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Alcohol and endometrial cancer risk in the NIH-AARP Diet and Health Study

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Abstract

Previous investigations have provided conflicting results regarding whether alcohol consumption affects endometrial cancer risk, although in many of these studies the highest category of alcohol intake examined was limited. Further, most were unable to resolve how alcohol associations are affected by beverage type, the presence of other endometrial cancer risk factors, or tumor characteristics. To address these issues, we prospectively evaluated the association between alcohol intake and incident endometrial cancer (n = 1,491) in a cohort of 114,414 US women enrolled in the NIH-AARP Diet and Health Study. We calculated relative risks (RR) and 95% confidence intervals (CI) using Cox proportional hazards regression. After adjustment for age, body mass index, smoking, and other potential confounders, the multivariable RRs (and 95% CIs) compared with nondrinkers were 0.97 (0.87–1.09) for > 0-< 12 grams of alcohol/day, 1.06 (0.87–1.31) for 12- < 24 grams/day, and 0.93 (0.71–1.20) for ≥ 24 grams/day (*P* trend = 0.90). There was, however, some suggestion of higher risks associated with alcohol consumption among lean women (body mass index, BMI, <25) and users of menopausal hormone therapy, with significant interactions with both parameters (respective interaction P-values of 0.002 and 0.005). The relationship was also enhanced, albeit non-significantly so, for low grade cancers. Our results do not support that alcohol is a strong contributor to endometrial cancer risk, but slight risk increases may prevail among some users or for selected tumor characteristics.

Keywords

alcohol; endometrial cancer; prospective study

INTRODUCTION

Endometrial cancer, the most common gynecological cancer in the US,[1] is well recognized as being affected by hormonal risk factors[2] and sex steroid hormones.[3] Although alcohol consumption is known to be associated with increased levels of circulating sex steroid hormones,[4–7] its relationship to endometrial cancer risk remains unclear.

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The association between alcohol intake and endometrial cancer has been studied in seven cohort [8–14] and numerous case-control studies,[15–27] and the evidence has been summarized in two reviews[28, 29] and recently a meta-analysis.[30] Studies have largely reported null results, although most investigations have been limited by the highest category of alcohol intake. Among the seven prospective cohort studies, five reported no association,[8–10, 13, 14] of which three [8, 9, 13] examined only limited ranges of alcohol intake (highest category of alcohol intake ranged from: ≥ 4 grams/day to ≥ 10 grams/day). In a meta-analysis of the seven prospective studies, Friberg and colleagues reported on a possible J-shaped relationship between alcohol intake and endometrial cancer risk with increased risk for intakes higher than two or more alcoholic drinks per day (≥26 grams/day): compared with non-drinkers, the relative risk (RR) was 1.14 (95% confidence interval (CI): 0.95–1.36) for 2–2.5 drinks per day (approximately >26–32.5 grams/day) and 1.25 (95% CI: 0.98–1.58) for >2.5 drinks per day (>32.5 grams/day).[30] This finding is of interest given that this level of consumption is consistent with observations of significantly elevated blood hormone levels observed elsewhere.[6, 7]

The majority of epidemiologic studies have examined alcohol relationships by beverage type [8, 10, 12, 14, 16, 17, 19, 21, 24, 26, 31] and according to established endometrial cancer risk factors.[8, 10, 12, 21, 24–27, 31] However, the results of these analyses have been inconclusive. In addition, no prior study has examined whether alcohol associations differ according to tumor characteristics, including tumor grade or stage, which may explain some of the inconsistencies across studies. To further assess these relationships, we analyzed data from the large prospective NIH-AARP Diet and Health Study.

MATERIAL AND METHODS

Study Population

The NIH-AARP Diet and Health Study design and methodology have been described in detail elsewhere.[32] In brief, the NIH-AARP Diet and Health Study was established in 1995–1996 by inviting 3.5 million AARP (formerly known as the “American Association of Retired Persons”) members in six states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia and Detroit, Michigan) to complete a baseline questionnaire. A total of 617,119 self-administered questionnaires were mailed back, of which 566,402 were non-duplicate and satisfactorily completed.

We excluded study participants who used a proxy respondent (n = 15,760); were male (n = 325,174); reported a previous diagnosis of cancer other than non-melanoma skin cancer (n = 23,950), a history of hysterectomy (n = 82,107) or unknown hysterectomy status (n = 2,927), or menstrual periods that stopped due to surgery (n = 1,830) or radiation or chemotherapy (n = 117); developed non-epithelial endometrial cancer during follow-up (n=108); or died or moved out of the study area (n = 15). The resulting cohort consisted of 114,414 women. The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the U.S. National Cancer Institute.

Cohort Follow-Up

Cohort members were followed through the U.S. Postal Service national database of address changes and for updated vital status through the U.S. Social Security Administration Death Master File and the National Death Index Plus. Incident endometrial cancers were identified by probabilistic linkages with cancer registries in the original recruitment areas and two common states of relocation (Arizona and Texas). The completeness of case ascertainment in this cohort has been reported previously, with an estimated sensitivity of approximately

90% and specificity of 99.5% with respect to identification of cases by cancer registry linkage.[33] Follow-up time was defined as time from study baseline (between 1995 and 1996) until diagnosis of any cancer, date of death, the date moved out of registry ascertainment area, or last follow-up (December 31, 2006). From baseline through December 31, 2006, 1,650 study subjects developed incident endometrial cancer and 1,491 are included in the analysis after the exclusions described in the previous section. Stage and grade was available for 56% (N=831) and 93% (N=1,384) of endometrial cases included in this analysis, respectively.

Alcohol and Covariate Assessment

The baseline questionnaire elicited information about demographic factors, anthropometry, reproductive factors, medical history, and diet. The 124-item food-frequency questionnaire asked about a study participant's usual alcohol intake at home and in restaurants in the preceding year. This included 10 frequency categories ranging from never to ≥ 6 times per day and 3 portion sizes for beer (< 12 ounces, one to two 12 ounce cans, > two 12 ounce cans), wine or wine coolers (< 4 ounces, 4–8, > 8), and liquor or mixed drinks (< 1 shot, 1–2, > 2 shots). We converted intake frequency and portion sizes to grams/day by multiplying beverage-specific values of consumption by their respective grams of alcohol equivalents: 12 ounce beer, 12.96 grams; 5 ounce wine or wine coolers, 13.72 grams; and 1.5 ounce liquor, 13.93 grams.[34] We then summed these values to obtain total daily alcohol consumption. Total alcohol intake from alcoholic drinks was categorized into four categories: 0 grams/day, >0 to < 12 grams/day, 12 to < 24 grams/day and ≥ 24 grams/day, which approximately equates to nondrinkers, <1 drink/day, 1 to <2 drinks/day, ≥2 drinks/day, respectively.

Statistical Analysis

Cox proportional hazards regression was used to estimate relative risks (RR) and 95% confidence intervals (CI) with age as the time metric. We present the RR and 95% CI for a model adjusted for age and body mass index (BMI), two important endometrial cancer risk factors, and a multivariable model that included the following covariates: age, BMI, smoking status, race, parity, oral contraceptive (OC) use, menopausal hormone therapy (MHT) use, and age at menopause. Total alcoholic beverage consumption was examined in addition to alcohol intake by beverage type (beer, wine, liquor). For covariates with missing data, women were coded into a separate category. Tests for linear trends across the alcohol categories were calculated by using a variable containing the median value of alcohol intake (grams/day) within the defined alcohol categories.

We also assessed interactions with BMI, smoking status, MHT use, age at menopause, OC use, and parity by using cross-product terms in the model as well as calculating joint effect risk estimates. The likelihood ratio test was used to determine the significance of interactions between alcohol intake and these variables. Alcohol associations were also examined by clinical characteristics of the tumor, specifically stage and grade.

For all analyses, *P*-values of < 0.05 were considered statistically significant. All tests of statistical significance were two-tailed. Analyses were performed using SAS software release 9.1.3 (SAS Institute, Cary, NC).

RESULTS

Selected characteristics of analyzed cohort

A total of 114,414 women contributed 1,066,722.6 person-years, with average follow-up of 5.2 years for cases and 9.4 years for non-cases. The mean ± standard deviation ages for entry

were 62.3 ± 5.3 years for cases vs. 61.6 ± 5.5 for non-cases; for ages at exit comparable values were 67.4 ± 5.8 years for cases and 71.0 ± 5.9 for non-cases. Most women were White (90%) and postmenopausal (90%). Women who were overweight (BMI=25–29.9 kg/m^2) or obese (BMI≥30 kg/m^2) at baseline contributed 31% and 21% of the total person years, respectively.

Baseline characteristics of the women included in our analyses are shown in Table 1 according to categories of alcohol intake. The majority (57%) were light alcohol consumers (>0 -< 12 grams/day), while 9% were moderate alcohol consumers (12 - < 24 grams/day), and 6% heavy alcohol consumers (≥24 grams/day). Compared with the nondrinkers, alcohol consumers were slightly more likely to have education beyond the high school level, and to be ever smokers and OC or MHT users. They were also less likely to be obese. The distributions of race/ethnicity, age at menarche, age at menopause, and parity were similar across alcoholic beverage intake categories.

As previously described in this cohort, endometrial cancer was positively associated with BMI and later age at natural menopause, and inversely associated with duration of OC use, parity, cigarette smoking, later age at menarche, and non-White races.[35]

Associations using baseline alcohol intake

Overall, baseline alcohol consumption was not statistically significantly associated with endometrial cancer risk (Table 2). No linear trends were observed between alcohol consumption and endometrial cancer in age and BMI-adjusted analyses (*P* trend = 0.66) or in analyses further adjusted for additional confounders (*P* trend = 0.90). Three percent of the cohort reported consuming 24 - > 36 grams/day, while another three percent reported more excessive drinking (≥36 grams/day). There was no evidence of any alteration in endometrial cancer risk among either of these groups.

We also examined endometrial cancer risk in relation to intake of specific alcoholic beverages. Among those reporting alcohol consumption at baseline, 36%, 62%, and 49% of the cohort consumed beer, wine, and liquor, respectively. The mean (standard deviation) of any alcohol intake among beverage-specific nondrinkers were 3.2 grams/day (12.1 grams/day), 2.7 grams/day (16.8 grams/day), and 2.3 grams/day (10.6 grams/day) for beer, wine, and liquor nondrinkers, respectively. No clear associations were found between these beverages and endometrial cancer risk before or after adjustment for the other alcoholic beverage types (Table 2). Given the strong inverse associations between cigarette smoking and endometrial cancer in this and other studies, we also examined the association only among never smokers (n = 50,118 women), and results remained essentially the same.

Interactions with alcohol intake

Table 3 summarizes the joint associations on endometrial cancer risk of alcohol consumption and selected endometrial cancer risk factors. Alcohol relationships were not modified by smoking status, OC use, or parity. However, alcohol associations were significantly modified by BMI, MHT use, and age at menopause (BMI *P* interaction = 0.002; MHT use *P* interaction = 0.005; age at menopause *P* interaction = 0.004). There was some suggestion that alcohol consumption was positively associated with risk among lean women, MHT users, and women with menopause onset at 55 years old or greater, although trends were not statistically significant. In contrast, significant inverse trends were observed among heavier women (p trend=0.04). In addition, the interaction between alcohol intake and age at menopause was no longer statistically significant among nonsmokers (*P* interaction = 0.120). We also examined a cross-tabulation of BMI and MHT use (data not shown). We found that alcohol intake was most clearly associated with increased

endometrial cancer risk among MHT users in lean women: compared with nondrinkers, increased risk was observed for >0–12grams/day (RR=1.33; 95% CI: 0.95 – 1.87), 12->24 grams/day (RR=1.60; 95% CI: 1.05–2.45), and ≥24 grams/day (RR=1.28; 95% CI: 0.73 – 2.23).

Tumor characteristics

Alcohol relationships did not appear to vary by stage at diagnosis (Table 4), but there was some indication of a slight increase in risk for lower grade tumors (*P* trend = 0.09) and a reverse trend for higher grade (III-IV) tumors (*P* trend = 0.04). This latter relationship was based on small numbers of endometrial cancer cases. Given the small numbers, we did not attempt to examine relationships among nonsmokers.

Sensitivity analyses

We performed several sensitivity analyses for the association between alcohol intake and endometrial cancer. We also adjusted individually for calendar time, calories, red meat, dietary fiber, coffee, and several endometrial cancer risk factors, including education, age at menarche, self-reported diabetes, self-rated health quality, and physical activity; results were essentially the same and are not shown here. In addition, given the positive correlation between alcohol intake and smoking (heavy drinkers are often heavy smokers), we adjusted for smoking dose and smoking status (never; former ≤ 20 cigs/day; former >20 cigs/day; current ≤ 20 cigs/day; current > 20 cigs/day; unknown), and results remained essentially the same. The results were also similar when we restricted the analysis to postmenopausal women.

The overall null association was similarly observed regardless of whether the reference was those who were nondrinkers, those who consumed the lowest category of alcohol (> 0-< 12 grams/day), or those who consumed less than the median of the lowest category of alcohol (<1 g/day). We also examined the risk associations with beverage-specific alcohol intake and exclusive beverage-specific alcohol intake compared with nondrinkers of any alcohol, and observed no statistically significant associations. In addition, we also excluded cases (N=278) identified in the first two years of follow-up to account for any preclinical symptoms that may have led women to stop drinking, and found similar associations as presented in Table 2.

DISCUSSION

The NIH-AARP Diet and Health Study provided a unique opportunity to prospectively examine the association of alcohol with endometrial cancer risk in a large cohort of women. Endometrial cancer risk was unaffected by amounts or types of alcoholic beverages consumed.

Five prospective studies[8–10, 13, 14] and 10 case-control studies[15, 17, 19, 20, 22–24, 26, 27, 31] also observed overall null associations, while a few others reported a positive or negative association between alcohol and endometrial cancer risk.[12, 16, 21, 25] We were particularly interested in examining the association with higher amounts of consumption (notably ≥ 24 grams/day), but found no evidence of increased risk even among these heaviest consumers. Similar to our null results, no association was observed in the Million Women Study [14] and in the National Breast Screening Study[11] with highest alcohol consumers, ≥ 15 drinks/week (i.e. ≥ 21 grams/day) and ≥30 grams/day respectively. Our results contrast with those of Setiawan and colleagues who had a comparable number of cases in the highest category of alcohol intake (≥ 24 grams/day) similarly based on intake during the year preceding the baseline questionnaire, but found a statistically significant two-fold increased risk.[12]

Another smaller cohort study similarly found an increased risk (RR=1.78) only among the highest alcohol consumers (>30 grams/day), but this was not statistically significant.[10]

We found some suggestion of higher risks associated with alcohol consumption among lean women, MHT users, and those with older ages at menopause with significant interactions with each parameter. Given the positive association between alcohol intake and smoking (heavy drinkers are often heavy smokers), we examined relationships among never smokers only. While interactions with obesity and MHT use remained statistically significant, the interaction for age at menopause was no longer significant (*P* interaction=0.120). The one cohort study that examined age at menopause reported observing no interaction with alcohol intake (*P* interaction = 0.39).[10] Similar to our data which suggest an increased endometrial cancer risk associated with alcohol intake among lean women, a previous study reported a stronger positive association in lean women (BMI<25 kg/m^2),[12] however others have found an inverse association[16] or stronger positive association[21] in heavier women. Earlier studies examining possible interactions between alcohol intake and MHT have not been consistent in their observations,[28] but our results align with reports that alcohol consumption is more strongly related to increased estradiol levels among MHT users than non-users.[36, 37] We also examined the joint association between BMI and MHT in its alcohol-endometrial cancer association, and our data suggest that moderate alcohol intake among lean women using MHT had the strongest increased risk. A limitation of the baseline questionnaire is that MHT formulation was not captured. While formulation was captured on the follow-up questionnaire, case numbers were too small to examine formula-specific interactions. Since estrogens alone are associated with much higher RRs than estrogen plus progestin formulations, future work needs to address the relationship between alcohol intake and MHT formulations.

The mechanisms by which alcohol, obesity, and estrogen influence endometrial cancer risk are not well understood. Adipose tissue is a significant site of endogenous estrogen production particularly among postmenopausal women,[38] a mechanism hypothesized to underlie the high risks of endometrial cancer observed among obese women. Alcohol consumption has been related to elevated circulating estrogen levels,[4–7] but an increased risk associated with alcohol may be undetectable among heavier women because of their generally higher estrogen levels. This notion was supported by a previous analysis that showed that most endometrial cancers among MHT users occurred in lean and moderately overweight women (BMI <30 kg/m^2) and most endometrial cancers among nonusers occurred in obese women (BMI≥30 kg/m^2).[35] We did not see this compensative effect of higher endogenous levels among MHT users. On the other hand, the modest levels of estrogen in MHT users may be more sensitive to the synergistic effect of increased estrogen associated with MHT and alcohol intake. However, we cannot rule out the possibility that we observed the effect modifications by BMI and MHT use by chance alone. Further studies are required to establish a relationship between alcohol intake and blood estradiol levels in women who are lean and type and use of MHT.

We also attempted to assess whether the alcohol-endometrial cancer association differed by endometrial cancer tumor characteristics and observed a slight increase in risk for lower grade tumors. Our finding, however, needs to be cautiously interpreted given that it was based on small numbers and no other published studies have reported this finding. We were not able to classify cases according to histologic type of tumor because of incomplete information among those selected for this alcohol analysis.

The major strengths of our study include the large, prospective evaluation of alcohol consumption on incident risk of endometrial cancer. In addition, the detailed NIH-AARP study questionnaire allowed for examination of the association between a wider range of

total and beverage-specific alcohol intakes with endometrial cancer risk and provided information on potential confounders and effect modifiers, which allowed for a thorough assessment of the independence of alcohol from other related factors and the joint effects between alcohol and these lifestyle factors, and tumor characteristics. However, the questionnaire asked about average drinking intake in the year prior to questionnaire completion date and included both drinking and non-drinking days, which did not allow for investigation of patterns of drinking (regular/irregular, binge/not binge)[39], duration of drinking, or of changes in lifetime drinking pattern. In addition, we could not separately assess cancer risk for nondrinkers and former drinkers. If nondrinkers are former drinkers who stopped drinking due to their illness,[40] our estimates might be biased towards the null.

In conclusion, our results do not support alcohol as a strong contributor to endometrial cancer risk, even with moderate or greater alcohol intake, except possibly an increased risk among women who are lean and are MHT users, or for low grade cancers. Future studies examining the association between alcohol and endometrial cancer should be conducted in large studies with lifetime alcohol consumption history to assess associations by beverage type, potential effect modifiers, and clinical characteristics of the tumors.

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Table 1

Select baseline characteristics by categories of alcohol intake among 114,414 women in NIH-AARP Diet and Health Study, 1995–2006

	Alcohol (grams/day)[a]							
	0 gram/day (N=31,773)		>0–<12 g/day (N=65,512)		12–>24 g/day (N=10,407)		≥24 g/day (N=6,722)	
	N	%	N	%	N	%	N	%
Median Alcohol (grams/day)	NA		1.31		15.79		39.43	
Race/ethnicity								
White	27,178	86%	60,097	92%	9,907	95%	6,338	94%
Non-White	4,595	14%	5,415	8%	500	5%	384	6%
Age (years)								
< 55	4,189	13%	11,387	17%	1,513	15%	1,122	17%
55–59	6,885	22%	16,031	24%	2,251	22%	1,570	23%
60–64	8,820	28%	17,427	27%	2,898	28%	1,904	28%
65–69	10,662	34%	18,575	28%	3,406	33%	1,951	29%
≥70	1,217	4%	2,092	3%	339	3%	175	3%
Education								
< High school	12,322	40%	18,180	28%	2,252	22%	1,598	24%
≥High school	18,317	60%	45,623	72%	7,956	78%	4,965	76%
Age at menarche (years)								
< 13	15,165	48%	31,281	48%	4,723	46%	2,998	45%
13–14	13,142	42%	28,014	43%	4,668	45%	3,058	46%
≥15	3,298	10%	6,038	9%	982	9%	648	10%
Age at menopause (years)								
Premenopausal	1,573	5%	4,564	7%	662	7%	450	7%
< 45	4,009	13%	6,492	10%	995	10%	730	11%
45–49	8,389	27%	16,170	26%	2,626	26%	1,797	28%
50–54	13,545	44%	29,277	46%	4,688	47%	2,830	44%
≥ 55	3,129	10%	6,619	10%	996	10%	593	9%
Body mass index (kg/m^2)								
< 25	11,903	39%	29,684	47%	6,191	61%	3,795	58%
25–<30	9,511	31%	20,502	32%	2,920	29%	1,927	29%

	Alcohol (grams/day)[α]							
	0 gram/day (N=31,773)		>0–<12 g/day (N=65,512)		12–>24 g/day (N=10,407)		≥24 g/day (N=6,722)	
	N	%	N	%	N	%	N	%
≥ 30	8,950	29%	13,583	21%	1,034	10%	833	13%
Smoking status								
Never smoker	17,017	55%	28,508	45%	3,156	31%	1,437	22%
Former smoker	10,010	32%	26,110	41%	5,032	50%	3,154	48%
Current smoker	3,799	12%	9,015	14%	1,905	19%	1,935	30%
Menopausal hormone therapy								
Never user	21,478	68%	37,884	58%	5,552	53%	3,828	57%
Ever user	10,295	32%	27,628	42%	4,855	47%	2,894	43%
Oral contraceptive								
Never user	20,960	67%	37,322	57%	5,628	54%	3,452	52%
Ever user	10,517	33%	27,779	43%	4,735	46%	3,215	48%
Parity (births)								
Nulliparous	5,447	17%	11,089	17%	2,011	19%	1,512	23%
1	3,579	11%	7,023	11%	1,057	10%	753	11%
2	7,750	25%	17,721	27%	2,816	27%	1,719	26%
≥ 3	14,830	47%	29,424	45%	4,504	43%	2,715	41%
Self-reported (yes):								
Heart disease	3,246	10%	4,067	6%	545	5%	361	5%
Diabetes	4,269	13%	3,044	5%	189	2%	149	2%

*Numbers may not add up to total because of missing values. Missing values were excluded from percentage calculations.

[α]Alcohol consumption the year preceding the baseline questionnaire. Grams/day approximately equates to the following number of drinks/day: 0g/day, nondrinkers; >0-<12g/day, ~<1 drink/day; >12-<24g/day, ~1-<2 drink/day; ≥24g/day, ~≥2 drink/day.

Table 2

Adjusted RR and 95% CI for endometrial cancer in relation to baseline alcohol intake in the NIH-AARP Diet and Health Study, 1995–2006

	Alcohol (grams/day)				
	0 g/day (N=31,773)	**>0 – <12 g/day (N=65,512)**	**12 – >24 g/day (N=10,407)**	**≥24 g/day(N=6,722)**	***P*-trend[α]**
Total Alcohol Intake, All Cases					
No. cases	461	841	122	67	
Person years	293,099	615,668	96,590	61,365	
RR, age and BMI adjusted (95% CI)[β]	1(ref)	0.98 (0.88–1.10)	1.07 (0.87–1.31)	0.90 (0.69–1.16)	0.66
RR, multivariate adjusted (95% CI)[γ]	1(ref)	0.97 (0.87–1.09)	1.06 (0.87–1.31)	0.93 (0.71–1.20)	0.90
Alcoholic Beverage, All Cases[δ]					
Beer					
No. cases	977	499	7	8	
Person years	679,004	371,498	8,593	7,627	
RR, age and BMI adjusted (95% CI)[β]	1(ref)	1.05 (0.93–1.18)	0.69 (0.33–1.46)	0.88 (0.44–1.76)	0.47
RR, multivariate adjusted (95% CI)[γ]	1(ref)	1.06 (0.94–1.20)	0.77 (0.37–1.63)	0.99 (0.49–1.99)	0.77
Wine					
No. cases	608	794	68	21	
Person years	396,971	601,101	49,179	19,472	
RR, age and BMI adjusted (95% CI)[β]	1(ref)	1.00 (0.88–1.13)	1.25 (0.96–1.62)	0.99 (0.63–1.53)	0.38
RR, multivariate adjusted (95% CI)[γ]	1(ref)	0.95 (0.84–1.07)	1.17 (0.90–1.53)	0.95 (0.61–1.48)	0.48
Liquor					
No. cases	805	616	47	23	
Person years	546,478	458,952	38,060	23,233	
RR, age and BMI adjusted (95% CI)[β]	1(ref)	0.96 (0.85–1.08)	0.95 (0.70–1.28)	0.73 (0.48–1.11)	0.18
RR, multivariate adjusted (95% CI)[γ]	1(ref)	0.98 (0.87–1.11)	0.99 (0.73–1.35)	0.77 (0.51–1.18)	0.30

[α] For linear trend test used a variable containing the median values of alcohol intake (grams/day) within defined alcohol categories.

[β] Adjusted for age (continuous) and body mass index (<25kg/m^2, 25–29, ≥30, missing)

[γ] Adjusted for age (continuous), body mass index (<25kg/m^2, 25–29, ≥30), smoking status (never, former, current), race/ethnicity (White, non-White), parity (nulliparous, 1,2, ≥3), oral contraceptive use (never, ever), oral menopausal hormone use (never, ever), and age at menopause (premenopausal, 45, 45–49, 50–54, ≥55). Unknown set as a separate category within each factor.

$^{\delta}$Additionally adjusted for categories of other alcoholic beverages

Table 3

Adjusted RR and 95% CI for endometrial cancer in relation to baseline alcohol intake by endometrial cancer risk factors in the NIH-AARP Diet and Health Study, 1995–2006

	Alcohol (grams/day)													
	0 g/day		>0 – <12 g/day			12 – >24 g/day			≥24 g/day					
	Case	RR	Case	RR	LB - UB	Case	RR	LB - UB	Case	RR	LB - UB	P trend[α]	*P* int[β]	*P* int[γ]
Body Mass Index														
< 25 kg/m^2	82	1(ref)	233	1.07	(0.83 – 1.38)	65	1.40	(1.00 – 1.94)	27	1.09	(0.70 – 1.70)	0.35	0.002	0.031
≥> 25 kg/m^2	364	1(ref)	589	0.90	(0.79 – 1.03)	55	0.74	(0.56 – 0.99)	37	0.73	(0.52 – 1.02)	0.04		
Smoking status														
Never	288	1(ref)	412	0.93	(0.80 – 1.09)	44	1.03	(0.75 – 1.42)	11	0.54	(0.30 – 0.99)	0.13	0.291	NA
Former	137	1(ref)	339	1.02	(0.83 – 1.25)	64	1.15	(0.85 – 1.56)	37	1.00	(0.70 – 1.46)	0.76		
Current	28	1(ref)	67	1.00	(0.64 – 1.56)	12	0.95	(0.48 – 1.88)	17	1.42	(0.77 – 2.62)	0.23		
Menopausal hormone therapy														
Never user	337	1(ref)	480	0.89	(0.77 – 1.02)	52	0.89	(0.66 – 1.20)	40	1.00	(0.72 – 1.39)	0.84	0.005	0.034
Ever user	124	1(ref)	361	1.18	(0.96 – 1.45)	70	1.33	(0.98 –1.79)	27	0.91	(0.59 – 1.38)	0.65		
Age at menopause (among postmenopausal women only)														
< 50 years	151	1(ref)	215	0.85	(0.69 – 1.05)	37	1.12	(0.77 – 1.62)	20	0.92	(0.57 – 1.47)	0.68	0.004	0.120
50–54 years	208	1(ref)	392	0.97	(0.82–1.15)	50	0.92	(0.67 – 1.26)	27	0.84	(0.56 – 1.26)	0.37		
≥ 55 years	62	1(ref)	134	1.20	(0.88 –1.63)	14	1.06	(0.59 – 1.93)	12	1.43	(0.77 – 2.69)	0.49		
Oral contraceptive														
Never user	348	1(ref)	571	0.98	(0.85– 1.12)	74	1.02	(0.79 – 1.32)	46	1.03	(0.75 – 1.40)	0.74	0.587	0.478
Ever user	113	1(ref)	270	0.96	(0.77 – 1.20)	48	1.12	(0.79 – 1.58)	21	0.75	(0.47 – 1.20)	0.46		
Parity (births)														
Nulliparous	105	1(ref)	188	0.95	(0.75 – 1.21)	24	0.80	(0.51 – 1.26)	24	1.13	(0.72 – 1.78)	0.72	0.560	0.780
1–2	158	1(ref)	313	1.00	(0.83 – 1.22)	46	1.12	(0.80 – 1.56)	21	0.84	(0.53 – 1.33)	0.67		
≥ 3	197	1(ref)	334	0.94	(0.79 – 1.13)	52	1.19	(0.87 – 1.62)	21	0.81	(0.51 – 1.27)	0.84		

[α] For linear trend test used a variable containing the median values of alcohol intake (g/day) within defined alcohol categories. Adjusted for age (continuous), body mass index (<25kg/m^2, 25–29, ≥30), smoking status (never, former, current), race/ethnicity (White, non-White), parity (nulliparous, 1,2,≥3), oral contraceptive use (never, ever), oral menopausal hormone use (never, ever), and age at menopause (premenopausal, <45, 45–49, 50–54,≥55). Unknown set as a separate category within each factor.

[β] Interaction was tested on the multiplicative scale by entering product terms in the multivariable Cox proportional hazard models and comparing the model without the interaction term using the likelihood ratio test.

$\gamma_{\text{Interaction tested only among non-smokers}}$

Table 4

Adjusted RR and 95% CI for endometrial cancer by stage and grade for categories of baseline alcohol intake in the NIH-AARP Diet and Health Study, 1995–2006

	Alcohol (grams/day)				
	0 g/day	**>0 – <12 g/day**	**12 – >24 g/day**	**≥ 24 g/day**	***P*-trend[α]**
Total Alcohol Intake, by Stage[β]					
In situ/Localized					
No. cases	211	373	51	30	
Person years	271,547	570,830	88,724	55,626	
RR, age and BMI adjusted (95% CI)[γ]	1(ref)	0.96 (0.81–1.14)	0.99 (0.73–1.35)	0.91 (0.62–1.33)	0.73
RR, multivariate adjusted (95% CI)[δ]	1(ref)	0.94 (0.79–1.11)	0.97 (0.71–1.32)	0.91 (0.62–1.35)	0.79
Regional/Distant Metastasis					
No. cases	45	96	19	4	
Person years	270,830	569,521	88,601	55,489	
RR, age and BMI adjusted (95% CI)[γ]	1(ref)	1.16 (0.81–1.65)	1.70 (0.99–2.93)	0.56 (0.20–1.57)	0.64
RR, multivariate adjusted (95% CI)[δ]	1(ref)	1.20 (0.84–1.73)	1.83 (1.05–3.18)	0.61 (0.22–1.72)	0.77
Total Alcohol Intake, by Grade[ε]					
Grade I					
No. cases	192	360	60	38	
Person years	271,550	570,683	88,781	55,641	
RR, age and BMI adjusted (95% CI)[γ]	1(ref)	1.00 (0.84–1.20)	1.26 (0.94–1.69)	1.23 (0.87–1.75)	0.09
RR, multivariate adjusted (95% CI)[δ]	1(ref)	0.96 (0.80–1.15)	1.20 (0.89–1.62)	1.21 (0.85–1.73)	0.09
Grade II					
No. cases	144	276	37	21	
Person years	271,286	570,439	88,637	55,585	
RR, age and BMI adjusted (95% CI)[γ]	1(ref)	1.05 (0.86–1.29)	1.08 (0.75–1.56)	0.95 (0.60–1.51)	0.84
RR, multivariate adjusted (95% CI)[δ]	1(ref)	1.04 (0.84–1.27)	1.07 (0.74–1.55)	0.98 (0.62–1.56)	0.95
Grade III-IV					
No. cases	86	145	16	6	

	Alcohol (grams/day)				
	0 g/day	**>0 – <12 g/day**	**12 – >24 g/day**	**≥ 24 g/day**	***P*-trend[α]**
Person years	271,062	569,769	88,587	55,509	
RR, age and BMI adjusted (95% CI)[γ]	1(ref)	0.90 (0.69–1.18)	0.72 (0.42–1.24)	0.43 (0.19–0.98)	0.03
RR, multivariate adjusted (95% CI)[δ]	1(ref)	0.92 (0.70–1.21)	0.74 (0.43–1.28)	0.44 (0.19–1.01)	0.04

[α] For linear trend test used a variable containing the median values of alcohol intake (g/day) within defined alcohol categories.

[β] SEER Summary Staging Manual 2000: in situ/localized, regional/distant metastasis

[γ] Adjusted for age (continuous) and body mass index (<25kg/m^2, 25–29, ≥30, missing)

[δ] Adjusted for age (continuous), body mass index (<25kg/m^2, 25–29, ≥30), smoking status (never, former, current), race/ethnicity (White, non-White), parity (nulliparous, 1,2,≥3), oral contraceptive use (never, ever), oral menopausal hormone use (never, ever), and age at menopause (premenopausal, <45, 45–49, 50–54,≥55). Unknown set as a separate category within each factor.

[ε] Grade I (well differentiated), II (moderately differentiated, III (poorly differentiated), IV (undifferentiated/anaplastic)