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Missed opportunities: Genetic counseling and testing among an ethnically diverse cohort of women with endometrial cancer

Jessica Lee [a], Lindsay R. Gubernick [b], Allison L. Brodsky [b], Julia E. Fehniger [a], Douglas A. Levine [a], Deanna Gerber [a], Shabnam A. Asgari [c], Anna Cantor [c], Jessica T. Martineau [c], Ophira M. Ginsburg [c], Julia A. Smith [c], Bhavana Pothuri [a,*]

[a] New York University Langone Health, Division of Gynecologic Oncology, Laura and Isaac Perlmutter Cancer Center, 240 East 38th Street, New York, NY, USA
[b] New York University School of Medicine, 550 First Avenue, New York, NY, USA
[c] New York University Langone Health, Laura and Isaac Perlmutter Cancer Center, High-Risk Cancer Program, 160 East 34th Street, New York, NY, USA

HIGHLIGHTS

- Women with endometrial cancer who have high-risk criteria for Lynch syndrome are not given genetic counseling referrals.
- Only one third of high-risk women underwent genetic testing for Lynch syndrome.
- There are women with Lynch syndrome who do not have loss of mismatch repair protein expression on tumor immunohistochemistry.

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ABSTRACT

Objectives. Lynch syndrome (LS) accounts for the majority of inherited endometrial cancers (EC), and the identification of probands presents a unique opportunity to treat and prevent multiple cancers. The diagnosis of EC can provide the indication for women with specific risk factors to undergo genetic testing (GT). We sought to evaluate genetic counseling referrals (GCR) and subsequent GT rates in an ethnically diverse group of high-risk women.

Methods. All women diagnosed with EC between 2011 and 2016 were identified. Risk factors for LS including age, family and personal histories of Lynch-related cancers and loss of tumor mismatch repair (MMR) protein expression were identified from laboratory and medical records. Standard two-sided statistical tests were used.

Results. Of 583 women diagnosed with EC, 184 (31.6%) were found to have at least one high-risk characteristic for LS. Among these high-risk women, 58% were given GCR and resulting in only 35% undergoing GT. Ten of the 65 high-risk women who had GT (15.4%) were diagnosed with Lynch syndrome, and all ten met high-risk criteria. Two women of Asian race had tumors exhibiting retained MMR protein expression despite germline testing demonstrating Lynch syndrome.

Conclusions. Many high-risk women do not receive GCR despite a high rate of germline mutations among these women. Improving GCR among high-risk women will lead to more subsequent GT to identify more Lynch syndrome families and prevent additional cancers. Among our ethnically diverse cohort, two women diagnosed with LS had retained MMR protein expression. GCR should be offered to women who possess high-risk characteristics despite normal MMR protein expression.

1. Introduction

Endometrial cancer is the most common gynecologic cancer in the United States with an estimated 63,230 new cases and 11,350 deaths in 2018 [1]. The frequency of inherited endometrial cancers is approximately 3–5% [2], and the majority of these are due to Lynch syndrome. Lynch syndrome is a cancer predisposition condition caused by an autosomal dominant germline mutation in an allele of one of the DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6* and *PMS2* or large deletions in the *EPCAM* gene that results in the epigenetic silencing of the adjacent *MSH2* gene. Individuals with Lynch syndrome have an increased risk of developing colorectal cancer and endometrial cancer as well as other cancers including ovarian, gastric, small bowel, urothelial,

* Corresponding author at: Division of Gynecologic Oncology, Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, 240 East 38th Street, 19th Floor, New York, NY 10016, USA.
E-mail address: bhavana.pothuri@nyumc.org (B. Pothuri).

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renal and hepatobiliary cancers [3]. The lifetime risk of endometrial cancer in women with Lynch syndrome is 40–60% [4–7]. Endometrial cancer presents as the first, or sentinel, cancer preceding the diagnosis of colon cancer in approximately 50% of women with Lynch syndrome [8].

Identification of a germline MMR mutation can prevent subsequent cancers through screening and prophylactic measures as well as provide an indication for cascade testing of affected individuals' family members to identify additional germline mutation carriers. Genetic counseling sessions with certified genetic counselors and physicians provide a venue to impart knowledge about cancer genetics and shape perceptions on cancer risks and in turn, allow women to make informed decisions regarding their genetic testing options. Positive results can enable patients and their family members to undergo risk-reducing screening and preventative measures for other related cancers.

The Amsterdam or Bethesda guidelines were initially used to identify those with significant risks of Lynch syndrome and recommend subsequent genetic testing; however, neither guideline provides high sensitivity and specificity in a reliable and consistent manner. The Amsterdam criteria has been shown to have low sensitivity (28–45%) but high specificity (99%), whereas the Bethesda criteria conversely has higher sensitivity (73–91%) but lower specificity (62–77%) [9]. The Amsterdam and Bethesda guidelines can miss up to 72% and 28% individuals with Lynch syndrome, respectively [10,11]. The Society of Gynecologic Oncology (SGO), the National Comprehensive Cancer Network (NCCN) and the American College of Medical Genetics (ACMG) have each designed their own criteria defining who is at sufficiently high risk for Lynch syndrome to recommend further genetic evaluation (Suppl Table 1) [12–14].

Over the last several years, immunohistochemistry (IHC) for MMR protein expression in tumor tissues has been increasingly used to screen patients for further investigation of germline mutation testing for Lynch syndrome. MMR IHC has been shown to be approximately 90% sensitive in detecting germline mutations [15]. The American College of Obstetrics and Gynecologists (ACOG) released an algorithm utilizing MMR IHC to assess the likelihood of Lynch syndrome in women with colorectal or endometrial cancer to stratify who should proceed with germline DNA testing [16].

In addition, women with loss of MMR IHC protein expression may be good candidates for targeted treatment options with the development of novel immunotherapy agents. This is especially salient with the 2017 FDA accelerated approval of biomarker-directed pembrolizumab in microsatellite instability–high or MMR-deficient tumors.

Previous studies have shown that rates of patients undergoing genetic counseling and testing are low in gynecologic cancers despite recommendations from professional organizations [17–19]. The objectives of this study were to identify high-risk individuals for Lynch syndrome from an ethnically diverse population of women with endometrial cancer and to evaluate the rates of genetic counseling referrals (GCR), genetic testing (GT) and germline mutations for Lynch syndrome.

2. Materials and methods

2.1. Data acquisition

After Institutional Review Board approval was obtained, all patients diagnosed with endometrial carcinoma at two academic tertiary care centers between November 2012 and December 2016 were identified. Patient demographics and clinical data including family history were abstracted from medical records. At our institutions, select somatic MMR IHC was initiated in 2014, and universal tumor testing started in early 2015. Tumor testing for the four common MMR proteins was performed on a formalin-fixed paraffin-embedded tissue blocks at a commercial laboratory (Esoterix Genetic Laboratories, LLC), with reflex MLH1 promoter methylation testing if the tumors exhibited loss of MLH1 and/or PMS2 protein expression. The tumor MMR IHC results were obtained from operative pathology reports. Genetic testing was performed at Myriad Genetics, Ambry Genetics, Invitae or GeneDx.

Provider-patient discussions on genetic counseling and GCR were identified from documentation in the medical record. GCR were provided based on the gynecologic oncologists' discretion. During this time period, we did not have formal referral policies in place for GCR, but referrals were generally recommended based one of the major guidelines listed in Suppl Table 1. For this study, we established that high-risk characteristics for Lynch syndrome included age < 50 at the time of endometrial cancer diagnosis, a positive family history defined as two or more family members with Lynch-related cancers, a positive personal history defined as at least one other metachronous or synchronous Lynch-related cancer, or evidence of MMR protein expression loss on tumor IHC. Women who were known to have Lynch syndrome or who had already undergone genetic testing prior to their endometrial cancer diagnosis were excluded from the study. Women who did not present for follow-up after their endometrial cancer diagnosis were also excluded.

All genetic counseling and testing were performed by the high-risk genetics team which includes certified genetic counselors and physicians specializing in high-risk genetics. Individuals who saw the genetic counseling team were identified from consultation notes or office notes indicating that the patient had been seen by a genetic counselor or other high-risk genetics provider. Patients who received GT were determined by a germline testing report in the medical record or by notations in the office notes reflecting a germline testing result.

2.2. Statistical analysis

Median values and standard deviations were used to describe continuous data, and categorical variables were displayed as totals and frequencies. Categorical variables were compared using the chi-square analyses, and continuous variables were compared using Wilcoxon signed-rank tests. All statistical analyses were performed using R Studio version 1.0.143. The two-sided significance was set at $p < 0.05$.

3. Results

From 2012 to 2016, 583 women were diagnosed with endometrial cancer and included in the study. Of these women, 155 women (155/583, 26.6%) were given GCR. Table 1 lists the patient and tumor characteristics of women categorized by whether they were provided GCR. Women given GCR had a younger age at diagnosis (median age of 55 years compared to 65 years, $p < 0.0001$) and had a lower body mass index (BMI) (median BMI 28.5 kg/m^2 vs 30.6 kg/m^2, $p = 0.003$). Among the entire cohort, 49.1% were non-Caucasian including 13.6% blacks, 14.6% Latinas and 9.9% Asians. There were higher proportions of Caucasians (61.3% vs 57.0%) and Asians (15.5% vs 7.9%) in the GCR group compared to the non-GCR group ($p = 0.02$). When evaluating tumor characteristics, there was a higher percentage of women with grade 1 or 2 disease among the GCR group versus the non-GCR group (78.7% vs 66.4%, $p = 0.004$), but there were no differences in disease stage or tumor histology between the two groups.

Among the entire cohort of endometrial cancer patients, ten out of 583 patients tested positive for a germline Lynch syndrome mutation (10/583, 1.7%). Table 2 lists the rates of GCR, GT and Lynch syndrome in the entire cohort and also by each high-risk characteristic evaluated. Of the 155 women who were given GCR, 97 (97/155, 62.6%) saw the genetics team and received GT. Of the 97 women who underwent GT, ten (10/97, 10.3%) were diagnosed with Lynch syndrome.

Evaluating by each high-risk characteristic, when looking at age, 82 women (82/583, 14.1%) were younger than 50 years old at the time of their endometrial cancer diagnosis. Forty-eight patients of this cohort (48/82, 58.5%) were provided GCR and of these 48 patients, 27 patients (27/48, 56.3%) underwent GT. Four out of the 27 young GT patients (4/27, 14.8%) were found to have Lynch syndrome. When evaluating family

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