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Patterns and Predictors of Genetic Referral among Ovarian Cancer Patients at a National Cancer Institute Comprehensive Cancer Center

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Abstract

Germline mutations (e.g., *BRCA1/2*) have prognostic and treatment implications for ovarian cancer (OVCA) patients. Thus, national guidelines recommend genetic testing for OVCA patients. The present study examines patterns and predictors of genetics referral in OVCA patients. Electronic medical record data were abstracted retrospectively from 557 OVCA patients treated from January 1, 2001, to December 31, 2015. Logistic regression models identified sociodemographic characteristics, disease/treatment characteristics, family history data, provider characteristics, and survival data that predicted genetics referral. Overall, 27.5% of patients received referral. Eleven variables predicting referral were selected during stepwise regression: younger age, White race, not having private insurance, professional school education, year of OVCA diagnosis, platinum sensitivity, female gynecologic oncologist, chemotherapy administered by a gynecologic oncologist, clinical trial enrollment, longer overall survival, and family history of OVCA. Genetics referral among OVCA patients was similar to rates reported nationwide. Unique predictive factors will contribute to quality improvement and should be validated at a multi-institutional level to ensure guideline concordant care is provided to all OVCA patients. Future research should identify both patient-level and provider-level factors associated with genetics referral.

Keywords

ovarian cancer; germline mutation; *BRCA1/2*; genetic testing; genetic counseling

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Data Availability: Anonymized data will be made available upon request.

INTRODUCTION

An estimated 15–20% of ovarian cancer (OVCA) cases are attributed to germline mutations, with the majority attributed to mutations in *BRCA1* and *BRCA2* (*BRCA1/2*).¹ *BRCA1/2* mutations have significant implications for both OVCA patients and their family members. For patients, *BRCA1/2* mutations are associated with platinum sensitivity and improved survival.² In addition, polyADP-ribose polymerase (PARPi) inhibitors have FDA approval for germline or somatic *BRCA1/2* mutations.³ Knowledge of genetic mutations may also impact clinical trial eligibility and enrollment as targeted therapeutic indications increase.⁴ Additionally, given improved survival among OVCA patients, *BRCA1/2* testing is important to identify those at increased risk for secondary malignancies (e.g., breast cancer).³ Finally, if a *BRCA1/2* mutation is identified, cascade testing can be initiated to identify mutations in at-risk relatives.⁵ Given the absence of effective early detection strategies for OVCA, cascade testing is critically important.⁵ Identification of at-risk relatives has the potential to save lives, through risk-reducing surgeries that substantially decrease mortality risks.⁶

For these reasons, 2014 guidelines from the Society for Gynecologic Oncology (SGO), National Comprehensive Cancer Network and National Society of Genetic Counselors recommend genetic testing (GT) for all OVCA patients.^{7–9} Despite this recommendation, only 20–30% of all OVCA patients receive GT,⁴ suggesting significant missed clinical opportunities.

Little is known about which OVCA patients are more or less likely to receive referral for genetic services. A recent SGO white paper identified factors associated with GT among OVCA patients across several key dimensions of care delivery, including patient and physician knowledge, time constraints, patient refusal, delays and/or denials by third party payers, limited availability of genetic counselors, and lack of reimbursement.⁴ However, these factors were identified through expert stakeholder consensus, rather than empirical data.

To address this gap, we utilized electronic medical records (EMR) of OVCA patients treated at a National Cancer Institute – Comprehensive Cancer Center (NCI-CCC) between 2001 and 2015. Our aims were to: (1) characterize frequency of genetic referral in OVCA patients in an NCI-CCC setting, and (2) identify patient, disease/treatment, and provider factors predictive of genetic referral for OVCA patients.

MATERIALS & METHODS

Procedures and Participants

All procedures were approved by an Institutional Review Board (Protocol #00025750). Eligible participants were women treated for advanced, epithelial OVCA between January 1, 2001, and December 31, 2015. All data were abstracted retrospectively using the EMR. Retrospective chart review was restricted to patients who had previously consented to participate in an institutional study protocol for a data repository; patients provided written informed consent for their biospecimens and associated case data to be used for ongoing research.

Measures

Patient demographic characteristics.—Data included age, race, education, marital status, number of children, and insurance type.

Disease and treatment characteristics.—Clinical data included year of OVCA diagnosis (2001–2013 [pre-guideline recommendations] or 2014–2015 [post-guideline recommendations]), tumor characteristics (site of origin, grade, stage, histotype), and treatment history (debulking status, platinum sensitivity, clinical trial enrollment, number of therapy lines).

Provider characteristics.—Data included gender of gynecologic oncologist (GYN/ONC) and type of chemotherapy provider (medical oncologist or GYN/ONC).

Family history.—Data included family history of breast cancer and OVCA.

Survival data.—Progression-free and overall survival in months was calculated from dates of diagnosis, disease progression, and death.

GT referral.—Categorized as yes (1) or no (0) based on orders placed.

Analytic strategy

First, descriptive statistics characterized the frequency of genetics referral. A forward stepwise logistic regression then examined predictors of GT referral. Given the lack of data on this topic, we set $p < 0.3$ as the model entry criterion and $p < 0.2$ as the criterion for staying in the model. Model goodness-of-fit was evaluated by Hosmer and Lemeshow's test,¹⁰ with a non-significant χ^2 ($p > 0.05$) indicating adequate goodness-of-fit. Finally, exploratory analyses compared predictors of GT referral for cases from 2001–2013 to cases from 2014–2015. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Preliminary and Descriptive Analyses.

A total of 557 women were eligible and included in the analyses (Table 1).

Frequency of GT Referral.

Overall, 27.5% of OVCA patients received genetic referral.

Predictors of GT Referral.

Eleven predictor variables were selected in stepwise logistic regression (Table 2). Eight variables were statistically significantly associated with greater likelihood of referral, including younger age ($OR_{Age\ 70-88} = 0.26$, 95% CI=0.11–0.57), White race ($OR_{Non-White} = 0.38$, 95% CI=0.15–1.01), being diagnosed with OVCA between 2014–2015 ($OR_{2014-2015} = 7.26$, 95% CI=3.48–15.15), platinum sensitivity ($OR_{No} = 0.49$, 95% CI=0.28–0.86), female GYN/ONC ($OR_{Female} = 1.88$, 95% CI=1.10–3.21), having chemotherapy

provided by a GYN/ONC ($OR_{No}=0.49$, 95% CI=0.30–0.78), clinical trial enrollment ($OR_{Yes}=1.74$, 95% CI=1.11–2.74), and longer overall survival ($OR_{61+ \text{ months}}=2.70$, 95% CI=1.47–4.98). Two additional variables selected into the model had suggestive, but non-statistically significant associations with greater likelihood of referral: not having private insurance ($OR_{non-private}=1.47$, 95% CI=0.91–2.40) and professional school education ($OR_{Professional \text{ School}}=1.85$, 95% CI=0.93–3.67). The model demonstrated adequate goodness-of-fit ($\chi^2=7.45$, $p=0.76$).

Exploratory analyses identified two predictors that emerged in stepwise regressions for both 2001–2013 and 2014–2015: age and platinum sensitivity (Table 3). Unique predictors of referral from 2001–2013 included race, GYN/ONC gender, chemotherapy provider, clinical trial enrollment, and overall survival. Number of therapy lines also predicted referral from 2014–2015.

DISCUSSION

Given the prognostic and treatment implications of germline *BRCA1/2* mutations in the context of OVCA, genetics referral is vital. Despite national guidelines suggesting 100% GT for OVCA patients, the national average is 20–30%.⁴ Identifying predictors of genetics referral among OVCA patients has the potential to increase guideline-concordant care. The present study addressed this question via EMR review.

Referral rates from our institution (27.5%) were consistent with national averages. Notably, our institution an NCI-CCC; some barriers to GT (e.g., access) are minimized in this setting. However, most OVCA patients are treated in low-volume, low-resource community hospitals that are less likely to deliver standard of care treatment.¹¹ Thus, the predictive factors identified in this study should be validated at a multi-institutional level to ensure guideline concordant care is provided to all OVCA patients.

Importantly, we observed an increase in referral rates from 2001–2013 (26%) to 2014–2015 (55%). There are multiple potential explanations for this finding. First, it may reflect the 2014 publication of guidelines for universal testing and, subsequently, increased provider awareness of GT recommendations. Also, before 2014, GT was only indicated for women with a family history of breast cancer and/or OVCA. Thus, the expansion to universal GT for OVCA patients may have resulted in increased referral rates. Second, the 2014 introduction of PARPi in clinical trials may have impacted rates of genetics referral. Finally, in 2013 actress Angelina Jolie announced that she had a pathogenic *BRCA1* mutation and had undergone risk-reducing mastectomy, leading to enormous public interest in GT.¹² Thus, the patterns observed here may be related to increased public awareness and acceptability of GT. However, it should be noted that our 2014–2015 cohort was quite small ($n=56$). A larger contemporary cohort is needed to confirm the pattern observed here.

In our population, 31% of women that received GT did have a pathogenic mutation. This is greater than the 15–20% of *BRCA1/2* positive OVCA patients reported in prior studies.¹ This may indicate that genetics referrals are provided for OVCA patients who are more

likely to carry *BRCA1/2* mutations based on factors beyond their diagnosis (e.g., age at diagnosis, personal cancer history, etc.).

Patient characteristics that predicted genetics referral included age, race, insurance status, education, platinum sensitivity, and family history of OVCA. Interestingly, some factors previously associated with genetics referral were *not* associated with GT in this study, including parity, partner status, histology, and disease stage.¹³ Because we selected only eleven predictors in the final logistic regression model, these additional factors may play a smaller role in predicting genetics referral.

Provider characteristics – including a female GYN/ONC and a GYN/ONC chemotherapy provider – were also associated with genetics referral. These unique predictors of genetics referral have not previously been identified. Rather, physician-level factors reported in the literature include lack of time, genetics training, and familiarity with guidelines.^{14–16} Our results may indicate that physician sociodemographics and oncology specialty also play a role in referral.

Given the low rates of genetics referral among OVCA patients, quality improvement measures are needed. In previous trials, strategies including EMR changes, workflow changes, care integration, and patient and provider education have resulted in a 40–352% increase in rates of genetics referral.^{14,15,17,18} Another approach is *BRCA1/2* testing of OVCA tumor tissue.¹⁹ Pilot testing has found somatic GT to be feasible, effective, and acceptable to patients and providers.²⁰ As the patient characteristics associated with GT in the present study are relatively immutable (e.g., sociodemographics, disease characteristics), systems-level initiatives such as these are necessary.

Strengths of our study include objective data on GT referral via EMR abstraction, a large sample size (N=557) representing a long time period (14 years), and only 1.7% missing data. Our sample was all advanced OVCA patients (Stage III/IV) and thus representative of the typical OVCA patient. Lastly, our findings are highly clinically significant, with the potential to impact cancer care delivery by identifying subpopulations of OVCA patients at risk for substandard care.

Nonetheless, limitations must be acknowledged. First, data are from a single institution and may not be generalizable across all practice settings. Second, most participants were White (93%) and highly educated (54% “some college” or more); results may not generalize to underserved populations.

This study addresses key gaps in knowledge regarding genetics referral among OVCA patients. Our results suggest some unique characteristics that might impact GT referral; future research across multiple institutions is needed to validate the predictors identified here. Future work should prospectively identify factors that will further enhance our current understanding, ultimately improving quality of care for OVCA patients.

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Table 1.

Patient sociodemographic characteristics, disease/treatment characteristics, family history, and provider characteristics, and survival data for participants (N=557).

	Mean (SD)	Range	N (%)
Patient Sociodemographic Characteristics			
Current Age (years)	61.6 (11.4)	27–88	
Race: % White			523 (94%)
Marital Status: % Married/Cohabiting			375 (67%)
Education			
HS/HS grad/vocational school			182 (33%)
Some college/college grad			232 (42%)
Professional school			66 (12%)
Unknown			77 (14%)
Children: % yes			448 (80%)
Insurance Type			
Private			270 (48%)
Non-private (Medicare, Medicaid, self-pay, medically needy)			287 (52%)
Disease/Treatment Characteristics			
Year of diagnosis			
2001–2013			501 (90%)
2014–2015			56 (10%)
Primary cancer site: % ovarian			494 (89%)
Grade: % high			542 (97%)
Stage			
III			432 (78%)
IV			125 (22%)
Histotype: % serous			482 (87%)
Debulking status: % optimal			462 (83%)
Platinum sensitivity: % yes			384 (69%)
Clinical trial enrollment: % yes			159 (29%)
Number of therapy lines	3.4 (2.7)	0–17	
Family History of Cancer			
History of breast cancer: % yes			119 (21%)
History of ovarian cancer: % yes			39 (7%)
Provider Characteristics			
Gender of gynecologic oncologist			
Male			458 (82%)
Female			99 (18%)
Type of chemotherapy provider			
Gynecologic oncologist			368 (66%)
Medical oncologist			189 (33%)
Survival Data			

	Mean (SD)	Range	N (%)
Progression-free survival (months)	18.1 (24.4)	0–172	
Overall survival (months)	47.1 (34.2)	0–194	

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Table 2.

Multiple logistic regression model for genetic referral.

Variable	# Referred to Genetic Counseling	Multivariable-adjusted odds ratio [95% confidence interval]
Age (Years)		
27–49	32	(ref)
50–59	56	1.11 [0.59, 2.08]
60–69	53	0.58 [0.31, 1.12]
70–88	20	0.26 [0.11, 0.57]
Race		
White	153	(ref)
Non-white	8	0.38 [0.15, 1.01]
Insurance Type		
Private	86	(ref)
Non-private	75	1.47 [0.91, 2.40]
Education		
HS/vocational school	49	(ref)
Some college/college grad	65	0.84 [0.51, 1.39]
Professional school	28	1.85 [0.93, 3.67]
Diagnosis Year		
2001–2013	130	(ref)
2014–2015	31	7.26 [3.48, 15.15]
Platinum Sensitive		
Yes	137	(ref)
No	24	0.49 [0.28, 0.86]
Gynecologic Oncologist Gender		
Male	118	(ref)
Female	43	1.88 [1.10, 3.21]
Chemotherapy Provider		
Gynecologic Oncologist	123	(ref)
Other	38	0.49 [0.30, 0.78]
Enrolled in clinical trial		
No	93	(ref)
Yes	68	1.74 [1.11, 2.74]
Overall Survival (months)		
0–36	42	(ref)
37–60	65	3.83 [2.16, 6.81]
61+	54	2.70 [1.47, 4.98]
Family history of ovarian cancer		
No	119	(ref)
Yes	42	2.20 [1.03, 4.72]

Table 3.

Multiple logistic regression models comparing variables associated with genetic referral 2001–2013 versus 2014–2015.

Variable	Multivariable-adjusted odds ratio [95% confidence interval]	
	2001–2013 (n=501)	2014–2015 (n=56)
Age (Years)		
27–59	(ref)	(ref)
60–88	0.50 [0.32, 0.78]	0.16 [0.03, 0.89]
Race		
White	(ref)	---
Non-white	0.31 [0.10, 0.99]	---
Platinum Sensitive		
Yes	(ref)	(ref)
No	0.56 [0.31, 1.00]	0.16 [0.03, 0.77]
Gynecologic Oncologist Gender		
Male	(ref)	---
Female	1.82 [1.04, 3.21]	---
Chemotherapy Provider		
Gynecologic Oncologist	(ref)	---
Other	0.52 [0.32, 0.85]	---
Enrolled in clinical trial		
No	(ref)	---
Yes	1.85 [1.17, 2.93]	---
Overall Survival (months)		
0–36	(ref)	---
37+	3.69 [2.11, 6.46]	---
Number of therapy lines		
0–3	---	(ref)
4+	---	5.69 [1.43, 22.69]