Tea Consumption and Ovarian Cancer Risk in a Population-Based Cohort

Susanna C. Larsson, MSc; Alicja Wolk, DMSc

Background: Substantial evidence from laboratory studies indicates that green and black tea preparations may protect against various cancers. Few epidemiologic studies, however, have examined the relationship specifically between tea consumption and risk of ovarian cancer.

Methods: We prospectively examined the association between tea consumption and risk of ovarian cancer in 61,057 women aged 40 to 76 years who were participants in the population-based Swedish Mammography Cohort. Participants completed a validated 67-item food frequency questionnaire at enrollment between 1987 and 1990 and were followed for cancer incidence through December 2004.

Results: During an average follow-up of 15.1 years, 301 incident cases of invasive epithelial ovarian cancer were ascertained. Tea consumption was inversely associated with the risk of ovarian cancer after controlling for potential confounders (P for trend, .03). Compared with women who never or seldom (less than monthly) consumed tea, the multivariate hazard ratios for those who consumed less than 1 cup per day, 1 cup per day, and 2 or more cups per day were 0.82 (95% confidence interval [CI], 0.62-1.08), 0.76 (95% CI, 0.56-1.04), and 0.54 (95% CI, 0.31-0.91), respectively. Each additional cup of tea per day was associated with an 18% lower risk of ovarian cancer (multivariate hazard ratio, 0.82; 95% CI, 0.68-0.99).

Conclusion: These results suggest that tea consumption is associated with a reduced risk of epithelial ovarian cancer in a dose-response manner.

Arch Intern Med. 2005;165:2683-2686

GREEN AND BLACK TEA POLYPHENOLS have been extensively studied as cancer chemopreventive agents. Although substantial evidence from in vitro and animal studies indicates that green and black tea preparations can inhibit carcinogenic processes, the possible protective role of tea consumption against the development of cancer in humans is unclear.1 Few epidemiologic studies, particularly prospective studies,2 have examined the association specifically between tea consumption and risk of ovarian cancer. The Iowa Women’s Health Study3 found no clear evidence of a relationship between tea consumption and ovarian cancer risk, but the number of cases was small. Case-control studies of tea consumption in relation to ovarian cancer have been inconsistent, with an inverse association observed in some1,4 but not in most studies.3,5-8

The paucity of prospective data on tea consumption in relation to ovarian cancer risk led us to examine prospectively this relationship among participants in the Swedish Mammography Cohort.

STUDY POPULATION

The population-based Swedish Mammography Cohort was established between 1987 and 1990, when all women aged 40 to 76 years and residing in Uppsala and Västmanland counties in central Sweden received a mailed invitation to participate in a mammography screening program together with a 6-page questionnaire.9 A total of 66,651 women, representing 74% of the source population, returned a completed questionnaire that solicited information about diet, education, parity, age at first birth, weight, and height. Data on age at menarche, age at menopause, and use of oral contraceptives and postmenopausal hormones were obtained from a complementary questionnaire from women in Uppsala County in connection with their mammography examination. In 1997, participants were mailed a follow-up questionnaire that was expanded to include details about lifestyle factors, medical history, reproductive factors, and exogenous hormone use. The study was approved by the ethics committees at the Uppsala University Hospital and the Karolinska Institutet in Stockholm.

For this analysis, we excluded women with erroneous or incorrect national registration numbers and women with implausibly high or low total energy intakes (ie, 3 SDs from the mean value for...
log-transformed energy). We also excluded women with a diagnosed cancer (except nonmelanoma skin cancer) and women who had undergone a bilateral oophorectomy before baseline, leaving 61,057 eligible women for this analysis.

DIETARY ASSESSMENT

Tea consumption was assessed at baseline as part of a 67-item food-frequency questionnaire. For each item, participants reported their usual average consumption during the previous 6 months, with 8 predefined response categories ranging from “never/seldom” to “4 or more times per day.” In a validation study in a random sample of 129 women from the cohort, the Spearman correlation coefficient between the mean of four 1-week weighed diet records and the food-frequency questionnaire was 0.81 for tea consumption.

CASE ASCERTAINMENT AND FOLLOW-UP

Incident cases of invasive epithelial ovarian cancer were identified through linkage with the National Swedish Cancer Registry and the Regional Cancer Registry that recorded all cancer diagnoses in the study area. Both the national and the regional cancer registries have been documented to be almost complete. Dates of death in the cohort were ascertained through the Swedish Death Register. For women who moved out of the study area, the date of moving was obtained from the Swedish Population Register.

STATISTICAL ANALYSIS

We computed person-time of follow-up for each woman from the date of enrollment to the date of diagnosis of ovarian cancer, the date of death, the date of a bilateral oophorectomy, the date of moving out from the study area, or December 31, 2004, whichever came first. After determining that the data conformed to the proportional hazards assumption, we used Cox proportional hazards models to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). The Cox models were stratified by age in months and the year of recruitment. The multivariate models were also simultaneously controlled for body mass index, education, parity, use of oral contraceptives, and intakes of total energy, fruit, vegetables, milk, liquor, beer, wine, and coffee. Tests of trend across categories of tea consumption were conducted by assigning the median value for each category and modeling this value as a single continuous variable. We used restricted cubic spline regression with 5 knots to flexibly model the relation between tea consumption and ovarian cancer incidence. Analyses were performed using SAS software (version 9.1; SAS Institute Inc, Cary, NC). All reported P values are 2-sided.

RESULTS

At baseline, 68% of the participants reported drinking tea (mainly black tea) at least once per month. The mean tea consumption among drinkers was 0.8 cups/d. Compared with women who never or seldom drank tea, women who drank tea were generally younger and leaner and more likely to have a postsecondary education (Table 1). Women with frequent consumption of tea tended to consume more fruits, vegetables, and beer, but to drink less coffee.

During 920,407 person-years of follow-up (mean, 15.1 years), 301 women were diagnosed as having invasive epithelial ovarian cancer. We observed an inverse association between tea consumption and risk of ovarian cancer (Table 2). Compared with women who never or rarely consumed tea, the multivariate HR for those who drank 2 or more cups of tea per day was 0.54 (95% CI, 0.31-0.91; P value for trend, .03). The results were unchanged after further adjustment for age at menarche, age at first birth, age at menopause, family history of breast cancer, and use of postmenopausal hormones. Spline regression analysis demonstrated a dose-response relationship between tea consumption and incidence of ovarian cancer

Table 1. Age-Standardized Baseline Characteristics of the Study Population According to Tea Consumption

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Never/Seldom*</th>
<th>&lt;1†</th>
<th>1</th>
<th>≥2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, No.</td>
<td>19,544</td>
<td>21,009</td>
<td>15,498</td>
<td>5006</td>
</tr>
<tr>
<td>Tea consumption, median</td>
<td>0</td>
<td>0.14</td>
<td>1.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Age, mean, y</td>
<td>55.3</td>
<td>53.3</td>
<td>53.1</td>
<td>51.2</td>
</tr>
<tr>
<td>BMI, mean</td>
<td>25.0</td>
<td>24.8</td>
<td>24.5</td>
<td>24.2</td>
</tr>
<tr>
<td>Postsecondary education, %</td>
<td>10</td>
<td>13</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Mean No. of child births</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Oral contraceptive use, %</td>
<td>52</td>
<td>55</td>
<td>55</td>
<td>56</td>
</tr>
<tr>
<td>Mean consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruits, servings/d</td>
<td>1.4</td>
<td>1.5</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Vegetables, servings/d</td>
<td>1.6</td>
<td>1.8</td>
<td>1.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Milk, servings/d</td>
<td>1.2</td>
<td>1.3</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Liquor, servings/wk</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Beer, servings/wk</td>
<td>1.0</td>
<td>1.1</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Wine, servings/wk</td>
<td>0.4</td>
<td>0.4</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Coffee, cups/d</td>
<td>2.6</td>
<td>2.5</td>
<td>2.2</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

* Seldom indicates less than or equal to 1 cup/mo.
† Less than 1 indicates 1 to 3 cups/mo and up to 5 to 6 cups/wk.
The protective effect against ovarian cancer.

consumption might have been too low to provide a pro-

H11350 liquor (2 categories), beer (3 categories), wine (3 categories), and coffee (4 categories).

States,7,8 Australia,6 and Italy5 found no association with

other cancers. Other case-control studies in the United

relate to none, was 0.5 (95% CI, 0.2-1.0) using healthy controls and 0.7 (95% CI, 0.3-1.6) using controls with

other cancers. Other case-control studies in the United

States;7,8 Australia,6 and Italy5 found no association with

tea consumption. In some case-control studies,5,8 the tea

consumption; coffee is not associated with ovarian cancer

coffee consumption among women with high tea con-

sumption; coffee is not associated with ovarian cancer risk in this cohort.14

To our knowledge, the Iowa Women’s Health Study2

is the only other prospective study that has examined the relationship between tea consumption and ovarian cancer risk. In the Iowa cohort of 107 ovarian cancer cases diagnosed among 35 369 postmenopausal women during 8 years of follow-up, weekly consumption of tea was associated with a significant 47% lower risk; however, there was no association with higher consumption (>1 cup/d). These unstable results might reflect limited statistical power. Case-control studies of tea consumption in relation to ovarian cancer have yielded inconsistent results. A case-control study in China4 reported significant inverse associations between consumption of green and black teas and risk of ovarian cancer; women who consumed tea had an approximately 60% lower risk compared with nondrinkers. Tea consumption was also associated with a reduction in ovarian cancer risk in a case-control study in the United States.3 In that study, the relative risk for drinking 5 or more cups of tea per day, relative to none, was 0.5 (95% CI, 0.2-1.0) using healthy controls and 0.7 (95% CI, 0.3-1.6) using controls with other cancers. Other case-control studies in the United

States;7,8 Australia,6 and Italy5 found no association with tea consumption. In some case-control studies,3,8 the tea consumption might have been too low to provide a protective effect against ovarian cancer.

Antioxidant polyphenols, including catechins, thea-

flavins, thearubigins, and flavanols (eg, quercetin), are abundantly present in both green and black teas and have been shown to inhibit carcinogenesis in cell studies and in animal models involving different organs.1 Several possible mechanisms have been proposed for the anticarcino-
genic properties of tea polyphenols, including inhibition of cell growth and angiogenesis and induction of apopto-
sis.1 Tea polyphenols may also protect against cancer through their strong antioxidant activity.15

The strengths of our study include a population-
based and prospective design, a large size, and a relatively large number of ovarian cancer cases, and a virtually complete cohort follow-up.10 Furthermore, the assessment of tea consumption by the food-

frequency questionnaire used in this study had a high

<table>
<thead>
<tr>
<th>Tea Consumption, Cups/d</th>
<th>Cases, No.</th>
<th>Person-Years of Follow-up</th>
<th>Age-Adjusted HR (95% CI)</th>
<th>Multivariate HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never/seldom†</td>
<td>111</td>
<td>289 686</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;14</td>
<td>102</td>
<td>319 064</td>
<td>0.84 (0.63-1.11)</td>
<td>0.82 (0.62-1.08)</td>
</tr>
<tr>
<td>1</td>
<td>72</td>
<td>235 091</td>
<td>0.79 (0.57-1.06)</td>
<td>0.76 (0.56-1.04)</td>
</tr>
<tr>
<td>≥2</td>
<td>16</td>
<td>76 566</td>
<td>0.58 (0.34-0.99)</td>
<td>0.54 (0.31-0.91)</td>
</tr>
<tr>
<td>P value for trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age in months (continuous); body mass index (quartiles); education (<high school, high school, university); parity (nulliparous, 1-2 children, ≥3 children); oral contraceptive use (ever, never); intake of total energy (continuous); and consumption of fruit (quartiles), vegetables (quartiles), milk (quartiles), liquor (2 categories), beer (3 categories), wine (3 categories), and coffee (4 categories).

†Seldom indicates less than or equal to 1 cup/mo.

‡Less than 1 indicates 1 to 3 cups/mo and up to 5 to 6 cups/wk.

Figure. Invasive epithelial ovarian cancer according to tea consumption. Multivariate hazard ratios calculated by restricted cubic spline Cox proportional hazards models that were adjusted for age in months (continuous); body mass index (quartiles); education (<high school, high school, university); parity (nulliparous, 1-2 children, ≥3 children); oral contraceptive use (ever, never); intake of total energy (continuous); and consumption of fruits (quartiles), vegetables (quartiles), milk (quartiles), liquor (2 categories), beer (3 categories), wine (3 categories), and coffee (4 categories). The solid curve represents point estimates; dashed curves, 95% confidence intervals.

COMMENT

In this large population-based prospective cohort study, tea consumption was significantly inversely associated with risk of ovarian cancer. We observed a 46% lower risk of ovarian cancer in women who drank 2 or more cups of tea per day compared with nondrinkers. This association does not depend on lower coffee consumption among women with high tea consumption; coffee is not associated with ovarian cancer risk in this cohort.14

Antioxidant polyphenols, including catechins, thea-

flavins, thearubigins, and flavanols (eg, quercetin), are abundantly present in both green and black teas and have been shown to inhibit carcinogenesis in cell studies and in animal models involving different organs.1 Several possible mechanisms have been proposed for the anticarcino-
genic properties of tea polyphenols, including inhibition of cell growth and angiogenesis and induction of apopto-
sis.1 Tea polyphenols may also protect against cancer through their strong antioxidant activity.15

The strengths of our study include a population-
based and prospective design, a large size, and a relatively large number of ovarian cancer cases, and a virtually complete cohort follow-up.10 Furthermore, the assessment of tea consumption by the food-

frequency questionnaire used in this study had a high
validity ($r=0.81$) when compared with multiple diet records.

As in any observational study we cannot entirely exclude the possibility that our findings are explained by uncontrolled or residual confounding. In this cohort, women with high tea consumption, compared with those who never or seldom consumed tea, seemed to be more health conscious in their behaviors in that they consumed more fruits and vegetables and were generally leaner. Hence, residual confounding by a healthy lifestyle should be considered as a potential explanation for the observed inverse association of tea consumption with the risk of ovarian cancer. Arguing against residual confounding, the results were similar in age-adjusted and multivariate models. We also cannot rule out chance as an alternative explanation for our findings. Nevertheless, the dose-response relationship of tea consumption with ovarian cancer risk makes chance less likely.

In summary, our results from a large population-based cohort of Swedish women suggest that tea consumption may lower the risk of ovarian cancer. Because prospective data on this relationship are scarce, our findings need confirmation by future studies.

Accepted for Publication: August 10, 2005.

Correspondence: Susanna C. Larsson, MSc, Division of Nutritional Epidemiology, The National Institute of Environmental Medicine, Karolinska Institutet, PO Box 210, SE-171 77 Stockholm, Sweden (susanna.larsson@mm.ki.se).

Funding/Support: This work was supported by research grants from the Swedish Cancer Foundation and the Swedish Research Council/Longitudinal Studies, Stockholm, Sweden.

Role of the Sponsor: Funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review or approval of the manuscript.

REFERENCES