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Alcohol consumption and endometrial cancer risk: The Multiethnic Cohort

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Abstract

The role of alcohol intake in the etiology of endometrial cancer is unclear. We examined the impact of alcohol intake on endometrial cancer risk among 41,574 postmenopausal African-American, Japanese-American, Latina, Native-Hawaiian and White women recruited to the prospective Multiethnic Cohort Study in 1993–1996. During an average of 8.3 years of follow-up, 324 incident invasive endometrial cancer cases were identified among these women. Data on alcohol intake and endometrial cancer risk factors were obtained from the baseline questionnaire. Relative risks (RRs) and 95% confidence intervals (CIs) for endometrial cancer associated with alcohol intake were estimated using log-linear (Cox) proportional hazard models stratified by age, year of recruitment, ethnicity and study center, and adjusted for several confounding factors. Increased alcohol consumption was associated with increased risk (p trend = 0.013). Compared to non-drinkers, women consuming ≥2 drinks/day had a multivariate RR of 2.01 (95% CI: 1.30, 3.11). There was no increase in risk associated with <1 drink/day (RR = 1.01; 95% CI: 0.77, 1.33) and 1 to <2 drinks/day (RR = 1.09; 95% CI: 0.62, 1.93). There was no clear effect modification by body mass index, postmenopausal hormone use, parity, oral contraceptive use or smoking status, though our power to detect such interactions was limited. Our results suggest that only alcohol consumption equivalent to 2 or more drinks per day increases risk of endometrial cancer in postmenopausal women.

Keywords

endometrial cance; cohort studies; alcohol intake; risk factors

Endometrial cancer is the most common gynecological cancer in the United States[1] and Europe.[2] The role of unopposed estrogens in the etiology of endometrial cancer is well established.[3] Daily alcohol use has been associated with higher levels of circulating estrogens in postmenopausal women in several studies.[4-11] Alcohol consumption has also been found to further increase blood estrogen levels in postmenopausal women who are taking estrogen replacement therapy.[12,13] It is therefore plausible that women who consume alcoholic beverages are at increased risk of endometrial cancer.

Relatively few epidemiologic studies have examined the relationship between alcohol consumption and endometrial cancer. Data from 3 prospective cohort studies offered little support for an association[14-16] and results from case-control studies are conflicting [reviewed

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in Ref. 17]. Bandera *et al.*[17] offered several explanations for these inconsistent findings which include small sample size, limited range of alcohol intake, and insufficient control of confounding factors. Because of the sparse and conflicting results to date, it has not been possible to draw any firm conclusion about the role of alcohol in the etiology of endometrial cancer. It is clear that further data, especially from a prospective study, regarding this topic are needed. We report here our analysis of the relationship between alcohol and endometrial cancer risk in the Multiethnic Cohort Study (MEC) which has a wide-range of alcohol exposure and comprehensive data on endometrial cancer risk factors.

Material and methods

Study population

The MEC is a prospective study designed to examine the association of diet, life-style and genetic factors with incidence of cancer and other chronic diseases. The details of the study design and baseline characteristics have been published.[18] Briefly, the recruitment of the cohort began in 1993 and was completed in 1996. Potential participants were identified through driver's license files from the Departments of Motor Vehicles, voter registration lists and Health Care Financing Administration data files. The cohort consists of >215,000 men and women (aged 45 to 75 years at baseline) and comprises mainly 5 self-reported racial/ethnic populations: African Americans, Japanese Americans, Latinos, Native Hawaiians and Whites living in Hawaii and California (mainly Los Angeles County). Each participant completed a self-administered mail baseline questionnaire that included diet, demographic factors, anthropometric measures, other lifestyle factors, history of prior medical conditions, family history of cancer and for women, menstrual and reproductive history and exogenous hormone use. The institutional review boards at the University of Hawaii and at the University of Southern California approved the study protocol.

Exclusion criteria

Women were excluded from the present analysis if they (*i*) had cancer other than nonmelanoma skin cancer before the date the baseline questionnaire was completed ($n = 5,526$), (*ii*) missing menopausal status ($n = 4,645$), premenopausal ($n = 13,382$), reported a hysterectomy or a bilateral oophorectomy on the questionnaire ($n = 27,510$), or (*iii*) had missing data on any of the following variables: education, BMI, age at menarche, parity, oral contraceptive (OC) use, HT use, smoking status, or vigorous physical activity ($n = 6,918$). After all exclusions, 41,574 postmenopausal women (15.7% African Americans, 31.5% Japanese Americans, 21.5% Latinas, 6.7% Native Hawaiians, and 24.5% Whites) were included in the analyses. Excluded subjects were slightly younger than to those who remained in the analyses but were similar with respect to distribution of endometrial cancer risk factors.

Follow-up and case identification

Follow-up began when participants completed the baseline questionnaire and continued to the first of the following endpoints: (*i*) diagnosis of endometrial cancer, (*ii*) diagnosis of other cancer (but not nonmelanoma skin cancer), (*iii*) death, or (*iv*) end of follow-up (December 31, 2002). Incident endometrial cancer cases were identified by record linkage to the Hawaii Tumor Registry, the Cancer Surveillance Program for Los Angeles County and the California State Cancer Registry. All of these tumor registries participate in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program of cancer registration. Cases of endometrial cancer had International Classification of Diseases for Oncology (ICD-O-2) code C54 (uterine corpus). Uterine sarcomas ($n = 20$) were not included in the case group. Deaths within the cohort were determined by annual linkage to state death certificate files in California and Hawaii, and periodically to the national death index. Case ascertainment and death information were complete through December 31, 2002. On average, cohort participants were

followed for 8.3 years. A total of 324 incident cases of endometrial cancer were identified during the follow-up period among the at-risk cohort.

Assessment of alcohol intake

Consumption of alcoholic beverages during the year preceding the baseline questionnaire was assessed by consumption frequency questions. Alcoholic drinks were classified into regular beer, light beer, red wine, white/pink wine (including champagne and sake) and hard liquor. Nine intake categories ranged from "never" to "4 or more times per day" and information on usual serving size was also requested. Mean daily alcohol intake was calculated using our extensive food composition table.[18] The total intake of alcohol was expressed in grams/day, and it was calculated by multiplying the volume of a drink by the percentage of alcohol content. Total alcohol intake was categorized into 4 categories: nondrinkers (0 g/day), <1 drink/day (>0 to < 12 g/day), 1 to <2 drinks/day (12 to <24 g/day) and ≥2 drinks/day (≥24 g/day). Regular and light beer were combined into a single beer variable and red and white wine were combined into a single wine variable since separate analysis resulted in small numbers of subjects within each stratum.

Statistical analysis

Hazard rate ratios (RRs) and corresponding 95% confidence intervals (CIs) for endometrial cancer incidence associated with alcohol intake were estimated using log-linear proportional hazard (Cox proportional hazard) models adjusted for (stratified on) age at recruitment (in 1-year age groups), year of recruitment (single years), race/ethnicity and study center (Hawaii/Los Angeles). Fine stratification by year of recruitment ensures that any change in the characteristics of the subjects over time of recruitment is adjusted for. The underlying time variable in the analysis was time from the date of enrollment to the date of endometrial cancer diagnosis, date of other cancer diagnosis, death or censoring. The RRs were estimated with and without adjustment for the following potential confounders: smoking status (never, past, current), age at menarche (≥12, 13–14, ≥15), age of natural menopause (<45, 45–49, 50–54, ≥55), BMI (continuous), parity (nulliparous, 1, 2–3, ≥4 children), duration and type of HT use (never, and per 5 year of past estrogen only therapy (ET), past estrogen-progestin therapy (EPT), current ET, current EPT use), duration of OC use (never, ≥5 years, >5 years), education (years), diabetes (no/yes), hypertension (no/yes), family history of endometrial cancer (no/yes). We also investigated possible effect modification of the relationship between alcohol intake and endometrial cancer by BMI (<25, 25 to <30, ≥30), HT use (never, past, current ET, current EPT), parity (nulliparous, parous), smoking status (never, past, current) and OC use (never, ever). The likelihood ratio test was used to determine the significance of the interaction between alcohol intake and the above variables with respect to endometrial cancer. The test compared a main effect, no interaction model with a full model containing a main effect and an interaction term for the variables of interest. Interaction terms were created using categories as described above, but the BMI categories were treated as continuous. Trend tests were conducted by treating each category as a continuous term in the multivariate models. All *p* values are 2-sided. Statistical analyses were performed in SAS version 9.1 (SAS Institute, Cary, NC) and STATA version 8 (StataCorp, College Station, TX).

Results

Baseline characteristics among postmenopausal women according to category of alcohol intake are shown in Table I. Among the cohort, 62.3% women were nondrinkers. The majority of alcohol drinkers in this study were White women. Drinkers tend to be leaner and more likely to be nulliparous than nondrinkers. Drinkers also reported a higher prevalence of ever OC use and a much higher prevalence of current smoking than nondrinkers. The distribution of age at

menarche, age at menopause, HT use, diabetes, hypertension and family history of endometrial cancer were roughly similar across the categories of alcohol intake.

Table II shows the association between alcohol intake and endometrial cancer. Increased consumption was associated with increased risk (p trend = 0.013). Compared to nondrinkers, women consuming ≥2 drinks/day had a multivariate RR of 2.01 (95% CI: 1.30, 3.11). There was no increase in risk associated with <1 drink/day (multivariate RR = 1.01; 95% CI: 0.77, 1.33) and 1 to <2 drinks/day (multivariate RR = 1.09; 95% CI: 0.62, 1.93). We also explored the association between endometrial cancer and specific type of alcoholic beverage. We observed a significant increase in risk with increasing wine (p trend = 0.007) and hard liquor (p trend = 0.015) consumption. Compared with nondrinkers, wine drinkers who consumed ≥2 drinks/day had a RR of 3.15 (95% CI: 1.63, 6.09). For liquor drinkers relative to nondrinkers, the RR of endometrial cancer for women who consumed 1 to <2 drinks/day was 2.25 (95% CI: 1.06, 4.77) and for women who consumed <2 drinks/day was 1.96 (95% CI: 0.98, 3.90). There were very few women who consumed ≥2 beers/day; although not statistically significant, intake of alcohol from beer was also adversely associated with endometrial cancer.

We explored the potential modifying effect of other endometrial cancer risk factors on the association between alcohol and endometrial cancer (Table III). We considered BMI, smoking, HT use, OC use, and parity because they were either known to influence or may influence sex steroid hormone levels in postmenopausal women.[5,19-22] For ease of presentation and because there was no evidence of association with this moderate consumption, we collapsed the 2 middle categories (<1 drink/day and 1 to <2 drink/day). Risk associated with consuming ≥2 drinks/day was stronger among lean women (RR = 2.88; 95% CI: 1.57, 5.31) than among overweight (RR = 1.22; 95% CI: 0.43, 3.44) or obese (RR = 1.34; 95% CI: 0.43, 4.11) women. The risk associated with drinking ≥2 drinks/day was also stronger among nulliparous women (RR = 3.56; 95% CI: 1.20, 10.59) than among parous women (RR = 1.82; 95% CI: 1.11, 2.99). Although the positive associations between alcohol and endometrial cancer appeared stronger among lean women or nulliparous women, the tests for interaction for both factors were not significant (p = 0.09). There was no statistically significant interaction between alcohol intake and HT use (p = 0.13), OC use (p = 0.54), or smoking status (p = 0.42).

Discussion

In this large multiethnic prospective study, we found a significant increase in endometrial cancer risk among postmenopausal women who consumed ≥2 alcoholic drinks/day. The positive association was observed for all types of alcohol beverages suggesting that alcohol *per se* is responsible for the increase in risk.

A potential biological mechanism by which alcohol may increase endometrial cancer risk is related to alcohol's impact on estrogen levels. The unopposed estrogen hypothesis for endometrial carcinogenesis is well accepted[3]; prolonged exposure to estrogens leads to increased mitotic proliferation of endometrial cells, resulting in increased DNA replication errors and somatic mutations which can lead to a malignant phenotype. Several studies have shown that alcohol intake increases endogenous serum levels of estrogen in postmenopausal women.[4-11] In the EPIC (European Prospective Investigation into Cancer and Nutrition) study, the largest published study on alcohol intake and sex-steroid hormone concentrations, a significant elevation in blood estrone levels was observed only among postmenopausal women who consumed more than 25 g of ethanol/day (~2 or more drinks/day) compared to nondrinkers[11]; consumers of ~2 drinks/day had a 24% increase in estrone levels, consumers of ~1.5 drinks/day had a nonsignificant increase of 10% and lower levels of consumption had no increase. The increased estrogen levels in women consuming alcohol is thought to be due either to a decrease in the metabolic clearance of estrogens or to increased production.[23]

To our knowledge, only 3 other prospective studies have examined the association between alcohol consumption and endometrial cancer risk.[14-16] A limited range of alcohol intake may explain the absence of association in 2 of these studies.[14,15] In the 2 no-effect cohort studies,[14,15] the lower bound of the highest category of alcohol intake included women who consumed 4 or 7 g of ethanol/day. The third study, the Netherlands Cohort Study, had a wider range of intake, with the highest category of women being those who reported ≥30 g ethanol/day[16]; compared to nondrinkers, a nonstatistically significant increase in risk was observed in this category (RR = 1.78; 95% CI 0.88, 3.60), with no increase in risk evident in the lower categories of alcohol intake. We found endometrial cancer risk to be elevated only among women who drank at least 2 drinks per day which supports the EPIC results if alcohol exerts its effect on endometrial cancer by increasing estrogen levels.

We examined possible interactions between alcohol intake and several risk factors on endometrial cancer risk. Although the interaction was not statistically significant, the positive association of alcohol intake with endometrial cancer risk appeared stronger among lean women than among overweight or obese women. It has been suggested that there is an upper limit beyond which unopposed estrogens do not induce further increase in the mitotic rate of endometrial cells.[24] Lean postmenopausal women who have low circulating levels of endogenous estrogens may be more sensitive to modest elevations in estrogen levels resulting from alcohol drinking than are overweight or obese women among whom higher estrogen levels might mask alcohol as an independent risk factor. Earlier studies examining possible interaction with BMI did not offer conclusive results.[17] Although not statistically significant, the association between alcohol intake and endometrial cancer was stronger in nulliparous women than in parous women; if this is true we have no explanation of why this should be. However, it is possible that the effect of alcohol on endometrial cancer risk was more observable among nulliparous women just because there were more drinkers and wider range of intake among these women compared to parous women. Future studies are needed to confirm our findings.

A previous study has shown that in postmenopausal women, the acute effects of alcohol on estrogen levels is more pronounced among normal weight women who are on ET than among women who are not using ET.[25] Based on this finding, a stronger positive association between alcohol and endometrial cancer among current ET users than among nonusers is expected. We did not observe a significant interaction of alcohol with HT use, but the small number of cases in certain categories (*e.g.* current ET users who drank >2 drinks/day) limited the power of our test for interaction. Only a few studies have evaluated the possible interaction between ET and alcohol on endometrial cancer and the results were not conclusive.[17]

The strengths of our study include its prospective design, exclusion of prevalent cancer cases at baseline, and the ability to control for potential confounding factors. Limitations include potential misclassification of self-reported alcohol intake (which would tend to be nondifferential because of the prospective design of our study, biasing the RRs toward the null), and limited power in the interaction analysis.

In summary, our cohort study demonstrated that postmenopausal women who consume 2 or more alcoholic drinks per day have an increased risk of endometrial cancer. There was no clear evidence for interaction of alcohol with other endometrial cancer risk factors. Further studies with sufficient numbers of heavy drinkers and detailed information on known risk factors for endometrial cancer are needed to corroborate our finding.

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TABLE I

BASELINE CHARACTERISTICS[1] AMONG POSTMENOPAUSAL WOMEN IN THE MULTIETHNIC COHORT ACCORDING TO CATEGORY OF ALCOHOL INTAKE

Characteristics	Alcohol consumption/day			
	Nondrinkers (0 g/day)	<1 drink/day (>0 to <12 g/day)	1 to <2 drinks/day (12 to <24 g/day)	≥2 drinks/day (≥24 g/day)
No. of women	25,878	11,546	1,873	2,277
Age at cohort entry, mean	62.0	60.1	60.3	60.3
Ethnicity, %				
African American	15.9	15.9	13.7	15.1
Japanese American	39.8	20.7	12.5	8.7
Latina	22.2	23.7	13.3	9.7
Native Hawaiian	6.7	6.3	7.1	6.9
White		33.3	53.3	59.6
Body mass index (kg/m^2), %				
<25	49.4	57.5	64.9	66.6
25 to <30	30.4	29.4	24.6	24.3
≥30	20.2	13.1	10.5	9.1
Age at menarche, %				
≤12	47.2	47.1	47.8	43.5
13–14	39.6	39.8	38.6	43.0
15+	13.1	13.1	13.6	13.5
Age at menopause, %				
<45	16.3	15.1	16.4	15.8
45–49	31.9	31.4	29.7	33.8
50–54	41.1	42.6	40.8	40.0
≥55	10.7	10.9	13.1	10.4
Nulliparous, %	11.0	12.7	14.9	17.4
Hormone therapy use, %				
Never	56.9	50.2	49.9	51.2
Past	16.7	17.7	16.2	19.5
Current ET	3.9	4.4	5.2	4.6
Current EPT	22.6	27.7	28.7	24.6

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Characteristics	Alcohol consumption/day			
	Nondrinkers (0 g/day)	<1 drink/day (>0 to <12 g/day)	1 to <2 drinks/day (12 to <24 g/day)	≥2 drinks/day (≥24 g/day)
Ever OC use, %	34.3	41.2	41.3	42.0
Current smokers, %	11.8	15.2	23.7	30.6
Diabetes, %	13.5	5.6	5.5	5.2
Hypertension, %	39.9	33.0	30.7	37.6
Family history of endometrial cancer, %	1.4	1.3	1.3	2.0

[1] Standardized to the age and ethnicity distribution of postmenopausal women in the study.

TABLE II

HAZARD RATE RATIOS (RRs) FOR ENDOMETRIAL CANCER IN RELATION TO ALCOHOL INTAKE IN THE MULTIETHNIC COHORT

	Nondrinkers (0 g eth/day)	<1 drink/day (>0 to <12 g eth/day)	1 to <2 drinks/day (12 to <24 g eth/day)	≥2 drinks/day (≥ 24 g eth/day)	*p* trend
Total intake					
No. cases	196	85	14	29	
RR[1] (95% CI)	1.00 (referent)	0.91 (0.70, 1.19)	0.89 (0.51, 1.55)	1.59 (1.05, 2.42)	0.191
Multivariate RR[1] (95% CI)	1.00 (referent)	1.01 (0.77, 1.33)	1.09 (0.62, 1.93)	2.01 (1.30, 3.11)	0.013
Beer					
No. cases	196	42	5	4	
RR[1] (95% CI)	1.00 (referent)	0.89 (0.63, 1.27)	1.40 (0.57, 3.46)	1.06 (0.39, 2.89)	0.962
Multivariate RR[1] (95% CI)	1.00 (referent)	1.04 (0.73, 1.49)	1.68 (0.67, 4.21)	1.46 (0.52, 4.12)	0.327
Wine					
No. cases	196	81	9	11	
RR[1] (95% CI)	1.00 (referent)	0.99 (0.75, 1.30)	1.07 (0.53, 2.14)	2.47 (1.30, 4.67)	0.120
Multivariate RR[1] (95% CI)	1.00 (referent)	1.14 (0.85, 1.52)	1.37 (0.68, 2.78)	3.15 (1.63, 6.09)	0.007
Hard liquor					
No. cases	196	44	8	10	
RR[1] (95% CI)	1.00 (referent)	1.03 (0.73, 1.46)	1.69 (0.81, 3.53)	1.42 (0.73, 2.76)	0.191
Multivariate RR[1] (95% CI)	1.00 (referent)	1.18 (0.82, 1.69)	2.25 (1.06, 4.77)	1.96 (0.98, 3.90)	0.015

[1]RRs were stratified by age at recruitment, year of recruitment, race/ethnicity and study center. Multivariate RRs were further adjusted for education, body mass index, age at menarche, age at menopause, duration and type of hormone therapy use, duration of oral contraceptive use, parity, smoking history, diabetes, hypertension and vigorous physical activity.

TABLE III

HAZARD RATE RATIOS (RRs) FOR ENDOMETRIAL CANCER IN RELATION TO ALCOHOL INTAKE BY OTHER RISK FACTOR CATEGORIES IN THE MULTIETHNIC COHORT

		Total intake		
	Nondrinkers	**<2 drink/day**	**≥2 drinks/day**	***p* trend**
BMI < 25				
No. cases	67	43	20	
Multivariate RR[1] (95% CI)	1.00 (referent)	1.00 (0.64, 1.56)	2.88 (1.57, 5.31)	0.013
BMI 25 to <30				
No. cases	52	29	5	
Multivariate RR[1] (95% CI)	1.00 (referent)	1.12 (0.67, 1.86)	1.22 (0.43, 3.44)	0.617
BMI ≥ 30				
No. cases	77	27	4	
Multivariate RR[1] (95% CI)	1.00 (referent)	0.84 (0.52, 1.35)	1.34 (0.43, 4.11)	0.759
Never HT				
No. cases	106	41	8	
Multivariate RR[1] (95% CI)	1.00 (referent)	0.93 (0.63, 1.37)	1.41 (0.64, 3.12)	0.825
Past HT				
No. cases	35	21	7	
Multivariate RR[1] (95% CI)	1.00 (referent)	1.08 (0.57, 2.06)	2.96 (1.06, 8.28)	0.130
Current ET				
No. cases	11	7	3	
Multivariate RR[1] (95% CI)	1.00 (referent)	2.49 (0.45, 13.85)	20.01 (0.34, 11191.4)	0.152
Current EPT				
No. cases	44	30	11	
Multivariate RR[1] (95% CI)	1.00 (referent)	0.99 (0.57, 1.71)	1.86 (0.83, 4.15)	0.269
Never smokers				
No. cases	120	50	9	
Multivariate RR[1] (95% CI)	1.00 (referent)	1.13 (0.78, 1.62)	2.38 (1.13, 5.01)	0.091
Past smokers				
No. cases	63	41	14	
Multivariate RR[1] (95% CI)	1.00 (referent)	0.98 (0.62, 1.52)	1.95 (0.98, 3.88)	0.205

		Total intake		
	Nondrinkers	**<2 drink/day**	**≥2 drinks/day**	***p* trend**
Current smokers				
No. cases	13	8	6	
Multivariate RR[1] (95% CI)	1.00 (referent)	0.47 (0.14, 1.58)	1.54 (0.33, 7.26)	0.967
Nulliparous				
No. cases	21	24	7	
Multivariate RR[1] (95% CI)	1.00 (referent)	2.39 (1.16, 4.93)	3.56 (1.20, 10.59)	0.006
Parous				
No. cases	175	75	22	
Multivariate RR[1] (95% CI)	1.00 (referent)	0.91 (0.68, 1.22)	1.82 (1.11, 2.99)	0.275
OC never				
No. cases	142	69	17	
Multivariate RR[1] (95% CI)	1.00 (referent)	1.10 (0.80, 1.50)	1.93 (1.10, 3.39)	0.076
OC ever				
No. cases	54	30	12	
Multivariate RR[1] (95% CI)	1.00 (referent)	0.83 (0.50, 1.36)	1.62 (0.76, 3.48)	0.640

[1]RRs were stratified by age at recruitment, year of recruitment, race/ethnicity and study center and adjusted for education, body mass index, age at menarche, age at menopause, duration and type of hormone therapy use, duration of oral contraceptive use, parity, smoking history, diabetes, hypertension and vigorous physical activity when appropriate.