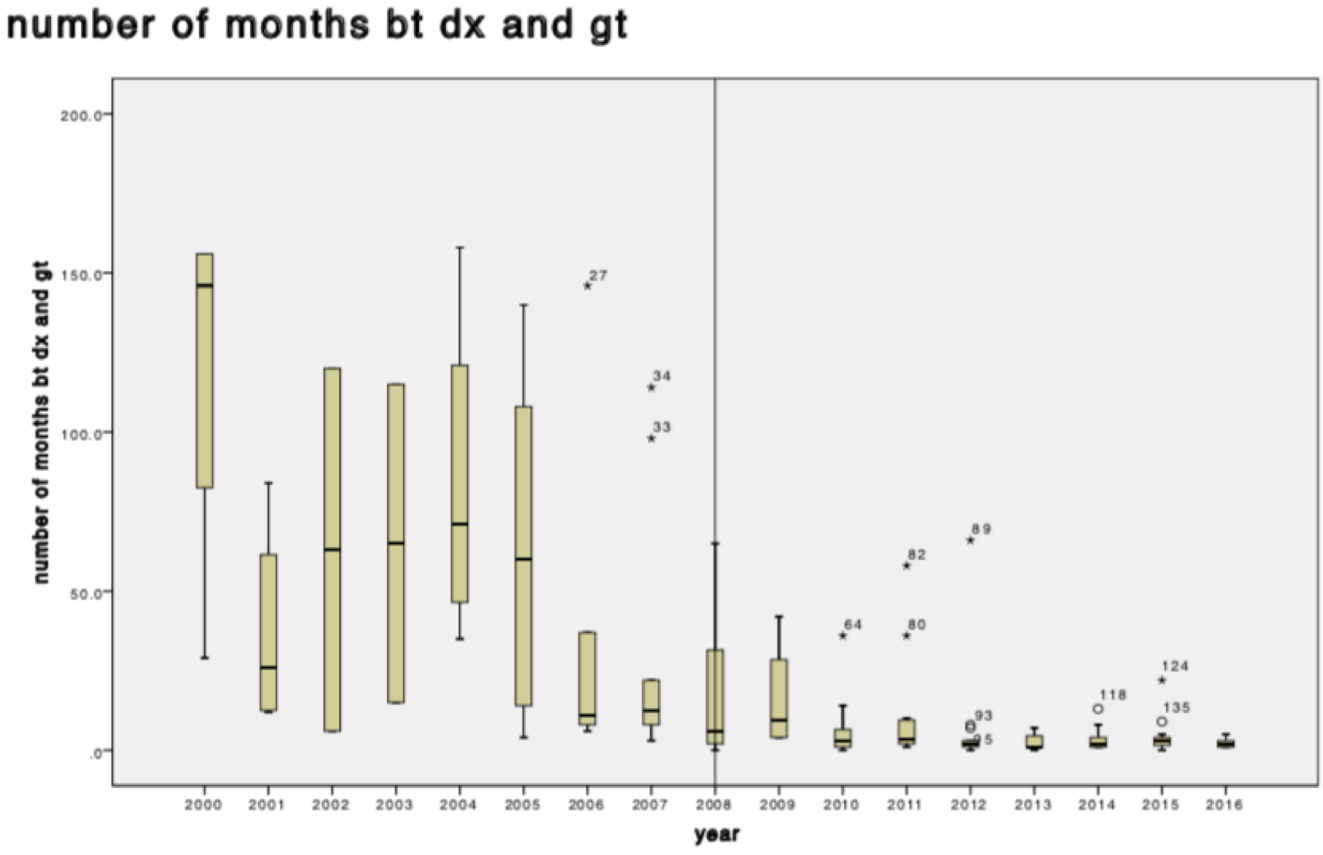

Figure 9. Modified box plot demonstrating time in months between diagnosis of breast cancer and first genetic counseling visit by year of diagnosis. Median values are indicated as thick horizontal lines and the quartile ranges as upper and lower edges. Outliers are shown as asterisks and open circles.

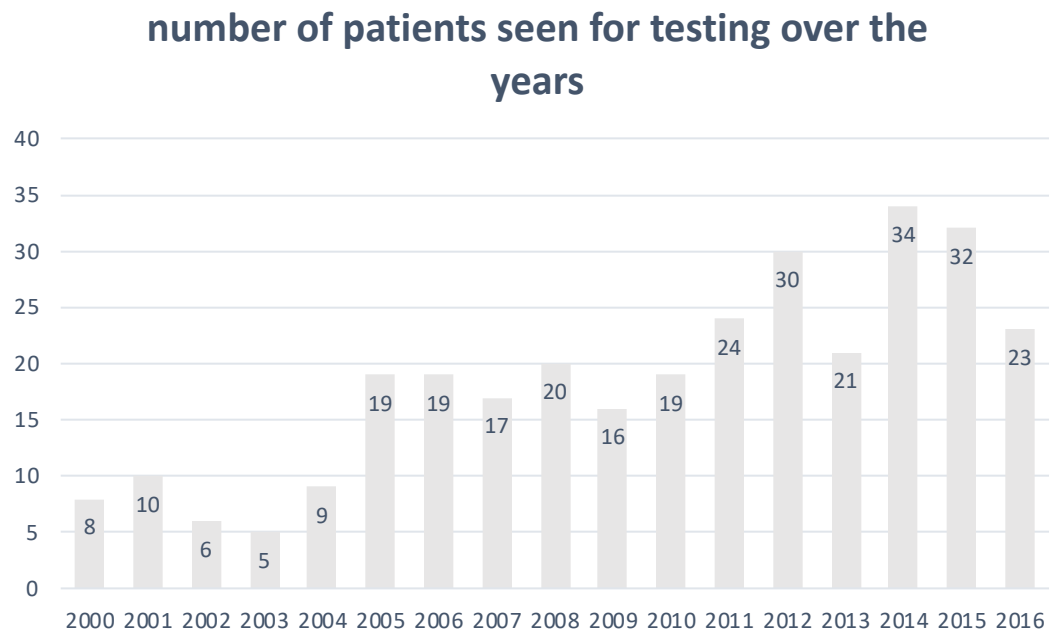

Figure 10. There is an increase in the number of young female patients seen for genetic testing over the years.

Table 12. Summary of the number of young female patients seen for genetic testing over the years.

year	N
2000	8
2001	10
2002	6
2003	5
2004	9
2005	19
2006	19
2007	17
2008	20
2009	16
2010	19
2011	24
2012	30
2013	21
2014	34
2015	32
2016	23

Table 13. Linear regression data between number of young female patients seen over the years. There is a positive correlation between the number and the years (coeffeicint of 1.52), with a p value of 4.57E-06.

Regression Statistics								
Multiple R	0.87382553							
R Square	0.76357107							
Adjusted R Square	0.74780914							
Standard Error	4.41003016							
Observations	17							
ANOVA								
	df	SS	MS	F	Significance F			
Regression	1	942.156863	942.156863	48.4440113	4.57484E-06			
Residual	15	291.72549	19.448366					
Total	16	1233.88235						
	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0%	Upper 95.0%
Intercept	-3033.0196	438.40599	-6.9182896	4.9078E-06	-3967.459855	-2098.5794	-3967.4599	-2098.5794
year	1.51960784	0.21832903	6.96017322	4.5748E-06	1.054250539	1.98496515	1.05425054	1.98496515

Table 14. Young female genetic testing results

genetic counseling at FBOCC	169
negative	99
BRCA1 positive	21
BRCA2 positive	18
PALB2 positive	1
TP53 positive	1
STK11 positive	1
BRCA1 VUS	6
BRCA2 VUS	7
PALB2 VUS	1
BRCA1/TP53	1
RAD51D VUS	1
BRIP1 VUS	1
TP53 VUS	4
declined testing	6
unknown results	1

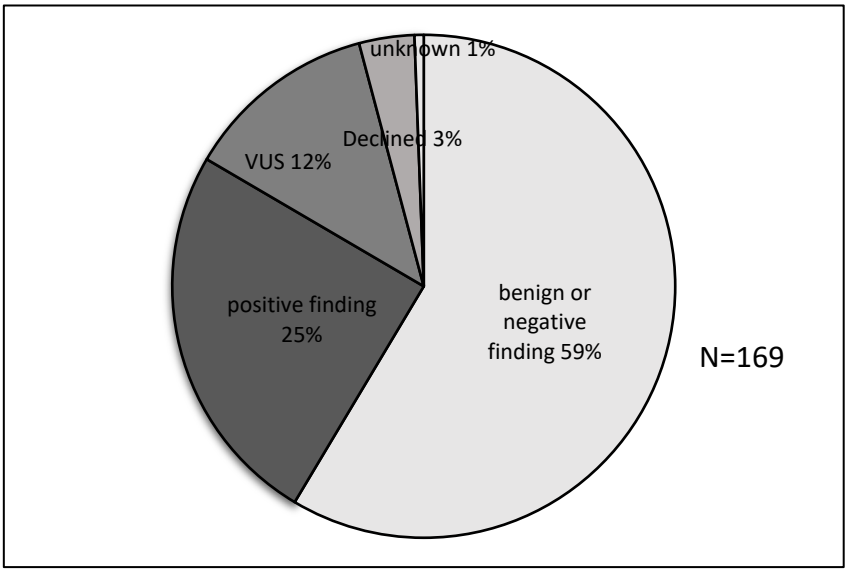

Figure 11. Despite the conventional understanding that only 10-15% of breast cancer cases are hereditary, in the younger population, there was a greater incidence of pathogenic mutations at 25%.

Table 15. Correlation between pathogenic variant findings and family history of breast cancer

	ACTUAL				PREDICTED						
	Negative	Positive	Totals		Negative	Positive	Totals		Chi-Square		
Family Hx br	63	30	93		68.0	25.0	93		0.070697983		declined or no info
No Family Hx br	54	13	67		49.0	18.0	67				9
	117	43	160		117	43	160				

There is no significant correlation between positive genetic test result and presence of breast cancer family history. P= 0.071.

Correlation between genetic testing (gt) and age at diagnosis

Case Processing Summary

		N	Marginal Percentage
gt	no	208	39.9%
	yes	313	60.1%
age at dx	16.00	1	0.2%
	17.00	1	0.2%
	19.00	1	0.2%
	22.00	4	0.8%
	23.00	1	0.2%
	24.00	10	1.9%
	25.00	8	1.5%
	26.00	10	1.9%
	27.00	16	3.1%
	28.00	25	4.8%
	29.00	43	8.3%
	30.00	45	8.6%
	31.00	48	9.2%
	32.00	63	12.1%
	33.00	70	13.4%
	34.00	81	15.5%
	35.00	94	18.0%
Valid		521	100.0%
Missing		3	
Total		524	
Subpopulation		17[a]	

Table 16

Likelihood Ratio Tests

Effect	Model Fitting Criteria: -2 Log Likelihood of Reduced Model	Likelihood Ratio Tests: Chi-Square	df	Sig.
Intercept	45.003[a]	.000	0	.
age	75.169	30.166	16	.017

The chi-square statistic is the difference in -2 log-likelihoods between the final model and a reduced model. The reduced model is formed by omitting an effect from the final model. The null hypothesis is that all parameters of that effect are 0.

P=0.017