Alcohol Consumption and Endometrial Cancer: Some Unresolved Issues

Elisa V. Bandera, Lawrence H. Kushi, Sara H. Olson, Wendy Y. Chen, and Paola Muti

Abstract: The role of hormonal factors, in particular unopposed estrogens, on endometrial cancer occurrence is well established. Progesterone deficiency has also been suggested as a possible risk factor. Alcohol use has been shown to be associated with elevated estrogen levels and reduced progesterone. Epidemiologic studies, however, have not offered much support for a positive association between alcohol intake and endometrial cancer, with results generally indicating no association or suggesting an inverse relationship with endometrial cancer. However, certain methodologic limitations, such as small sample size, limited range of alcohol intake, and confounding may have explained those findings. Moreover, there are some unexplored aspects of the possible effect of alcohol, such as the possible interaction with use of exogenous estrogens, and other factors, that need clarification.

Introduction

Endometrial cancer is the most common female genital cancer in the United States, ranking fourth among cancers in women in age-adjusted incidence (1). According to the American Cancer Society (2), 38,300 new cases and 6,600 deaths due to this disease were expected in the year 2001. The role of hormonal factors in the etiology of endometrial cancer is well established (1), as most of the major risk factors of endometrial cancer have in common an increased exposure of the endometrium to unopposed estrogens. Although not as widely accepted, other endogenous hormones have been implicated; in particular progesterone deficiency and increased levels of androgens may increase endometrial cancer risk (1).

Alcohol use has been associated with higher levels of circulating estrogens in pre- and postmenopausal women (3), reduced progesterone levels in premenopausal women (3), and elevated androstenedione and testosterone in premenopausal women (4). The most consistent result emerging from studies in postmenopausal women is that, among estrogen replacement therapy (ERT) users, alcohol causes a rapid and substantial elevation in circulating estradiol (5). As alcohol drinking seems to induce a hormonal profile, which has been associated with an increased risk of endometrial cancer, an association between alcohol consumption and endometrial cancer might be expected. However, epidemiologic studies have offered little support for such an association, with most studies suggesting no association (6–16) or even an inverse association between alcohol and endometrial cancer risk (17,18). In contrast, two studies reported a positive association (19,20). These conflicting results could be explained by methodological limitations of previous studies or inadequate exploration of this hypothesis. The literature reviewing the effect of alcohol use on female hormonal levels has been elegantly reviewed by others (3,5,21). The purpose of this article is not to be a comprehensive review of the epidemiologic literature evaluating alcohol and endometrial cancer. Rather, it aims to point out several aspects of this relationship that have previously received little attention, and that warrant further evaluation of a possible role of alcohol in the etiology of endometrial cancer.

Alcohol Consumption and Endometrial Cancer: Epidemiologic Evidence

The relationship between alcohol intake and endometrial cancer has been evaluated in relatively few epidemiologic studies. As shown in Table 1, of 13 case-control studies that have examined this association, two found an increased risk (19,20), two observed an inverse relation (17,18), and the remaining reported odds ratios (ORs) fluctuating around 1 with confidence intervals (CIs) that included the null value (6–10, 12–14,16). In addition, two cohort studies (11,15) failed to find a significant association between total alcohol consump-
Table 1. Case-Control and Cohort Studies Evaluating Alcohol Consumption and Endometrial Cancer$^a$

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Location</th>
<th>Size</th>
<th>Comparison (Cases in the Drinking Category)</th>
<th>OR or RR (95% CI)</th>
<th>Smoking</th>
<th>ERT/HRT</th>
<th>OC</th>
<th>BMI</th>
<th>Fat Intake</th>
<th>Total Energy Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Italy</td>
<td>206/206</td>
<td>&gt;4 drinks/day vs. 0 (9 cases)</td>
<td>4.3 (1.0–18.4) $P$ trend: 0.02</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>USA</td>
<td>351/2,247</td>
<td>Nondrinker vs. ≤150 g/week (29 cases)</td>
<td>1.8 (1.1–3.0)</td>
<td>Yes (yes/no)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Japan</td>
<td>239/8,920</td>
<td>Daily vs. less (not specified)</td>
<td>0.5 (0.2–1.7)</td>
<td>Yes (ever/never)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>USA</td>
<td>103/236</td>
<td>Drinker vs. nondrinker (17 cases)</td>
<td>0.6 (0.3–1.3)</td>
<td>Yes (&quot;cigarette habit&quot;)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Switzerland and North Italy</td>
<td>274/572</td>
<td>&gt;1 glass per day vs. none (97 cases)</td>
<td>1.2 (not shown) $P$ trend: 0.6</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>USA</td>
<td>400/297</td>
<td>&gt;4 drinks/week vs. none (50 cases)</td>
<td>0.7 (0.4–1.3)</td>
<td>Yes (nonsmoker, former, current)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>China</td>
<td>268/268</td>
<td>Ever drinking regularly vs. none (18 cases)</td>
<td>1.2 (0.6, 2.6)</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>20</td>
<td>Italy</td>
<td>726/2,123</td>
<td>≥2 drinks/day vs. none (87 cases)</td>
<td>1.6 (1.2–2.2)</td>
<td>Yes (never, ever)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>Greece</td>
<td>145/298</td>
<td>Yes vs. no, rarely (40 cases)</td>
<td>0.7 (0.4–1.4)</td>
<td>Yes (never, ever)</td>
<td>Yes (Only 2 cases and 5 controls)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>13</td>
<td>Hawaii</td>
<td>332/511</td>
<td>Yes vs. no (78 cases)</td>
<td>0.9 (0.6–1.4) $P$ trend: 0.4</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>USA</td>
<td>739/2,313</td>
<td>≥14 drinks/week vs. none (31 cases)</td>
<td>1.3 (0.8–2.1) $P$ trend: 0.8</td>
<td>Yes (never, former, current)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>18</td>
<td>Canada</td>
<td>552/562</td>
<td>&gt;8.3 g of absolute alcohol vs. none (108 cases)</td>
<td>0.7 (0.5–1.0)</td>
<td>Ever smoked (yes/no)</td>
<td>Yes</td>
<td>Yes</td>
<td>Weight</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>16</td>
<td>Sweden</td>
<td>709/3,368</td>
<td>≥24 g/day vs. nondrinkers</td>
<td>0.9 (0.7–1.2) $P$ for trend: 0.44</td>
<td>Yes (never, former, recent/current)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Case-control studies

Cohort studies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Location</th>
<th>Size</th>
<th>Comparison (Cases in the Drinking Category)</th>
<th>OR or RR (95% CI)</th>
<th>Smoking</th>
<th>ERT/HRT</th>
<th>OC</th>
<th>BMI</th>
<th>Fat Intake</th>
<th>Total Energy Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>US</td>
<td>167/25,170 (5 yr follow-up)</td>
<td>≥24 g/day (approx. 1/3 beer/day) vs. none (32 cases)</td>
<td>1.0 (0.7, 1.6) $P$ trend: 0.37</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>Sweden</td>
<td>133/11,659</td>
<td>≥24 drinks/week vs. none (7 cases)</td>
<td>1.3 (0.6–2.8) $P$ trend &gt; 0.05</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Weight</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

$^a$: Size = cases/controls for case-control studies or cases/total number of subjects for cohort studies. Parazzini et al., 1995 (20), is an update from the study by La Vecchia et al., 1986 (19). Abbreviations: OR, odds ratio; RR, relative risk; CI, confidence interval; ERT, estrogen replacement therapy; HRT, hormone replacement therapy; OC, oral contraceptives; BMI, body mass index; ?, uncertain.
tion and endometrial cancer. Overall, these results do not provide strong evidence that alcohol may affect the risk of endometrial cancer. However, a closer look at these studies reveals some limitations and some understudied aspects of this potential association that warrant further consideration of this hypothesis.

Methodologic Issues

The largely null findings regarding alcohol intake and endometrial cancer risk in epidemiologic studies may be explained by differing characteristics of the population studied, including the prevalence of estrogen use, age distribution, and menopausal status. Also potentially important are the distribution of alcoholic beverage type, the range of alcohol intake, which varied considerably across studies, as well as methodological differences in ascertainment of alcohol intake. Studies have been generally confronted with a small number of drinkers and a limited range of exposure. This is illustrated in Table 1, where it can be seen that all risk estimates were based on fewer than 100 cases in the exposed categories. Furthermore, measurement error undoubtedly occurred as a consequence of the limitations in ascertainment of intake in some studies, affecting the ability to detect an association. The methodologic issues in estimating alcohol consumption are well known (22) and will not be discussed here.

The differential evaluation of effect modifiers and control for potential confounding factors across studies may have also led to inconsistent results. These factors are considered in more detail below.

Possible Confounders/Effect Modification

Estrogen replacement therapy: The majority of the studies do not provide details regarding exogenous hormone use. Despite the consistent finding of increased estrogen levels associated with alcohol consumption among postmenopausal women on ERT previously mentioned, only five epidemiologic studies evaluated the possible interaction between ERT and alcohol on endometrial cancer (9,11,14,16,20; Table 2). Of these, two case-control studies reported a nonsignificant interaction, with a positive association of alcohol intake with endometrial cancer risk that was stronger or limited to ERT users (14,20). In contrast, two case-control studies (9,16) and a cohort study (11) failed to find an interaction. It should be noted these studies had very limited statistical power to evaluate this interaction. If the relationship between alcohol and endometrial cancer is indeed limited to ERT users, failing to stratify by ERT use may result in an underestimation of the association. Clearly, this is an area that needs further evaluation.

Oral contraceptive use: An independent inverse association between the estrogen-progestin combination type of oral contraceptive use and endometrial cancer risk is well documented (1). Consumption of alcoholic beverages has been found to be more prevalent among oral contraceptive users after adjusting for age (9). Despite the potential for negative confounding, only 7 (9,13,16–20) of the 15 studies (see Table 1) examining the relationship between alcohol and endometrial cancer risk adjusted for oral contraceptive use. It should be noted that in some of these studies the prevalence of oral contraceptive use was very low. For example, in the study by Kalandidi et al. (12) only 2 cases and 5 controls used oral contraceptives. Furthermore, two of the 15 studies were conducted among postmenopausal women (11,16). In that the protective effect of oral contraceptives has been shown to continue for years after discontinuing use (23), considering prior oral contraceptive use as a possible confounder may be important even among postmenopausal women.

Possible effect modification by oral contraceptive use has received little attention (Table 2). Of the 15 studies of alcohol and endometrial cancer, only three evaluated a possible interaction with conflicting results. An inverse relationship with alcohol limited to oral contraceptive users was found in a case-control study (9). In that they did not seem to have adjusted these analyses for smoking, residual negative confounding by cigarette smoking may explain their results. In contrast, two other studies found no interaction (11,16).

Menopausal status: Previous studies have generally not evaluated possible effect modification by menopausal status, but two case-control studies reported a significant inverse association limited to premenopausal women (9,14). Though these findings were based on a very small number of subjects, they may in part reflect the interaction of alcohol intake with oral contraceptive use noted above. In contrast, another case-control study reported no association for premenopausal women, but a suggestion of increased risk of endometrial cancer associated with alcohol intake only for postmenopausal women (20). Two studies limited to postmenopausal women found no association between alcohol and endometrial cancer risk (11,16). Although the results of studies evaluating the possible interaction between alcohol and menopausal status on endometrial cancer risk do not offer a clear picture, they highlight the need to further evaluate this association separately in pre- and postmenopausal women.

Body mass index: A strong positive association between body mass index (BMI) and endometrial cancer risk in pre- and postmenopausal women is well established (23). Because BMI has been found to be inversely related to alcohol consumption in women (24,25), failing to adjust for this variable may result in negative confounding. As shown in Table 1, all but three (6,8,20) studies adjusted for this variable, with conflicting results. Obesity may increase endometrial cancer risk by altering female sexual hormonal levels in premenopausal (by increasing anovulatory menstrual cycles and, therefore, reducing progesterone levels) and postmenopausal women (by increasing levels of bioavailable estrogens; 26). Because alcohol intake may also affect estrogen and progesterone levels
its effect may be different in lean and obese women. Of the 15 studies of alcohol intake and endometrial cancer, eight examined a possible interaction with BMI but did not offer conclusive results (Table 2). One study found a stronger positive association between alcohol and endometrial cancer for obese women (20), whereas other studies found an inverse association limited to leaner women (18) or a stronger inverse relationship for obese women (17). Five studies found no evidence of interaction (9,11,14–16).

The possible role of BMI as a confounder/modifier of the relationship between alcohol intake and endometrial cancer needs clarification since both influence women’s hormonal milieus.

Cigarette smoking: Another issue to consider is the possible confounding effect of cigarette smoking, which has been fairly consistently shown to have an inverse association with endometrial cancer risk, particularly among postmenopausal women (23). Given the known correlation between tobacco use and alcohol consumption, if cigarette smoking is not taken into account, negative confounding may occur. As shown in Table 1, only a few studies considered smoking as a potential confounder, and only in broad categories of smoking status (7,12,14,17,18,20). To our knowledge, the relationship between alcohol and endometrial cancer has not been evaluated after taking into account the effect of smoking history or smoking intensity. It is noteworthy that the only two studies that reported a positive association with alcohol intake were conducted in Italy (19,20), where wine, which is less correlated with smoking than other alcoholic beverages, was the most prevalent alcoholic beverage consumed.

Dietary factors: A potential confounder of the relationship between alcohol and endometrial cancer is total energy intake, as obesity is an established risk factor for the disease and alcohol is an important contributor to total energy intake. Studies have suggested that alcohol calories are added to the diet, rather than replacing calories derived from foods, resulting in an overall increase in total energy intake (27). However, the relationship between alcohol and obesity is complex. As previously noted, alcohol consumption has been repeatedly found to be associated with lower body weight (27) and this relationship has not been explained by higher physical activity levels among drinkers (28,29). Consequently, evaluating the relationship between total energy intake and endometrial cancer without disentangling calories from alcohol and nonalcohol calories may lead to an erroneous interpretation. Most studies evaluating the relationship between alcohol and endometrial cancer did not consider total energy intake or calories from alcohol as a potential confounder. The study by Levi et al. (8) reported a significant dose-response relationship with an OR for the highest tertile of alcohol consumption of 1.6. This OR was substantially attenuated after total energy intake was included in the model (1.2, \( P \) for trend > 0.05). More research is needed to clarify

Table 2. Evaluation of Interactions in Case-Control and Cohort Studies of Alcohol Consumption and Endometrial Cancer

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Location</th>
<th>Menopausal Status</th>
<th>BMI</th>
<th>OC Use</th>
<th>ERT/HRT Use</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>USA</td>
<td>No interaction</td>
<td>Stronger inverse association among obese women</td>
<td>No interaction</td>
<td>NR</td>
<td>No interaction</td>
</tr>
<tr>
<td>9</td>
<td>USA</td>
<td>Inverse association only for premenopausal women</td>
<td>No interaction</td>
<td>Inverse association limited to OC users (unadjusted for smoking)</td>
<td>No interaction</td>
<td>Increased risk in smokers, decreased risk in nonsmokers</td>
</tr>
<tr>
<td>20</td>
<td>Italy</td>
<td>Increased risk only in postmenopausal women (NS)</td>
<td>Stronger positive association for obese women (NS)</td>
<td>NR</td>
<td>Stronger positive association for ERT users (NS)</td>
<td>Stronger positive association for never smokers (NS)</td>
</tr>
<tr>
<td>14</td>
<td>USA</td>
<td>Inverse association only in premenopausal women (SS, but based on 4 cases, 36 controls)</td>
<td>No interaction</td>
<td>NR</td>
<td>Increased risk in current users, decreased risk in never users (NS)</td>
<td>No interaction</td>
</tr>
<tr>
<td>18</td>
<td>Canada</td>
<td>NR</td>
<td>Suggestion of inverse association limited to leaner women</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>16</td>
<td>Sweden</td>
<td>N/A (postmenopausal women)</td>
<td>No interaction</td>
<td>No interaction</td>
<td>No interaction</td>
<td>NR</td>
</tr>
<tr>
<td>Cohort studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>USA</td>
<td>N/A (postmenopausal women)</td>
<td>No interaction</td>
<td>NR</td>
<td>No interaction</td>
<td>NR</td>
</tr>
<tr>
<td>15</td>
<td>Sweden</td>
<td>NR</td>
<td>No interaction (not shown)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

a: Abbreviations: ERT, estrogen replacement therapy; OC, oral contraceptives; BMI, body mass index; N/A, not applicable; NS, not statistically significant; NR, not reported.
the interrelation between alcohol intake, total energy intake, BMI, and endometrial cancer.

Other dietary factors may confound the association between alcohol and endometrial cancer, as drinking may affect overall dietary patterns, and this could alter the risk of this disease. For instance, in the study by Swanson et al. (9) among female moderate drinkers, alcohol drinkers tended to consume fewer nonalcohol calories and less fat than non-drinkers. The most consistent finding from other studies examining the relationship between nutrient intake and alcohol consumption among women in the United States has been an inverse association between carbohydrate consumption and alcohol drinking (24,28–30). Although the relationship between carbohydrate consumption and endometrial cancer has received little attention, a modest negative relationship with complex carbohydrates was reported in a population-based case-control study after controlling for BMI and total energy intake among other factors (31). Further, the lower carbohydrate intake among drinkers may contribute to their lower body size, and reinforces the need to adjust for BMI when evaluating the role of alcohol on endometrial cancer risk.

Several other dietary factors have been implicated in the etiology of endometrial cancer, with an increased risk associated with dietary fat and a decreased risk with fruit and vegetable consumption (32) and several phytochemicals (13,33). The potential effect modification of alcohol intake on these associations is an additional aspect of relevance, which has been frequently overlooked. For example, a biological interaction between alcohol and folate intakes has been reported for breast cancer (34).

**Effect by Alcoholic Beverage Type**

Of the 15 studies evaluating the association between alcohol and endometrial cancer listed in Table 1, all but five (6,10,12,15,19) considered the separate effects of the different alcoholic beverages. Overall, results are inconclusive because most risk estimates did not reach statistical significance, as they were based on very few cases. An exception are two European studies that found increased risks of endometrial cancer for wine and liquor drinkers, with ORs of 1.7 (P for trend < 0.05; CI not shown) and 5.2 (P for trend < 0.05; CI not shown), respectively, in one study (8), and 1.6 (95% CI, 1.2–2.2) and 1.6 (95% CI, 1.1–2.2), respectively, in the other study (20). It should be noted that these two studies were conducted in populations where drinking wine, and perhaps liquor, is more prevalent and socially accepted than in the United States. Furthermore, these two studies did not adjust for total energy intake, which perhaps resulted in an overestimate of the magnitude of the association.

An interesting finding that has emerged from some studies is the suggestion of an inverse relationship with wine and beer and increased risk associated with liquor consumption (11,35). Although these results were not statistically significant, it is worth noting here that wine and beer contain phytochemicals (36,37) that may be associated with decreased risk of cancer. It is possible that alcohol increases endometrial cancer risk but the antioxidants and phytoestrogens in alcoholic beverages counteract that effect when alcohol is consumed at moderate levels. At high drinking levels, however, the ethanol content may overpower the effect of the potentially chemopreventive agents in alcoholic beverages. If it is true that moderate amounts of wine and beer decrease risk and liquor increases it, this may explain the conflicting results found in previous studies for total alcohol. The possible differential effects of wine, beer, and liquor at different levels of intake must be clarified.

**Conclusions**

Studies evaluating the role of alcohol intake on endometrial cancer risk have generally not been supportive of a relationship. However, an effect cannot yet be ruled out. Limitations of previous investigations and unanswered aspects of this potential relationship justify a closer look into this hypothesis. A lower risk of endometrial cancer is found among women with lower BMI, oral contraceptive users, and smokers, all factors associated with alcohol drinking. Of the 15 studies evaluating the relationship between alcohol and endometrial cancer, only five considered these three potential confounders simultaneously (9,11,16–18), and two of them found an inverse relationship (17,18) and two reported no association (9,11,16). However, none of the four studies seemed to have adjusted for smoking history; thus, the possibility of residual negative confounding remains. It should be noted here that some of these studies may have adjusted for all these potential confounders but did not report it.

The role of alcohol intake on endometrial cancer risk cannot be adequately evaluated without taking into account, along with other known risk factors for the disease, cigarette smoking history, oral contraceptive use, ERT use, energy intake from alcohol and nonalcohol sources, and BMI. Even if alcohol is unrelated or weakly inversely related to endometrial cancer in all groups combined, it may be associated with increased risk in selected subgroups, such as women using ERT or those with low intake of folate. Possible effect modification by menopausal status, BMI, ERT, oral contraceptive use, and smoking status needs further evaluation. To maximize the range of intake of alcohol, it may be beneficial to examine this association in multiethnic and geographically diverse populations. Moreover, information should be collected on frequency, quantity, and duration of use of wine, beer, and liquor to ensure a better estimate of total alcohol intake as well as possible differences in risk by type of beverage.

Endometrial cancer is a disease largely explained by hormonal factors. All the factors discussed here (e.g., oral contraceptives, ERT, cigarette smoking, and BMI) are related to alcohol consumption and have the potential of modifying estrogen levels. Understanding the interrelationship of all these factors with alcohol and its impact in endometrial cancer risk could provide important insights into the etiology and prevention of this disease.
References


