Prospective Multicenter Randomized Intermediate Biomarker Study of Oral Contraceptive versus Depo-Provera for Prevention of Endometrial Cancer in Women with Lynch Syndrome

Karen H. Lu1, David S. Loose5, Melinda S. Yates1, Graciela M. Nogueras-Gonzalez2, Mark F. Munsell2, Lee-may Chen6, Henry Lynch8, Terri Cornelison9, Stephanie Boyd-Rogers1, Mary Rubin6, Molly S. Daniels1,3, Peggy Conrad7, Andrea Milbourne1, David M. Gershenson1, and Russell R. Broaddus4

Abstract

Women with Lynch syndrome have a 40% to 60% lifetime risk for developing endometrial cancer, a cancer associated with estrogen imbalance. The molecular basis for endometrial-specific tumorigenesis is unclear. Progestins inhibit estrogen-driven proliferation, and epidemiologic studies have shown that progestin-containing oral contraceptives (OCP) reduce the risk of endometrial cancer by 50% in women at general population risk. It is unknown whether they are effective in women with Lynch syndrome. Asymptomatic women ages 25 to 50 with Lynch syndrome were randomized to receive the progestin compounds Depo-Provera (depo-MPA) or OCP for three months. An endometrial biopsy and transvaginal ultrasound were conducted before and after treatment. Endometrial proliferation was evaluated as the primary endpoint. Histology and a panel of surrogate endpoint biomarkers were evaluated for each endometrial biopsy as secondary endpoints. A total of 51 women were enrolled, and 46 completed treatment. Two of the 51 women had complex hyperplasia with atypia at the baseline endometrial biopsy and were excluded from the study. Overall, both depo-MPA and OCP induced a dramatic decrease in endometrial epithelial proliferation and microscopic changes in the endometrium characteristic of progestin action. Transvaginal ultrasound measurement of endometrial stripe was not a useful measure of endometrial response or baseline hyperplasia. These results show that women with Lynch syndrome do show an endometrial response to short-term exogenous progestins, suggesting that OCP and depo-MPA may be reasonable chemopreventive agents in this high-risk patient population.

Introduction

Lynch syndrome, or hereditary nonpolyposis colorectal cancer syndrome (HNPCC), is an autosomal-dominant inherited condition characterized by early-onset colon cancer and endometrial cancer. In women with Lynch syndrome, risk of endometrial cancer equals or exceeds risk of colon cancer. Women with Lynch syndrome gene mutations have a 40% to 60% lifetime risk of developing endometrial cancer, compared with 3% for the general population (1, 2). Endometrial cancer tends to occur at an earlier age in women with Lynch syndrome (mean age of diagnosis–48 years; refs. 3, 4). In the general risk patient population, endometrial cancer, especially endometrioid-type, is known to be an estrogen-driven malignancy. Progesterone is well-known to antagonize the effects of estrogen. Accordingly, the Cancer and Steroid Hormone Study (CASH) has shown that use of progestin-containing oral contraceptive pills (OCP) reduces the risk of endometrial cancer by 50% in women at general population risk (5). It is unclear whether OCP are effective in high-risk women, such as women with Lynch syndrome.

The goal of this short-term 3-month phase II biomarker endpoint study was to examine the effects of progestin-containing OCP or depo-medroxyprogesterone acetate (depo-MPA) on the endometrium of women with Lynch syndrome.
syndrome. Given the substantial risk of endometrial cancer in these women, it is essential to determine whether progestins are able to induce the characteristic microscopic changes in the endometrium of Lynch syndrome women, similar to those observed in average-risk women. As a step toward determining the chemopreventive potential of OCP and depo-MPA in this population, we examined the short-term effect of depo-MPA and OCP on the endometrium of women with Lynch syndrome using markers of progestin responsiveness, including pre- and posttreatment endometrial histology, endometrial epithelial proliferation index, and a panel of endometrial gene expression biomarkers of estrogen action. Gene expression biomarkers were selected on the basis of previous microarray studies and targeted gene expression analysis identifying estrogen-responsive genes in the endometrium, including several markers that are differentially expressed in estrogen-related endometrial cancer (6–11).

Materials and Methods

Patients

The Institutional Review Boards at MD Anderson Cancer Center (Houston, TX), University of California, San Francisco (San Francisco, CA), and Creighton University (Omaha, NE) approved the study (trial registration ID: NCT00033358). Women between the ages of 25 and 50 with a known mutation in MLH1, MSH2, or MSH6 were eligible. In addition, women who had a personal history of a Lynch syndrome-associated cancer and who fulfilled Amsterdam criteria based on family history were eligible. Additional inclusion criteria included no prior hysterectomy, no history of prior pelvic radiation, no chemotherapy before initiation of study. Women also had to have no medical contraindication to use of OCP or depo-MPA, including known or suspected pregnancy, undiagnosed vaginal bleeding, active thrombophlebitis or past history of thromboembolic disorders or cerebral vascular disease, gallbladder disease, history of diabetes, coronary artery disease, or a current tobacco smoker age of 35 years or more.

On day 5 to 10 of the menstrual cycle, corresponding to the endometrial proliferative phase, a transvaginal ultrasound (TVS) and then an endometrial biopsy using a 3 and 4 mm pipelle were conducted for each participant. Half the biopsy was placed into formalin for routine histologic processing, pathologic assessment, and Ki67 immunohistochemistry. The remaining half was frozen under liquid nitrogen and used for subsequent quantitative real-time PCR (qRT-PCR) assays. The TVS measured the endometrial stripe and the size, morphology, and any abnormalities of the uterus and ovaries. Women were randomized to receive OCP (LoOvral, 0.3 mg ethinyl estradiol and 0.3 mg norgestrel daily for 21 days followed by 7 days of placebo) or a single dose of 150 mg depo-MPA. For women randomized to the OCP arm, the second TVS and endometrial biopsy were conducted on day 4 to 10 after initiation of the fourth pack of study medication. For women randomized to the depo-MPA arm, the second TVS and endometrial biopsy were conducted on day 90 ± 5 days. Women were considered invaluable if they missed more than 4 consecutive nonplacebo pills and/or missed a total of more than 10 nonplacebo pills during a 4-month period.

Assays

All endometrial biopsies were microscopically examined. The baseline biopsies were examined to confirm proliferative phase histology and to rule out the presence of endometrial hyperplasia or carcinoma. Posttreatment biopsies were evaluated for response to progestin treatment. The response was considered good if the glands were inactive or secretory and there was lack of epithelial cell mitotic figures, and if there was evidence of stromal predecidualization, characterized by stromal cells with increased eosinophilic cytoplasm and acquisition of epithelioid shape. A poor response was characterized by the absence of stromal cell pseudo-decidualization, the absence of inactive endometrial glands, or the presence of proliferative-type endometrial epithelial glands with mitotic figures. The presence of endometrial hyperplasia or carcinoma in the posttreatment biopsy was characterized as a pathologic response. Ki67 immunohistochemistry (MIB-1, Dako) was conducted as per manufacturer’s instructions; its expression was determined by microscopically quantifying the percentage of endometrial epithelial cells with positively stained nuclei.

Estrogen is well-known to be a stimulator of endometrial proliferation and uterine growth. We have previously characterized a panel of genes that are expressed in the endometrium and modulated by estrogen (Supplementary Table S1; refs. 6–14). Importantly, these genes are differentially expressed in endometrial carcinoma with several showing significantly higher expression in endometrioid-type carcinomas (estrogen-related) compared with nonendometrioid carcinomas (not related to estrogen excess). This panel includes IGF-1, IGF-1R, IGF-2, EIG121 (a.k.a. KIAA1324), RALDH2 (a.k.a. ALDH1A2), sFRP1, sFRP4, and survivin (a.k.a. BIRC5). IGFBP1 was also analyzed as a positive control for tissue action of progesterone. All quantitative real-time PCR assays for genes in this panel were conducted from the frozen endometrial biopsy using an ABI7700 instrument (Life Technologies). All assays were validated using standards comprising a synthetic oligonucleotide that corresponds exactly to the amplicon that was measured in sample RNA to ensure linearity of signal and to determine the lower limit of detection of each assay. Assays must have been able to detect a minimum of 1,000 molecules of target and were linear (r2 > 0.98) over a concentration range of at least 5 logs. Each sample was assayed in quadruplicate including a negative control that was minus the reverse transcriptase. This negative control served to measure any contaminating DNA in the RNA samples. All transcripts were normalized using the transcripts 18S mRNA, β-actin (ACTB), and 36B4 (a.k.a. RPLP0). Assays for these 3 transcripts were conducted on each sample and “gNORM” was calculated as the geometric mean of the normalizer transcripts.
Statistical analysis
The primary outcome was the change in Ki-67 expression before and after treatment. We analyzed these changes within, as well as between, treatment groups. Secondary endpoints included the change from pre- to posttreatment in histology and endometrial thickness (as measured by TVS), as well as the estimation of the frequency of endometrial abnormalities in this patient population on presentation. Another secondary endpoint included the examination of the change in expression of estrogen-induced genes measured by qRT-PCR.

Measurements of each potential surrogate endpoint biomarker were taken before and after hormone treatment. Although the actual data values observed were used in the analysis of the trial, for simplicity in the computation of sample size we assumed only that the value for a given biomarker increased or decreased. If the treatment had no effect, then the probability of a marker increasing (or decreasing) was 0.50. This study was designed to have 80% power to detect a change in this probability to 0.82 within each treatment arm. Using an exact test (2-sided) with a significance level of 0.05, we needed 22 patients in a treatment arm to detect a change in the proportion of patients in that arm with markers increasing (or decreasing) from 0.50 to 0.82 with 80% power. To allow for an approximate 15% dropout rate, we enrolled 51 patients total on this multicenter trial.

This was an exploratory study, and any biomarkers found to be elevated or depressed was of interest. However, as there were 9 potential biomarkers of special interest (Ki67 immunohistochemistry and qRT-PCR of 8 estrogen-modulated genes), to achieve an overall type I error rate of 5% we tested each biomarker at the nominal level of 0.05/9 = 0.0056. The proportion of patients with a marker increasing (or decreasing) had to have been 0.86 for us to be able to detect a statistically significant change in the proportion of patients with markers increasing (or decreasing) from 0.50 and maintain an overall significance level of 0.05.

Paired plots showing pre- and posttreatment values (so called “box plots”) were examined for each biomarker. Paired t tests (or signed rank test) were used to compare the biomarkers. In addition, to determine whether patterns of changes in the biomarkers were associated with treatment, we conducted a multivariate analysis of the data. We examined the correlation in the changes following treatment among the biomarkers using either Pearson or Spearman correlations as appropriate.

Results
A total of 51 women were enrolled, and their demographics are summarized in Table 1. There were no significant differences between the treatment arms for age, race, mutation status, BMI, parity, or gravity. Twenty-four women had an MLH1 mutation, 22 women had an MSH2 mutation, and 2 women had an MSH6 mutation. In addition, 2 women fulfilled Amsterdam criteria and had a history of colon cancer. One patient was Amsterdam positive, had a history of a benign ovarian tumor, and had previously undergone a unilateral salpingo-oophorectomy.

As shown in Fig. 1, both depo-MPA and OCP caused a dramatic decrease in endometrial epithelial proliferation as measured by Ki-67-positive cells [depo-MPA mean pre-51.8%, mean post-13.1% (P < 0.001) and OCP mean pre-48.3%, mean post-3.1% (P < 0.001)]. When histology was examined (Table 2), 20 of 23 patients in the depo-MPA group and 22 of 23 patients in the OCP group showed inactive and/or secretory-type glands (Fig. 2A). Interestingly, the 3 patients who had a poor histologic response to treatment were all in the depo-MPA group, the arm in which...
treatment compliance was not an issue (Fig. 2B). An additional patient, who had a normal endometrial biopsy at baseline and was randomized to receive OCP, was found to have a focus of complex hyperplasia without atypia in a background of inactive glands on her 3-month biopsy (pathologic response; Fig. 2C). Two of 51 patients had baseline endometrial abnormalities [3.9%, 95% confidence interval (CI) 0.5–13.5]. Both abnormalities were complex atypical hyperplasia (Supplementary Fig. S1), and both were found to have grade 1 endometrioid endometrial carcinoma in the subsequent hysterectomy.

Transvaginal ultrasound measurement of baseline endometrial thickness revealed a mean of 5.5 mm (range 2.6–10.1) for the depo-MPA arm and a mean of 6.5 mm (range 2.0–19.0) ($P = \text{NS}$) for the OCP arm. Despite the changes in endometrial histology posttreatment, the mean follow-up endometrial thickness was not significantly decreased, with the mean in the depo-MPA arm of 4.5 mm (range 1.0–9.3) and 4.5 mm (range 2.0–10.0) in the OCP arm (Table 2).

In addition to Ki-67, transcripts for 8 different estrogen-modulated genes were quantified (Fig. 3). We also analyzed the endometrial expression of $IGFBP1$, which is well-known to be induced by progesterone (15, 16), to verify tissue action of OCP and depo-MPA. $IGFBP1$ was significantly induced in the posttreatment endometrial biopsies for both treatment arms (Fig. 3). For both treatment groups, the posttreatment endometrial biopsies had significantly altered expression of $IGF-1$, $IGF-2$, sFRP1, sFRP4, and survivin transcripts. For the depo-MPA group, $EIG121$ was also decreased in the posttreatment biopsy. These results are consistent with the fact that progesterone typically antagonizes the biologic effects of estrogen. For 2 of the 3 poor histologic responders (all 3 in the depo-MPA group), endometrial tissue was available for molecular analyses. In contrast to patients with a good histologic response, the 2 poor responders showed elevated sFRP1, sFRP4, and survivin in the posttreatment endometrial biopsies (Fig. 4).

### Table 2. Histology and endometrial thickness

<table>
<thead>
<tr>
<th></th>
<th>Depo-MPA ($N = 25$)</th>
<th>OCP ($N = 26$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proliferative</td>
<td>23</td>
<td>24</td>
<td>0.999</td>
</tr>
<tr>
<td>Not Proliferative</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pathologic</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Follow-Up Biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>20</td>
<td>22</td>
<td>0.233a</td>
</tr>
<tr>
<td>Poor</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pathologic</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No Biopsy</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Baseline endometrial thickness (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>5.5</td>
<td>6.5</td>
<td>0.189</td>
</tr>
<tr>
<td>Range</td>
<td>2.6–10.1</td>
<td>2.0–19.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Follow-up endometrial thickness (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.5</td>
<td>4.5</td>
<td>0.933b</td>
</tr>
<tr>
<td>Range</td>
<td>1.0–9.3</td>
<td>2.0–10.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Change in Endometrial Thickness (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.9</td>
<td>1.7</td>
<td>0.225b</td>
</tr>
<tr>
<td>Range</td>
<td>−5.0–6.0</td>
<td>−1.0–5.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

aExcludes "No biopsy" group.
bTwo patients on depo-MPA and 3 patients on OCP did not have follow-up endometrial thickness.

### Discussion

While women with Lynch syndrome have a substantial lifetime risk for the development of endometrial cancer, studies regarding the efficacy of preventive strategies are few.
We previously reported that surgical prevention with hysterectomy and bilateral salpingo-oophorectomy is highly effective for the prevention of endometrial and ovarian cancer in this high-risk population (17). Whether OCP or depo-MPA are effective chemopreventive agents for women with Lynch syndrome, as they are for women in the general population, is unknown. As a step toward determining the chemopreventive potential of OCP and depo-MPA in this population, we examined the short-term effect of depo-MPA and OCP on the endometrium of women with Lynch syndrome using several endometrial tissue markers of progestin-responsiveness. With each woman as her own control, after 3 months of treatment we observed a significant decrease in endometrial epithelial proliferation (Ki-67) in both the depo-MPA and OCP arms. Histologically, 20 of the 23 women in the depo-MPA arm and 22 of 23 women in the OCP arm showed the presence of inactive and/or secretory-type glands. While the endpoint of this study was not efficacy, the significant response both with Ki-67 and histology suggests that both depo-MPA and OCP may be reasonable chemopreventive agents in this high-risk cohort.

Interestingly, 3 women in the depo-MPA arm had a poor histologic response, although all 3 showed a significant decrease in Ki-67. Given the small numbers of nonresponders overall, it would be difficult to conclude that OCPs were more effective than depo-MPA. In addition, longitudinal studies will be necessary to determine whether poor histologic response to progestins such as depo-MPA can be a marker for increased risk of endometrial cancer in women with Lynch syndrome. The 1 woman in the OCP arm who had a focus of endometrial hyperplasia without atypia in a background of inactive glands had a pretreatment biopsy that showed normal proliferative endometrium. It is possible that this small focus of hyperplasia had been present before treatment and was missed with pipelle sampling. After completion of the study, the patient chose to remain on OCP and had a dilation and curettage 4 months later showing benign endometrium.

As a secondary endpoint, we found that the point estimate of endometrial abnormalities in women with Lynch syndrome under age 50 was 3.9% (95% CI, 0.5–13.5). Both women were completely asymptomatic and had complex atypical hyperplasia on their baseline biopsy. Both went on to have a hysterectomy, and both were found to have grade 1 endometrial cancer. Given that the median age of women was 36.8 in the depo-MPA arm and 37 in the OCP arm, the finding of complex endometrial hyperplasia (CAH) and cancer in 2 asymptomatic women highlights that these women are at extremely high risk of developing endometrial cancer. The point estimate of endometrial hyperplasia/cancer in the general population is difficult to ascertain, but there are some data from large studies of hysterectomy specimens derived from patients with uterine prolapse. One study of 372 women with hysterectomies for uterine prolapse (84% of patients older than 55 years of age) found 4 cases (1.1%) of simple/complex hyperplasia with atypia or endometrial carcinoma. Another study of 644 similar hysterectomies from women with a mean age of 59.7 years found 12 patients (1.9%) with incidental endometrial complex hyperplasia or carcinoma. In both of these studies, the patient age was significantly older than the median age of 36.8–37 years for this study.
As another secondary endpoint, we examined the ultrasound measurement of the endometrial stripe in women before and after treatment. While 1 of the 2 women with baseline CAH had a thickened endometrial stripe (19 mm), the other woman did not (7 mm). Of note, the patient with the 19 mm stripe had had a TVS 6 weeks earlier (outside the study) in which the stripe was measured at 7 mm. For the other women in the study, there was no significant difference with respect to the change in endometrial thickness. The 3 patients with poor response in the depo-MPA treatment group had changes in endometrial thickness of 3.0, 0, and 3.6 mm. The 1 patient with a pathologic response in the follow-up biopsy (in the OCP treatment group) had no change in endometrial thickness from before therapy to after therapy. Therefore, measurement of endometrial stripe as a correlate of response to progestin is not useful. In addition, consistent with other published studies, ultrasound measurement of endometrial stripe is not a sensitive screening method for detecting endometrial abnormalities.

As an additional secondary endpoint, we examined a panel of qRT-PCR biomarkers of estrogen action in the endometrium. First, we showed the feasibility of conducting a number of transcript assays using endometrial tissue obtained from a pipelle. Second, we found a statistically significant decrease in the expression of EIG121, IGF-1, sFRP-1, sFRP4, and survivin in the posttreatment biopsies. Therefore, these molecular biomarkers can be modulated by short-term exogenous progestins (OCP and depo-MPA). Third, we found that the women who received depo-MPA who had a poor histologic response (only 2 of 3 had tissue available for qRT-PCR) showed elevated posttreatment sFRP1, sFRP4, and survivin compared with baseline biopsy values. The survivin protein inhibits apoptosis and is increased in multiple tumor types, including endometrial cancers (14, 20–24). While both OCP and depo-MPA decreased survivin in the endometrium, the 2 poor responders showed an increase in survivin. The proteins encoded by RALDH2, sFRP1, and sFRP4 are all thought to act as "brakes" to inhibit physiologic estrogen-induced endometrial proliferation. In this way, normal endometrial growth induced by estrogen is controlled. The enzyme encoded by RALDH2 catalyzes the synthesis of retinoic acid, a known inhibitor of uterine growth (7). Both sFRP1 and sFRP4 act as molecular antagonists to ligands in the Wnt signaling pathway (25), binding to Wnt7a to act as "brakes" to decrease Wnt-associated proliferation in the endometrium. In this study, sFRP1 and sFRP4 expression were downregulated by both OCP and depo-MPA.
OCP and depo-MPA. Considering progesterone’s known antagonism of estrogen action, we speculate that under conditions of endometrial quiescence induced by long-term progestin exposure, expression of such estrogen-regulated genes is turned off. The abnormally elevated posttreatment levels of sFRP1, sFRP4, and survivin observed in the 2 nonresponders may represent biomarkers predictive of an even greater increased risk of endometrial cancer development in these women, but this will require longitudinal studies to verify. From Fig. 4, it can be seen that the baseline endometrial expression of these genes is quite variable, but the vast majority of posttreatment biopsies have a narrower range of gene expression. This, plus our observations of different gene expression in the 2 nonresponders, introduces the concept of assessing tissue biomarkers following some type of exogenous stimulus/treatment rather than in untreated tissues. In other words, expression of biomarkers in response to a stimulus may be more informative than a baseline measure of a tissue biomarker. We are particularly intrigued whether molecular analysis of gene transcripts after a progestin challenge may be a clinically useful test to identify which women with Lynch syndrome are at particularly high risk for endometrial cancer.

This study also highlights the challenges in conducting phase II gynecologic chemoprevention trials in high-risk populations. We screened over 700 women to enroll 51 over a 6-year period (data not shown). Primary reasons for exclusion included no identified Lynch syndrome mutation, not wanting to come off OCP before enrollment, not willing to take depo-MPA, unwilling to undergo 2 endometrial biopsies, smoker and over the age of 35 years, planned pregnancy, prior or planned hysterectomy, high cholesterol, or not having flexibility to undergo baseline endometrial biopsy on days 5 to 10 of menstrual cycle. On the basis of our experience from this trial, 3 factors are necessary for the completion of phase II gynecologic chemoprevention trials—(i) steady commitment of the research staff at all sites for recruitment of participants, (ii) multidisciplinary and multi-institutional commitment and cooperation from geneticists, gastrointestinal, and gynecologic services, and (iii) sponsor (NCI) patience in keeping the study open as long as there is steady accrual.

In conclusion, this phase II biomarker study found that women with Lynch syndrome have a normal response to short-term exogenous progestins, based on histology and proliferation indices, compared with previous reports in the general population (26, 27). This suggests that oral contraceptives and depo-MPA may be reasonable chemopreventive agents for this high-risk cohort, as they are in women at general population risk (5). In addition, young women with Lynch syndrome who are asymptomatic have a high baseline rate of complex atypical hyperplasia and endometrial cancer. Finally, while requiring coordinated, multi-institutional efforts, we showed the capacity to complete a phase II chemoprevention study in women with Lynch syndrome.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: K.H. Lu, D.S. Loose, T. Cornelison, R.R. Broaddus
Development of methodology: D.S. Loose, L. Chen
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K.H. Lu, D.S. Loose, L. Chen, H. Lynch, S. Boyd-Rogers, M. Rubin, M.S. Daniell, P. Conrad, A. Millbourne, D.M. Geneshenon, R.R. Broaddus
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.H. Lu, D.S. Loose, M.S. Yates, G.M.
References


Grant Support

This work was supported by the National Cancer Institute (N01-CN-05127 and P50CA098258).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received January 16, 2013; revised March 22, 2013; accepted April 16, 2013; published OnlineFirst May 2, 2013.
Cancer Prevention Research

Prospective Multicenter Randomized Intermediate Biomarker Study of Oral Contraceptive versus Depo-Provera for Prevention of Endometrial Cancer in Women with Lynch Syndrome


Updated version
Access the most recent version of this article at: doi:10.1158/1940-6207.CAPR-13-0020

Supplementary Material
Access the most recent supplemental material at:
http://cancerpreventionresearch.aacrjournals.org/content/suppl/2013/05/02/1940-6207.CAPR-13-0020.DC1
http://cancerpreventionresearch.aacrjournals.org/content/suppl/2013/08/06/1940-6207.CAPR-13-0020.DC2

Cited articles
This article cites 27 articles, 9 of which you can access for free at:
http://cancerpreventionresearch.aacrjournals.org/content/6/8/774.full.html#ref-list-1

Citing articles
This article has been cited by 10 HighWire-hosted articles. Access the articles at:
http://cancerpreventionresearch.aacrjournals.org/content/6/8/774.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.