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Prevalence of occult gynecologic malignancy at the time of risk reducing and nonprophylactic surgery in patients with Lynch syndrome

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HIGHLIGHTS

- Surgeons should consider the possibility of malignancy in patients with Lynch syndrome who are undergoing risk-reducing surgery.
- Surgeons should consider pre-operative testing and sending operative specimens for frozen pathology to determine the need for staging.

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ABSTRACT

Objective. The primary aim of this study was to determine the prevalence of occult gynecologic malignancy at the time of risk reducing surgery in patients with Lynch Syndrome. A secondary aim was to determine the prevalence of occult gynecologic malignancy at the time of surgery for non-prophylactic indications in patients with Lynch Syndrome.

Methods. A retrospective review of an Inherited Colorectal Cancer Registry found 76 patients with Lynch syndrome (defined by a germline mutation in a DNA mismatch repair gene) or hereditary nonpolyposis colorectal cancer (HNPCC) (defined by Amsterdam criteria) who had undergone hysterectomy and/or salpingo-oophorectomy for a prophylactic or non-prophylactic indication. Indications for surgery and the prevalence of cancer at the time of each operation were reviewed.

Results. 24 of 76 patients underwent prophylactic hysterectomy and/or bilateral salpingo-oophorectomy for Lynch syndrome or HNPCC. In 9 of these patients, a benign indication for surgery was also noted. 4 of 24 patients (17%, 95% CI = 5–38%) were noted to have cancer on final pathology. 20 of 76 patients (26%) undergoing operative management for any indication were noted to have occult malignancy on final pathology.

Conclusions. Patients should be counseled about the risks of finding gynecologic cancer at the time of prophylactic or non-prophylactic surgery for Lynch syndrome and HNPCC, and the potential need for additional surgery.

Introduction

Lynch syndrome (LS) is an autosomal dominantly inherited condition caused by a germline mutation in one of four DNA mismatch repair genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Loss of expression of MSH2 is also associated with mutations in *EPCAM* [1–5]. Lynch syndrome is part of hereditary nonpolyposis colorectal cancer (HNPCC), where affected families are defined by family history criteria known as the Amsterdam criteria. Only a fraction of HNPCC families can be shown to have a germline mutation, but HNPCC along with microsatellite instability is a reasonable surrogate for Lynch syndrome when genetic testing is not possible or fails to reveal a mutation.

LS confers up to an 80% lifetime risk of developing colorectal cancer. However, women with LS are also at an increased risk for developing endometrial and ovarian malignancies. Cancers of the stomach, pancreas, upper urinary tract, biliary tract, small intestine, skin, and brain also occur with increased frequency [6–8].

Women with LS have a 19–71% lifetime risk of developing endometrial cancer. This wide range is due to a variation in risk according to the particular mismatch repair gene mutated. The risk of endometrial cancer among women with a *MSH6* mutation is greater than the risk of colorectal cancer [9–12]. The lifetime risk of ovarian cancer in LS ranges from 3 to 14% [13,14].

For women with LS, management options for the risk of endometrial and ovarian cancer include: surveillance with endometrial sampling,

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transvaginal ultrasound, and CA-125; chemoprevention with oral contraceptives; and risk-reducing surgery. Risk-reducing hysterectomy and bilateral salpingo-oophorectomy is effective at preventing endometrial and ovarian cancers [15], is cost-effective over screening alone [16], and is typically recommended for women who have completed childbearing [17].

The prevalence of gynecologic malignancy at the time of risk-reducing surgery in LS has not been described as a primary outcome in the literature. The presence of malignancy at the time of risk-reducing surgery may change the recommended operation to more radical surgery and/or staging. This may expose the patient to more potential risk for complications at the time of surgery or even a second surgery if the possibility of cancer is not planned for in advance. Knowing the prevalence of malignancy at the time of risk-reducing surgery would help guide surgeons in counseling a patient regarding their potential risks and need for a more extensive procedure.

The primary aim of this study was to determine the prevalence of occult gynecologic malignancy at the time of risk-reducing surgery in patients with LS. A secondary aim of this study was to determine the prevalence of occult gynecologic malignancy at the time of surgery for non-prophylactic indications in patients with LS.

Methods

This study is a retrospective chart review of the David G. Jagelman Inherited Colorectal Cancer Registry. The Cleveland Clinic Sanford R. Weiss, M.D., Center for Hereditary Colorectal Neoplasia maintains the registry. Information is stored and organized in the Cologene™ database and the registry is approved by the Cleveland Clinic Institutional Review Board. The registry tracks outcomes in patients with inherited colorectal cancer, including patients with LS and HNPCC. Among other outcomes, the database contains the surgical history of these patients. It has been following patients with HNPCC since 1989 and with LS since 1994. All prophylactic procedures were performed between September 1999 and April 2012, with the addition of a single prophylactic surgery included from 1985 with the indication of family history of gynecologic cancer. All non-prophylactic procedures were performed between March 1950 and October 2009. All procedures were performed between March 1950 and April 2012.

Patients eligible for inclusion in the study were defined as women with LS, defined by the presence of a deleterious mismatch repair gene mutation, or HNPCC (those whose families satisfied Amsterdam 1 Criteria, Amsterdam 2 Criteria, or Amsterdam-like Criteria [18–20, Table 1], and who underwent hysterectomy and/or right, left, or bilateral salpingo-oophorectomy. Patients with a pre-operative diagnosis of gynecologic malignancy or with inadequate medical records were excluded. Patients meeting Amsterdam criteria, with a mutation not associated with gynecologic malignancy or with microsatellite stable tumors (i.e. Colorectal Cancer Type X), were also excluded. The database was queried and 197 patients were identified that met the inclusion criteria. 70 patients were excluded for a pre-operative diagnosis of gynecologic malignancy, 44 were excluded for inadequate medical records, 3 patients were excluded for a GERM-1 mutation, and 4 patients were excluded for microsatellite stable tumors. After excluding ineligible patients and patients with inadequate medical records, there were 76 patients available for our analysis. These 76 individuals were from 65 families.

The indications for operative management and the prevalence of cancer at the time of each operation were reviewed. Indications for gynecologic surgery were classified as prophylactic and non-prophylactic. Prophylactic operations were subdivided into groups of prophylactic only vs. prophylactic and benign. Non-prophylactic operations were subdivided into benign; spread of primary tumor or secondary debulking of non-gynecologic cancer to gynecologic organs; and premalignant conditions (i.e. hyperplasia, cervical intraepithelial neoplasia). Data were collected and managed using REDCap electronic data capture tools hosted at the Cleveland Clinic [21]. The lower and upper limits of the 95% confidence interval for a proportion were determined by the Wilson procedure with a correction for continuity [22,23].

Table 1
Definitions of Amsterdam Criteria.

Amsterdam I criteria
-At least 3 relatives with histologically confirmed colorectal cancer, 1 of whom is a first degree relative of the other 2; familial adenomatous polyposis (FAP) should be excluded;
-At least 2 successive generations involved;
-At least 1 of the cancers diagnosed before age 50.
Amsterdam II criteria
-At least 3 relatives with histologically confirmed Lynch Syndrome-associated cancer, 1 of whom is a first degree relative of the other 2; familial adenomatous polyposis (FAP) should be excluded;
-At least 2 successive generations involved;
-At least 1 of the cancers diagnosed before age 50.
Amsterdam-like criteria
-2 or more relatives with colorectal cancers and 1 relative with and advanced adenoma *
-2 or more successive generations
-1 or more diagnosed before 50 years
-1 should be 1st degree to other 2

*Advanced adenoma: high-grade (severe) dysplasia (any size); >25% villous architecture; adenoma >1 cm diameter; 3 (or more) adenomas (of any size) in one procedure; or 1 adenoma, any size at or under 40 years of age.

Results

Demographic details, genotypes, and surgeries performed in the 76 patients with LS/HNPCC are shown in Table 2. Of these 76 patients, 24

Table 2
Characteristics of all patients.

	Prophylactic (n = 24)	Non-prophylactic (n = 52)	All patients (n = 76)
Race			
Caucasian	22	47	69
Asian	1	0	1
Black	1	3	4
Unknown		2	2
Average age at surgery	46.8 (Range 32–61)	46.0 (Range 30–78)	46.2 (Range 30–78)
Familial mutation			
MLH1	*8*	15	23
MSH2	*9*	*5*	*14*
MSH6	*2*	*1*	*3*
PMS2	*1*	*0*	*1*
Amsterdam criteria/HNPCC	*4*	*31*	*35*
Operations			
LSO	0	2	2
BSO	1	0	1
TH-BSO	22	41	63
TH-RSO	0	2	2
TH-LSO	0	1	1
SCH-BSO, followed by LEEP	1	0	1
TH only	0	6	6
Gynecologic cancers***			
Endometrial	3	11	14
Ovarian	1	8	9

*As determined by deleterious mutation or abnormal IHC.
**1 patient had prior hysterectomy.
***Three patients had both endometrial and ovarian malignancy in the non-prophylactic group.
BSO, bilateral salpingo-oophorectomy.
LSO, left salpingo-oophorectomy.
RSO, right salpingo-oophorectomy.
LEEP, loop electrosurgical excision procedure.
SCH, supracervical hysterectomy.
TH, total hysterectomy.