Featured Article

Endometriosis and Its Treatment with Danazol or Lupron in Relation to Ovarian Cancer

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Abstract

Purpose: It has been hypothesized that circulating androgens may be involved in the development of ovarian cancer. The androgenic medication, danazol, and the antiandrogenic medications, leuprolide and nafarelin, are commonly used in the treatment of endometriosis. We assessed the associations between the use of these medications and ovarian cancer.

Experimental Design: We pooled information on self-reported use of danazol and leuprolide/nafarelin from two population-based case-control studies of incident ovarian cancer, comprising 1373 cases and 1980 controls. Odds ratios for the association between danazol and ovarian cancer, and leuprolide/nafarelin and ovarian cancer were adjusted for age, parity, oral contraceptive use, and family history of ovarian cancer. These analyses were repeated among the 120 cases and 124 controls who reported having had endometriosis.

Results: Danazol users (n = 19) were at a significantly elevated 3.2-fold (95% confidence interval, 1.2–8.5) risk of developing ovarian cancer, whereas leuprolide/nafarelin users (n = 23) were not at significantly elevated risk (odds ratio, 1.0; 95% confidence interval, 0.4–2.4). Similar results were obtained among the subset of women with endometriosis.

Conclusions: Danazol, but not leuprolide/nafarelin, increased the risk of ovarian cancer. This supports the hypothesis that androgen excess may be associated with the development of ovarian cancer.

Introduction

Ovarian cancer is the leading cause of death from gynecologic cancer, yet its etiology is unknown. Sex hormones, including androgens, have been hypothesized to have potentially mutagenic effects on the ovarian epithelium (1). To test whether exogenous androgens may be associated with ovarian cancer, we examined the effects of medications used for endometriosis, which have opposing effects on androgens. Danazol (17-α-ethinylestradiol) is a synthetic androgen that binds to androgen receptors and sex hormone-binding globulin resulting in a 3-fold increase in free testosterone (2). Leuprolide (lupron) and nafarelin (Synarel) are gonadotropin-releasing hormone analogues, which, with repeated doses, suppress the secretion of follicle-stimulating hormone and luteinizing hormone, causing a hormonal milieu similar to that seen during menopause (3). Each medication is prescribed for symptomatic treatment of endometriosis, although all have other therapeutic uses. Because danazol and luprolide/nafarelin have opposing effects on androgen levels, we hypothesized that they would differentially impact ovarian cancer risk.

Materials and Methods

We pooled data on danazol and lupron/nafarelin use from two ovarian cancer case-control studies. The characteristics of these studies have been described elsewhere (4). Briefly, both studies used a population-based, case-control design to study epithelial ovarian cancer. One study was conducted in Eastern Pennsylvania (5). It recruited women ages 20–69 from 39 hospitals in the region and ascertained controls, frequency matched to cases by age, and area of residence, by random digit dialing or Healthcare Finance Administration files. A total of 767 cases (88% of eligible subjects) and 1367 controls (72% of eligible subjects) were enrolled. The other study was conducted in Hawaii/Los Angeles (6). It recruited women ages 18–87 from any of the major hospital centers on the island of Oahu. Controls, frequency matched to cases by age, race, and location, were identified from within a state-wide population registry or Healthcare Finance Administration files. A total of 606 cases (65% of eligible subjects) and 613 controls (72% of eligible subjects) were enrolled. A total of 1373 cases and 1980 controls was enrolled in the combined analysis.

Both studies carried out standardized in-person interviews using modified versions of a single questionnaire. This questionnaire based recall for reproduction events on a life calendar with important events during a woman’s life used to enhance her memory for date-related information. Danazol use and lupron/nafarelin use were captured as follows. In one study (5), subjects were simply asked to identify any hormonal drug use. Information was available on potentially important confounding variables related to ovarian cancer risk such as age (continuous), gravidity (continuous), oral contraceptive use (dichotomous), and family history of ovarian cancer (categorical). Women were categorized as having endometriosis if they had been informed by a doctor or other health professional that they

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had endometriosis or infertility from endometriosis. Subjects were also categorized as having endometriosis if they reported taking medications to treat endometriosis. One hundred and twenty cases and 124 controls reported having endometriosis.

To test the appropriateness of pooling the data estimates from the two studies, we calculated a $\chi^2$ statistic for heterogeneity. In none of the analyses did we find statistically significant heterogeneity between two studies.

Pooled ORs, with corresponding 95% CIs were calculated as the primary measure of effect size. Because both studies used frequency rather than individual matching and matched on the basis of broad criteria, such as age within 5–10-year intervals, we used unconditional logistic regression models to adjust for any additional effects of potential confounding variables. Included in the models were age and gravidity as continuous variables, and oral contraceptive use and family history of ovarian cancer as dichotomous (yes/no) variables.

Because both danazol and lupron are prescribed primarily for the treatment of endometriosis, which is in itself a risk factor for ovarian cancer, we repeated our multivariable analyses including only women with a history of endometriosis. Among women with endometriosis, we also examined the effect of other treatments on ovarian cancer risk. Only data from one of the studies (5) was available for this last analysis.

### Results

The proportion of women reporting danazol or luprolide/nafarelin use was low, with only 19 women reporting danazol use and only 23 reporting luprolide/nafarelin use (Table 1). Compared with women who had never used either danazol or lupron, women who used danazol had fewer pregnancies ($P < 0.05$). As expected, women who used danazol or luprolide/nafarelin were much more likely to have been diagnosed with endometriosis ($P < 0.001$). Women who used luprolide/nafarelin were younger ($P < 0.001$), more educated ($P = 0.05$), less gravid ($P < 0.005$), and more likely to use oral contraceptives ($P = 0.001$) than women who used neither danazol or luprolide/nafarelin.

After adjusting for age, gravidity, oral contraceptive use, and family history of ovarian cancer, women who used danazol had over three times the risk for ovarian cancer compared with users of neither danazol nor lupron/nafarelin (adjusted OR for users, 3.2; 95% CI, 1.2–8.5; Table 2). Luprolide/nafarelin was not associated with ovarian cancer risk (adjusted OR, 1.0; 95% CI, 0.4–2.4). The odds of ovarian cancer associated with danazol use of 1–3 months duration as compared with nonuse was 1.6 (95% CI, 0.3–8.3) and for ≥4 months duration was 4.7 (95% CI, 1.3–17.3). In contrast, the odds of ovarian cancer with luprolide/nafarelin use of 1–3 months duration was 0.4 (95% CI, 0.1–1.9) and for ≥4 months duration was 1.8 (95% CI, 0.6–5.6). Five women used both danazol and luproide. When we excluded these women from the analyses, the OR for danazol (adjusted OR, 3.4; 95% CI, 1.0–10.8) and the OR for luprolide/nafarelin changed little (adjusted OR, 0.7; 95% CI, 0.3–2.0).

Restricting the adjusted analyses to include only women diagnosed with endometriosis, danazol use was still associated with an increased risk of ovarian cancer (OR, 2.9; 95% CI, 1.0–8.5), whereas the association between luprolide/nafarelin use and ovarian cancer remained nonsignificant (OR, 1.4; 95% CI, 0.5–4.1). Other treatments for endometriosis including oral contraceptive use (OR, 0.5; 95% CI, 0.3–0.9), hysterectomy (OR, 0.6; 95% CI, 0.3–1.2), and infertility drug use (OR, 1.2; 95% CI, 0.6–2.4), were not significantly related to elevated ovarian cancer risk among women with endometriosis.

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2 The abbreviations used are: OR, odds ratio; CI, confidence interval.
Danazol Use

In this pooled analysis, danazol was an independent risk factor for ovarian cancer. The occurrence of ovarian cancer was 3.2 times higher among women who used danazol compared with women who used neither drug. The association between danazol use and ovarian cancer persisted among a subset of women with endometriosis. Luprolide and nafarelin, on the other hand, were not significantly related to ovarian cancer risk. Indeed, none of the other treatments for endometriosis (oral contraceptives, hysterectomy, infertility drug use, surgical treatment, and other hormone use) significantly elevated ovarian cancer risk.

Our findings support the hypothesis that circulating androgens may be involved in the development of ovarian cancer. Androgens have been shown to stimulate the growth of ovarian epithelial cells in vivo, leading to ovarian neoplasm (7). Most ovarian cancer tumors express androgen receptors, and ovarian cancer cell growth is inhibited in vitro by antiandrogens (8, 9). Furthermore, in a prospective study, women who developed ovarian cancer had 50% higher levels of circulating androgens than women who did not develop the disease (10).

Although we considered the possibility that women who used danazol had more severe endometriosis compared with lupron users, we know of no evidence to this effect. Danazol was developed in the 1970s and quickly became the most common treatment for endometriosis. Lupron was approved by the Food and Drug Administration for use in the treatment of endometriosis in 1990. Both danazol and lupron are equally effective; however, because of the androgenic side effects of danazol, lupron is now the preferred medication (3).

Selection and information biases were minimized in this pooled analysis by the population-based study design, large sample size, structured interviews, and detailed data collection on danazol and lupron use. However, the study was limited by the few women using danazol or lupron and by the derivation of data on medication use from self-reports.

Despite these limitations, our data suggest that danazol use increases the risk of ovarian cancer among women with endometriosis. This potential for risk may moderate enthusiasm for the use of danazol in treating endometriosis, particularly should our findings be replicated. Less clear is any concern about the use of exogenous androgens in women without endometriosis. Female body builders sometimes take androgens to increase muscle mass. Increasingly, postmenopausal women are also taking androgenic drugs for this same purpose as well as to enhance libido. Additional study of the long-term effects of exogenous androgen use in women is essential.

**Discussion**

**Table 2** ORs and 95% CIs of ovarian cancer risk in relation to danazol and lupron use

<table>
<thead>
<tr>
<th>Medication</th>
<th>Cases</th>
<th>Controls</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
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<tbody>
<tr>
<td>All women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danazol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither medication</td>
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<td>1962</td>
<td>3.1 (1.2–8.3)</td>
<td>3.2 (1.2–8.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lupron or nafarelin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither medication</td>
<td>1354</td>
<td>1962</td>
<td>0.9 (0.4–2.2)</td>
<td>1.0 (0.4–2.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>9</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women with endometriosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danazol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither medication</td>
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<td>113</td>
<td>2.9 (1.0–8.5)</td>
<td>2.9 (1.0–8.5)</td>
</tr>
<tr>
<td>Yes</td>
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<tr>
<td>Lupron or nafarelin</td>
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<td></td>
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<td></td>
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<tr>
<td>Neither medication</td>
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<td>113</td>
<td>1.3 (0.6–4.4)</td>
<td>1.4 (0.5–4.1)</td>
</tr>
<tr>
<td>Yes</td>
<td>9</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age and gravidity as continuous variables and oral contraceptive use, and family history of ovarian cancer use as dichotomous variables.

**References**

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