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Women with HNPCC: A Target Population for the Chemoprevention of Gynecologic Cancers

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1. ABSTRACT

Hereditary nonpolyposis colorectal cancer syndrome (HNPCC) is an autosomal-dominant inherited cancer susceptibility syndrome that is associated with increased risk of development of endometrial and ovarian cancers. Therefore, women with HNPCC are candidates for chemoprevention of gynecological cancers. Although there have been a number of clinical trials examining chemoprevention strategies for colorectal cancer in HNPCC, the information regarding gynecological cancers in HNPCC remains limited. The purpose of this review is to provide an analytical background about the current knowledge regarding gynecological cancers in patients with HNPCC.

2. INTRODUCTION TO HNPCC

Hereditary nonpolyposis colorectal cancer syndrome (HNPCC), or Lynch Syndrome, is an autosomal-dominant inherited cancer susceptibility syndrome. HNPCC is caused by a mutation in one of the genes in the DNA mismatch repair gene family, including *MLH1*, *MSH2*, *MSH6*, *PMS1*, and *PMS2*. These mutations result in a somewhat limited tumor profile, which includes carcinomas of the colon, endometrium, ovary, and ureter. Because of the defect in DNA mismatch repair, these cancers have a characteristic molecular alteration, microsatellite instability. Traditionally, most HNPCC patients have been identified and cared for by gastroenterologists, colorectal surgeons, and

gastrointestinal medical oncologists. Hence, only recently, it has been realized that gynecological tumors actually play a major role in HNPCC. Consequently, much of the clinical and basic science focus of research in HNPCC has concentrated on colorectal cancer. The rationale for such a focus is largely due to the findings that the cumulative incidence of colorectal cancer in HNPCC (men and women) is 82%, while the cumulative incidence of endometrial cancer and ovarian cancer is 60% and 12%, respectively (1,2). However, it is imperative to note that the cancer risks are strikingly different in men and women. Women with HNPCC have a 60% lifetime risk of developing endometrial cancer, but only a 39-54% lifetime risk of developing colorectal cancer. In men, there is an estimated 74-83% risk of colorectal cancer (1,2).

3. GYNECOLOGICAL CANCERS IN WOMEN WITH HNPCC

Most women with HNPCC have been identified as carriers of mutation because colorectal cancer was diagnosed in the woman or family member at a relatively young age. Because endometrial cancer is so common in women with HNPCC, we hypothesized that in a proportion of women with HNPCC, gynecologic cancers presented first, before the development of colorectal cancer (3). To test this hypothesis, five different hereditary cancer registries were examined for women with dual colorectal/gynecological cancers. A total of 117 women with dual primary cancers from 223 Amsterdam families were identified. We found that 51% of these women had an endometrial or ovarian cancer diagnosed first. For these women, the median number of years between the diagnosis of a gynecological cancer and the diagnosis of colorectal cancer was 11 years. Therefore, for about 50% of women with HNPCC, gynecologists and gynecological oncologists may actually be the first members of the health care team with the opportunity to identify new mutation carriers. Early identification of a patient at the time of initial gynecological cancer diagnosis is crucial in proactively managing and reducing the risk to the patient for subsequent colorectal cancer.

4. HNPCC-ASSOCIATED ENDOMETRIAL CANCER

Clearly, gynecological cancers are important in HNPCC. What, then, do we know about these tumors? Effective chemoprevention strategies depend on detailed clinical, pathologic, and molecular knowledge of the targeted cancer. Our knowledge of HNPCC associated endometrial cancer is not detailed, but it is far greater than our understanding of HNPCC associated ovarian cancer. In HNPCC, microsatellite instability results from germline mutation of a DNA mismatch repair gene (most commonly, *MLH1* and *MSH2*). Microsatellite instability can also be detected in sporadic endometrial and colorectal cancers secondary to methylation of the *MLH1* promoter (4). It has been known for some time that sporadic, MSI-high endometrial cancer due to *MLH1* methylation is associated with almost exclusively endometrioid tumors, higher FIGO grade, and advanced stage (5-7). In comparison to sporadic MSI-high endometrial cancers with *MLH1* methylation, we have found that HNPCC associated endometrial cancer, while sharing the common molecular abnormality of microsatellite instability, actually includes a broader spectrum of tumor histotypes, including endometrioid adenocarcinoma, papillary serous carcinoma, clear cell carcinoma, and malignant mixed mullerian tumor. In fact, the endometrial tumor spectrum for HNPCC more closely mirrored that of the general population than that for *MLH1* methylation (8). Importantly, analysis of these HNPCC endometrial cancers revealed that nearly 25% of them had pathological features (deep myometrial invasion greater than 50% the myometrial wall thickness; cervix involvement; lymph node or adnexal metastasis) that would necessitate adjuvant therapy following hysterectomy (8). Thus, because approximately one-quarter of endometrial cancers are associated with such adverse clinical characteristics, chemoprevention can potentially make a big impact.

Endometrial complex hyperplasia with atypia (CAH) is a well-recognized precursor for endometrioid adenocarcinoma, the most common histological subtype of endometrial cancer. It is known that approximately 29% of women with CAH detected on endometrial biopsy will progress to endometrial cancer (9). For HNPCC-associated colon cancer, it has been hypothesized that colon adenomas, especially proximal ones, are more likely to progress to colonic adenocarcinoma, and progress more rapidly, than adenomas in the general population (10-12). A similar hypothesis could be posed for CAH in HNPCC-associated endometrial cancer, but at this time we do not have sufficient data to address this issue. At MDACC, we have encountered two women with HNPCC who had CAH following an endometrial biopsy. At hysterectomy, both of these women had endometrial endometrioid adenocarcinoma, grade 1, associated with complex hyperplasia. Neither tumor was invasive. Therefore, our limited information at this time suggests that CAH is indeed a part of the pathogenesis of endometrial endometrioid tumors in HNPCC. However, there is no data for the rate of cancer progression in HNPCC associated CAH.

5. HNPCC-ASSOCIATED OVARIAN CANCER

Data regarding ovarian cancer in HNPCC is quite limited. A previous study examined the medical records of 80 ovarian cancer patients from HNPCC families based on germline mutation or clinical criteria (13). The majority (94%) of these tumors were epithelial cancers. Approximately 56% were papillary serous ovarian cancer, and 18% were endometrioid ovarian cancer. Surprisingly, 84% of women had Stage I or II disease. In contrast, more than 70% of women with sporadic ovarian cancer presented with advanced stage disease. Many of the ovarian cancer cases reported in this study were several decades old and predated the establishment of many of the current guidelines for pathologically distinguishing borderline tumors from invasive cancers. A study in which there is careful centralized pathological review of the ovarian tumor slides from women with HNPCC would be useful to further characterize ovarian cancer in HNPCC.

6. UTILITY OF PROPHYLACTIC SURGERY

Once women have completed childbearing, it might be reasonable to assume that a prophylactic hysterectomy and bilateral salpingo-oopherectomy (BSO) is an option to reduce the gynecological cancer risk in women with HNPCC. At this time, there is insufficient evidence in the literature to recommend for or against prophylactic surgery. In a manuscript that is currently undergoing editorial review, we examined 315 women with documented HNPCC germline mutations from three different cancer registries. Women who had undergone prophylactic hysterectomy +/- BSO were matched to mutation positive women who did not have surgery. For the prophylactic surgery group, none of the women developed endometrial, ovarian, or primary peritoneal cancer. In the control group, 33% of the women developed endometrial cancer, and 5% developed ovarian cancer. Therefore, this study provides evidence for the protective benefit of prophylactic hysterectomy and BSO in the prevention of endometrial and ovarian cancer in women with HNPCC.

7. SCREENING FOR GYNECOLOGICAL CANCERS IN HNPCC

Screening information for endometrial cancer in HNPCC is currently limited. Clinical guidelines recommend such screening to begin between the ages of 25 and 35 (14). The frequency of such screening is entirely unclear. As part of an NCI-sponsored chemoprevention study, we are currently investigating oral contraceptives and depo-provera as possible chemopreventive agents for endometrial cancer in HNPCC. For this study, women undergo baseline and 3 month post-treatment endometrial biopsies and transvaginal ultrasounds. A component of this study is to examine, by quantitative PCR, a series of endometrial tissue biomarkers that may give us clues as to identifying women who are particularly at risk and who should be screened more often. To date, this chemopreventive study has enrolled 34 women, and we anticipate completing this study in about 2 years.

8. CONCLUSION

In the United States, the understanding of the gynecological manifestations of HNPCC, and, in fact, HNPCC in general, would be greatly accelerated by the establishment of a centralized study group for HNPCC. We especially encourage the gynecologic community to participate in research efforts, given the substantial risk of gynecologic cancers in women with HNPCC. Such centralized efforts would greatly enhance the success of chemoprevention trials in this patient population.

9. ACKNOWLEDGEMENT

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Abbreviations: HNPCC: Hereditary nonpolyposis colorectal cancer syndrome; CAH: Endometrial complex hyperplasia with atypia; BSO: bilateral salpingo-oopherectomy

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