# Alcohol, Wine, and Risk of Epithelial Ovarian Cancer

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## Abstract

**Moderate alcohol intake can influence sex hormone levels and affect ovarian function as well as increasing breast cancer risk. This suggests that alcohol might also influence ovarian cancer risk. We have evaluated this among 696 Australian women with histologically confirmed epithelial ovarian cancer and 786 cancer-free control women, selected at random from the electoral roll. Sociodemographic information and a detailed reproductive history were collected in a face-to-face interview, and information about diet and alcohol consumption was obtained from a food frequency questionnaire. Logistic regression was used to calculate adjusted odds ratios (OR) and 95% confidence intervals (95% CI). Overall, 59% of women drank <1 standard drink/week and only 5% of cases and 8% of controls drank an average of ≥2 standard drinks/day. Compared with nondrinkers, the OR for women who drank an average of ≥2 standard drinks/day was 0.49 (95% CI = 0.30–0.81). This effect did not vary for the different subtypes but was restricted to wine (OR = 0.56, 95% CI = 0.33–0.93 for ≥1 glass/day *versus* nondrinkers) with no effect for beer (OR = 1.26, 95% CI = 0.65–2.46) or sherry/spirits (OR = 1.07, 95% CI = 0.59–1.95). Combining our results with the six previous population-based studies gave a pooled OR of 0.72 (95% CI = 0.54–0.97) for the highest alcohol intake group *versus* nondrinkers. These data suggest that alcohol does not increase risk of ovarian cancer. In this Australian population, the inverse association with alcohol was due solely to wine consumption and so may be a consequence of antioxidants and/or phytoestrogens in wine rather than the alcohol itself.** (Cancer Epidemiol Biomarkers Prev 2004;13(4):592–599)

## Background

Regular moderate alcohol consumption has been associated with increased levels of circulating estrogens, particularly among postmenopausal women taking hormone replacement therapy (HRT; Ref. 1). Higher alcohol intake has also been associated with lower levels of progesterone (2) and higher levels of androstenedione (3) among premenopausal women. Other reported consequences of moderate to high alcohol intake in women include increased menstrual symptoms, infertility and spontaneous abortion (4, 5), and derangements of menstrual cycle and reproductive hormone function (6). Animal studies have also shown that chronic alcohol exposure leads to ovarian failure in rats (7). It is now generally accepted that drinking alcohol increases a woman's risk of developing breast cancer, although the effect is not large with about 10% increase in risk seen for each additional alcoholic drink/day (8, 9). The mechanism underlying the alcohol-breast cancer link is not clear, although it may be due at least in part to the effect of alcohol on sex hormone levels (10). These data suggest that alcohol consumption might also influence the risk of ovarian cancer.

Previous epidemiological studies have variously reported a positive (11, 12), inverse (13, 14), or null (15–17) association between alcohol consumption and risk of ovarian cancer. However, many of these studies had limited power to detect an effect because of small numbers, particularly for higher levels of alcohol intake. It is also becoming increasingly clear that risk factors vary for the different histological subtypes of ovarian cancer (18). For example, cigarette smoking has not clearly been associated with ovarian cancer risk overall, but recent studies have consistently shown that women who smoke have ~2-fold increased risk of developing mucinous ovarian cancers (19–21). To date, few studies have evaluated either the association between alcohol and different histological subtypes of ovarian cancer or the effects of different types of alcohol.

The present study was conducted to evaluate the association between alcohol intake and ovarian cancer risk in a large population-based case-control study conducted in Australia between 1990 and 1993. In addition, we have brought together all of the published data evaluating the association between alcohol consumption and epithelial ovarian cancer to comprehensively examine this association.

## Methods

The methods have been described previously in full (22). Briefly, between August 1990 and December 1993, histologically confirmed incident cases of primary epithelial ovarian cancer were ascertained through the major

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treatment centers in the three most populous Australian states (New South Wales, Victoria, and Queensland). With consent from their treating doctor, eligible women aged between 18 and 79 years were invited to take part in the study. Among 925 eligible cases identified, 50 (5%) died prior to interview, 12 (1%) could not be traced, and 41 (4%) either refused or their doctor did not consent, giving a participation rate of 89%. Tissue from each case was reviewed by an independent pathologist in each state to confirm the diagnosis and histological type of the cancer. Control women, frequency matched to the cases for age (within 10-year bands) and urban/rural district of residence, were selected at random from the electoral roll (enrolment to vote is compulsory in Australia) and sent a letter inviting them to take part in the study. Women who reported a history of ovarian cancer or bilateral oophorectomy were excluded. Of the 1527 potential control women selected, 192 (13%) could not be traced and 162 (11%) were found to be ineligible, and of the remaining 1173, 855 (73%) agreed to take part in the study. To ensure comparability between cases and controls, the 28 case women who were not on the electoral roll were excluded from all analyses.

All women provided detailed information in a standardized face-to-face interview, and full histories of pregnancy, lactation, and contraceptive use were obtained by a life calendar from age 15 to 50. Most women (90% of cases and 95% of controls) also provided dietary data via a self-completed food frequency questionnaire adapted for the Australian population from the instrument developed and validated by Willett *et al.* (23). The food frequency questionnaire asked about usual consumption in the 12 months prior to cancer diagnosis for cases or interview for controls. It included questions on frequency of drinking different types of alcohol (*i.e.*, red wine, white wine and champagne, beer, low-alcohol beer, sherry and port, and spirits). This information was used to estimate a woman's average total daily alcohol intake (in grams). The food frequency questionnaire also included questions on consumption of foods and beverages that contain caffeine, including coffee, tea, cola drinks, and chocolate. Caffeine consumption was considered a potential confounder of the association between alcohol and ovarian cancer based on a previous report (17); therefore, total caffeine intake was calculated based on the estimated caffeine content of the following food items: coffee (assumed to be instant) 70 mg/250 ml cup, tea 30 mg/250 ml cup, cola 36 mg/375 ml can, and chocolate (assumed to be milk chocolate) 10 mg/50 g bar.

Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to estimate the relative risk (RR) of ovarian cancer associated with different levels of alcohol intake. Multiple logistic regression models were used to simultaneously adjust for possible confounders including age (in years), age squared, level of education (post-high school *versus* lower), body mass index (BMI; <65th, 65–85th, and >85th percentiles), parity, duration of oral contraceptive (OC) use (never, <24, 24–59, 60–119, and ≥120 months), smoking history (never, past, or current), and caffeine intake (quintiles). Other potential confounders, including family history of breast or ovarian cancer, use of HRT, use of talc in the perineal region, and history of tubal ligation or hysterectomy, were not included in the final models because their inclusion had no appreciable effect on the OR for the variables of interest. To test for heterogeneity across levels of known risk factors for ovarian cancer (*e.g.*, age and menopausal status), a term for the interaction between the level of wine consumption and the risk factor of interest was added to the adjusted model. A two-sided $P$ value of <0.05 for the likelihood ratio test for addition of the interaction term to the model was taken as evidence of heterogeneity.

**Systematic Review.** Medline (1966–2003) was used to identify articles that reported data on alcohol intake in relation to ovarian cancer and additional studies were identified from the reference lists of these articles. Studies that did not report a measure of relative risk (RR) were excluded as were those that had no control for potential confounders other than age and/or race. Summary ORs (using a random effects model), tests for heterogeneity of the individual study results, and forest plots were generated using the Stata statistical package (24). This was done for all studies combined and also separately for population-based and hospital/clinic-based studies because, *a priori*, we were concerned that alcohol consumption among a control group of hospitalized women might not accurately reflect that in the general population.

## Results

Complete data were available for 696 cases and 786 controls. Overall, 33% of cases and 24% of controls reported no alcohol consumption in the 12 months prior to cancer diagnosis for cases or interview for controls. One third of the women (31% of cases and 32% of controls) drank some alcohol but less than an average of 1.8 g/day (<1 standard drink/week), and only 5% of cases and 8% of controls reported drinking an average of ≥25 g/day of alcohol (2 standard drinks). Most women drank more than one form of alcohol. Wine was most popular, with 60% of women reporting some wine consumption (59% white wine and 29% red wine) while one-third of the women reported drinking each of the other types of alcohol considered: beer (32%), sherry and/or port (32%), and spirits (36%). Overall, about one-half of the alcohol consumed by the women came from wine, with about one-quarter from beer and one-quarter from sherry, port, and spirits.

Consumption of any alcohol was associated with a reduced risk of ovarian cancer with an adjusted OR of 0.71 (95% CI = 0.55–0.92) among drinkers relative to nondrinkers. Even an average consumption of <1.8 g/day of alcohol (<1 standard drink/week) was associated with a 20% reduction in risk of ovarian cancer (OR = 0.79, 95% CI = 0.59–1.05). Increasing consumption of alcohol was associated with a decreasing risk of ovarian cancer, with ~50% reduction in risk (OR = 0.49, 95% CI = 0.30–0.81) seen among women who reported an average consumption of ≥25 g/day of alcohol (2 standard drinks) compared with nondrinkers (Table 1). This trend was, however, only of marginal statistical significance when nondrinkers were excluded from the analysis. There were no statistically significant differences between borderline and invasive cancers or between the different histologic subtypes.

When intake of different types of alcohol was considered (Table 2), wine drinkers had a lower risk of ovarian cancer than both self-reported nondrinkers and women who reported drinking only beer or spirits. There was also a statistically significant trend toward lower risk with increasing wine consumption ($P$ for trend = 0.01 excluding nondrinkers). This association persisted after adjustment for consumption of other types of alcohol and was especially strong for consumption of red wine (OR = 0.15, 95% CI = 0.05–0.45 for >1 glass/day relative to nondrinkers) compared with white wine (OR = 0.62, 95% CI = 0.38–1.01), although few women ($n$ = 27) drank an average of >1 glass/day of red wine. In contrast, although beer drinkers had a lower risk of ovarian cancer than nondrinkers, there was no trend in risk with increasing beer consumption and the association disappeared after adjustment for consumption of other types of alcohol. The pattern for fortified wines and spirits was similar to that seen for beer.

We then considered whether the inverse association between wine consumption and risk of ovarian cancer varied according to other characteristics of the women. The effect was somewhat stronger among younger women (OR = 0.35 for ≥1 glass/day *versus* no alcohol at age <50 years compared with 0.61 at age ≥50 years), although the difference with age was not statistically significant ($P_{interaction}$ = 0.7). The association was significantly stronger among women with a higher level of education (OR = 0.34 *versus* 0.76 among women who attended school only; $P_{interaction}$ = 0.02), those who had never smoked (OR = 0.28 *versus* 0.82 among smokers; $P_{interaction}$ = 0.005), and those who had used the OC

**Table 1. Total alcohol intake and risk of ovarian cancer by tumor type**

| Alcohol (standard drinks)[a] | Cases (%) | Controls ($n$ = 786; %) | Adjusted OR[b] | 95% CI | Test for trend | Excluding nondrinkers |
|---|---|---|---|---|---|---|
| All cancers ($n$ = 696) | | | | | | |
| None | 32.8 | 23.8 | 1.0 | | | |
| <1/wk | 31.0 | 31.6 | 0.79 | 0.59–1.05 | | |
| 1–6/wk | 22.7 | 29.1 | 0.66 | 0.48–0.90 | | |
| 1–1.9/day | 8.2 | 7.9 | 0.78 | 0.50–1.23 | | |
| ≥2/day | 5.3 | 7.6 | 0.49 | 0.30–0.81 | $P$ = 0.003 | $P$ = 0.07 |
| Invasive cancers ($n$ = 570) | | | | | | |
| None | 32.6 | 23.8 | 1.0 | | | |
| <1/wk | 30.7 | 31.6 | 0.84 | 0.62–1.14 | | |
| 1–6/wk | 23.5 | 29.1 | 0.73 | 0.53–1.02 | | |
| 1–1.9/day | 8.4 | 7.9 | 0.85 | 0.53–1.36 | | |
| ≥2/day | 4.7 | 7.6 | 0.46 | 0.27–0.79 | $P$ = 0.009 | $P$ = 0.05 |
| Borderline cancers ($n$ = 126) | | | | | | |
| None | 33.3 | 23.8 | 1.0 | | | |
| <1/wk | 32.5 | 31.6 | 0.68 | 0.40–1.15 | | |
| 1–6/wk | 19.1 | 29.1 | 0.47 | 0.26–0.85 | | |
| 1–1.9/day | 7.1 | 7.9 | 0.66 | 0.27–1.58 | | |
| ≥2/day | 7.9 | 7.6 | 0.70 | 0.30–1.61 | $P$ = 0.12 | $P$ = 0.9 |
| Serous cancers ($n$ = 360) | | | | | | |
| None | 32.5 | 23.8 | 1.0 | | | |
| <1/wk | 32.5 | 31.6 | 0.90 | 0.64–1.27 | | |
| 1–6/wk | 21.4 | 29.1 | 0.72 | 0.49–1.05 | | |
| 1–1.9/day | 8.1 | 7.9 | 0.88 | 0.51–1.51 | | |
| ≥2/day | 5.6 | 7.6 | 0.61 | 0.35–1.17 | $P$ = 0.09 | $P$ = 0.3 |
| Endometrioid and clear cell cancers ($n$ = 147) | | | | | | |
| None | 32.0 | 23.8 | 1.0 | | | |
| <1/wk | 31.3 | 31.6 | 0.92 | 0.55–1.52 | | |
| 1–6/wk | 23.1 | 29.1 | 0.85 | 0.49–1.47 | | |
| 1–1.9/day | 8.8 | 7.9 | 1.34 | 0.62–2.88 | | |
| ≥2/day | 4.8 | 7.6 | 0.52 | 0.20–1.33 | $P$ = 0.4 | $P$ = 0.5 |
| Mucinous cancers ($n$ = 105) | | | | | | |
| None | 28.6 | 23.8 | 1.0 | | | |
| <1/wk | 36.2 | 31.6 | 0.85 | 0.49–1.50 | | |
| 1–6/wk | 21.9 | 29.1 | 0.56 | 0.30–1.06 | | |
| 1–1.9/day | 7.6 | 7.9 | 0.57 | 0.22–1.45 | | |
| ≥2/day | 5.7 | 7.6 | 0.44 | 0.16–1.20 | $P$ = 0.03 | $P$ = 0.07 |
| Other histological types ($n$ = 84) | | | | | | |
| None | 40.2 | 23.8 | 1.0 | | | |
| <1/wk | 18.3 | 31.6 | 0.34 | 0.17–0.68 | | |
| 1–6/wk | 28.1 | 29.1 | 0.67 | 0.36–1.24 | | |
| 1–1.9/day | 8.5 | 7.9 | 0.65 | 0.25–1.67 | | |
| ≥2/day | 4.9 | 7.6 | 0.37 | 0.12–1.18 | $P$ = 0.15 | $P$ = 0.5 |

[a]Assuming 12.5g of alcohol = 1 standard drink.
[b]OR adjusted for age (in years), age squared, level of education, BMI, smoking status (never, past, or current), duration of OC use, parity, and caffeine intake (quintiles).

**Table 2. Alcohol type and risk of ovarian cancer compared with nondrinkers**

| Alcohol (drinks) | Cases (%) | Controls (%) | Adjusted OR[a] | 95% CI | Adjusted OR[b] | 95% CI |
|---|---|---|---|---|---|---|
| Nondrinkers[c] | 32.8 | 23.8 | 1.0[c] | Reference | 1.0[c] | Reference |
| Wine | | | | | | |
| None[d] | 13.7 | 9.7 | 1.13 | 0.77–1.67 | 1.20 | 0.77–1.91 |
| <1/wk | 30.0 | 37.3 | 0.64 | 0.48–0.86 | 0.68 | 0.48–0.96 |
| 1–6/wk | 17.1 | 19.5 | 0.72 | 0.50–1.00 | 0.77 | 0.51–1.19 |
| ≥1/day | 6.5 | 9.8 | 0.53 | 0.34–0.83 | 0.56 | 0.33–0.93 |
| | | | $P = 0.01$[e] | | $P = 0.01$[e] | |
| Beer | | | | | | |
| None[d] | 37.4 | 42.8 | 0.72 | 0.54–0.95 | 1.21 | 0.77–1.91 |
| <1/wk | 17.0 | 18.5 | 0.76 | 0.54–1.07 | 1.28 | 0.78–2.10 |
| 1–6/wk | 8.8 | 11.3 | 0.59 | 0.39–0.89 | 0.94 | 0.55–1.61 |
| ≥1/day | 4.2 | 3.7 | 0.83 | 0.46–1.51 | 1.26 | 0.65–2.46 |
| | | | $P = 0.8$[e] | | $P = 0.5$[e] | |
| Sherry/spirits | | | | | | |
| None[d] | 21.3 | 22.7 | 0.74 | 0.54–1.02 | 1.21 | 0.77–1.91 |
| <1/wk | 29.2 | 33.2 | 0.72 | 0.54–0.96 | 1.16 | 0.75–1.80 |
| 1–6/wk | 11.6 | 14.4 | 0.67 | 0.46–0.97 | 1.08 | 0.64–1.82 |
| ≥1/day | 5.2 | 6.0 | 0.68 | 0.40–1.14 | 1.07 | 0.59–1.95 |
| | | | $P = 0.6$[e] | | $P = 0.5$[e] | |

[a]OR adjusted for age (in years), age squared, level of education, BMI, smoking status (never, past, or current), duration of OC use, parity, and caffeine intake (quintiles).
[b]OR also adjusted for consumption of other types of alcohol (none, <1/week, 1–6/week, or ≥1/day).
[c]Reference category for calculation of ORs but excluded from trend tests.
[d]Women who did not drink that type of alcohol but who did drink other types of alcohol.
[e]Trend tests calculated after excluding nondrinkers.

pill (OR = 0.40 *versus* 0.81 among nonusers; $P_{interaction}$ = 0.003). It was also somewhat stronger among women who had a family history of breast and/or ovarian cancer (OR = 0.29 *versus* 0.59 among those with no family history; $P_{interaction}$ = 0.06). There was no significant variation with menopausal status, BMI, or use of HRT.

We also considered whether the apparent inverse association between ovarian cancer risk and wine consumption could be due to cases having reduced their alcohol intake in the months prior to their diagnosis with cancer. Likely, such changes would be greater for women with more advanced disease or who experienced gastrointestinal and/or abdominal symptoms prior to their diagnosis. The association between wine and ovarian cancer risk did not vary significantly with stage of disease. Compared with nondrinkers, the ORs for consumption of ≥1 glass/day of wine were 0.60 (95% CI = 0.26–1.36) for women with borderline disease, 0.50 (95% CI = 0.23–1.07) for women with early cancer (stage 1 or 2), and 0.60 (95% CI = 0.34–1.05) for women with advanced cancer (stage 3 or 4). The association was somewhat stronger among women who did not experience gastrointestinal or abdominal symptoms (OR = 0.26, 95% CI = 0.09–0.79 for ≥1 glass/day) than among women with these symptoms (OR = 0.60, 95% CI = 0.37–0.95), whereas the opposite pattern would be expected if these symptoms had caused women to reduce their alcohol intake prior to diagnosis.

**Summary of Literature.** We identified 24 other reports that included data on alcohol intake and ovarian cancer. Two of these (25, 26) were excluded because they reported results for a subset of subjects that were also included in a more comprehensive report, leaving a total of 22 separate studies. Four studies were excluded because they did not report RRs for the association between alcohol and ovarian cancer (27–30) and an additional five studies were excluded because they presented only crude (11, 15) or age/race-adjusted (31–33) estimates with no control for other potentially important confounders.

The results of the remaining six population-based and eight hospital-based studies are shown in Table 3 and Fig. 1 together with the results of the present study. There was statistically significant heterogeneity when the results of all 14 studies were considered together (heterogeneity $\chi^2$ = 26.5, $df$ = 13, $P$ = 0.01), suggesting that combining the data would be inappropriate.

There was still some variability when only the seven population-based studies (including the present study) were considered, but this did not reach statistical significance ($\chi^2$ = 10.8, $df$ = 6, $P$ = 0.09). Five of the six previous population-based studies were conducted in the United States. One case-control study (13) and the only cohort study (14) both reported statistically significant reductions in risk of ovarian cancer associated with alcohol. Three others reported a nonsignificant reduction in risk (16, 34, 35) while one reported a nonsignificant increase in risk (17). Combining the results of these six studies with the present study gave a pooled OR of 0.72 (95% CI = 0.54–0.97).

There was less variability among the results of the seven hospital-based studies ($\chi^2$ = 8.1, $df$ = 6, $P$ = 0.2). Two studies reported an inverse association between alcohol and ovarian cancer (36, 37) that was statistically significant in one (36), one reported no association (38), and four reported nonsignificant increases in risk of ovarian cancer associated with alcohol (12, 39–41). Combining the results of all seven hospital-based studies gave a pooled OR of 1.10 (95% CI = 0.83–1.44). When the two studies that had simply compared drinkers and nondrinkers were excluded, the pooled OR was unchanged (1.10, 95% CI = 0.79–1.52).

**Table 3. Summary of results from previous studies of alcohol and ovarian cancer that included adjustment for confounding together with the results of the present study**

| Study | Country | Study population (cases/controls) | Alcohol comparison (standard drinks/wk)[a] | RR (95% CI) | Trend |
|---|---|---|---|---|---|
| *Population-based studies* | | | | | |
| Gwinn *et al.* (13) | United States | 433/2915, age < 55 yr | ≥20 *vs.* none[b] | 0.5 (0.2–0.9)[c] | – |
| Whittemore *et al.* (16) | United States | 188/539 (259 population, 280 hospital) | ≥20 *vs.* none | 0.66 (0.3–1.5) ($P$ = 0.34)[d,e] | No trend |
| Kushi *et al.* (14) | United States | Cohort n = 29,083 (139 cases) | > 6 *vs.* none[b] | 0.49 (0.24–1.01)[c] | $P$ = 0.01 |
| Kuper *et al.* (17) | United States | 563/523 | >21 *vs.* none | 1.35 (0.80–2.26)[c] | $P$ = 0.2 |
| Goodman *et al.* (34) | United States | 558/607 | ≥14 *vs.* none | 0.84 (0.55–1.28)[d,f] | $P$ = 0.7 |
| Schouten *et al.* (35) | Holland | Case-cohort: 214/2211 (members of subcohort) | >8.3 *vs.* none[b] | 0.85 (0.52–1.42)[c] | $P$ = 0.5 |
| Webb *et al.* | Australia | 696/786 | ≥14 *vs.* none[b] | 0.49 (0.30–0.81)[c] | $P$ = 0.003 |
| *Hospital-based studies* | | | | | |
| Hartge *et al.* (39) | United States | 296/343 (hospital discharge lists) | ≥14 *vs.* none | 1.5 (0.8–2.8)[g] | $P$ = 0.14 |
| Kato *et al.* (36) | Japan | 417/8920 (other cancers) | ≥7 (daily) *vs.* none | 0.38 (0.16–0.90)[g] | – |
| La Vecchia *et al.* (12) | Italy (1983–1990) | 801/2114 | ≥21 *vs.* none | 1.3 (0.9–1.8)[c] | $P$ < 0.05 |
| Polychronopoulou *et al.* (40) | Greece | 189/200 (hospital visitors) | Trend glass/day ≥21 *vs.* none (estimate) | 1.06 (0.82–1.36)[c] 1.2 (0.6–2.5)[h] | $P$ = 0.7 |
| Nandakumar *et al.* (41) | India | 97/194 (suspected cancer, not confirmed) | With or without history of consumption | 1.3 (0.2–8.0)[i] | – |
| Tavani *et al.* (38) | Italy (1992–1999) | 1031/2411 (acute non-neoplastic, non-hormone-related) | >20[b] *vs.* never | 1.09 (0.76–1.57)[f] | $P$ = 0.4 |
| Yen *et al.* (37) | Taiwan | 86/369 (nonmalignant, nongynecological conditions) | Yes *vs.* no | 0.71 (0.20–2.51)[i] | – |
| *Studies of women with alcoholism (standardized for age only)* | | | | | |
| Adami *et al.* (42) | Sweden | 1013 women with alcoholism, 1965–1983 (4 cases) | Diagnosis of alcoholism | 1.9 (0.5–4.9) | – |
| Tønnesen *et al.* (43) | Denmark | 3093 women with alcoholism, 1954–1987 (6 cases) | Diagnosis of alcoholism | 0.9 (0.3–1.8) | – |
| Sigvardsson *et al.* (44) | Sweden | 15,508 alcoholic and 15,508 matched nonalcoholic women (65 and 53 cases, respectively) | History of alcohol abuse *vs.* not | 1.2 (0.9–1.8) | – |
| Lagiou *et al.* (45) | Sweden | 36,856 women with alcoholism, 1965–1994 (76 cases) | Diagnosis of alcoholism | | |
| | | | Age < 60 yr | 0.76 (0.58–1.00) | – |
| | | | Age ≥ 60 yr | 0.99 (0.70–1.36) | – |

[a]Comparison for highest *versus* lowest group only shown.
[b]Approximate, assuming 1 drink = 12.6 g of alcohol.
[c]Multivariate including smoking.
[d]Further adjustment for smoking and/or coffee had little effect.
[e]95% CI estimated from $P$ value using test-based limits (49).
[f]Multivariate excluding smoking and caffeine.
[g]Adjusted for age and/or race; further adjustment had little effect.
[h]Estimated using β and SE calculated from reported continuous OR and 95% CI.
[i]Limited adjustment for age and education/income (37) or geographic region/marital status (41).

In addition to the above studies, we identified four reports from cohort studies of women with alcoholism conducted in Scandinavia (42–45). Overall, these found little evidence for an association between a diagnosis of alcoholism and risk of ovarian cancer (Table 3), although, in the largest study, a 24% reduction in risk was seen among alcoholics under age 60 (45). These studies were not included in the meta-analysis above because they had no adjustment for potential confounders other than age.

## Discussion

Data from this large population-based study of ovarian cancer suggest that alcohol consumption, specifically wine drinking, may be associated with a reduced risk of ovarian cancer. The apparent protective effect was seen at even low to moderate levels of alcohol or wine intake and did not differ appreciably for borderline and invasive cancers or for the different histologic subtypes of ovarian cancer. After adjusting for wine consumption,

there was no association between consumption of either beer or sherry/spirits and ovarian cancer risk. There was some suggestion that the greatest protective effect of wine was seen among women already at lower risk of ovarian cancer because they were younger, better educated, nonsmokers, or OC users. The only exception to this pattern was the stronger effect seen among women with a family history of breast or ovarian cancer.

A reduction in risk among women drinking alcohol is consistent with the results of five of the six previous population-based studies (13, 14, 16, 34, 35). To date, only one population-based study has reported an increased risk associated with alcohol and this study did not control for caffeine intake, a strong risk factor for ovarian cancer in their data that is also likely to be associated with alcohol intake (17). Pooling the results of the present study with the previous population-based studies suggested that women in the highest alcohol groups had a significantly lower risk of ovarian cancer. In contrast, there was no association between alcohol intake and ovarian cancer when the results of the seven hospital-based studies were combined. The results of hospital-based studies are, however, difficult to interpret because alcohol consumption reported by women who are hospitalized may not accurately reflect that among women in the general population.

The observation that the reduction in risk was associated only with wine intake and not other types of alcohol suggests that the apparent protective effect might be due to something other than the alcohol in wine. Six of the previous studies attempted to separate the effects of different types of alcoholic beverage. In the majority of these studies, the reference group for each type of alcohol included women who drank other types of alcohol (12, 13, 35, 38); thus, the results are hard to interpret. In one study, wine, beer, and spirits drinkers were compared with complete nondrinkers, and as in the present study, the authors reported a stronger protective effect for wine, particularly red wine, than for either beer or spirits (34).

It is, however, difficult to know whether the apparent protective effect seen for wine and not other alcohol is real. Although several studies have assessed consumption of different types of alcohol in relation to breast cancer risk, each type of alcohol has been implicated in different studies and the totality of evidence suggests that the source of the alcohol is not important (46). This is consistent with the hypothesis that it is the effect of alcohol on circulating estrogen levels that increases breast cancer risk. The absence of a positive association between alcohol and ovarian cancer suggests that any effect of moderate alcohol intake on hormone levels and/or ovarian function is not sufficient to increase risk of ovarian cancer appreciably. Unlike spirits and beer, wine, particularly red wine, contains high levels of antioxidants as well as resveratrol, a phytoestrogen with anticancer properties (47); thus, it is plausible that wine could influence cancer risk independently of the alcohol it contains.

It is important to consider whether the observed effects could be due to bias or confounding. If cases had changed their alcohol intake around the time of their cancer diagnosis or had simply underestimated their usual alcohol intake as a consequence of their disease, one might expect that the underreporting would be greatest, and thus the OR lowest, among women diagnosed with more advanced disease or who had gastric and abdominal symptoms. This was not the case.

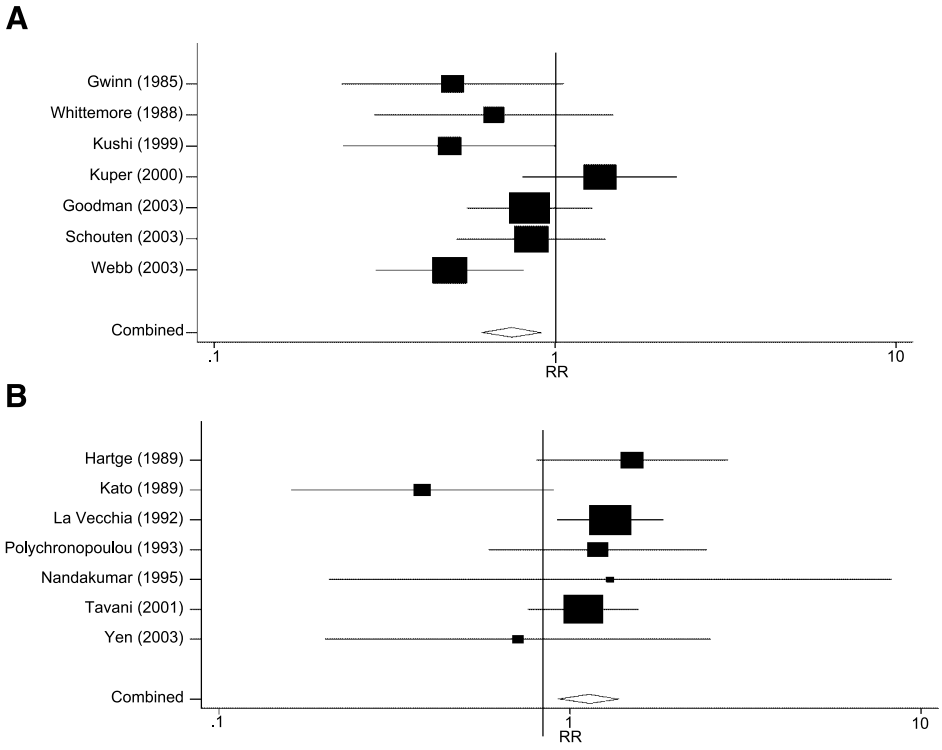


*Fig. 1.* Diagrammatic representation of study findings of the relation between the highest measured level of alcohol intake and ovarian cancer risk for (**A**) population-based and (**B**) hospital/clinic-based studies. *Center of each square,* RR of the study. *Horizontal line,* 95% CI. The size of the square is proportional to the amount of information from the study. *Open diamonds,* pooled RRs and their 95% CIs.

It is also possible that controls may have systematically overestimated their alcohol intake. Using population alcohol intake data from the 1989 Australian National Health Survey (48) and adjusting for age, we would have expected 27% of the control population to have drunk no alcohol within the last 12 months and 49% to drink alcohol more than once a week compared with the observed 24% and 46%, respectively. The expected and observed proportions of women drinking beer (13% and 15%), wine (29% and 29%), and fortified wine and spirits (19% and 21%) more than once a week were also reassuring close. Furthermore, the apparent protective effects were seen only for wine, particularly red wine, and it is unlikely that cases would selectively underestimate and/or controls selectively overestimate their intake of wine and not other types of alcohol. Adjustment for known ovarian cancer risk factors that were also significantly associated with wine consumption in this population (age, level of education, smoking, caffeine intake, OC use, parity, and BMI) had little effect on the effect estimates (crude OR = 0.48, 95% CI = 0.32–0.73; adjusted OR = 0.53, 95% CI = 0.34–0.83); thus, it is unlikely that the strong inverse effect seen is due to residual confounding by these factors.

Taken together, the results of this and the six previous population-based studies suggest that, compared with nondrinkers, women who consume alcohol have a reduced risk of ovarian cancer. In this study and the one previous study that evaluated the effects of drinkng wine, beer, and spirits separately compared with nondrinkers, the strongest inverse associations were seen for wine, particularly red wine. It is thus possible that the high levels of antioxidants and phytoestrogens found in wine could reduce risk of ovarian cancer. Further data evaluating the association between different types of alcohol and ovarian cancer risk are required to confirm these results.

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