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Primary Peritoneal Cancer After Bilateral Salpingo-oophorectomy in Two Patients With Lynch Syndrome

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Abstract

Background—Women with Lynch syndrome or hereditary nonpolyposis colorectal carcinoma (HNPCC) have a 40-60% lifetime risk of endometrial cancer and a 7-12% lifetime risk of ovarian cancer. Risk-reducing surgery, including hysterectomy and bilateral salpingo-oophorectomy (BSO), is currently recommended once childbearing is complete. We describe two cases of primary peritoneal cancer following BSO in women with Lynch syndrome or HNPCC.

Cases—The first patient was a 44 year-old woman who underwent hysterectomy with BSO for benign disease. She presented 12 years later with a pelvic mass and was diagnosed with a high-grade serous primary peritoneal cancer. Genetic testing showed a mutation in the *MSH2* DNA mismatch repair gene. The second case was a 58 year-old woman who had a hysterectomy and BSO for endometrial cancer. She developed a high-grade serous primary peritoneal cancer 8 years later and was found to have a mutation in the *PMS2* DNA mismatch repair gene.

Conclusion—Women with Lynch syndrome or HNPCC should be counseled that they may be at risk for developing primary peritoneal cancer despite undergoing gynecologic cancer risk-reducing surgery. The magnitude of this risk remains to be determined.

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INTRODUCTION

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is an autosomal dominant inherited cancer susceptibility syndrome caused by a germline mutation in one of the deoxyribonucleic acid (DNA) mismatch repair genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*). It is associated with early age at cancer diagnosis and the development of multiple types of cancer including cancer of the colon and rectum, endometrium, stomach, ovary, small bowel, ureter and renal pelvis. The lifetime risk of endometrial cancer for women with Lynch syndrome or HNPCC is 40 to 60% and the lifetime risk of ovarian cancer is 7 to 12%.^{1, 2} Similar to women with *BRCA1* and *BRCA2* mutations, it is currently recommended that risk-reducing hysterectomy and bilateral salpingo-oophorectomy (BSO) be offered to all women with Lynch syndrome or HNPCC aged 35 years or older who do not wish to preserve fertility.^{3, 4}

Previous studies in women with *BRCA* mutations have reported the development of primary peritoneal cancer following risk-reducing BSO.⁵⁻⁷ A systematic MEDLINE search (keywords “hereditary non-polyposis colorectal cancer (HNPCC)”, “Lynch syndrome”, and “primary peritoneal cancer”, English language, 1950 to 2009) revealed no reports of primary peritoneal cancer in women with Lynch syndrome or HNPCC. The current report describes two cases of primary peritoneal cancer following BSO in individuals with Lynch syndrome or HNPCC.

CASES

Case 1

A woman underwent hysterectomy with BSO at age 44 for benign disease. She presented 12 years later at the age of 56 with a pelvic mass. At surgical exploration, the mass was found to be unresectable and biopsies revealed poorly-differentiated adenocarcinoma. Immunoperoxidase studies revealed positive staining for cytokeratin 7 and negative staining for cytokeratin 20 in neoplastic cells, favoring a gynecologic malignancy. The patient was treated with chemotherapy and pelvic radiation therapy, followed by exploratory laparotomy with excision of the mass. Final pathology was consistent with a serous carcinoma representing a primary peritoneal carcinoma. She was treated with additional chemotherapy. The patient was subsequently diagnosed with a transitional cell carcinoma of the urethra, as well as synchronous adenocarcinomas of the colon and rectum. She ultimately died of recurrent urethral cancer at the age of 63.

The patient's family history was significant for her mother diagnosed with endometrial cancer at age 40, one sister diagnosed with endometrial cancer at age 38 and another sister diagnosed with pancreatic cancer at age 48. In addition, one maternal uncle was diagnosed with colon cancer at age 60 and another maternal uncle died at age 68 from metastatic cancer to the liver from an unknown primary tumor. The patient underwent genetic counseling and molecular studies were performed on the patient's colon and rectal tumor specimens to evaluate for Lynch syndrome or HNPCC. Immunohistochemistry demonstrated intact nuclear staining for the *hMLH1* and *PMS2* proteins, weak staining for the *hMSH6* protein, and absent staining for the *hMSH2* protein. Microsatellite instability

(MSI) analysis showed allelic shift in 3 of the 6 markers examined, classifying the tumor as MSI-high. Tissue from the patient's primary peritoneal tumor was no longer available for molecular studies. The patient subsequently underwent germline genetic testing that demonstrated a deleterious mutation in the *MSH2* gene consisting of a deletion of exons 9 and 10, resulting in premature truncation of the *MSH2* protein.

Case 2

A 58 year-old woman underwent hysterectomy with BSO for endometrial cancer. She was found to have a grade 2 endometrioid adenocarcinoma of the endometrium invading 4 of 14 mm of the myometrium. The ovaries showed no evidence of malignancy and pelvic washings were negative. She received no further treatment. Eight years later, she presented with a 10 cm pelvic mass and underwent exploratory laparotomy with excision of the mass. Final pathology showed it to be a high-grade serous carcinoma consistent with a primary peritoneal cancer. The patient was treated with chemotherapy. She is currently three months post-treatment and is without evidence of disease.

The patient's family history was significant only for her mother diagnosed with colon cancer at the age of 58. The patient underwent genetic counseling and molecular studies were performed on her endometrial cancer specimens. Immunohistochemistry demonstrated intact nuclear staining for the *hMLH1*, *hMSH2* and *hMSH6* proteins, but absent staining for the *PMS2* protein. Microsatellite instability (MSI) analysis showed allelic shift in 5 of the 7 markers examined, classifying the tumor as MSI-high. In addition, no hypermethylation of the *MLH1* promoter was detected. The patient subsequently underwent germline genetic testing that demonstrated a deleterious frameshift mutation in the *PMS2* gene (c. 736_741delCCCCCTins11). Molecular studies were subsequently performed on the patient's primary peritoneal tumor specimens and intact nuclear staining was noted for the *hMLH1*, *hMSH2*, *hMSH6* and *PMS2* proteins. In addition, the tumor was found to be microsatellite stable.

COMMENT

In both cases, there was no evidence of ovarian cancer at the time of BSO. In addition, the primary peritoneal cancers were diagnosed 8 and 12 years following BSO, decreasing the likelihood that they were associated with an undiagnosed occult ovarian cancer. The primary peritoneal tumor samples were unavailable for the first patient. In the second patient, the molecular studies on the primary peritoneal tumor specimen did not confirm the *PMS2* mismatch repair gene mutation. However, the sensitivity of immunohistochemistry and MSI testing in detecting Lynch syndrome or HNPCC associated *PMS2* mutations in tumor specimens from malignancies other than colorectal and endometrial cancers is unknown. It remains unclear if the primary peritoneal cancers in these two patients were attributable to their underlying germline Lynch syndrome or HNPCC mutations. However, given these two cases, women with Lynch syndrome or HNPCC should be counseled that they may be at risk for developing primary peritoneal cancer despite undergoing risk-reducing hysterectomy and BSO.

Similarly, primary peritoneal cancer following risk-reducing BSO has been described in women with *BRCA1* and *BRCA2* mutations.⁵⁻⁷ A recent multi-center, prospective study by Kauff and colleagues⁷ reported primary peritoneal cancer in 3 of 509 women (0.6%) with a *BRCA* mutation following risk-reducing BSO. The median time from risk-reducing surgery to the development of primary peritoneal cancer in this study was 16 months, with a mean follow-up of 40 months. Although there are currently no guidelines for monitoring *BRCA* mutation carriers for primary peritoneal cancer following BSO, these women are counseled regarding this possibility prior to undergoing risk-reducing surgery.

Interestingly, one of the individuals in the current report was found to have a mutation in the *PMS2* gene. A recent study by Senter *et al.*⁸ reported on 55 mono-allelic *PMS2* mutation carriers with Lynch syndrome-associated cancers. They noted 5 cases of endometrial cancer and estimated the cumulative endometrial cancer risk to age 70 to be only 15%. In addition, they reported no cases of ovarian or primary peritoneal cancer. Although the current case adds to the spectrum of potential Lynch syndrome or HNPCC associated cancers reported in individuals with *PMS2* mutations, further study is needed to confirm the cancer risks and determine if specific screening and preventive recommendations are needed for individuals with *PMS2* mutations.

In summary, we report two cases of primary peritoneal cancer following BSO in women with Lynch syndrome or HNPCC. It remains unclear if these cancers were attributable to the underlying Lynch syndrome or HNPCC germline mutations. However, these findings suggest that women with Lynch syndrome or HNPCC be counseled that they may be at risk for developing primary peritoneal cancer despite undergoing risk-reducing hysterectomy and BSO. They should also be informed that screening for primary peritoneal cancer is currently investigational, with limited information available regarding the risks and benefits. Longer follow-up and further study is needed to better characterize the risk of primary peritoneal cancer in women with Lynch syndrome or HNPCC.

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Précis

Women with Lynch syndrome or hereditary nonpolyposis colorectal carcinoma should be counseled that they may be at risk for developing primary peritoneal cancer, despite undergoing gynecologic cancer risk-reducing surgery.