

Commentary

See related article by Lu et al., p. 774

Chemoprevention of Endometrial Cancer in Lynch Syndrome: A Step Forward

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Abstract

Lynch syndrome is one of the most common hereditary cancer syndromes. Although Lynch syndrome is associated with increased risk for developing colorectal, endometrial, and other cancers specialized screening, risk-reducing surgery, and chemoprevention offer promise for reducing morbidity and mortality. Frequent colonoscopic surveillance has proven effective for early detection and prevention of Lynch syndrome-associated colorectal cancer; however, the optimal strategy for managing endometrial cancer risks in women with germline mutations in DNA mismatch repair genes has yet to be determined. In this issue of *Cancer Prevention Research*, Lu and colleagues report their findings of a phase II prospective, multicenter randomized trial comparing the effects of oral contraceptive pills and Depo-Provera on endometrial proliferation in women with Lynch syndrome. Although short-term hormonal treatment with either modality altered endometrial proliferation indices, it remains unknown whether hormonal suppression actually reduces endometrial cancer risk in women with Lynch syndrome. This trial represents the first of its kind in evaluating agents which might offer protection against Lynch syndrome-associated endometrial cancer and provides preliminary data regarding potential biomarkers for early detection of endometrial neoplasia. The investigators' experience with this trial also offers insights regarding the various technical and scientific challenges inherent in chemoprevention research. *Cancer Prev Res*; 6(8); 755–9. ©2013 AACR.

Lynch Syndrome—An Ideal Population for Cancer Prevention Research

Lynch syndrome is one of the most common cancer predisposition syndromes estimated to affect as many as 1 in 370 individuals (1). Germline mutations in *MSH2*, *MLH1*, *MSH6*, and *PMS2* compromise DNA mismatch repair (MMR) leading to accumulation of replication errors and increased risk for developing cancer. Although Lynch syndrome was originally described as hereditary nonpolyposis colorectal cancer on the basis of the high incidence of colorectal cancer in affected families, further study of these kindreds revealed increased risk for other extracolonic cancers. Endometrial cancers are the second most common tumors occurring in patients with Lynch syndrome; a recent study estimated cumulative risk for endometrial cancer of 54% for *MLH1*, 21% for *MSH2*, and 16% for *MSH6* carriers (2) with these Lynch syndrome-associated tumors devel-

oping approximately a decade earlier than sporadic endometrial cancers. While the high lifetime risk for colorectal cancer (estimated at 40%–80%; ref. 3) has been the primary focus of cancer prevention efforts, for many women with Lynch syndrome, the risk of endometrial cancer is comparable or even exceeds their risk of colorectal cancer.

Identification of individuals at risk for Lynch syndrome-associated cancers provides an opportunity to change the natural history of the disease for these patients and their families. Estimates suggest that as many as 1 in 35 colorectal cancers (4) and 1 in 10 young (<age 50) endometrial cancers are associated with Lynch syndrome (5). As most Lynch syndrome-associated tumors have distinctive phenotypes of mismatch repair deficiency, testing for DNA microsatellite instability (MSI) and/or abnormalities in expression of DNA MMR proteins by immunohistochemistry (IHC) has been incorporated into the histopathologic evaluation of colorectal cancer tumors at many institutions. Given the high cancer risks and potential for risk-reducing interventions, cost-effectiveness models support screening for Lynch syndrome in cancer-affected as well as in cancer-unaffected individuals (6, 7). The key assumption is that presymptomatic identification of at-risk individuals will lead to implementation of interventions that reduce the likelihood that they will develop cancer or die from Lynch syndrome-associated cancers (8).

So what interventions are effective for reducing morbidity and mortality due to Lynch syndrome-associated cancers?

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In the case of colorectal cancer, endoscopic screening has proven to be extremely effective for both early detection and prevention of colorectal neoplasia. Colonoscopy, with removal of premalignant polyps, is associated with significant decreases in colorectal cancer incidence, morbidity, and mortality among individuals at average, moderate, and high risk for colorectal cancer, including individuals with Lynch syndrome. Longitudinal observational data from Lynch syndrome cohorts from several European countries have provided convincing evidence that early and frequent colonoscopy in MMR mutation carriers reduces cancer incidence and mortality (9, 10). Observations that Lynch syndrome-associated colorectal cancer tumors show accelerated neoplastic transformation have led to recommendations for colonoscopy every 1 to 2 years beginning at age 20–25 (11).

Unfortunately, when it comes to risk reduction for endometrial cancer, currently available strategies for early detection and/or prevention are not nearly as effective. Although endometrial cancer screening with transvaginal ultrasound and/or endometrial biopsy beginning at age 30 to 35 years has been recommended, evidence suggests the sensitivity of these tests for detecting endometrial neoplasia is limited, at best (11, 12). To date, the only intervention proven to be effective for prevention of Lynch syndrome-associated endometrial cancers is hysterectomy (13). Consequently, women who carry MMR mutations currently face a choice between potentially ineffective endometrial surveillance and prophylactic hysterectomy, which offers more definitive endometrial cancer risk reduction in exchange for risks of surgical complications and loss of fertility (14).

The Rationale for Chemoprevention in Lynch Syndrome

Cancer chemoprevention is the concept of taking a medication or other type of chemical agent to prevent, suppress, or reverse the process of carcinogenesis in asymptomatic individuals. In identifying patients who may benefit from chemoprevention, their risk of developing cancer must be weighed against the risks and side effects from the study agent/medication. Therefore, the ideal chemoprevention study would involve subjects from a population at high-risk and a study agent with a favorable side-effect profile.

Interest in cancer chemoprevention is growing among certain groups of patients. Hormonal modulators such as tamoxifen, raloxifene, and aromatase inhibitors have been associated with significant reductions in risk for breast cancer (15, 16) and uptake of these is increasing among women with abnormal breast histology or genetic predisposition, which place them at high risk for breast cancer. Among women with germline *BRCA1* and *BRCA2* gene mutations, use of oral contraceptive pills (OCP) has been associated with significant reductions in ovarian cancer risk (17), providing an alternative to prophylactic oophorectomy for premenopausal women. Endometrial cancer, like breast cancer, is presumed to be an estrogen-driven malig-

nancy. As use of progestin-containing OCPs has been associated with a reduction in the risk of endometrial cancer in the general population in observational and case-control studies (18, 19), a chemoprevention study using progestins in women with Lynch syndrome seems both reasonable and feasible.

In this issue of the *Cancer Prevention Research*, Lu and colleagues report on the results of their short-term phase II randomized chemoprevention study examining the effects progestin-containing OCPs or depo-medroxyprogesterone acetate (depoMPA) on endometrial proliferation in women with Lynch syndrome (20). Women ages 25 to 50 years with a clinical diagnosis of Lynch syndrome underwent baseline transvaginal ultrasound and endometrial biopsy and then were randomized to receive one of two hormonal interventions for 3 months followed by repeat transvaginal ultrasound and endometrial biopsy. The primary outcome was change in endometrial proliferation pre-post treatment, measured by Ki67 expression on endometrial biopsies. Secondary endpoints included changes in endometrial histology, endometrial thickness (measured by transvaginal ultrasound), and expression of 8 estrogen-modulated genes previously found to be differentially expressed in endometrial carcinomas (21).

After screening more than 700 potentially eligible subjects, 51 asymptomatic women were ultimately enrolled in this study. Two subjects had histologic abnormalities detected on the baseline/pretreatment endometrial biopsies that ultimately led to the diagnosis of grade 1 endometrial carcinoma. Forty-six women completed 3 months of treatment with either OCP or depoMPA. Posttreatment endometrial biopsies showed dramatic decrease in endometrial proliferation in all but 3 subjects. Interestingly, individuals whose endometrial biopsies showed a histologic response to progestin all had concomitant decrease in expression of IGF-I, sFRP1, sFRP4, and survivin, whereas the 3 nonresponders had elevated expression of these genes in endometrial tissues.

What do we learn from this study? In brief, these findings show that the majority of women with Lynch syndrome have the same physiologic response to progestin exposure as would be expected in "normal" endometrium. The primary outcome was change in endometrial proliferation before and after treatment, and as the authors acknowledge, the use of this as a surrogate endpoint is problematic, as the clinical significance of progestin effect on endometrial proliferation with respect to risk for either sporadic or Lynch syndrome-associated endometrial cancer is unknown. Consequently, it would be a leap to interpret a normal physiologic response to progestins as evidence that these would be effective for endometrial cancer chemoprevention. However, the investigators' finding of differences in the gene expression profiles between subjects with non-hormone-responsive and hormone-responsive endometrium does provide some interesting clues regarding the biology of endometrial neoplasia in Lynch syndrome. Further study is warranted to validate whether these gene expression profiles are similar to those found in carcinomas and

determine whether this finding may be predictive of risk for neoplastic transformation.

It is interesting to compare this endometrial cancer chemoprevention trial with the Colorectal Adenoma/Carcinoma Prevention Programme 2 (CAPP2), which was also conducted in subjects with Lynch syndrome. This multinational, randomized, placebo-controlled trial investigated the effects of aspirin and resistant starch on the clinically unambiguous endpoints of incidence of advanced colorectal neoplasia or cancer (22). Nine hundred and thirty seven subjects with Lynch syndrome recruited through 43 centers were randomized to take aspirin, starch, combination, or placebo for a mean duration of 29 months. Although preliminary analyses showed no effect of either agent on the primary endpoints of incidence of colorectal adenomas or carcinomas, long-term follow up showed that subjects randomized to aspirin had a significant reduction in incidence of both colorectal cancer (HR 0.41, 95% confidence interval, 0.19–0.86), as well as extracolonic cancers (including endometrial cancer; ref. 23).

In the discussion of their manuscript, Lu and colleagues offer candid insights regarding the scientific and technical challenges they encountered in conducting chemoprevention research in endometrial cancer. Although the sample size for this phase II trial was modest, the study took 6 years to complete because the investigators had to screen more than 700 potential subjects to enroll 51 women. This high screen failure rate was due in large part to the fact that many of the potentially eligible women were either planning to become pregnant or were already using hormonal birth control and were reluctant to discontinue this for the 4-month wash-out period required before randomization. While the successful completion of this study is a testament to the commitment of the study staff, the significant investment of time and money required for this small phase II study raises questions about whether a future phase III randomized trial of hormonal agents would even be feasible in this population.

Is a Randomized Trial Always Necessary?

Many individuals are unwilling to take medications or supplements for cancer chemoprevention because they are reluctant to accept the risk of side effects. However, in this study, a significant proportion of potential subjects did not want to participate in the trial because they were already using the study agent (or a comparable alternative) and would have to discontinue the hormonal birth control they were already using in order to enroll in the study. Oral contraceptives and depo MPA are clinically available and have a favorable side-effect profile. If the use of hormonal contraceptives is already so common among women with Lynch syndrome, we may not need a larger randomized trial to gain information about the effect of these agents on endometrial cancer risk. These data may already be available through observational, multinational cohort studies currently underway or through secondary analyses of data from other studies, such as CAPP2. Observational cohort studies have reported associations between aspirin use and reduced

risk for sporadic endometrial cancer (24), and a larger (3,000 subject) CAPP3 chemoprevention study to define the optimum dose of aspirin required for cancer prevention in patients with Lynch syndrome is already being planned (25). Analyzing these data with regard to use of hormonal birth control would seem logical. Furthermore, incorporating collection of endometrial biopsy specimens during surveillance of study participants, although logistically challenging, would provide the opportunity to collect the longitudinal data needed to define the pathogenesis of Lynch syndrome-associated endometrial cancer and to identify and validate whether elevated expression of sFRP1, sFRP4, and survivin could be used as biomarkers for early detection.

All in all, the endometrial cancer chemoprevention study conducted by Lu and colleagues represents an important step forward but ultimately leaves us with more questions than answers. Why is the endometrium of women with MMR gene mutations at such high risk for neoplastic transformation? Are these tumors driven by estrogen like sporadic endometrial cancers? What additional factors are associated with risk for endometrial cancer? How effective is exposure to exogenous progestins in modifying risk? Is nonresponsiveness to exogenous progestins a risk factor for endometrial cancer? Can gene expression profiles be used as biomarkers to predict risk for endometrial cancer?

We know surprisingly little about the molecular mechanisms involved in the pathogenesis of Lynch syndrome-associated endometrial cancers. Compared with sporadic endometrial cancers, Lynch syndrome-associated tumors are more likely to arise at younger ages, be located in the lower uterine segment, exhibit features of MMR deficiency, and feature endometrioid histology. Endometrial cancers arising in the setting of somatic *MLH1* methylation and epigenetic silencing are almost exclusively endometrioid histology (96.2%) and tend to be high grade or show a distinctive "undifferentiated" histology (26). Endometrial cancers with MMR deficiency due to Lynch syndrome and *MLH1* methylation are frequently lumped together in studies of MSI-high tumors, making it difficult to decipher whether Lynch syndrome-associated endometrial cancers are associated with different survival outcomes than sporadic endometrial cancers. More research is needed to understand the mechanisms leading to endometrial carcinogenesis in Lynch syndrome.

Despite the limitations of this small study, the investigators should be commended for expanding the field and attempting to gain as much as possible out of this study by combining feasibility testing of a chemopreventive intervention with collection of exploratory data for biomarker discovery and validation. It is actually the secondary findings from this study that provide the most valuable additions to the literature. The incidental finding of stage I endometrial cancer in baseline biopsies of 2 of 51 (3.9%) asymptomatic subjects provides justification for offering endometrial biopsy to women with Lynch syndrome. The finding that transvaginal ultrasound measurements of the endometrial stripe did not correlate with

endometrial response to hormonal treatment corroborates anecdotal reports that this modality is of limited use for screening/surveillance in research and/or clinical care. Finally, the collection of pre/post treatment endometrial biopsies will provide material to test future candidate biomarkers.

Women with Lynch syndrome are at high risk for cancer and represent an ideal population for cancer chemoprevention. Given the risks and side effects associated with prophylactic hysterectomy, most women are eager for alternatives to surgery and the risk-benefit profile of any number of potential chemoprevention agents would appear favorable. Lu and colleagues have shown that OCPs and depo-MPA induce an expected physiologic endometrial response when administered to premenopausal women with Lynch syndrome. Whether this effect is associated with a reduction in incidence of endometrial cancer in this high-risk group of women remains unknown. Further research needs to be conducted to

elucidate the molecular mechanisms that lead to endometrial carcinogenesis in Lynch syndrome and to determine what impact, if any, hormonal or anti-inflammatory treatment might have for modifying cancer risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Conception and design: E. Stoffel, C. Walsh

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E. Stoffel, C. Walsh

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E. Stoffel, C. Walsh

Writing, review, and/or revision of the manuscript: E. Stoffel, C. Walsh

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E. Stoffel, C. Walsh

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