Original Article

Alcohol consumption and the risk of endometrial cancer: a meta-analysis

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Epidemiologic findings are inconsistent concerning the association of endometrial cancer risk with alcohol consumption. Therefore, we conduct a meta-analysis of studies that assessed the association of alcohol consumption and the risk of endometrial cancer. A systematic literature search up to April 2010 was performed in MEDLINE and EMBASE, and study-specific risk estimates were pooled using a random-effects model. In the present study, six prospective and 14 case-control studies were included. Alcohol intake was not significantly associated with the risk of endometrial cancer among prospective studies (relative risk (RR): 1.04; 95% confidence interval (CI): 0.91-1.18) or among case-control studies (odds ratio (OR): 0.89; 95% CI: 0.76-1.05). However evidence from the results of our stratified analyses revealed that increased risk of endometrial cancer was associated with liquor consumption (RR: 1.22; 95% CI: 1.03-1.45) but null association with wine and beer consumption. In conclusion, alcohol consumption is not associated with the risk of endometrial cancer. Future studies should also examine whether the relation varies according to different type of alcoholic beverages.

Key Words: alcohol consumption, endometrial cancer, risk, association, meta-analysis

INTRODUCTION

Despite a recent decline in the incidence rate of endometrial cancer, it remains the most common female gynecologic malignancy. According to International Agency for Research on Cancer in 2005, it was diagnosed in 199,000 women worldwide and 50,000 women died of the disease.[1] The main etiologic hypothesis for the development of endometrial cancer is exposure to high levels of estrogen in conjunction with inadequate progesterone.[2-3] Other factors shown to increase the risk include obesity and nulliparity, which are thought to possibly act through increased circulating concentrations of unopposed estrogens.[4]

In addition, some life-style factors may also exert effects on the risk of gynecologic cancer.[5] Our recent meta-analysis concluded the inverse association of endometrial cancer risk with cigarette smoking.[6] Alcohol use is correlated with endogenous hormone level. Daily alcohol consumption has been suggested to be associated with higher levels of circulating estrogens in postmenopausal women.[7] It has also been found to further increase blood estrogen levels in postmenopausal women who are taking estrogen replacement therapy.[8] Since estrogens have a role in endometrial cancer, factors associated with low concentrations of circulating estrogens may reduce the risk of this malignant disorder. Therefore, alcohol consumption might have effects on the risk of endometrial cancer.

During last three decades, many epidemiological studies have evaluated the association between alcohol consumption and endometrial cancer risk. However, results of these studies were not entirely consistent; the impact of alcohol consumption on the risk of endometrial cancer is still unclear. Thus, we conducted a meta-analysis to summarize those studies. We also investigated whether the association between alcohol consumption and endometrial cancer risk differed by type of alcoholic beverage or smoking status.

MATERIALS AND METHODS

Search strategy

A systematic literature search up to April 2010 was performed in MEDLINE and EMBASE to identify relevant studies. Search terms included "alcohol", "beer", or "wine", "liquor", "lifestyle", combined with "endometrial

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cancer", "uterine corpus cancer", or "endometrial carcinoma". The search was limited to English-language articles. The titles and abstracts were scanned to exclude any clearly irrelevant studies. The full texts of the remaining articles were read to determine whether they contained information on the topic of interest. Furthermore, to find any additional published studies, a manual search was performed by checking all the references of retrieved articles. All searches were conducted independently by two authors. At last the results were compared, and any questions or discrepancies were resolved through iteration and consensus.

Study selection

To be eligible, studies had to fulfill the following four inclusion criteria: 1) they had a prospective or case-control study design; 2) the exposure of interest was alcohol consumption; 3) the outcome of interest was endometrial cancer incidence or mortality; 4) relative risk (RR) estimates (or odds ratio (OR) estimates in case-control studies) with their corresponding 95% confidence interval (CI) (or sufficient data to calculate) were reported; 5) they should adjusted for potential endometrial cancer risk such as age, BMI, or parity. Studies in particular populations (cohorts of alcoholics or brewery workers) were not included.

The primary literature search identified 180 records. After screening the titles and abstracts, 150 articles were excluded because they were either laboratory studies, review articles, or irrelevant to the current study. We identified 30 potentially relevant articles concerning alcohol consumption and endometrial cancer risk.[9-38] Four articles[9,12,14,15] were excluded because their risk estimates and 95% CI were not given. Three were excluded because they did not adjust for any potential risk factors.[10,17,18] One used cancer patients to be the control.[11] One publication was excluded because it was a duplicate of a previous report from the same study population,[13] and one enrolled women hospitalized with alcoholism.[16] Finally, six prospective and 14 case-control studies were included in the meta-analysis.[19-38]

Data extraction

Information from studies was extracted independently by two researchers. The following data were collected: the first author's last name, the year of publication, the country in which the study was performed, the years of follow-up or the study period, the study design, the type of controls for case-control studies (population- or hospital-based controls), the age range of study participants, the sample size (cases and controls or cohort size), the exposure of alcohol consumption, the type of alcoholic beverage, the covariates controlled for in the analysis, and the risk estimates with corresponding 95% CI. If a study provided several risk estimates, the most completely adjusted estimate was extracted.

Statistical analyses

Study-specific risk estimates were extracted from each paper, and log risk estimates were weighted by the inverse of their variances to obtain a pooled risk estimate. Studies were combined by use of the DerSimonian and Laird random-effects model, which considers both within- and between-study variation. Our primary analysis compared the risk of endometrial cancer in ever alcohol use to never use. Several studies did not report a risk estimate for ever alcohol use. For these studies, a summary estimate for ever alcohol use was generated using reported risk estimate for each alcohol use category. This summary estimate was used in the meta-analysis for calculation of the overall RR for ever alcohol use. In addition, for analysis of potential interactions, we conducted subgroup analyses by the location of the study (US versus other countries), and adjustment for hormone replacement therapy (HRT) use. Summary estimates were also calculated for the type of alcoholic beverage (beer, wine and liquor).

Q and I^2 statistics were used to examine whether the results of studies were homogeneous. To avoid type II errors due to low power, the significance level was set at 0.10 instead of the more traditional 0.05 level. When statistical heterogeneity was detected, the sources of heterogeneity were explored and sensitivity analysis was performed. Publication bias was evaluated with Egger's regression asymmetry test in which *p*-values less than 0.10 was considered representative of statistically significant publication bias. Statistical analyses were conducted using STATA 10.0 software (STATA Corp, College Station, TX). All statistical tests were two-sided.

RESULTS

Studies identified

We identified six prospective and 14 case-control studies on the association between alcohol consumption and risk of endometrial cancer.[19-38] Table 1 presents the basic characteristics of each study included in our meta-analysis. Three of six prospective studies were conducted in Europe,[20,22,24] two in the US,[19,23] and one in Canada.[21] Of the 14 case-control studies included in the meta-analysis, seven were from the US,[26,28,29,31,32,34,37] four from Europe,[25,30,35,36] two from Asia,[27,28] and the remaining one was from Canada.[33]

Ever alcohol use

The risk estimates of endometrial cancer for ever alcohol use in individual prospective and case-control studies and summary estimates are shown in Figure 1. The summary risk estimate for cohort studies was 1.04 (95% CI: 0.91-1.18) with no statistically significant heterogeneity among these studies (Q=6.93, p=0.226). The pooled estimate of all case-control studies was 0.89 (95% CI: 0.76-1.05) which also showed that alcohol consumption was not associated with the risk of endometrial cancer; but there was indication of heterogeneity among studies (Q=50.73, p<0.001). By using a stepwise process, we determined that most of the heterogeneity was accounted for four studies by Gapstur *et al*., Friberg *et al*., Storm *et al*. and Hosono *et al*.[19,24,37,38] As an additional sensitivity analysis, we calculated summary risk estimate for endometrial cancer and alcohol intake with and without these studies. When these four studies were excluded, the remaining studies were homogenous (Q=11.29, p=0.256), and the summary estimate was 0.90 (95% CI: 0.80-1.00) which also did not significantly change the total estimate.

Table 1. Characteristics of cohort and case–control studies of alcohol consumption and endometrial cancer risk

Study (reference)	Country	Study period	Design	Age, y	Case, n	Cohort size/ controls	Exposure	RR/OR	95% CI	Adjustments
Gapstur et al, 1993 (19)	US	1986-1990	Cohort	55-69 PMP	167	25170	<4 g/d >4 g/d	0.7 1.0	0.5-1.1 0.7-1.6	age, BMI, number of live births, age at menopause, HRT
Terry et al, 1999 (20)	Sweden	1967-1992	Cohort	42-81	133	11659	<2 drinks/w 2-4 drinks/w ≥4 drinks/w	1.7 1.2 1.3	1.03-2.8 0.6-2.4 0.6-2.8	age, PA, weight, parity
Jain et al, 2000 (21)	Canada	1980-1993	Cohort	40-59	221	56837	2 quartile 3 quartile 4 quartile	1.01 0.78 1.0	0.69-1.46 0.52-1.18 0.67-1.50	age, energy, BMI, smoke, OC, HRT, education, livebirths, age at menarche
Loerbroks et al, 2007 (22)	Netherlands	1986-1997	Cohort	55-69 PMP	280	62573	Any	1.06	0.78-1.43	age, BMI, parity, OC, PA, hypertension, age at first birth, age at menopause, smoking
Setiawan et al, 2008 (23)	US	1993-2002	Cohort	45-79 PMP	324	41574	<1 drink/d 1-2 drink/d ≥2 drink/d	1.01 1.09 2.01	0.77-1.33 0.62-1.93 1.30-3.11	age, year, race, center, education, BMI, age at menarche, age at menopause, HRT, OC, parity, smoking, diabetes, hypertension, PA
Friberg et al, 2009 (24)	Sweden	1987-1997	Cohort	40-76	687	61,226	3.4 g/d 3.4-9.9 g/d ≥10 g/d	1.01 1.01 1.09	0.84-1.22 0.80-1.27 0.71-1.67	age, BMI and smoking
La Vecchia et al, 1986 (25)	Italy	1983-1984	HCC	<75	206	206	<2 drinks/d 2-3 drinks/d 3-4 drinks/d ≥4 drinks/d	1.59 1.57 3.44 4.33	0.80-3.18 0.77-3.21 1.03-11.51 1.02-18.43	age, marital status, BMI, education, parity, diabetes, hypertension, age at menarche and at menopause, OC and other female hormone use
Webster et al, 1989 (26)	US	1980-1982	PCC	20-54	351	2247	None 1-49 g/d 50-149 ≥150	1.83 1.61 1.11 1	1.11-3.01 1.04-2.49 0.68-1.81	age, race, parity, OC, smoking
Shu et al, 1991 (27)	China	1988-1990	PCC	18-74	286	268	Any	1.2	0.6-2.6	age, parity, weight
Swanson, et al, 1993 (28)	US	1987-1990	PCC	20-74	400	297	Any	0.82	0.53-1.26	age, education, smoking, age at menarche, OC, Quetelet'si ndex, body fat distribution

Abbreviation: RR, relative risk; CI, confidence intervals; PCC, population-based case-control; HCC, hospital-based case-control; OC, oral contraceptive; BMI, body mass index; HRT, hormone replacement therapy; PMP, postmenopausal.

Table 1. Characteristics of cohort and case–control studies of alcohol consumption and endometrial cancer risk (con.)

Study (reference)	Country	Study period	Design	Age, y	Case, n	Cohort size/ controls	Exposure	RR/OR	95% CI	Adjustments
Austin et al, 1993 (29)	US	1985-1988	HCC	40-82	103	236	Any	0.64	0.32-1.28	age, race, schooling, BMI, obesity, cigarette, HRT, parity
Parazzini et al, 1995 (30)	Italy	1983-1993	HCC	25-74	726	2123	0-1 drink/d 1-2 drinks/d >2 drinks/d	1.1 1.4 1.6	0.9-1.4 1.1-1.8 1.2-2.2	age, education, quetelet index, parity, menopausal status, smoking, OC, HRT, diabetes, hypertension
Newcomb et al, 1997 (31)	US	1991-1994	PCC	18-84	739	2313	Any	1.07	0.86-1.33	age, smoking, education, weight, HRT, and parity
Goodman et al, 1997 (32)	US	1985-1993	PCC	18-84	332	511	Ever	0.90	0.60-1.36	age, ethnicity, pregnancy, OC, estrogen, diabetes, Quetelefs index
Jain et al, 2000 (33)	Canada	1994-1998	PCC	30-79	552	562	2 quartile 3 quartile	0.85 0.72	0.63-1.18 0.52-0.99	energy, age, weight, smoke, diabetes, OC, HRT, education, live births, age at menarche
Littman et al, 2001 (34)	US	1985-1991	PCC	45-71 PMP	679	944	1-3 drinks/m 1-3 drinks/w 4-6 drinks/w >1 drinks/d	0.95 0.95 0.77 0.95	0.71-1.3 0.68-1.3 0.52-1.1 0.66-1.4	age, residence, energy intake, HRT, smoking, BMI
Weiderpass et al, 2001 (35)	Sweden	1994-1995	PCC	50-74 PMP	709	3368	Any	1.0	0.83-1.21	smoking, age, BMI, parity, age at menopause, age at last birth, HRT, OC , diabetes
Petridou et al, 2002 (36)	Greece	1999	HCC	Not provided	84	84	Yes	0.63	0.27-1.49	age, education, height, BMI, age at menarche, pregnant, age at first pregnancy, no. of children, menopausal status
Storm et al, 2006 (37)	US	1999-2002	PCC	50-79 PMP	511	1412	<7 drinks/w ≥7 drinks/w	0.63 0.72	0.50-0.78 0.44-1.18	age, race
Hosono et al, 2008 (38)	Japan	2001-2005	HCC	20-79	148	1468	<1 drinks/w 1-2 drinks/w 3-4 drinks/w ≥5 drinks/w	0.71 0.77 0.67 0.37	0.39-1.29 0.40-1.50 0.31-1.43 0.17-0.82	age, smoking, BMI, exercise, menstrual status, age at menarche, menstruation, parity, diabetes, hypertension, OC, HRT, flushing after drinking.

Abbreviation: RR, relative risk; CI, confidence intervals; PCC, population-based case-control; HCC, hospital-based case-control; OC, oral contraceptive; BMI, body mass index; HRT, hormone replacement therapy; PMP, postmenopausal.

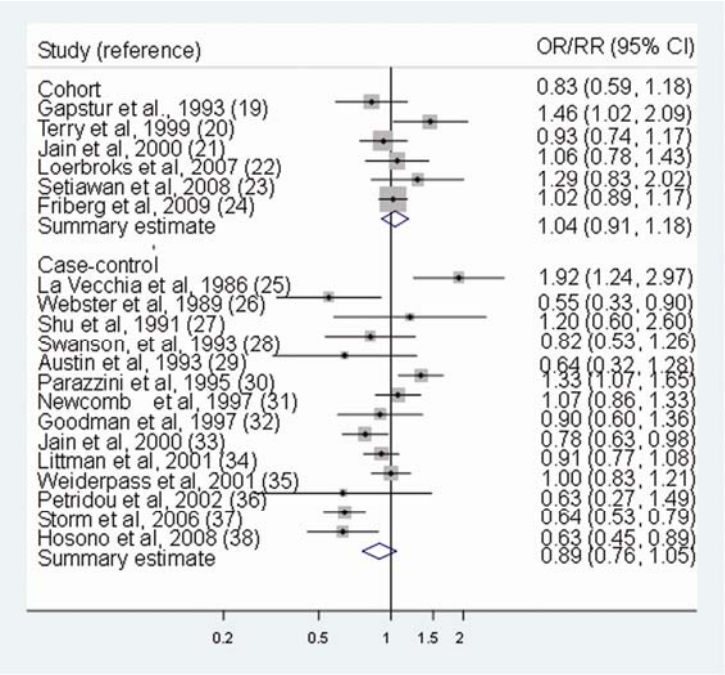

Figure 1. In prospective and case-control studies, risk estimates of endometrial cancer associated with alcohol consumption. Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight, i.e., the inverse of the variance); horizontal lines indicate 95% confidence intervals (CIs); diamonds indicate summary risk estimate with its corresponding 95% CI.

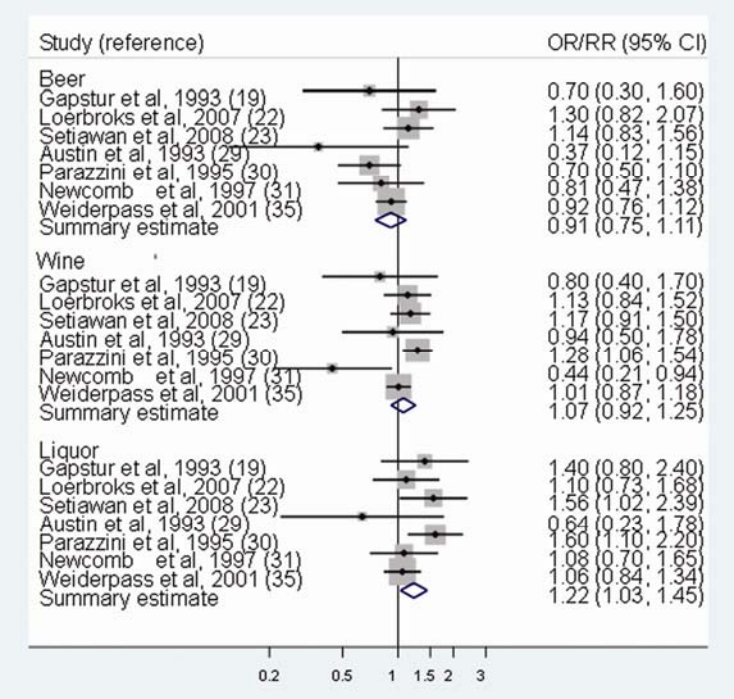

Figure 2. Risk estimates of endometrial cancer associated with alcohol consumption, stratified by the type of alcoholic beverage. Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight, i.e., the inverse of the variance); horizontal lines indicate 95% CIs; diamonds indicate summary risk estimate with its corresponding 95% CI.

Egger's test suggested no statistically significant asymmetry of the funnel plot for prospective (p=0.507) or case-control (p=0.747) studies, indicating no evidence of substantial publication bias.

In prospective studies, stratified analysis by geographic region and adjustment for HRT use did not show any statistically significant difference in summary estimates between strata. In case-control studies, stratified analysis by geographic region and adjustment for HRT use also suggested no clear association between ever alcohol use and endometrial cancer risk (data was not shown).

Type of alcohol

Three prospective and 4 case-control studies were included in the analysis of the association between different type of alcoholic beverage and endometrial cancer risk (Figure 2).[19,22,23,29-31,35] The individual risk estimates and summary estimates of endometrial cancer for specific alcohol intake are shown in Figure 1. Beer intake was not

significantly associated with endometrial cancer risk (RR: 0.91; 95% CI: 0.75-1.11). Compared to non-drinkers, wine drinkers had a RR of 1.07 (95% CI: 0.92-1.25) which showed that wine consumption was not associated with the risk of endometrial cancer. For liquor drinkers relative to nondrinkers, the RR of endometrial cancer for women was 1.22 (95% CI: 1.03-1.45) which indicated that liquor use could statistically significantly increase the risk of endometrial cancer.

Effect modification by HRT use

One prospective study and three case-control studies have examined the association between alcohol intake and risk of endometrial cancer according to HRT status.[23,31,35,38] Based on the results from those studies, the association was not statistically significant among HRT users (RR: 1.16; 95% CI: 0.90-1.51) and among non-HRT users (RR: 0.81; 95% CI: 0.60-1.09).

Effect modification by smoking status

One prospective study and three case-control studies have examined the association between alcohol intake and risk of endometrial cancer according to smoking status.[23,26,31,38] Based on the results from these studies, the association was not statistically significant among smokers (RR: 0.88; 95% CI: 0.64-1.21) and among non-smokers (RR: 0.86; 95% CI: 0.62-1.20).

DISCUSSION

Our meta-analysis has assessed the relationship between alcohol intake and endometrial cancer risk. The major points from our research are as follows. First, neither prospective studies nor case-control studies found that alcohol intake was associated with endometrial cancer risk. Second, we noted that liquor consumption, not other types of alcohol beverage, could significantly increase the risk of endometrial cancer.

There are several biological mechanisms through which alcohol might increase the risk of endometrial cancer development. Many studies have shown a positive association between alcohol intake and estrogen levels,[7,8,39] which in turn, may contribute to the development of endometrial cancer through increased mitotic activity of endometrial cells, increased number of DNA replication errors, and somatic mutations resulting in the malignant phenotype.[2] An important determinant of estrogen levels in women is use of unopposed HRT, which is consistently associated with an increased risk of endometrial cancer,[3] Furthermore, it has been suggested that alcohol consumption increases estradiol levels particularly in postmenopausal women who are on HRT.[40] However, our studies have indicated that alcohol consumption is not associated with the risk of endometrial cancer and no significant interaction with use of HRT has been found. In addition, moderate alcohol intake has also been shown to improve insulin sensitivity and reduce fasting insulin concentrations.[41] Insulin has been shown to stimulate the growth of endometrial stromal cells by binding to insulin receptors in endometrium.[42] These counteracting mechanisms by which alcohol might be associated with endometrial cancer risk probably cancel each other. This might explain the apparent absence of association.

An interesting finding that has emerged from our study is the suggestion of increased risk associated with liquor consumption and a null association with wine and beer consumption. It is very difficult to know the reason. But it is worth noting that wine and beer contain phytochemicals that may be associated with decreased risk of cancer.[43] In addition, wine, particularly red wine, contains high levels of antioxidants as well as resveratrol, a phytoestrogen with anticancer properties.[44] It is possible that alcohol increases endometrial cancer risk but the antioxidants and phytoestrogens in alcoholic beverages counteract that effect when alcohol is consumed at moderate levels. If it is true, this may explain the results found in our studies for total alcohol. The possible differential effects of wine, beer, and liquor must be clarified in the future study.

Nevertheless, our meta-analysis has several limitations. First, a limitation of our approach is that only articles published in the English language were included. Limited resources prevented us from including articles published in other languages. Second, all studies we included are observational. Observational studies, even when well controlled, are susceptible to various biases. Prospective cohort studies are less susceptible to bias than case-control studies, because, in the prospective design, information on exposures is collected before the diagnosis of the disease. In our meta-analysis, the pooled results of prospective studies also showed a null association between alcohol intake and endometrial cancer risk. Third, individual studies may have failed to adjust for potential confounders such as oral contraceptive use and menopausal status in the data analysis which could influence the relationship between alcohol consumption and endometrial cancer risk. Moreover, other factors may be influencing the estimates for the association between alcohol and endometrial cancer risk, since non-alcohol drinkers may differ from the general population of alcohol drinkers concerning other exposures such as physical activity, or fruit and vegetable intake. And the studies included in our meta-analysis rarely considered confounding or interaction from these variables. Fourth, our results are likely to be affected by some misclassification of alcohol consumption. Only one of the six prospective studies updated the information about alcohol drinking status during follow-up.[24] And changes in alcohol consumption throughout life may lead to misclassification. Misclassification of alcohol drinking status may have been introduced in the other five prospective studies that assessed it at baseline only. Fifth, the relationship between amount of alcohol intake and endometrial cancer risk should be considered, but we did not have enough information to do dose-response analysis. Because some articles that we included in our study have no dose-response analysis between alcohol consumption and endometrial cancer. Moreover, although a few studies showed the dose-response data, there was no uniform criterion for dose to conduct further stratified analysis. Additionally, as presented in Table 1, most included studies which conducted dose stratified analysis showed no significant dose-dependent association. Finally, heterogeneity may have been introduced by different measure methods among studies, such as different type of alcohol consumed and different assessment methods.

In conclusion, our meta-analysis of all prospective and case-control studies demonstrates that alcohol consumption is not associated with the risk of endometrial cancer. Future studies should also examine whether the relation varies according to different type of alcohol beverage.

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AUTHOR DISCLOSURES

Qingmin Sun, Linlin Xu, Bo Zhou, You Wang, Yali Jing and Bin Wang, no conflicts of interest.

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Original Article

Alcohol consumption and the risk of endometrial cancer: a meta-analysis

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饮酒与子宫内膜癌发病风险的相关性：統合分析

流行病学研究饮酒与子宫内膜癌发病风险的相关性結果并不一致，因此我们进行一项統合分析(meta-analysis)来评估子宫内膜癌发病风险与饮酒的相关性。从 MEDLINE 和 EMBASE 数据库，系统性地搜索 2010 年 4 月前的相关文献，用随机效应模式对风险评估结果进行加权。纳入了 6 个前瞻性研究和 14 个病例对照研究。结果发现在前瞻性研究中，饮酒与子宫内膜癌发病风险无相关性(RR 值为 1.04，95%可信区间是 0.91-1.18)，病例对照研究中同样无相关性(OR 值为 0.89，95%可信区间是 0.76-1.05)。然而，分层分析结果却发现，饮蒸餾酒者有較高的子宫内膜癌的发病风险(RR 值为 1.22，95%可信区间是 1.03-1.45)，葡萄酒与啤酒则无相关性。总言之，饮酒与子宫内膜癌的发病风险无相关性。未来的研究應檢测子宫内膜癌风险与饮酒的關聯性是否依酒的種类而異。

關鍵字：饮酒、子宫内膜癌、发病风险、相关性、統合分析