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Genetic Risk Assessment for Women with Epithelial Ovarian Cancer: Referral Patterns and Outcomes in a University Gynecologic Oncology Clinic

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Abstract

Little is known about genetic service utilization and ovarian cancer. We identified the frequency and outcome of genetic counseling referral, predictors of referral, and referral uptake for ovarian cancer patients. Using pathology reports, we identified all epithelial ovarian cancer patients seen in a university gynecologic oncology clinic (1/04–8/06). Electronic medical records (EMR) were used to document genetic service referral, time from diagnosis-to-referral, point-in-treatment at referral, personal/family cancer history, demographics, and genetic test results. Groups were compared using chi-squared and Fisher's exact test for categorical variables and t-tests for continuous variables. The study population consisted of 376 women with ovarian cancer, 72 (19 %) of who were referred for genetic counseling/testing, primarily during surveillance. Of those referred, 42 (58 %) had personal or family genetic counseling and 34 (47 %) were ultimately tested or identified due to known family mutation. Family history and prior cancer were associated with referral. Family history, living in a larger community, higher-stage disease, and serous

histology were associated with undergoing genetic counseling. Risk assessment identified 20 BRCA1/2 (5.3 %) and 1 HNPCC (0.3 %) mutation carriers. Based on recent estimates that 11.7–16.6 % of women with ovarian cancer are BRCA carriers and 2 % are HNPCC carriers, results suggest under-identification of carriers and under-utilization of genetic services by providers and patients. Interventions to increase medical providers' referrals, even in a specialized oncology clinic, are necessary and may include innovations in educating these providers using web-based methods. Ease of referral by the introduction of an electronic cancer genetic referral form represents another new direction that may increase genetic risk assessment for high-risk women with ovarian cancer.

Keywords

Ovarian cancer; Genetic risk assessment; BRCA; HNPCC; Genetic counseling

Introduction

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States, with an estimated 22,240 women that will be diagnosed this year and 14,030 who will die from the disease (Siegel et al. 2013). The prognosis of this disease is stage dependent, suggesting early detection may be the best way to improve survival outcomes. Modern screening strategies have, to date, lacked sufficient positive predictive value to be used in the general population. However, screening may be effective in selected populations at higher baseline risk, increasing interest in identifying women at elevated hereditary susceptibility.

Genes responsible for the development of ovarian cancer have been identified and genetic testing is commercially available. Germ-line mutations in BRCA1 and BRCA2, associated with Hereditary Breast/Ovarian cancer (HBOC), are reported to occur in 11.7–16.6 % of ovarian cancers, making ovarian cancer one of the most common hereditary malignancies (Alsop et al. 2012; Pal et al. 2005; Prat et al. 2005; Risch et al. 2001). Mutations in germline mismatch repair genes (MLH1, MSH2, MSH6 and PMS2), associated with hereditary nonpolyposis colorectal cancer (Lynch syndrome), are implicated in an additional 2 % of ovarian cancer cases (Malandier et al. 2006). While hereditary risk assessment and genetic testing may have complex medical and psychological implications for patients (Broadstock et al. 2000; Lapointe et al. 2012; Meiser et al. 2008), a priori risk stratification enables physicians to provide cost-effective tailored screening and prevention options. These options have demonstrated improved outcomes in women at substantial risk (20–25 %), including increased life expectancy for first degree relatives (Kwon et al. 2010; Lancaster et al. 2007).

Research suggests genetic testing be considered for all women with invasive ovarian cancer, high-grade epithelial tumors, or any serous tumor (Alsop et al. 2012; Gilks and Prat 2009; Metcalfe et al. 2009; Pal et al. 2005; Trainer et al. 2010), and the Society of Gynecologic Oncologists (SGO) has established guidelines endorsing referral of high-risk patients (Lancaster et al. 2007). Regardless of these recommendations, barriers to identifying BRCA mutations in women with ovarian cancer continue to exist. Lacour et al. (2008) surveyed

237 women with ovarian cancer about their knowledge and willingness to undergo BRCA testing and concluded despite lack of knowledge, more than 80 % were willing to be tested if it affected their therapy or would benefit their family. Subsequent U.S. studies documenting women's actual use of genetic services to identify BRCA mutations found under-usage of genetic counseling for women with ovarian cancer. Referrals are low especially in African-Americans but increased physician referral rates are noted when systematic methods for identifying high-risk women were introduced (Daniels et al. 2009; Hughes et al. 2003; Meyer et al. 2010). International studies similarly report low use of referral for counseling and testing among ovarian cancer patients (Alsop et al. 2012; Metcalfe et al. 2009). We were unable to identify any studies assessing referral rates for ovarian cancer patients with suspected Lynch syndrome despite inclusion of this group in the SGO guidelines (Lancaster et al. 2007). These studies suggest little is known about genetic service utilization by women with ovarian cancer, including how successfully women at increased genetic risk are being recognized and referred.

We sought to identify the frequency and outcome of referral for genetic risk assessment for women with ovarian, fallopian tube (FTC) and primary peritoneal cancer (PPC)¹ treated at a university gynecologic oncology clinic at a nationally designated Comprehensive Cancer Center and factors predicting their referral and referral uptake.

Methods

Participants and Procedures

After obtaining approval from the University of Minnesota's Institutional Review Board, we conducted a retrospective review of the electronic medical records (EMR) for women treated at the Women's Cancer Center (WCC) from January 2004 to August 2006 for suspected or recurrent ovarian, fallopian tube (FTC), or primary peritoneal (PPC) carcinoma¹. Using ICD-9 codes, 429 patients were identified. The ICD-9 codes used for identification included 183.0 (malignant neoplasm of ovary), 183.2 (malignant neoplasm of fallopian tube), 158.8 (malignant neoplasm of specified parts of the peritoneum), V10.43 (personal history of malignant neoplasm of ovary). The time frame was selected based on the introduction and availability of a single EMR system (Allscripts). The final analysis included 376 (82 %) patients verified by pathology reports as having epithelial tumors, the most common tumor associated with BRCA1/2 or Lynch syndrome. Fifty-three cases were omitted based on pathology reports indicating non-epithelial tumor histology, the most frequent of which was granulosa cell tumor.

The gynecologic oncologists in the Women's Cancer Center do not directly order genetic testing, but complete a hand-recorded order referral form to refer patients to a genetic counselor, a member of the Cancer Genetics Program, stationed in the clinic. Initiation of the genetic counseling process was defined as the original date a genetic counseling referral was discussed and documented in the EMR. The genetic counselor, responsible for setting up the counseling appointment following referral, proceeds by contacting the patient by telephone. A patient's decision to decline a risk assessment referral, a counseling

¹PPC and FTC are considered part of the spectrum of the HBOC Syndrome.

appointment, or the decision to self-refer to another testing center is not routinely recorded in the patient's EMR. Patients were not required to use a counselor in or to be tested at the Cancer Genetics Program to be part of the study. The date of genetic counseling was defined as the date of the initial counseling visit. Patients receiving counseling in the Cancer Genetics Program saw one of two certified genetic counselors. Decisions about what guidelines were used for ordering testing and which genes were to be tested were left to the discretion of the genetic counselor based on their assessment.

When test results were positive, the gene mutation present was not consistently reported in patients' EMRs. Within our clinical setting, genetic testing by the Cancer Genetics Program is performed by a CLIA-approved facility. Tumors were tested for microsatellite instability and immunohistochemistry in patients selected for Lynch syndrome testing if their ovarian cancer followed a colon cancer diagnosis. For patients selected for Lynch syndrome testing following an ovarian cancer diagnosis without a colon cancer diagnosis, genetic testing was performed based on family history. Referral outcome was tracked in patients' EMR records for a minimum of 4 years. Subjects were placed into two groups as delineated in Fig. 1, those referred for genetic services and those not referred. Within the referred group, two subgroups were identified: those seen by a genetic counselor and those not seen. Patients seen for counseling were divided into those who completed and did not complete testing. Those completing testing were identified as testing gene positive or negative. Patients seen in the WCC and referred by providers other than the gynecologic oncologists also were included.

Other patient data considered in this analysis included state of residence (Minnesota/other), home community size (population <10,000, 10,000–49,999, >50,000), diagnosis, histology (serous, clear cell, endometriosis, mucinous, adenocarcinoma—type not specified, other/unknown), year/age at diagnosis, stage, previous or subsequent cancer diagnosis (breast, colorectal, endometrial, other), and family cancer history.

Additional data collected on referred patients, included treating oncologist, referring provider, the number of biological children, time from initial diagnosis to referral, and referral outcome (genetic counselor visit, time from referral-to-counselor visit, gene test results). Point-of-care at referral was documented as: 1) Pre-initial diagnosis, 2) Newly diagnosed: post staging surgery/pre-chemotherapy, 3) During initial chemotherapy, 4) Surveillance: post-chemotherapy during 1st remission, 5) At recurrence, 6) During treatment for recurrence, 7) Family member tested. A genetic counselor (A.L.) reviewed documented personal/family cancer history, identified risk for BRCA1, BRCA2, or Lynch syndrome, and placed patients in one of seven familial cancer-risk categories based on NCCN Guidelines Panel (2006) existing at the time of the study (Table 1) (Daly et al. 2006). The study genetic counselor reviewed the referred patient's family history that had been recorded in the EMR by the treating oncologist. For a referred patient who subsequently met with a Cancer Genetics Program counselor, histories documented by the oncologist and by the genetic counselor were not compared.

Data Analysis

All values were reported as percentages or means±standard deviation (SD) unless otherwise noted. Comparisons by group were performed using chi-squared and Fisher's exact tests when applicable for categorical variables and t-tests for continuous variables. The number of patients with missing information for each variable is presented, however they are not included in analyses. A p-value less than or equal to 0.05 was considered statistically significant. All analyses were performed using SAS version 9.2.

Results

Patient Characteristics and Associations with Genetic Service Referral

Among 376 eligible patients, the mean age at diagnosis was 55.3±13.3 years (range=18–91). Patient characteristics and descriptive statistics by referral status are detailed in Table 2. The majority (81 %) were not referred for genetic counseling, resided in Minnesota (88 %), had stage III-IV disease (67 %), were diagnosed since 2000 (87 %), lived in larger/metro communities (population >50,000; 48 %), and had serous tumors (55 %).

Seventy-two (19 %) patients were referred for genetic counseling. The majority were referred by the seven gynecologic oncologists ($n=54$, 75 %) with a 14 % group referral rate (range=0–21 %). Characteristics of patients referred by the oncologists versus other providers were not compared. Patients referred were more likely to have a family cancer history indicating significant-to-high familial risk ($P<0.0001$), a cancer diagnosis prior to ovarian cancer ($P<0.0001$), and to be younger ($P=0.06$; mean age=52.6). Another cancer diagnosis post-ovarian cancer occurred for 8 (14 %) referred and 24 (8 %) non-referred; none of the latter were subsequently referred for counseling. Among those with other cancers, the most frequent pre-ovarian cancer was breast; post-ovarian diagnosis, breast and endometrial cancers occurred with similar frequency.

Referred Patients and Associations with Attending Genetic Counseling

Of those who were referred for genetic counseling, 42 (58 %) attended a formal consultation. Patient characteristics and descriptive statistics based on whether a genetic counselor was seen are detailed in Table 3. The mean time from diagnosis-to-referral was 21±29.3 months (range=0–116) and referral-to-genetic counseling was 5.4±10.2 months (range=0–45). Patients were referred most frequently at a surveillance visit (38 %), and the majority of patients referred had children (78 %). Those seen for counseling were more likely to live in larger communities ($P=0.007$), have stage III/IV cancer ($P=0.01$), serous tumors ($P=0.007$) and a family cancer history indicating significant-to-high familial risk ($P=0.02$).

Detailed testing and results for the 42 patients seen for counseling are described in Fig. 1. A total of 21 women were ultimately identified as gene positive (15 BRCA1, 4 BRCA2, 1 BRCA unknown and 1 HNPCC). Of note, 8 were not tested and did not have family members who had tested gene positive. It was unclear how many not tested were not offered testing. However, based on EMR information, one cancelled a testing appointment ("too upset"), one declined testing based on religion, two were to "check" insurance coverage for

testing, and documentation of reasons for the 4 remaining were unavailable or equivocal. The remaining 34 (81 %) were identified as gene positive ($n=21$) or negative ($n=13$). Of the 21 gene positive patients, 4 were told testing was not necessary as they had one or more first degree relatives with breast or ovarian cancer who had tested BRCA1 or BRCA2 positive and therefore these women were designated gene positive based upon personal cancer history and the identification of a familial mutation. Among them, 4 were tested at another center located in the same metropolitan or regional area. For the BRCA unknown, patient medical records forwarded by another cancer center were available in the EMR but did not identify which BRCA germ-line mutation had been identified. One woman's test results indicated a BRCA2 genetic variant of uncertain significance.

Discussion

In this fee-for-service comprehensive cancer clinic, 72 (19 %) women were referred or ultimately identified for risk assessment from our study population of 376 patients, and 20 (5.3 %) were identified as BRCA1/2 and 1 (0.3 %) as HNPCC mutation carriers. Based on recent estimates that 11.7–16.6 % of women with ovarian cancer are BRCA carriers and 2 % are HNPCC carriers, results suggest under-identification of carriers and under-utilization of genetic services by providers and patients. Our findings occurred despite the high possibility of identifying a mutation among women with ovarian cancer being seen by gynecologic oncologists at a cancer center.

The frequency of BRCA1/2 germ-line mutations in women with ovarian cancer is unclear. Earlier studies reported 5 % to 10 % of ovarian cancers are associated with these mutations (Berchuck et al. 1998) while more recent research describes higher rates, ranging from 11.7 % to 16.6 % (Alsop et al. 2012; Metcalfe et al. 2009; Pal et al. 2005; Zhang et al. 2011). The prevalence of mutations has been reported to be particularly high among women diagnosed in their forties (24.0 %), in women with serous ovarian cancer (18.0 %), and in women of Jewish origin (29.4 %) (Zhang et al. 2011). The frequency of HNPCC mutations in women with ovarian cancer is estimated to be 2 % (Malandar et al. 2006).

As expected, higher familial risk and a cancer diagnosis prior to ovarian cancer were significant predictors for referral in our ovarian cancer population. Family history is a promising referral indicator, although it will miss patients with no obvious suggestive family history (Alsop et al. 2012; Pal et al. 2005). Despite a clearly documented high risk family history by the oncologist and subsequent categorization as high/significant familial risk, the majority of patients at this risk level were not referred. In addition, family history for 18 % of the study population ($n=73$) was categorized as potentially significant, meaning incompletely documented by providers. Few of these patients were referred, some of whom may have been mutation carriers and a more complete family history by providers may have resulted in referral.

Earlier age at ovarian cancer diagnosis was only marginally ($P=0.06$) associated with referral, even though cancer at a young age is a hallmark of heredity and age of ovarian cancer onset has been identified as a strong predictor of BRCA1/2 mutation status (Alsop et al. 2012). These results suggest younger age at diagnosis was not necessarily part of the

referral criteria used by our providers. An ovarian cancer diagnosis before age 50 has been reported for 61 % of BRCA1 and 24 % of BRCA2 carriers (Kwon et al. 2010; Risch et al. 2001; The Breast Cancer Linkage Consortium 1999). Surprisingly, the mean age of those referred in our study, the majority of whom were BRCA1 positive, was over 50 years old while only 30 (25 %) of 120 women less than 50 years old at diagnosis were referred. Lynch-associated ovarian cancer tends to occur even earlier with 42 years reported as the median age of diagnosis (range=31–48) (Domanska et al. 2007; Malander et al. 2006; Schmeler et al. 2006; Watson et al. 2001) making early onset ovarian cancer an important indicator for genetic testing referral (Watson et al. 2001).

Referrals were independent of point-in-care and were made throughout patients' clinical course. This differs from other studies of breast and ovarian cancer patients which have reported conflicting results. Meyer et al. (2010) reported ovarian cancer patients were less likely to be referred as time elapsed after their first visit. Contrasting findings are reported by Arden-Jones et al. (2005) who surveyed breast cancer patients and health professionals' views and found the majority of providers and patients believed genetic testing added too much additional stress when offered at the time of diagnosis. Providers treating ovarian cancer may be mindful of its threatening prognosis compared to breast cancer, thereby prompting providers to address issues early and to promote referral throughout the disease course as the prognosis allows. Uptake of counseling referral did not vary by the point-in-care at which referral was made. Our findings, similar to Daniels et al. (2009), suggest women with ovarian cancer remain open to counseling through treatment and follow up.

Living in a larger community, having advanced stage at diagnosis, a significant familial cancer risk, and serous histology were associated with increased use of genetic counseling. Larger communities are likely to provide women with greater access to genetic information and services, consistent with research reporting that uptake of cancer genetic testing is associated with more knowledge about it (Hughes et al. 2003). When an individual is part of a family at increased hereditary risk, research indicates risk assessment is more likely to be discussed within the family (Claes et al. 2003; Hughes et al. 2003; Koehly et al. 2003; Mellon et al. 2006) which is likely to promote more knowledge about cancer susceptibility and counseling. In our study, more knowledge may have been a key factor associated with higher use of genetic counseling by women at increased risk. In addition to seeking information from the family, cancer-genetics information is being more commonly sought in non-traditional media (Case et al. 2004; Markman et al. 2006). The internet is now a leading source of information about cancer genetics (Case et al. 2004). Many women with ovarian cancer have sought assistance from web-based decision support programs (Markman et al. 2006) and it has been associated with utilization of genetic counseling for BRCA1/2 mutations (Armstrong et al. 2006). Finally, the women who saw a genetic counselor tended to have a more advanced stage at diagnosis, suggesting they may have been aware of their serious prognosis and of the corresponding timeliness to pursue genetic counseling.

Explanation of the increased frequency of women electing to have counseling who had serous versus non-serous tumors is unclear but may be consistent with assuming a relative high proportion of BRCA carriers in our referred population. There is evidence genetic risk varies by histological subtype (Gates et al. 2010) with a greater proportion of serous ovarian

cancers in BRCA mutation carriers (Lakhani et al. 2004; Watson et al. 2001). Lynch-associated ovarian cancers are more often endometrioid (Schlich-Bakker et al. 2007).

Testing of all ovarian cancer patients is not cost effective. Therefore it is important to identify women at increased hereditary risk who have a high probability of carrying BRCA or HNPCC mutations for referral for genetic assessment. There are several possible reasons for our identification of fewer mutation carriers than what has been observed in other studies.

First, the number of existing genetic referrals by providers may have been insufficient to identify all of the BRCA and Lynch mutations. This could be due to incomplete documentation of family history; lack of providers' understanding of indicators for genetic mutation, notably earlier age at diagnosis and a second cancer diagnosis post-ovarian cancer; or limited provider time to discuss risk assessment fully with patients. Our results especially indicate less provider awareness of hereditary-risk indicators for Lynch syndrome compared to HBOC. In Lynch syndrome carriers, not only is ovarian cancer diagnosed at an earlier age, it often is the sentinel cancer, and is more likely to be associated with a synchronous endometrial or colorectal cancer (Watson et al. 2001). In our study, 15 women had a synchronous endometrial or colorectal cancer at diagnosis, only 5 (33 %) of these were referred compared to 22 patients (72 %) referred with ovarian and breast cancer.

Second, other gynecologic oncologists or health care providers who offer genetic testing without referral to genetics professionals may demonstrate a different/higher uptake of genetic testing. However, we identified no research addressing this option for providers treating women with ovarian or another hereditary cancer. Results of a national survey indicate most physicians refer patients for genetic testing for cancer susceptibility rather than directly ordering tests (Wideroff et al. 2005). These survey findings and the lack of research studying medical providers' use of testing without referral to genetic professionals may be influenced by two constraints: National Comprehensive Cancer Network (NCCN) and professional organizations' guidelines highly recommending genetic counseling as an integral part of cancer genetic testing (Lancaster et al. 2007; NCCN Guidelines Panel 2012; Robson et al. 2010) and providers own lack of confidence in interpreting test results (Freedman et al. 2003). In a related study, O'Neill et al. (2008) offered genetic susceptibility testing for relatives of patients with lung cancer using solely a web-based format. Interest was high and 44 of 116 (39 %) eligible participants decided to be tested. O'Neill suggests while this uptake rate may be lower than desirable, it does not differ from decisions made in the presence of a trained health professional. A recent development, the offer of genetic susceptibility tests directly to consumers by commercial entities, usually through Internet portals (see list, (Robson et al. 2010), has raised concerns about the adequacy of counseling for this type of test availability. We found no studies comparing uptake rates for these portals compared to test uptake following provider referral.

Third, the success of any hereditary risk assessment program depends not only on referral but also on patient uptake. Barriers to patients' using genetic services suggested by our findings include difficulty accessing services for those living in smaller communities and lack of knowledge that increased genetic risk is associated with a personal history of a

second cancer or ovarian cancer before age 50. In our population, additional barriers also may be represented by whether patients' recognized the benefits of early detection for at-risk family members, including their adult children and the relevancy of genetic counseling regardless of stage of disease at diagnosis. The majority of women in our study had children. In other studies of women with ovarian cancer, parity has been associated with the use of genetic testing (Metcalf et al. 2009).

Many patient barriers associated with low uptake may be addressed by increased cancer education for physicians, the public, and patients (Metcalf et al. 2009; Skinner et al. 2002). However, use of health interventions other than education alone may be necessary to impact some patient-related barriers. Barriers associated with being treated at a community vs. teaching hospital (Metcalf et al. 2009), lower education, lower income, and increased depression (Lerman et al. 1999) may affect use of risk assessment and education alone may be insufficient to modify these barriers. For example, heavier media attention has been suggested as a means of reducing cancer disparities associated with socioeconomic barriers (Viswanath et al. 2006) and might be included in a communication intervention to increase genetic counseling uptake for women with ovarian cancer. Additionally, there is extensive health research which finds some individuals avoid, ignore, and/or deny rather than seek information. Informational styles, which can influence subsequent health decisions, must be considered when addressing ways to overcome barriers.

Patients' decisions to decline genetic services may have prevented some mutation detection in our study population and may have been affected by their not seeking sufficient information about genetic services. Ways in which patients seek or avoid information to make informed decisions also might be included in developing intervention trials to impact individuals' use of cancer genetic risk assessment (Case et al. 2005). Future intervention trials designed to address education, communication and decision-making within the referral process might provide further insight as to how to improve uptake of genetic services following referral.

In designing intervention trials to promote hereditary risk assessment promising internet methods (eHealth) beginning to be developed may provide innovative ways to deliver educational and other health-related interventions (Dutta et al. 2010; Strecher 2007; Thomson and Hoffman-Goetz 2007). Users find these attractive because of their convenience, availability and anonymity (Strecher 2007). Challenges include finding the optimal fit of Internet programming to the needs and preferences of cancer patients at increased hereditary risk.

Practical Implications

Research regarding uptake rates for genetic risk assessment for women has focused on breast rather than ovarian cancer. Ropka et al. (2006) concluded, reviewing breast cancer genetic testing, that clinical characteristics and research methodological issues represent major factors contributing to the variability in published breast cancer risk assessment uptake rates. Similar factors, such as variation in research design and selection of the population studied, make it difficult to compare uptake rates for different hereditary cancers. Results of our study cautiously suggest women with ovarian cancer may have used genetic

testing at a lower frequency than women with breast cancer at hereditary risk, who demonstrate on average a 59 % testing uptake rate (range=20–96) (Broadstock et al. 2000; Schwartz et al. 2005) compared to 47 % in our study. Research suggests 26 % of colorectal cancer patients request information about Lynch syndrome testing (Keller et al. 2004; Ropka et al. 2006). However, when high-risk healthy members of hereditary colon cancer families have been contacted directly and invited to participate in genetic counseling/testing at no cost, Aktan-Collan et al. (2007) reported 76–86 % accepted; more accepted when approached by family members than by letter. Other uptake studies report a 51 % (Hadley et al. 2003) and 67 % (Gritz et al. 2005) response rate by healthy members of HNPCC families when invited to have counseling/testing and a 63 % uptake for HNPCC testing by affected individuals (Gritz et al. 2005). Compared to women with ovarian cancer, a higher proportion of breast and colon cancer patients may opt for genetic testing due to their knowledge of screening or treatment benefits, especially when genetic services are offered at no cost. Such benefits have yet to be identified for women with ovarian cancer.

It is difficult to know the extent to which our study group is representative of women reported in studies of BRCA/MMR mutation prevalence in ovarian cancer. Looking more closely at two of the few available studies demonstrates the methodological complexity of genetic testing uptake research for women with ovarian cancer. Reviewing medical records (2002 to 2006), Alsop et al. (2012) reported BRCA1/2 germ-line mutations in 14.1 % of ovarian cancer patients, including 16.8 % of serous patients (high-grade serous, 22.6 %). These subjects were part of an Australian-wide population-based project. Metcalfe et al. (2009) reported approximately 13 % of ovarian cancer in Ontario, Canada were attributable to a mutation in BRCA1/2.

Based on the above findings, caution must be taken in comparing rates, rate differences, and rate changes across hereditary ovarian cancer studies. Incentives to women with ovarian cancer who choose to use genetic services are only beginning to be recognized. For example, review of breast cancer genetic testing studies recommend intervention studies include additional outcomes such as psychological impact or a patient's satisfaction with their decision (Ropka et al. 2006) to undergo risk assessment.

Study Limitations

There are several limitations to our study. In our retrospective design, we were restricted to identifying genetic counseling referrals and testing results as reported in the EMR. It is likely that a small portion of referrals and even test results may not have been recorded. The gynecologic oncologists who referred the least might have discussed risk assessment and made a referral without recording it in the EMR. It also is possible that BRCA1/2 germ-line mutation prevalence actually is lower in our population. A cohort selection bias cannot be ruled out. Mutation prevalence varies among national (ethnic) groups and may be influenced by founder mutations (Fackenthal and Olopade 2007). Several factors are likely to weigh against a low BRCA mutation prevalence rate in our study population: the clinic has a state-wide referral base and Minnesota's ovarian cancer incidence rate interval, 11.9-to-12.6 per 100,000, places it in the second highest rate interval category by state (U.S. Cancer Statistics Working Group 2012). While Minnesota's Ashkenazi Jewish population (0.9 %) is lower

than that of the U.S. population (2.1 %), Minnesota's ancestry background is strongly German, Norwegian, and Swedish, representing about 66 % of Minnesota's population (Fackenthal and Olopade 2007), and these are among the nationalities in which BRCA1/2 founder mutations have been identified (Gritz et al. 2005). This ethnic demographic is what most likely contributes to the relatively high ovarian cancer rate in Minnesota. The family/personal history of women in our study further suggests women in our geographic region are not likely to be at lower genetic risk for BRCA germ-line mutations. About 30 % of our study group was categorized as having a significant or high family/personal history suggesting inherited cancer susceptibility. More than half of these at-risk women were not referred.

Research Recommendations

Our study indicates ovarian cancer patients at increased genetic risk are under-referred and genetic services are under-utilized when referrals are made by gynecologic oncologists within a university-based, fee-for-service clinic. Future improvement in mutation detection will depend on identifying and mitigating both patient and physician barriers to testing. Newer NCCN guidelines (2012) and recent studies (Alsop et al. 2012) recommending all women with epithelial ovarian cancer be referred for risk assessment as well as Medicare's reimbursement for risk assessment of all women with ovarian cancer may contribute to increased use of genetic services. However, despite new guidelines, socioeconomic and psychosocial barriers to patient uptake remain. Research has identified many barriers that were beyond the scope of our study. Barriers include approaching the patient in a clinical (versus research) setting, concerns about insurance discrimination, minority ethnicity, lower socioeconomic status and medical distrust, all of which suggest access to affordable and equitable care may be a significant barrier (Armstrong et al. 2005; Balmana et al. 2004; Culver et al. 2001; Forman and Hall 2009). Intervention trials investigating ways to attract news media attention surrounding genetic risk assessment (Viswanath et al. 2006) or those that examine factors affecting or impeding genetics information seeking and decision making (Case et al. 2005) represent promising directions to expand provider and patient use of genetic risk assessment. Lastly, in anticipation of targeted therapy which may specifically benefit ovarian cancer patients with BRCA mutations, further research is needed to design organizational changes within health systems to streamline the delivery of genetic services (Alsop et al. 2012; Wideroff et al. 2005). We are currently investigating the use of a referral form embedded in the EMR that is immediately faxed to the genetic counselor upon an ovarian cancer patient being seen by a gynecologic oncologist.

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Fig. 1.

Distribution of study patients by genetic counseling referral, visit with counselor, gene testing, and testing results. ¹One patient did not see genetic counselor but was ultimately identified. ²Three patients did not actually get tested, but received genetic counseling with their families and family members were tested

Table 1

Categories of personal/family cancer risk for women with ovarian cancer

Risk category^a	Description
High ^b	<p>Hereditary Breast/Ovarian Cancer (HBOC) syndrome</p> <p>One of the following: 1) have a personal history of breast cancer, 2) of Ashkenazi Jewish ancestry, 3) close relative^c with breast cancer age 50 or ovarian cancer at any age, OR a first or second degree relative with a known BRCA mutation, 4) close male relative with breast cancer.</p> <p>Hereditary Nonpolyposis Colorectal Cancer (HNPCC) syndrome</p> <p>One of the following: 1) a personal history of a synchronous endometrial or metachronous colorectal cancer with the first cancer diagnosed <50 OR 2) a first or second degree relative with a known mismatch repair gene mutation.</p>
Significant ^d	<p>HBOC syndrome</p> <p>At least one 1st degree relative with a cancer known to be associated with hereditary ovarian cancer risk.</p> <p>HNPCC syndrome</p> <p>At least one 1st degree relative with a cancer known to be associated with HNPCC.</p>
Potentially significant	Further information needed to assess significance, including age of onset in affected family members; or history of a cancer that is frequently misreported [e.g., stomach or unknown cancer in female relative].
Insignificant	Family history of some cancers but unlikely to be associated with hereditary ovarian cancer risk
Negative	No reported family history of cancers.
Unknown/unavailable	Family history unknown due to adoption, estrangement, etc.
Missing information	No information regarding family history in medical chart.

^aCategories based on NCCN guidelines at time of study (Daly et al 2006)^bGenetic risk assessment recommended for women with greater than approximately 20–25 % chance of having an inherited predisposition to HBOC or HNPCC^cFirst, second or third degree relative^dGenetic risk assessment recommended for women with greater than approximately 5–10 % chance of having an inherited predisposition to HBOC or HNPCC

Table 2

Comparison of patient characteristics by groups not referred and referred for genetic counseling

	<u>Overall</u>		<u>Not referred</u>		<u>Referred</u>		<i>P</i> -value
	N	%	N	%	N	%	
TOTAL	376		304	80.85	72	19.15	
Residence – State							0.69
Minnesota	329	87.50	265	87.17	64	88.89	
Other	47	12.50	39	12.83	8	11.11	
Residence – Community Size							0.68
<10,000	148	39.36	121	39.80	27	37.50	
<50,000	46	12.23	35	11.51	11	15.28	
>50,000/Metro	182	48.40	148	48.68	34	47.22	
Diagnosis							1.00
Ovarian or fallopian tube	357	94.95	288	94.74	69	95.83	
Primary peritoneal	19	5.05	16	5.26	3	4.17	
Histology							0.99
Serous	206	54.79	168	55.26	38	52.78	
Clear Cell	28	7.45	22	7.24	6	8.33	
Endometrioid	25	6.65	20	6.58	5	6.94	
Mucinous	26	6.91	20	6.58	6	8.33	
Adenocarcinoma	32	8.51	27	8.88	5	6.94	
Low malignant potential	7	1.86	6	1.97	1	1.39	
Other/Unknown	52	13.83	41	13.49	11	15.28	
Cancer FIGO stage							0.44
Stage I	78	23.21	62	23.22	16	23.19	
Stage II	32	9.52	22	8.24	10	14.49	
Stage III	168	50.00	135	50.56	33	47.83	
Stage IV	58	17.26	48	17.98	10	14.49	
Missing	40		37		3		
Year of diagnosis							0.24
1972–1989	9	2.39	9	2.96	0	0.00	
1990–1999	41	10.90	31	10.20	10	13.89	
2000–2006	326	86.70	264	86.84	62	86.11	
Family/personal cancer-risk category							<0.0001
Negative	34	9.04	34	11.18	0	0.00	
Insignificant	105	27.93	94	30.92	11	15.28	
Potentially significant	73	19.41	69	22.70	4	5.56	
Significant	44	11.70	36	11.84	8	11.11	
High	72	19.15	26	8.55	46	63.89	
Missing	45	11.97	43	14.14	2	2.78	
Unknown/unavailable	3	0.80	2	0.66	1	1.39	
Other cancer before ovarian							<0.0001

	<u>Overall</u>		<u>Not referred</u>		<u>Referred</u>		<i>P</i> -value
	N	%	N	%	N	%	
Breast	17	4.52	5	1.64	12	16.67	0.14
Colorectal	4	1.06	2	0.66	2	2.78	
Endometrial	2	0.53	1	0.33	1	1.39	
Other	12	3.19	10	3.29	2	2.78	
None	341	90.69	286	94.08	55	76.39	
Other cancer after ovarian							
Breast	8	2.13	4	1.32	4	5.56	
Colorectal	4	1.06	3	0.99	1	1.39	
Endometrial	8	2.13	7	2.30	1	1.39	
Other	14	3.72	10	3.29	4	5.56	
None	342	90.96	280	92.11	62	86.11	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	P value
Age at diagnosis	376	55.3 (13.3)	304	55.9 (13.2)	72	52.6 (13.7)	0.06

Table 3

Comparison of patient characteristics among referred patients by whether they saw a genetic counselor (GC)

	<u>Overall</u>		<u>Did not see GC</u>		<u>Saw GC</u>		<i>P</i> -value
	N	%	N	%	N	%	
Total	72		30	41.67	42	58.33	
Residence – State							0.26
Minnesota	64	88.89	25	83.33	39	92.86	
Other	8	11.11	5	16.67	3	7.14	
Residence – Size of City							0.007
<10,000	27	37.50	14	46.67	13	30.95	
<50,000	11	15.28	8	26.67	3	7.14	
>50,000/Metro	34	47.22	8	26.67	26	61.90	
Diagnosis							1.00
Ovarian or fallopian tube	69	95.83	29	96.67	40	95.24	
Primary peritoneal	3	4.17	1	3.33	2	4.76	
Histology							0.007
Serous	38	52.78	11	36.67	27	64.29	
Clear cell	6	8.33	2	6.67	4	9.52	
Endometrioid	5	6.94	3	10.00	2	4.76	
Mucinous	6	8.33	6	20.00	0	0.00	
Adenocarcinoma	5	6.94	1	3.33	4	9.52	
LMP	1	1.39	0	0.00	1	2.38	
Other/unknown	11	15.28	7	23.33	4	9.52	
Cancer FIGO stage							0.01
I–II	26	37.68	16	55.17	10	25.00	
III–IV	43	62.32	13	44.83	30	75.00	
Missing	3		1		2		
Family/personal cancer-risk category							0.02
Negative	0	0.00	0	0.00	0	0.00	
Insignificant	11	15.28	7	23.33	4	9.52	
Potentially significant	4	5.56	3	10.00	1	2.38	
Significant	8	11.11	1	3.33	7	16.67	
High	46	63.89	16	53.33	30	71.43	
No report	2	2.78	2	6.67	0	0.00	
Unknown/unavailable	1	1.39	1	3.33	0	0.00	
Other cancer prior to ovarian							0.88
Breast	12	16.67	5	16.67	7	16.67	
Colorectal	2	2.78	1	3.33	1	2.38	
Endometrial	1	1.39	0	0.00	1	2.38	
Other	2	2.78	0	0.00	2	4.76	
None	55	76.39	24	80.00	31	73.81	
Patient point-in-care at referral							0.21

	<u>Overall</u>		<u>Did not see GC</u>		<u>Saw GC</u>		<i>P</i> -value
	N	%	N	%	N	%	
At diagnosis	15	20.83	9	30.00	6	14.29	
During initial chemotherapy	13	18.06	6	20.00	7	16.67	
Visit for Surveillance	27	37.50	12	40.00	15	35.71	
At time of recurrence	8	11.11	1	3.33	7	16.67	
During treatment for recurrence	4	5.56	2	6.67	2	4.76	
Prior to ovarian cancer diagnosis	3	4.17	0	0.00	3	7.14	
Family member tested near diagnosis	2	2.78	0	0.00	2	4.76	
Biological children							1.00
Yes	53	77.94	22	78.57	31	77.50	
No	15	22.06	6	21.43	9	22.50	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	P value
Age at diagnosis (years)	72	52.6 (13.7)	30	53.3 (15.1)	42	52.1 (12.8)	0.72
Time from diagnosis to referral (mths)	67	21.1 (36.8)	30	21.2 (44.9)	37	21.0 (29.3)	0.99