

Null Results in Brief

Long-term Alcohol Consumption and Risk of Endometrial Cancer Incidence: A Prospective Cohort Study

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Abstract

Alcohol consumption has been hypothesized to increase the risk of endometrial cancer. We used data from the prospective population-based Swedish Mammography Cohort including 61,226 women to examine the association between alcohol and endometrial cancer incidence. Alcohol consumption was assessed with validated food frequency questionnaires at baseline 1987 to 1990 and at follow-up in 1997. During a mean follow-up of 17.6 years, 687 endometrial cancer cases were identified in the Swedish cancer registries. We found no association between alcohol consumption and endometrial cancer risk after adjustment for age,

body mass index, and smoking. The multivariable rate ratios (95% confidence intervals) for the three upper categories of long-term alcohol consumption as compared with no consumption were 1.01 (0.84-1.22) for <3.4 g/d, 1.01 (0.80-1.27) for 3.4 to 9.9 g/d, and 1.09 (0.71-1.67) for ≥ 10 g/d, respectively. The association did not differ by age, body mass index, folic acid intake, or postmenopausal hormone use in stratified analysis. In conclusion, our results suggest that low alcohol consumption (up to one drink per day) is unlikely to substantially influence risk of endometrial cancer. (Cancer Epidemiol Biomarkers Prev 2009;18(1):355-8)

Introduction

Alcohol consumption has been positively associated with higher estrogen levels among postmenopausal women (1-5) and could therefore be expected to increase the risk of endometrial cancer. Alcohol consumption has been investigated in several epidemiologic studies, most showing no association (6-18), some showing positive associations (19-22), and some negative associations (23, 24). Given the inconclusive results, we sought to address prospectively whether alcohol consumption is associated with risk of endometrial cancer. We used self-reported data on alcohol consumption with repeated assessment from the Swedish Mammography Cohort, a population-based prospective cohort study of more than 60,000 women.

Materials and Methods

The population-based Swedish Mammography Cohort (25) includes women from central Sweden who were 40 to 76 years of age at enrollment between 1987 and 1990. Alcohol and dietary intake data were collected at baseline 1987 to 1990, and in 1997 by self-administered food-frequency questionnaires. The Spearman rank correlation coefficient between food frequency question-

naires and weighted records for four 1-week periods for alcohol consumption was 0.9.¹

We performed a linkage of the cohort with the National Swedish Cancer Register through December 31, 2005 and with the Regional Cancer Register in the study area through December 31, 2007, these registries have been estimated to be almost 100% complete (26). Furthermore, by linkage with the nationwide Swedish In-patient Register, we identified women who had a hysterectomy for reasons other than endometrial cancer. Dates of death or migration from the study area were ascertained by linkage with the Swedish Death Register and the National Swedish Population Register, respectively. After exclusions, 61,226 women remained for this analysis, including 687 incident endometrial (adenocarcinoma) cancer cases.

We calculated person-years of follow-up for each woman from the date of mammography to the date of endometrial cancer diagnosis, the date of a hysterectomy, the date of death from any cause, the date of migration out of the study area during December 31, 2005 to December 31, 2007 (since for this time period we only have regional information on cancer incidence), or the end of follow-up on December 31, 2007, whichever came first. The relative risks (RR) of endometrial cancer [with 95% confidence intervals (CI)] were calculated using Cox proportional hazards models stratified on age in months. Multivariate models were adjusted for age, body mass index (BMI), and smoking. We also calculated the RR of endometrial cancer (with 95% CI) using updated

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¹ Wolk A: unpublished data.

Table 1. Age-standardized baseline characteristics of women in the Swedish Mammography Cohort according to alcohol consumption

	Alcohol consumption			
	Nondrinkers	<3.4	3.4-9.9	≥10.0
Median (g/d)	0 (n = 20,000)	1.80 (n = 24,376)	4.94 (n = 14,320)	12.41 (n = 2,530)*
Characteristics				
Age (y)	57.5	53.4	49.8	48.9
BMI (kg/m ²)	25.5	24.7	24.0	23.5
Age at menarche (y)	13.3	13.2	13.2	13.2
No. of children	2.2	2.1	2.0	2.0
Oral contraceptive use (%)	36.5	42.3	46.8	50.7
Age at menopause (y)	49.9	50.1	50.3	50.5
Postmenopausal hormone therapy (%)	41.3	49.0	54.3	60.1
Total energy intake (kcal)	1,596	1,582	1,588	1,616
Education ≥12 years (%)	10.1	13.0	15.4	17.3
History of diabetes (%)	5.7	3.9	2.7	2.7
History of smoking (%)	21.1	28.6	37.5	44.3

NOTE: All values other than age have been directly standardized according to the age distribution of the cohort.

*This amount corresponds to approximately one drink per day.

information on alcohol from the second questionnaire, and by using the average alcohol consumption for the time period January 1, 1998 to December 31, 2007 from the two questionnaires. The statistical significance of interactions was tested by adding an interaction term to the Cox model, simultaneously containing the main variable and age in months. All *P* values were two-sided. We had 80% power to detect a RR of >1.40 for the highest versus the lowest quartile ($\alpha = 0.05$). The study was approved by the Ethics Committees at the Uppsala University Hospital (Uppsala, Sweden) and the Karolinska Institutet (Stockholm, Sweden).

Results

Table 1 shows the distribution of known and potential risk factors for endometrial cancer in the cohort by categories of alcohol consumption. Women with high alcohol consumption were younger, had a lower BMI, more among them used oral contraceptives and postmenopausal hormones, were more educated, had less diabetes, and tended to smoke more. Other characteristics did not vary substantially with respect to alcohol consumption.

Overall, alcohol consumption at baseline was not associated with endometrial cancer risk in neither age-adjusted nor multivariable analyses adjusting for BMI and smoking (Table 2). We further investigated the association with long-term alcohol consumption using updated information from the second questionnaire in the cohort (Table 2). In the analysis additionally adjusted for education, age at menopause, age at menarche, oral contraceptive use, postmenopausal hormone use, parity, history of diabetes, and total energy intake, RRs for the three upper categories of alcohol consumption as compared with the lowest one were 1.01 (95% CI, 0.85-1.20), 0.94 (95% CI, 0.75-1.18), and 1.09 (95% CI, 0.71-1.68), respectively. To eliminate the possible residual confounding by smoking, we did an analysis confined to never smokers only (including 20,516 women and 287 cases). RRs for the three upper categories of alcohol consumption as compared with the lowest one were 0.93 (95% CI, 0.71-1.22), 0.96 (95% CI, 0.68-1.37), and 0.78 (95% CI, 0.31-1.94), respectively.

By stratifying the cohort, we also examined whether the observed association differed according to age, BMI, folic acid intake, or postmenopausal hormone use. Results from these analyses did not show any suggestions for effect modification (data not shown).

Table 2. RRs and 95% CIs of alcohol consumption in relation to endometrial cancer for 61,226 women in the Swedish Mammography Cohort

Alcohol consumption (g/d)	Nondrinkers	<3.4	3.4-9.9	≥10.0
Baseline				
No. of cases	268	273	122	24
Person-years	339,949	431,546	259,097	45,748
Age-adjusted RR (95% CI)*	1.00 (ref)	0.91 (0.77-1.08)	0.77 (0.61-0.96)	0.87 (0.57-1.34)
Multivariable adjusted RR (95% CI) †	1.00 (ref)	1.01 (0.85-1.20)	0.95 (0.75-1.19)	1.12 (0.73-1.71)
Long-term				
No. of cases	221	300	141	25
Age-adjusted RR (95% CI)*	1.00 (ref)	0.90 (0.75-1.08)	0.81 (0.65-1.01)	0.83 (0.55-1.27)
Multivariable adjusted RR (95% CI) †	1.00 (ref)	1.01 (0.84-1.22)	1.01 (0.80-1.27)	1.09 (0.71-1.67)

*Rate ratios from Cox proportional hazards models adjusted for age in months.

†Rate ratios from Cox proportional hazards models adjusted for age in months, BMI (<20, 20-25, 26-30, >30) and smoking (never/ever/missing).

‡In the longitudinal analysis, alcohol consumption is treated as a cumulative average of the alcohol intake at the two measurements.

Discussion

In this population-based prospective cohort study, we found no relation between alcohol consumption and endometrial cancer risk. Our results are in agreement with previous studies, showing no association between alcohol consumption and endometrial cancer risk (6-18), but not with studies showing either an increase or decrease in risk in relation to endometrial cancer (19-24).

There are several biological mechanisms through which alcohol might increase the risk of endometrial cancer development. Alcohol has been shown to increase the levels of estrogen (1-5), which in turn, have been shown to increase endometrial cancer risk by stimulating the proliferation of endometrial cells (27). However, moderate alcohol intake has also been shown to improve insulin sensitivity and reduce fasting insulin concentrations (28). Insulin has been shown to stimulate the growth of endometrial stromal cells by binding to insulin receptors in endometrium (29). Hyperinsulinemia may increase the levels of free estrogens through decreasing concentrations of circulating sex hormone binding globulin (30, 31). Finally, hyperinsulinemia through decreasing levels of IGF1 increases circulating free IGF-1, which by binding and activating IGF-1 receptors in the endometrium, stimulates cell proliferation (32-37). These two counteracting mechanisms by which alcohol might be associated with endometrial cancer risk probably cancel each other. This may explain the apparent absence of association.

The major strengths of our study include its prospective, population-based design, and the completeness of identification of endometrial cancer cases through the Swedish cancer registries. Furthermore, we had information on all major potential confounders. One limitation in our study was the low amount of alcohol consumed among the women, which made it impossible to assess the effect of larger amounts of alcohol. In conclusion, our results show that low alcohol consumption (up to one drink per day) is unlikely to substantially influence the risk of endometrial cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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