# Alcohol Consumption in Relation to Endometrial Cancer Risk[1]

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## Abstract

**We analyzed data from a population-based case-control study of Wisconsin women to evaluate the relationship of alcohol consumption to endometrial cancer risk. Cases ($n$ = 739) were identified from a statewide tumor registry; controls ($n$ = 2313) were selected randomly from driver's license lists and Medicare beneficiary files. Alcohol consumption and other factors were ascertained by telephone interview. Compared with abstainers, the multivariable relative risk for recent consumption of two or more drinks per day was 1.27 [95% confidence interval (CI) 0.78–2.07]; increasing consumption was not associated with risk of disease ($P$ for trend, 0.82). The relative risk for early adulthood consumption of two or more drinks per day was 1.00 (95% CI, 0.58–1.73), with no suggestion of a trend ($P$ = 0.26). Although the sample size was limited, a significant inverse association was suggested in premenopausal women consuming one drink per day or more (0.20, 95% CI 0.06–0.71). Beverage-specific consumption was not associated with risk. This study suggests that, unlike breast cancer, endometrial cancer is not positively associated with alcohol intake.**

## Introduction

Recent evidence suggests that alcohol intake positively influences endogenous estrogens (1–5), which, in addition to exogenous estrogens, are strong determinants of endometrial cancer risk (6, 7). However, alcohol consumption has been quite inconsistently associated with endometrial cancer incidence (8–14). Whereas two Italian studies observed an increased risk of endometrial cancer in relation to alcohol consumption (8, 9), other studies have found no association (10, 11, 15) or have found inverse relationships (12–14). The inverse association in these latter studies appeared strongest among premenopausal women. Our population-based case-control study of endometrial cancer provided an opportunity to examine age and beverage-specific alcohol consumption as well as other personal characteristics.

## Subjects and Methods

All participants were Wisconsin female residents ages 40–79 years. Incident invasive endometrial cancer cases (diagnosed between 1991 and 1994) were identified by a statewide mandatory cancer registry. According to an institutionally approved protocol, the physician of record for each eligible case was contacted by mail to obtain permission to approach the subject. Eligibility was limited to cases with listed telephone numbers, driver's licenses verified by self-report (if less than 65 years old), and if more than 65 years old, a Medicare card ($n$ = 856). A total of 745 cases (87% of eligible cases) participated in the study interview. The reasons for nonparticipation included physician refusal ($n$ = 6), subject refusal ($n$ = 53), inability to locate subject ($n$ = 2), and death ($n$ = 50). Of the interviewed cases, 98% had histological confirmation of invasive endometrial carcinoma.

Community controls were selected randomly from lists of licensed drivers (if less than 65 years old) and Medicare beneficiary files compiled by the Health Care Financing Administration (if 65–79 years old). The controls were selected at random to yield an age distribution similar to that of the cases and met the eligibility criterion of having a listed telephone number. Controls were eligible for the study if they reported no previous diagnosis of uterine cancer. Of the 4362 eligible controls, 521 (11.8%) refused, 35 (0.8%) could not be located, and 88 (2.0%) were deceased. A total of 3718 (85.2%) completed the study interview. Postinterview exclusions included 1304 control subjects who reported a history of hysterectomy and 6 women for whom interviews were determined to be unreliable. In all, 2408 control subjects were available for analysis.

During the structured 45-min telephone interview, the subject's usual history of alcohol consumption in their 20s ("young adult") and 5 years before the interview ("recent consumption") was ascertained. Data on consumption of beer, wine, and liquor were collected separately. In addition, we obtained exogenous hormone use, reproductive experiences, physical activity, medical and family history, and demographics prior to an assigned reference date. For cases, this was the date of diagnosis of the endometrial cancer. For comparability, control subjects were assigned a reference date that corresponded to the average diagnosis date for similarly aged cases (within 5-year strata) interviewed during the same month. Trained study staff conducted interviews by telephone without prior knowledge of the subjects' disease status. For 82% of cases and 95% of the controls, the interviewer remained unaware of the case-control status of the subject until the end of the interview.

Age was defined as the age at diagnosis or at the reference date. We assumed one drink of beer, wine, or liquor contained approximately equivalent amounts of alcohol (13 g; Ref. 16). Parity was the number of full-term pregnancies (defined as

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*Table 1* Characteristics (%) of endometrial cases and controls

| Characteristics | Cases ($n$ = 739) | Controls ($n$ = 2313) |
|---|---|---|
| Smoking status | | |
| Never | 60 | 54 |
| Former | 27 | 28 |
| Current | 13 | 18 |
| Education | | |
| <High school | 18 | 17 |
| High school diploma | 49 | 51 |
| Some college | 21 | 19 |
| College graduate | 12 | 13 |
| Relative weight (tertiles, kg/m$^2$) | | |
| 1 (<23.6) | 19 | 30 |
| 2 (23.6–27.4) | 22 | 30 |
| 3 (≥27.5) | 52 | 32 |
| Unknown | 7 | 8 |
| Hormone replacement use | | |
| Never | 57 | 69 |
| Former | 24 | 18 |
| Current | 19 | 13 |
| Parity | | |
| Nulliparous | 17 | 10 |
| 1 | 11 | 8 |
| 2 | 25 | 22 |
| ≥3 | 47 | 60 |

*Table 2* Adjusted RRs and 95% CIs for endometrial cancer by alcohol consumption

| Drinks per week | Cases | Controls | Age-adjusted RR, 95% CI | Multivariate RR,[a] 95% CI |
|---|---|---|---|---|
| Recent consumption | | | | |
| None | 157 | 500 | 1.0 | 1.0 |
| Any | 582 | 1813 | 1.06, 0.86–1.30 | 1.07, 0.86–1.33 |
| <1 | 262 | 684 | 1.23, 1.01–1.62 | 1.22, 0.96–1.56 |
| 1–2 | 126 | 469 | 0.85, 0.65–1.12 | 0.86, 0.65–1.14 |
| 3–6 | 115 | 364 | 1.05, 0.79–1.40 | 1.11, 0.83–1.50 |
| 7–13 | 48 | 204 | 0.77, 0.53–1.12 | 0.81, 0.55–1.19 |
| ≥14 | 31 | 92 | 1.15, 0.73–1.81 | 1.27, 0.78–2.07 |
| Continuous | | | 0.99, 0.98–1.02 ($P$ = 0.67) | 1.00, 0.98–1.02 ($P$ = 0.82) |
| Young adult | | | | |
| None | 113 | 394 | 1.0 | 1.0 |
| Any | 613 | 1906 | 1.16, 0.92–1.47 | 1.17, 0.92–1.50 |
| <1 | 225 | 703 | 1.18, 0.91–1.53 | 1.16, 0.88–1.53 |
| 1–2 | 186 | 526 | 1.26, 0.96–1.66 | 1.28, 0.96–1.71 |
| 3–6 | 127 | 441 | 1.06, 0.79–1.42 | 1.09, 0.80–1.49 |
| 7–13 | 52 | 157 | 1.08, 0.73–1.60 | 1.19, 0.78–1.80 |
| ≥14 | 23 | 79 | 1.09, 0.65–1.84 | 1.00, 0.58–1.73 |
| Continuous | | | 0.99, 0.97–1.01 ($P$ = 0.31) | 0.99, 0.97–1.01 ($P$ = 0.26) |

[a] Adjusted for age, smoking status, education, relative weight, use of hormone replacement therapy, and parity.

pregnancies longer than 6 months resulting in a live birth or stillbirth). A woman was classified as "postmenopausal" if she reported having undergone natural menopause or bilateral oophorectomy prior to the diagnosis date or reference date. Women who reported a hysterectomy were not eligible.

Odds ratios and 95% CIs[3] from multivariable logistic regression models were used to evaluate RRs (17). The models included terms for established risk factors for endometrial cancer including age (5-year categories), smoking status (three categories), hormone replacement use (three categories), relative weight tertiles (kg/m$^2$), education (four categories), and parity (four categories). Six cases and 95 controls were excluded from all models because of unknown alcohol consumption information, leaving 739 cases and 2313 controls for analysis.

**Reliability Study.** To assess the reliability of the questionnaire, 183 control subjects were reinterviewed after 6 months. The Spearman correlation coefficient between the average number of drinks per week reported in the two interviews was $r$ = 0.81 for both the recent period and for the young adult period (the decade of the 20s).

## Results

As compared with the controls, the women with endometrial cancer were more likely to be nulliparous, never smokers, and hormone replacement users and had higher relative weight and higher educational level (Table 1). These characteristics were considered potential confounders and we therefore controlled for them in all analyses.

Overall, alcohol consumption was not associated with endometrial cancer risk. Compared to abstainers, women consuming two drinks per day or more in the recent past had a RR of endometrial cancer of 1.27 (95% CI, 0.78–2.07); for the early life period, the RR was 1.00 (95% CI, 0.58–1.73; Table 2). Increasing recent ($P$ for trend, 0.82) and past ($P$ for trend = 0.26) consumption were not associated with increased risk. The multivariate adjusted estimates differed minimally from estimates obtained after adjustment for age only, suggesting that confounding was unlikely to have introduced substantial bias.

The relation of alcohol and endometrial cancer among various subgroups was examined (Table 3). The association between alcohol and cancer risk appeared to be inverse for premenopausal women who consumed, on average, at least one drink per day (RR, 0.20; 95% CI, 0.06–0.71). Consistent with this finding, younger women (≤55 years of age) who were daily drinkers had a reduced risk of endometrial cancer (RR, 0.58; 95% CI, 0.28–1.21). Similar inverse associations were observed for these subgroups in the earlier life period (data not shown). Relative weight did not appear to modify the relation between alcohol intake and risk of endometrial cancer ($P$ = 0.72); nor did use of hormone replacement therapy ($P$ = 0.15) or smoking ($P$ = 0.14). Limited sample size, however, constrained the evaluation of an alcohol effect in certain subgroups.

Type of alcoholic beverage consumed did not appear to be associated with risk. Variables for the different beverage types were entered simultaneously in a model. For the recent time period, the RRs associated with at least one drink per day were: for beer, the most commonly consumed beverage, 0.81 (95% CI, 0.47–1.38); for wine, 0.44 (95% CI, 0.21–0.94); and for hard liquor, 1.08 (95% CI, 0.70–1.65). However, when a model was fit with terms for total alcohol and beer (or wine or liquor), the results confirmed that alcohol in specific beverages was not associated with increased risk (for beer, $P$ = 0.08; for wine, $P$ = 0.3; and for liquor, $P$ = 0.2). Similarly, risk did not vary according to type of alcoholic beverage consumed in the earlier life period (data not shown).

## Discussion

Overall, in this large study, the risk of endometrial cancer was not related to alcohol intake, regardless of whether the con-

[3] The abbreviations used are: CI, confidence interval; RR, relative risk.

*Table 3* Adjusted RRs of endometrial cancer according to recent alcohol consumption (one or more drinks per day) and selected characteristics

| | Cases/controls | RR, 95% CI[a] | *P* interaction[a,b] |
|---|---|---|---|
| Abstainer | 157/500 | 1.0 | |
| Age | | | |
| ≤55 years | 17/71 | 0.58, 0.28–1.21 | |
| >55 years | 62/225 | 1.07, 0.73–1.57 | 0.11 |
| Menopausal status | | | |
| Premenopausal | 4/36 | 0.20, 0.06–0.71 | |
| Postmenopausal | 69/260 | 1.05, 0.72–1.53 | 0.007 |
| Relative weight (tertiles, kg/m$^2$) | | | |
| 1 (<23.6) | 24/120 | 0.92, 0.49–1.75 | |
| 2 (23.6–27.4) | 17/86 | 0.79, 0.40–1.56 | |
| 3 (≥27.5) | 34/61 | 1.27, 0.74–2.19 | 0.72 |
| Hormone replacement use | | | |
| Never | 30/180 | 0.70, 0.43–1.13 | |
| Former | 25/61 | 1.19, 0.62–2.28 | |
| Current | 24/54 | 1.56, 0.70–3.49 | 0.15 |
| Smoking status | | | |
| Never | 27/96 | 0.75, 0.45–1.26 | |
| Former | 38/105 | 1.52, 0.84–2.77 | |
| Current | 14/95 | 0.68, 0.30–1.57 | 0.14 |

[a] As appropriate, adjusted for age, smoking status, education, relative weight, hormone replacement therapy use, and parity.
[b] From continuous term, as appropriate, among abstainers and daily drinkers.

sumption was early in life or more recent. There was, however, a modest inverse association with increasing alcohol consumption in younger women.

Despite the consistent positive association observed between alcohol intake and many cancers, including breast cancer (18–20), only two of seven previous studies of endometrial cancer found a positive association with alcohol (8, 9). In those studies, a significant positive trend was observed with increasing consumption; LaVecchia *et al.* (8) reported a 4-fold increase in risk for women consuming four or more drinks per day compared with nondrinkers. In contrast, all other studies, including a large follow-up study (11), have found null or weakly inverse associations (10–15). Most consistent among this latter group is the inverse association among young or premenopausal women (12, 13). In the study of Webster *et al.* (12), a strong inverse relationship was observed among the very obese. The disparate results in prior research may be due to a number of factors, including differences in the ages, menopausal status, and hormone replacement status of study subjects, yielding subgroups at relatively greater (or lower) risk. Additionally, the beverages most commonly consumed varied in these studies. In our study, beer was the most frequently consumed beverage. Also, usual beverage type varied with age, with liquor consumption more common at older ages. Finally, and perhaps importantly, investigations have differed with respect to usual intake levels; for example, the highest level of alcohol consumption ranged from 28 drinks/week (Italy; Ref. 8) to only about 2 drinks/week (Iowa; Ref. 11). Finally, the size of the previous studies frequently limited the ability to exclude chance as an explanation for study findings.

Some limitations should be considered in interpreting our results. The study achieved high participation levels (87% of eligible cases and 85% of eligible controls), which suggests that selection bias, if any, would be limited. Because all information in this study was based on reports from women themselves, some bias in reporting may have occurred. However, the validity of reported recent alcohol consumption among nonalcoholic populations has, in general, been shown to be high (20). Evidence from studies of other cancer cases suggests that the accuracy of recalled alcohol consumption is similar for patients and for control subjects (23, 24), indicating that recall bias is unlikely to have had an important effect on the results of the present study. In our study population, the reliability of reported alcohol consumption appeared to be good, even for intake at 20–29 years of age. Other data in this population suggest that alcohol consumption in the distant past is reported with reasonable reliability (25). The likelihood of information bias was decreased further because our interviewers were blinded as to the case or control status for more than 80% of the participants. Finally, although confounding is always a concern, age-adjusted estimates were similar to the multivariate RRs, suggesting that confounding was unlikely to have introduced bias into this analysis.

Alcohol may increase endogenous estrogen levels in both premenopausal and postmenopausal women (2–5), possibly by delaying metabolism and prolonging half-life (25). However, not all studies have observed this association (26–28). In a recent randomized controlled cross-over study of postmenopausal women, neither plasma estrone nor estradiol was altered acutely by alcohol intake, except among current users of hormone replacement therapy (29), suggesting that the relationship may also depend on other characteristics of consumers. Although an association between alcohol and endogenous estrogens may plausibly support the consistently positive relation of alcohol and breast cancer incidence (30), it is not at all clear why the effect for endometrial cancer is null or inverse. Thus, the results of this study appear provocatively discordant with an alcohol-hormone link in women.

This large study provides additional evidence that, unlike breast cancer incidence, endometrial cancer risk is not positively associated with alcohol consumption. The lack of consistency in the effect of alcohol in the breast and endometrium is intriguing and deserves further study.

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