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Long-term alcohol intake and risk of endometrial cancer in the Nurses' Health Study, 1980–2010

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Background: Previous epidemiologic studies have shown inconsistent results for the association between alcohol intake and endometrial cancer risk. Most of the studies, however, assessed alcohol intake after cancer diagnosis, or measured alcohol intake at baseline only.

Methods: We prospectively examined the association between alcohol intake and endometrial cancer risk in the Nurses' Health Study with 68 067 female participants aged 34–59 years in 1980. Alcohol intake was measured several times with validated dietary questionnaires. We calculated cumulative average alcohol intake to represent long-term intakes of individual subjects. Using Cox proportional hazards models, we estimated incidence rate ratios (RRs) and 95% confidence intervals (CIs) for endometrial cancer risk after controlling for several risk factors simultaneously.

Results: We identified a total of 794 invasive endometrial adenocarcinoma from 1980 to 2010. We found an inverse association among alcohol drinkers (multivariable RR = 0.81; 95% CI: 0.68–0.96) compared with nondrinkers. Women with light alcohol intake of <5 g per day ($\sim$half drink per day) had a 22% lower risk of endometrial cancer (multivariable RR = 0.78; 95% CI: 0.66–0.94). Higher intake of alcohol, however, did not provide additional benefits against endometrial cancer: multivariable RRs for 5–14.9 g ($\sim$1 drink), 15–29.9 g ($\sim$2 drinks), or $\geqslant$30 g ($\geqslant$2 drinks) versus 0 g per day were 0.88, 0.83, and 0.78 (95% CI: 0.49–1.25), respectively. The lower risk among drinkers ($\sim$half drink per day) appeared to be stronger for obese women, but no significant interaction by body mass index was found.

Conclusions: This study provides prospective evidence for an inverse association between light alcohol intake ($\sim$half drink per day) in the long term and endometrial cancer risk, but above that level no significant association was found.

Endometrial cancer is the most common gynaecological cancer in the United States (De Vivo *et al*, 2008), and the major risk factors are related to an increased exposure of the endometrium to unopposed oestrogens, along with insulin resistance and hyperinsulinaemia (Kaaks *et al*, 2002). Lifestyle factors including dietary behaviours that may influence those hormonal factors in the long term may enhance or decrease endometrial cancer risk (Je *et al*, 2011; Ganmaa *et al*, 2012; Ollberding *et al*, 2012; Campagnoli *et al*, 2013; Dieli-Conwright *et al*, 2013; Inoue-Choi *et al*, 2013; Nagle *et al*, 2013). The recent prospective cohort studies and meta-analysis of coffee consumption and endometrial cancer risk showed that long-term high coffee consumption reduced the risk of endometrial cancer substantially, possibly through the hormonal modulation of coffee consumption (Je *et al*, 2011; Je and Giovannucci, 2012).

Alcohol intake has been associated with higher levels of oestrogens (Gavaler and Van Thiel, 1992; Hankinson *et al*, 1995; Madigan *et al*, 1998; Onland-Moret *et al*, 2005; Rinaldi *et al*, 2006;

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Danforth *et al*, 2009) and could therefore be expected to increase the risk of endometrial cancer. However, alcohol intake has been shown to improve insulin sensitivity and reduce fasting insulin concentrations as well (Davies *et al*, 2002). Several epidemiologic studies examined the association between alcohol intake and endometrial cancer risk, showing no association or inverse associations among women who consumed moderate alcohol intake, whereas high alcohol intake showed an increased risk (Friberg *et al*, 2010; Turati *et al*, 2010; Sun *et al*, 2011). Most of the epidemiologic studies were of retrospective design, which measured the past alcohol intake after diagnosis. A few prospective studies have been published, and most of the studies measured alcohol intake at baseline only, which may not represent long-term intakes of individual subjects. As alcohol may affect carcinogenesis over an extended period of time, the cumulative average alcohol intake might provide a better estimate of the long-term effects of alcohol intake.

Our large prospective cohort study, the Nurses' Health Study (NHS), has repeatedly measured intakes of alcoholic beverages, beer, wine, or liquor from validated food frequency questionnaires (FFQs) from 1980, and long-term alcohol intake in grams per day could therefore have been estimated among individuals. To further clarify the role of alcohol among different subgroups, we conducted stratified analyses by several important endometrial cancer risk factors.

MATERIALS AND METHODS

Study population. The NHS cohort was established in 1976, when 121 700 female registered nurses from 11 states in the United States of America aged 30–55 years completed a baseline questionnaire that included items on risk factors for cancer and cardiovascular disease and major medical events. Every 2 years, follow-up questionnaires have been mailed to update information; the follow-up rate has been at least 90% for each follow-up cycle. Dietary information, which was first asked in 1980 using a validated semiquantitative FFQ, was updated every 2–4 years. We excluded from our analysis women who did not complete the 1980 FFQ (more than 10 blank items or implausibly high or low energy intake <500 or >3500 kcal per day), died or reported any type of cancer (except for non-melanoma skin cancer) before 1980 and had a history of hysterectomy. Women with missing body mass index (BMI, $kg\,m^{-2}$) in 1978 or 1980 were also excluded at baseline since obesity is an important risk factor for endometrial cancer (but could re-enter the analysis once information on BMI was available). After these exclusions, 68 067 women formed our baseline population. During each follow-up cycle, we censored women who died, were diagnosed with any cancer including endometrial cancer, or had their uterus removed in the previous cycle. For the expanded FFQ assessment after 1980, women with more than 70 blank food items and total caloric intakes <600 or >3500 kcal per day were also excluded.

Ascertainment of endometrial cancer cases. From 1978 forward, women were asked to report on their questionnaires any new diagnosis of endometrial cancer. For woman who reported a diagnosis of cancer, we sought permission to obtain the relevant medical records and pathology report, which provided information on tumour stage, histologic type and grade. Study physicians blinded to all questionnaire data reviewed the documents to verify diagnosis and establish an exact date of diagnosis. Case definition for endometrial cancer was invasive type I epithelial adenocarcinoma (stages IA–IV) diagnosed between 1980 and 2010 ($n=794$). Noninvasive ($n=355$), nonepithelial ($n=69$), or a type of epithelial cancer other than adenocarcinoma ($n=69$; i.e., clear-cell, squamous cell, etc.) were not included in the analysis. Stage and grade of tumours included in the analysis was available for 96.6% ($n=767$) and 97.6% ($n=775$), respectively. Deaths in the cohort were identified by reports from family members and the US Postal Service and a search of the National Death Index; at least 98% of deaths were ascertained (Stampfer *et al*, 1984).

Assessment of alcohol and dietary intake. Previous studies have shown that our FFQs have reasonable validity and reproducibility for individual foods (Willett *et al*, 1985; Salvini *et al*, 1989). We used information obtained from responses on the eight FFQs assessed in 1980, 1984, 1986, 1990, 1994, 1998, 2002, and 2006. There were nine possible responses for each alcohol intake question, ranging from 'almost never' to '6+ servings per day'. Consumption of beer, wine, and liquor was ascertained in separate items. Each participant was asked how often, on average, she consumed each type of alcoholic beverage over the previous year, using standardised portion of each beverage (a 12-oz bottle or a can of beer, a 4-oz glass of wine, or a 1.5-oz serving of liquor). Alcohol intake (in g per day) was calculated as the sum of the daily number of drinks multiplied by the average alcohol content per type of each alcoholic beverage (beer 12.8 g, light beer 11.3 g, wine 11.0 g, liquor 14.0 g), using information obtained from US Department of Agriculture food-composition sources. Alcohol intake as measured by FFQ was highly correlated with intake, as calculated from diet record assessment completed by a sample of study participants (Spearman's $r=0.90$) (Giovannucci *et al*, 1991). As a covariate, we calculated glycaemic load (GL) by multiplying the carbohydrate content of each food by its glycaemic index (GI), which is a measure of the relative postprandial blood glucose response per gram of carbohydrates, and then multiplying this value by the frequency of consumption and summing these values for all foods (Salmeron *et al*, 1997). Total coffee intake as a confounder was assessed since we previously found a significant lower risk of endometrial cancer among high coffee drinkers, and they tended to consume high alcohol as well (Je *et al*, 2011). The frequency of coffee consumption assessed by the FFQs was converted to cups per day (237 ml = an 8 oz cup).

Assessment of covariate data. On the 1976 initial questionnaire, we collected information about menopausal status, postmenopausal hormone (PMH) use, oral contraceptive (OC) use, parity, age at last birth, age at menarche, age at menopause, smoking, weight, height, and history of diabetes and hypertension. Information on duration of OC use and parity was asked on each questionnaire through 1984, whereas most other covariate data have been updated on all subsequent biennial questionnaires, except for height and age at menarche. Updated BMI was calculated using height reported at baseline and weight reported at each cycle. Those missing weight in one follow-up cycle had their weight carried forward from the previous cycle, whereas those missing weight for two consecutive cycles were excluded until they reported their weight. Pack-years of smoking were calculated by multiplying the duration and dose of smoking; one pack-year is equivalent to having smoked one pack per day for 1 year.

Statistical methods. For each participant, we calculated person-time from the return date of the1980 baseline questionnaire to the date of any cancer diagnosis (except non-melanoma skin cancer), death from any causes, hysterectomy, or the end of follow-up, 1 June 2010, whichever came first. To represent the long-term intake for individual subjects as accurately as possible and to reduce random within-person variation, we used cumulative average intake calculated from all available dietary questionnaires up to the start of each 2-year follow-up. For example, dietary data from 1980 FFQ was used for the 1980–1984 follow-up period; the average of 1980 and 1984 intakes was used for the 1984–1986 follow-up period; the average of 1980, 1984, and 1986 intakes were used for 1986–1990 follow-up period; the average of 1980, 1984, 1986, and

1990 intakes were used for 1990–1994 follow-up period, and so on. We categorised daily alcohol intake into five categories: nondrinkers, 0.1–4.9 g per day (~0.5 drink per day), 5.0–14.9 g per day (~1 drink per day), 15.0–29.9 g per day (~2 drinks per day), and ⩾30.0 g per day (2+ drinks per day). Cox proportional hazard regression models with follow-up months as a primary time scale were used to estimate incidence rate ratios (RRs) and 95% confidence intervals (CIs) of developing endometrial cancer in each category of alcohol intake compared with nondrinkers as a reference (Cox, 1972). To control as finely as possible for confounding by age, calendar time, and any possible two-way interactions between these two time scales, we stratified the analysis jointly by age in months and 2-year follow-up cycle. We tested the proportional hazard assumption by including interaction terms between alcohol consumption and duration of follow-up, and the assumption was unlikely to be violated.

In multivariable models, we adjusted the following covariates (see Tables 2–4 for details on how covariates were controlled in multivariable models): BMI, age at menopause, age at menarche, parity and age at last birth, duration of OC use, PMH use, pack-years of smoking, coffee intake, GL, and total energy intake. Linear trends across increasing alcohol intake were tested using the median value of each alcohol intake category as continuous variable to minimise the influence of outliers. To test for a possible curvilinear association between alcohol intake and endometrial cancer risk, we created a quadratic term that squared this linear variable and included it in a separate model with the linear term. Alcoholic beverage types were also evaluated by entering beer, wine, and liquor consumption into a model with or without adjusting for other beverage type, with nondrinkers of a specific beverage type as the reference category.

As sensitivity analyses, we excluded nondrinkers who reported that they had greatly decreased their alcohol drinking during the past 10 years on the baseline 1980 FFQ; allowed 4–8 years of lag time to examine the possibility that preclinical disease influenced dietary assessment; stopped updating alcohol intake when women were diagnosed with type 2 diabetes; or used baseline alcohol intake only. To assess whether the relationship between alcohol intake and endometrial cancer risk varied across categories of other risk factors, we performed stratified analyses by BMI, smoking status, OC use, menopausal status, and PMH use (among postmenopausal women). To provide increased power for subgroup analyses, the two upper categories of alcohol intake were combined. Tests of interaction between alcohol categories and potential effect modifiers were assessed by entering the cross-product terms into the model. SAS PROC PHREG with SAS version 9.3 was used for all analyses above (SAS Institute Inc., Cary, NC, USA).

RESULTS

During 1 422 149 person-years of follow-up, we ascertained a total of 794 incident cases of invasive endometrial adenocarcinoma among the 68 067 women who were eligible for analysis. Among the 794 cases, 385 (48.5%) cases were classified as well differentiated, 277 (34.9%) as moderately differentiated; and 113 (14.2%) as poorly differentiated, and the remaining 19 (2.4%) were not specified. Most of the cases belonged to early stage of endometrial cancer, stages I/II ($n=694$, 87.4%), whereas 73 (9.2%) of cases were at stages III/IV and the remaining 27 (3.4%) were not specified. For the study period, 1980–2010, approximately 77.8% of the participants reported drinking alcohol, the majority of which were light alcohol drinkers (0.1–4.9 g per day, 54.5%), whereas the rest of alcohol drinkers consumed moderate (5–14.9 g per day, 29.5%), high (15–29.9 g per day, 11.3%), or heavy alcohol (⩾30 g per day, 4.7%). Table 1 shows the characteristics of participants categorised at the midpoint of follow-up (1994), according to cumulative average alcohol intake. Compared with nondrinkers, women who consumed greater amounts of alcohol tended to be smokers, coffee drinkers, consume foods with low GL, and used OCs. In addition, they tended to have a lower prevalence of diabetes, lower BMI, and be nulliparous.

In the age-adjusted model, we found a significant inverse association between alcohol intake and endometrial cancer risk (Table 2). Compared with nondrinkers, women who drank alcohol had a 32% (95% CI: 20–43%) reduction in the risk of endometrial cancer. The age-adjusted RRs for the four upper categories of long-term alcohol intake (0.1–4.9, 5–14.9, 15–29.9, and ⩾30 g per day) were 0.72, 0.67, 0.59, and 0.54 (95% CI: 0.35–0.85) (P-value for linear trend = 0.001) (Table 2). The inverse associations were attenuated after multivariable adjustment, and BMI was a primary confounder in the multivariable model. Compared with non-drinkers, women who drank alcohol had a 19% (95% CI: 4–32%) risk reduction. The multivariable-adjusted RR for light alcohol intake (0.1–4.9 g per day) remained statistically significant even after the multivariable adjustment (multivariable RR = 0.78; 95% CI: 0.66–0.94). Above that level of alcohol intake, however, no significant inverse association were found (P-value for a linear trend = 0.66). For the test of a possible curvilinear association, we found no evidence with nonlinear trend, in the age-adjusted as well as the multivariable-adjusted models.

We attempted to exclude from nondrinkers women who reported no alcohol intake in all the FFQs for the study period, but reported that they decreased alcohol intake greatly in the past 10 years at 1980 FFQ, considered as former drinkers ($n=22$ cases), and the multivariable RRs for the five alcohol categories were: 0.79 (95% CI: 0.66–0.96), 0.89, 0.85, and 0.79, which were similar to the findings from the main analyses. When we stopped updating alcohol intake once women were diagnosed with type 2 diabetes, the multivariable RRs for the alcohol categories were: 0.77 (95% CI: 0.65–0.93), 0.86, 0.82, and 0.78. When we allowed 4–7.9 years of lag time from intake measurement to endometrial cancer incidence ($n=729$ cases), the significant inverse association with light alcohol drinking was slightly stronger (RR = 0.74; 95% CI: 0.61–0.89). When we used baseline alcohol intake only, the inverse association with light alcohol drinking was slightly attenuated but remained statistically significant (RR = 0.81; 95% CI: 0.68–0.96).

We also examined endometrial cancer risk in relation to specific type of alcoholic beverages (beer, wine, or liquor). Thirty two per cent of the participants reported drinking beer, 70% drank wine, and 54% drank liquor (Table 3). By type of alcoholic beverages, we found no evidence that the benefit of alcohol was restricted to one type of alcoholic beverage after the multivariable adjustment and the other alcoholic beverages. Light alcohol intake from wine, however, tended to be associated with lower risk of endometrial cancer (RR = 0.85; 95% CI: 0.71–1.02). A strong nonsignificant inverse association was found among high beer drinkers, but there was a very small number of cases included in that category ($n=3$ cases) (P-value for linear trend = 0.08). Table 4 shows the associations of alcohol intake and endometrial cancer risk among subgroups stratified by selected endometrial cancer risk factors. Overall, the associations did not vary substantially by smoking status ($P=0.93$), OC use ($P=0.22$), menopausal status ($P=0.38$), or PMH use among postmenopausal women ($P=0.21$) (Table 4). The inverse association with light alcohol intake (<5 g per day) tended to be stronger among obese (BMI ⩾30 kg m^{-2}) (RR = 0.63; 95% CI: 0.48–0.83), but the interaction by BMI was not statistically significant ($P=0.16$). We attempted to examine relationships between alcohol intake and endometrial cancer by tumour characteristics using the data on tumour stage and grade. The inverse association with alcohol intake appeared to be stronger for late stage of tumours (stages III/IV) or high grade of tumours (grade III) (Supplementary Table).

Table1. Age-standardised 1994 (midpoint) participant characteristics, by categories of alcohol intake in US women for the Nurses' Health Study

	Category of alcohol intake				
Characteristics	**Nondrinkers**	**0.1–4.9 g per day**	**5.0–14.9 g per day**	**15–29.9 g per day**	**⩾30 g per day**
Age (years) (mean, s.d.)	59.8 (7.3)	58.8 (7.2)	59.2 (7.1)	60.1 (6.9)	61.0 (6.6)
BMI (kg m^{-2}) (mean, s.d.)	27.4 (5.8)	26.8 (5.3)	25.4 (4.4)	25.1 (4.4)	25.3 (4.7)
Total physical activity (MET-h per week) (mean, s.d.)	17.6 (22.2)	19.4 (24.0)	21.7 (24.6)	21.7 (26.9)	19.3 (23.0)
Ever smoked (%)	36.5	54.6	67.4	76.9	83.8
Diabetes (%)	9.0	5.6	2.9	3.0	3.7
Hypertension (%)	35.1	32.8	28.7	33.0	40.0
Age at menarche (years) (mean, s.d.)	12.4 (1.8)	12.4 (1.7)	12.5 (1.7)	12.6 (1.6)	12.6 (1.7)
Oral contraceptive use (%)	44.0	48.5	52.5	55.4	54.6
Nulliparous (%)	6.0	5.9	6.8	7.7	9.0
Parity among parous women (mean, s.d.)	3.1 (1.4)	3.2 (1.4)	3.1 (1.4)	3.1 (1.4)	3.1 (1.4)
Age at last birth (years) (mean, s.d.)	31.8 (4.5)	31.5 (4.4)	31.3 (4.3)	31.2 (4.4)	31.0 (4.5)
Postmenopausal (%)	76.4	77.7	78.3	80.1	80.6
Age at menopause (years) (mean, s.d.)[a]	50.2 (3.7)	50.2 (3.5)	50.2 (3.6)	50.1 (3.6)	50.0 (3.3)
PMH use (%)[a]	44.7	50.8	56.8	57.2	51.2
Coffee intake (cups per day) (mean, s.d.)	2.0 (1.8)	2.4 (1.6)	2.7 (1.5)	2.7 (1.5)	2.7 (1.5)
Dietary glycaemic load (mean, s.d.)	111.8 (35.7)	109.4 (33.0)	103.4 (32.1)	98.2 (31.2)	91.5 (31.3)
Alcohol (g per day) (mean, s.d.)	0	1.8 (1.4)	9.0 (2.8)	20.9 (4.2)	39.7 (9.6)
Beer (g per day)	0	0.3 (0.5)	1.4 (2.3)	3.4 (5.8)	8.5 (14.0)
Wine (g per day)	0	1.0 (1.0)	4.3 (3.3)	8.8 (7.5)	10.5 (12.2)
Liquor (g per day)	0	0.5 (0.7)	3.2 (3.4)	8.7 (7.7)	20.6 (15.2)

Abbreviations: BMI = body mass index; MET-h = metabolic equivalent task hours; PMH = postmenopausal hormone.
[a]Among postmenopausal women.

Table 2. RR of endometrial cancer for categories of cumulative average alcohol intake, follow-up 1980–2010

			Category of alcohol intake				
	Nondrinkers	**Drinkers**	**0.1–4.9 g per day**	**5.0–14.9 g per day**	**15–29.9 g per day**	**⩾30 g per day**	***P*-value for trend**
Median (g per day)	0	4.1	1.5	8.8	20.1	36.6	
Person-years	315 374	1 106 776	603 020	326 213	125 029	52 515	
Cases, *n*	221	573	329	165	58	21	
Age-adjusted RR (95% CI)[a]	1.00 (ref.)	0.68 (0.58–0.80)	0.72 (0.60–0.86)	0.67 (0.55–0.82)	0.59 (0.44–0.79)	0.54 (0.35–0.85)	0.001
Multivariable-adjusted RR (95% CI)[b]	1.00 (ref.)	0.81 (0.68–0.96)	0.78 (0.66–0.94)	0.88 (0.71–1.09)	0.83 (0.61–1.14)	0.78 (0.49–1.25)	0.66

Abbreviations: CI = confidence interval; RR = relative risk.
[a]Simple model was stratified by age (in months) and 2-year follow-up cycle.
[b]Multivariable model further adjusted for BMI (in kg m^{-2}; continuous), age at menopause (pre-/unknown menopause, <45, 45–46, 47–48, 49–50, 51–52, or ⩾53 years), age at menarche (<12, 12, or >12 years), parity and age at last birth (nulliparous, 1–2 and <30, 1–2 and ⩾30, 3–4 and <30, 3–4 and ⩾30, ⩾5 and <30, or ⩾5 and ⩾30 years), duration of oral contraceptive use (never, <3, 3–5, or >5 years), postmenopausal hormone use (premenopausal, postmenopausal, and never used hormones, postmenopausal and past hormone users, postmenopausal and current oestrogen hormone users, or postmenopausal and current oestrogen and progesterone hormone users), smoking status (never, >0–10, >10–20, >20–30, >30–40, >40 pack-years), physical activity (<9, 9–<18, or ⩾18 metabolic equivalent task hours per week), history of hypertension (yes or no), cumulative average intakes of total energy (kcal per day, continuous), coffee intake (<1, 1, 2–3, or ⩾4 cups per day; 1 cup = 237 ml), and glycaemic load (quartiles).

DISCUSSION

In this large prospective cohort study over a 30-year follow-up, we found a significant lower risk of endometrial cancer among alcohol drinkers compared with nondrinkers. Women with light alcohol intake of <5 g per day (approximately half drink per day) had a 22% lower risk of endometrial cancer compared with nondrinkers. Higher intakes of alcohol, however, did not provide additional benefits against endometrial cancer.

The inverse association with light alcohol intake for endometrial cancer risk observed in this cohort is consistent with the results

Table 3. RR of endometrial cancer risk for categories of cumulative average alcoholic beverage intake, follow-up 1980–2010

			Category of alcohol intake			
	Nondrinkers	Drinkers	0.1–4.9 g per day	5.0–14.9 g per day	⩾15 g per day	*P*-value for trend
Beer						
Median (g per day)	0	0.9	0.9	7.0	28.8	
Person-years	964 311	457 838	376 586	62 759	18 493	
Cases (*n*)	564	230	202	25	3	
Age-adjusted RR (95% CI)[a]	1.00 (ref.)	0.80 (0.68–0.93)	0.83 (0.70–0.97)	0.78 (0.52–1.16)	0.26 (0.08–0.82)	0.007
Multivariable-adjusted RR (95% CI)[b]	1.00 (ref.)	0.90 (0.76–1.05)	0.91 (0.77–1.07)	0.97 (0.65–1.46)	0.35 (0.11–1.11)	0.08
Multivariable-adjusted RR (95% CI)[c]	1.00 (ref.)	0.92 (0.78–1.09)	0.92 (0.77–1.10)	0.97 (0.64–1.46)	0.35 (0.11–1.09)	0.08
Wine						
Median (g per day)	0	1.6	1.0	8.4	22.0	
Person-years	429 184	992 965	773 612	176 322	43 031	
Cases (*n*)	273	521	410	91	20	
Age-adjusted RR (95% CI)[a]	1.00 (ref.)	0.75 (0.64–0.87)	0.76 (0.65–0.88)	0.73 (0.57–0.92)	0.69 (0.44–1.09)	0.09
Multivariable-adjusted RR (95% CI)[b]	1.00 (ref.)	0.86 (0.74–1.01)	0.84 (0.72–0.99)	0.98 (0.76–1.26)	0.98 (0.61–1.57)	0.58
Multivariable-adjusted RR (95% CI)[c]	1.00 (ref.)	0.87 (0.73–1.04)	0.85 (0.71–1.02)	0.98 (0.74–1.29)	1.00 (0.62–1.61)	0.49
Liquor						
Median (g per day)	0	1.3	0.9	8.0	25.7	
Person-years	659 255	762 895	560 416	150 753	51 726	
Cases (*n*)	386	408	298	85	25	
Age-adjusted RR (95% CI)[a]	1.00 (ref.)	0.84 (0.73–0.96)	0.83 (0.71–0.96)	0.93 (0.73–1.17)	0.69 (0.46–1.04)	0.15
Multivariable-adjusted RR (95% CI)[b]	1.00 (ref.)	0.94 (0.81–1.09)	0.90 (0.77–1.05)	1.17 (0.92–1.50)	0.92 (0.60–1.41)	0.68
Multivariable-adjusted RR (95% CI)[c]	1.00 (ref.)	1.02 (0.86–1.20)	0.96 (0.80–1.14)	1.25 (0.96–1.62)	0.98 (0.64–1.51)	0.51

Abbreviations: CI = confidence interval; RR = relative risk.

[a]Simple model was stratified by age (in months) and 2-year follow-up cycle.

[b]Multivariable model further adjusted for BMI (in kg m^{-2}; continuous), age at menopause (pre-/unknown menopause, <45, 45–46, 47–48, 49–50, 51–52, or ⩾53 years), age at menarche (<12, 12, or >12 years), parity and age at last birth (nulliparous, 1–2 and <30, 1–2 and ⩾30, 3–4 and <30, 3–4 and ⩾30, ⩾5 and <30, or ⩾5 and ⩾30 y), duration of oral contraceptive use (never, <3, 3–5, or >5 years), postmenopausal hormone use (premenopausal, postmenopausal, and never used hormones, postmenopausal and past hormone users, postmenopausal and current oestrogen hormone users, or postmenopausal and current oestrogen and progesterone hormone users), smoking status (never, >0–10, >10–20, >20–30, >30–40, and >40 pack-years), physical activity (<9, 9–<18, or ⩾18 metabolic equivalent task hours per week), history of hypertension (yes or no), cumulative average intakes of total energy (kcal per day, continuous), coffee intake (<1, 1, 2–3, or ⩾4 cups per day; 1 cup = 237 ml), and glycaemic load (quartiles).

[c]Multivariable model adjusted for the same covariates in the multivariable model[b] and further adjusted for categories of other type of alcoholic beverages (0, 0.1–4.9, 5–14.9 or ⩾15 g of alcohol per day).

from the recent meta-analysis (Friberg *et al*, 2010) of seven prospective studies (Gapstur *et al*, 1993; Terry *et al*, 1999; Loerbroks *et al*, 2007; Kabat *et al*, 2008; Setiawan *et al*, 2008; Allen *et al*, 2009; Friberg and Wolk, 2009). The meta-analysis reported a J-shaped association between risk and number of drinks of alcohol per day: consumption of up to 13 g of alcohol per day (~one drink) seemed to be associated with a modestly lower risk, whereas exposure to more than two drinks (>26 g of alcohol) per day may increase risk (Friberg *et al*, 2010). Another meta-analysis (Sun *et al*, 2011) of 6 prospective studies (Gapstur *et al*, 1993; Terry *et al*, 1999; Jain *et al*, 2000; Loerbroks *et al*, 2007; Setiawan *et al*, 2008; Friberg and Wolk, 2009) and 14 case–control studies (La Vecchia *et al*, 1986; Webster and Weiss, 1989; Shu *et al*, 1991; Austin *et al*, 1993; Swanson *et al*, 1993; Parazzini *et al*, 1995; Goodman *et al*, 1997; Newcomb *et al*, 1997; Jain *et al*, 2000; Littman *et al*, 2001; Petridou *et al*, 2002; Strom *et al*, 2006; Hosono *et al*, 2008) included results stratified by the type of alcoholic beverages (beer, wine, and liquor), and revealed that increased risk of endometrial cancer among liquor alcohol drinkers (RR = 1.22; 95% CI: 1.03–1.45), whereas null associations were found with wine and beer consumption (Sun *et al*, 2011). In our analysis, compared with nondrinkers, the RR in liquor drinkers was 1.02, and RRs in beer and wine drinkers were 0.92 and 0.87, respectively, and any of the associations by type of alcoholic beverage intake were not statistically significant, suggesting no clear evidence that the benefit of alcohol was restricted to one type of beverage.

Most of prospective studies included in the meta-analyses assessed alcohol intake at baseline only, except for one study that used an average intake with two measurements (Friberg and Wolk, 2009). Since a single measure of alcohol intake did not consider the change in alcohol consumption during the study period, it can lead to non-differential exposure misclassification. Moreover, we cannot rule out the possibility that the lowered RR observed in women drinking up to one drink per day found in the meta-analysis was due to the inclusion of former drinkers in the reference category who were likely to have health problems (Friberg *et al*, 2010). In our analysis, we used a cumulative average alcohol intake that took into account the past alcohol intake. Some of the women classified by nondrinkers based on several FFQs assessed during the study period reported that they had greatly decreased alcohol intake in the past 10 years, which indicated that they used to be drinkers. To prevent potential bias from 'sick quitters' in the reference category, we attempted to conduct a sensitivity analysis by excluding those women from nondrinkers and the results remained similar to the findings in the main analysis.

A relationship between long-term alcohol intake and risk of endometrial cancer is biologically plausible. In addition to

Table 4. Multivariable RR and 95% CI for endometrial cancer in relation to cumulative alcohol intake stratified by endometrial cancer risk factors in the Nurses' Health Study, 1980–2010[a]

		Category of alcohol intake									
		0 g per day		0.1–4.9 g per day		5.0–14.9 g per day		⩾15 g per day			
Covariates	Total no. of cases	No. of cases	RR	No. of cases	RR (95% CI)	No. of cases	RR (95% CI)	No. of cases	RR (95% CI)	*P*-value for trend	*P*-value for interaction
Body mass index (kg m^2)											
<25	258	53	1.00 (ref.)	93	0.89 (0.63–1.27)	72	1.05 (0.71–1.54)	40	0.97 (0.61–1.54)	0.80	
25–29.9	239	52	1.00 (ref.)	111	1.00 (0.70–1.41)	54	0.99 (0.65–1.50)	22	0.92 (0.54–2.59)	0.77	0.16
⩾30	297	116	1.00 (ref.)	125	0.63 (0.48–0.83)	39	0.80 (0.53–1.20)	17	0.74 (0.42–1.28)	0.81	
Smoking status											
Never	403	153	1.00 (ref.)	173	0.81 (0.65–1.02)	51	0.73 (0.52–1.02)	26	1.02 (0.66–1.60)	0.96	0.93
Ever	391	68	1.00 (ref.)	156	0.78 (0.58–1.05)	114	0.94 (0.68–1.29)	53	0.69 (0.47–1.02)	0.34	
OC use											
Never user	487	139	1.00 (ref.)	197	0.84 (0.67–1.05)	102	1.00 (0.76–1.32)	49	0.94 (0.65–1.34)	0.71	0.22
Ever user	305	82	1.00 (ref.)	132	0.68 (0.51–0.91)	61	0.68 (0.47–0.97)	30	0.66 (0.42–1.06)	0.32	
Menopausal status											
Premenopausal	96	33	1.00 (ref.)	40	0.83 (0.50–1.37)	17	0.84 (0.43–1.61)	6	0.64 (0.25–1.67)	0.45	0.38
Postmenopausal	667	181	1.00 (ref.)	281	0.78 (0.64–0.95)	138	0.84 (0.66–1.06)	67	0.79 (0.58–1.08)	0.54	
PMH use[b]											
Never	273	91	1.00 (ref.)	114	0.75 (0.56–1.01)	48	0.89 (0.60–1.31)	20	0.74 (0.44–1.26)	0.66	0.21
Ever	394	90	1.00 (ref.)	167	0.81 (0.62–1.07)	90	0.83 (0.60–1.14)	47	0.86 (0.58–1.27)	0.80	

Abbreviations: CI = confidence interval; RR = relative risk.

[a]Multivariable model was stratified by age (in months) and 2-year follow-up cycle and further adjusted for BMI (in kg m^{-2}; continuous), age at menopause (pre-/unknown menopause, <45, 45–46, 47–48, 49–50, 51–52, or ⩾53 years), age at menarche (<12, 12, or >12 years), parity and age at last birth (nulliparous, 1–2 and <30, 1–2 and ⩾30, 3–4 and <30, 3–4 and ⩾30, ⩾5 and <30, or ⩾5 and ⩾30 years), duration of oral contraceptive use (never, <3, 3–5, or >5 years), postmenopausal hormone use (premenopausal, postmenopausal, and never used hormones, postmenopausal and past hormone users, postmenopausal and current oestrogen hormone users, or postmenopausal and current oestrogen and progesterone hormone users), smoking status (never, >0–10, >10–20, >20–30, >30–40, >40 pack-years), physical activity (<9, 9–<18, or ⩾18 metabolic equivalent task hours per week), history of hypertension (yes or no), cumulative average intakes of total energy (kcal per day, continuous), coffee intake (<1, 1, 2–3, or ⩾4 cups per day; 1 cup = 237 ml), and glycaemic load (quartiles).

[b]Among postmenopausal women.

exposure to excessive oestrogen levels, chronic hyperinsulinaemia also have a role in endometrial carcinogenesis (Kaaks *et al*, 2002). Insulin can stimulate the growth of endometrial cells by binding to insulin receptors in the endometrium (Nagamani and Stuart, 1998) and by increasing circulating free insulin-like growth factor-1 through decreasing the levels of insulin-like growth factor-binding protein-1 (Irwin *et al*, 1993; Weiderpass *et al*, 2003). Alcohol intake has been associated with reduced fasting insulin concentrations and improved insulin sensitivity (Davies *et al*, 2002; Joosten *et al*, 2010), and thus may lower the risk of endometrial cancer by relieving chronic hyperinsulinaemia. A meta-analysis on the relationship between alcohol consumption and risk of type 2 diabetes showed a significant inverse association with 0.1–48 g of alcohol consumption, whereas no risk reduction was observed in consumers of ⩾48 g per day (Koppes *et al*, 2005). In our analysis, the inverse associations with higher amount of alcohol intake were attenuated and became nonsignificant after the multivariable adjustment. Despite the potential benefits of alcohol consumption, heavy alcohol intake may increase the risk of endometrial cancer. Several studies showed a positive association between alcohol intake and oestrogen levels (Gavaler and Van Thiel, 1992; Hankinson *et al*, 1995; Madigan *et al*, 1998; Onland-Moret *et al*, 2005; Rinaldi *et al*, 2006; Danforth *et al*, 2009). Although mechanisms by which alcohol drinking increases oestrogen levels are still not completely understood, it has been postulated that alcohol intake stimulates ovarian theca cells to produce androgens through increased LH secretion, stimulates adrenal cortex to produce androgens through increased ACTH secretion, or increases aromatase activity in the liver, leading to a higher conversion of androgens into oestrogens (Rinaldi *et al*, 2006). Prolonged exposure of excessive oestrogens may result in endometrial carcinogenesis, through increased mitotic activity of endometrial cells, increased the number of DNA replication errors, and somatic mutations leading to the malignant phenotype (Akhmedkhanov *et al*, 2001). Owing to the harmful effect of heavy alcohol use, the potential benefits of alcohol consumption on insulin sensitivity and fasting insulin concentrations may be negated to some extent.

We found a stronger inverse association with light alcohol intake among obese women, which is similar to the recent finding in the NIH-AARP Diet and Health Study (Yang *et al*, 2011). The prospective study showed an inverse association between alcohol intake and endometrial cancer risk among overweight or obese women (BMI ⩾25 kg m^{-2}), whereas there was some suggestion of higher risks associated with alcohol intake among lean women (BMI <25 kg m^{-2}) (*P*-value for interaction by BMI = 0.002). Although speculative at present, there might be several explanations for the inverse association among obese women. Obese women tend to have insulin resistance and higher levels of insulin compared with lean women, and potential abilities of alcohol

intake to improve those conditions may have led to reduced risk of endometrial cancer. As overweight or obese postmenopausal women already have high levels of oestrogens, the potential harmful effect of alcohol to elevate oestrogen levels may not be pronounced among those women. On the other hand, lean women who tend to have low insulin resistance and normal fasting insulin levels may be more likely to be affected by increased oestrogens resulting from alcohol intake.

We attempted to examine whether the association between alcohol intake and endometrial cancer risk varied by endometrial cancer characteristics, and observed relatively lower risk of endometrial cancer among alcohol drinkers when the tumours at diagnosis were late stages or high grade of tumours. The results by tumour grade tended to be consistent with those reported in the NIH-AARP diet and health study (Yang *et al*, 2011). However, the interpretation for the subanalysis should be cautious based on a relatively small number of cases included in each analysis.

An important strength of our study is the prospective design. Retrospective case–control studies, which consist of the majority of literature on this subject, can be prone to recall bias, resulting from differential measurement error among cases and controls in recalling past alcohol intake. As our study assessed alcohol intake before cancer diagnosis, we can avoid the methodological bias. Our study assessed alcohol intake repeatedly with long follow-up period, which allowed us to calculate long-term alcohol intake that may be the most biologically relevant to examine the risk of endometrial cancer. The details of alcohol intake in the several FFQs used in this analysis allowed for the calculation of alcohol in grams per day, thereby enhancing the precision of our exposure. Furthermore, the repeated measurements allowed us to conduct several sensitivity analyses to assess the robustness of the main results. In addition to using cumulative average intake that represents lifetime intake of subjects during the study period, we also attempted to exclude former drinkers before 1980 from the referent nondrinking category to make sure that any potential bias of 'sick quitter' explained the lower risk of endometrial cancer among alcohol drinkers compared with nondrinkers. A relatively large number of cases in our cohort enabled us to conduct subgroup analyses, which is useful to examine the potential mechanisms how alcohol might be associated with endometrial cancer.

Despite these strengths, some limitations of our study must be taken into considerations.

Alcohol drinking is often correlated with smoking and coffee consumption behaviours. In our data, we also found that alcohol drinking was correlated with low BMI and low GL intake. All of the factors such as smoking, coffee consumption, low BMI, and low GL have been associated with low risk of endometrial cancer (Viswanathan *et al*, 2005; Cui *et al*, 2011; Je *et al*, 2011; Zhang *et al*, 2014). Although we attempted to carefully control for the potential confounders in the multivariable model, residual confounding remains possible. We additionally conducted the analysis by restricting women to those without the factors, and still found similar inverse association with light alcohol intake in the subgroups. Since we had few cases ($n=4$ cases) who consumed very high alcohol intake (>45 g per day) in our cohort, the long-term effects of heavy alcohol use on endometrial cancer risk cannot be investigated. As the recent meta-analysis provided an evidence of an increased risk for endometrial cancer for intakes higher than two alcoholic drinks per day (Friberg *et al*, 2010), we cannot rule out the possibility of potential harmful effect of heavy alcohol consumption. Finally, our findings from the cohort of US female registered nurses may limit the generalisability, but the homogeneity can minimise some variations by socioeconomic status or other potential confounders.

In conclusion, this study provides prospective evidence for an inverse association between light alcohol intake (approximately half drink per day) in the long term and endometrial cancer risk, but above that level no significant association was found. Our findings may have some public health implications, given the large number of women consuming relatively light alcohol and the increasing incidence of endometrial cancer in Western countries. Further studies examining the association between heavy alcohol intake and endometrial cancer risk should be conducted in large studies with repeated measurements of alcohol intake.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors have read and approved the final version submitted for publication. YJ and EG developed study concept and design, and contributed to critical revision of the manuscript for important intellectual content. YJ wrote the manuscript and conducted statistical analysis. ID collected the data. YJ, ID and EG contributed to discussion and reviewed the manuscript.

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