

REVIEW OF ALCOHOL :ASSOCIATION WITH ENDOMETRIAL CANCER

Introduction

Despite a recent decline in the incidence rate of endometrial cancer, it remains the most common cancer of the female reproductive tract (Hill and Austin, 1996). It is known that hormonal factors play a central role in the aetiology of endometrial cancer (Brinton *et al.*, 1993). Two previous reports (CC/98/23 and CC/99/8) have reported on the relationship between alcohol consumption and breast cancer. This review will examine the relationship, if any, between alcohol intake and endometrial cancer.

Hormone dependence of endometrial cancer

Most risk factors for endometrial cancer are related to reproductive factors that affect a woman's hormonal status. Endometrial cancer is frequently related to a history of menstrual irregularities, infertility and anovulation (Peterson, 1968). Known risk factors for the disease include early age at menarche, nulliparity and late menopause, all of which prolong the years of menstruation (Parazzini *et al.*, 1991). In other words, a hyperoestrogenic state seems to be directly related to risk of endometrial cancer. "Artificial" hyperoestrogenism can be induced by oestrogen replacement therapy and also by the use of certain oral contraceptive preparations (Weiss and Sayvetz, 1980; Van Leeuwen and Rookus, 1989). Weiderpass *et al.* (1999) have observed that in postmenopausal women, oral use of oestradiol 1-2 mg daily increased the relative risk of endometrial cancer and endometrial atypical hyperplasia, with odds ratio (OR) for at least 5 years of use compared with never use of 3.0 (95% CI 2.0-4.0) and 8.3 (4.0-17.4), respectively.

Endometrial cancer and diet

There is also a strong relationship between endometrial cancer and obesity (see Hill and Austin, 1996 for review), and it has been postulated that diet affects endometrial cancer risk. Many epidemiological studies have examined the impact of various aspects of diet on endogenous hormone levels. Studies in vegetarians consuming low-fat diets have demonstrated increased urinary excretion of oestrogens and decreased plasma oestrogen levels (Armstrong *et al.*, 1981; Goldin *et al.*, 1982). In women placed on a low-fat diet, there was an apparent shift in oestrogen metabolism towards the less active oestrogen metabolites (Longcope *et al.*, 1987).

A number of studies have linked alcohol consumption to an increased risk of breast cancer, and these have been evaluated previously (CC/98/23 and CC/99/8). The

potential association with breast cancer is of interest here, given the aetiological similarities between breast cancer and endometrial cancer, particularly with regard to their apparent association with female sex hormone levels. The relationship between alcohol consumption and levels of female sex hormones has been investigated in several studies, the findings of which are summarised in Appendix 1. Alcohol intake was associated with an increase in oestrogen levels in 10 studies, a decrease in one study and no change in five studies. Appendix 2 summarises the results of studies assessing the relationship between alcohol intake and endometrial cancer. Two reported a positive association between alcohol and endometrial cancer, six reported no clear association and six reported a possible protective effect of alcohol. These will be discussed in more detail below.

Association of endometrial cancer with alcohol

Positive association

Two studies (Parazzini *et al.*, 1995; La Vecchia *et al.*, 1986) have reported that alcohol ingestion is related to a higher incidence of endometrial cancer. In the study of Parazzini *et al.* (1995), a hospital-based case-control study carried out in Northern Italy, 726 patients with endometrial cancer were compared with 2123 controls, non-hysterectomised patients admitted for acute non-gynaecological, non-hormone related, non-neoplastic conditions. Alcohol consumption was based on the number of alcoholic drinks per day (0, >0≤1, >1≤2, >2), and also on duration of alcohol drinking (never, <25, ≥25 years). Relative risk (RR) estimates for number of alcoholic drinks ingested per day were 1.0, 1.1, 1.4, 1.6 and 11.33 ($p < 0.001$). There was no relation between duration of alcohol consumption and risk of endometrial cancer. The authors concluded that their findings suggested a link between alcohol drinking and endometrial cancer risk, although they admitted that several inconsistencies in their data leave the causality of this association in doubt.

| | | | | |
|--|--|---|---|---|
| Parazzini <i>et al.</i> (1995) Northern Italy | Hospital-based case-control 726 patients, 2123 controls | Alcoholic drinks/day (0, >0≤1, >1≤2, >2) Duration of | RR estimates 1.1, 1.3, 1.6 Trend p value < 0.001 | “These findings suggest a potential link between alcohol drinking |
|--|--|---|---|---|

| | | | | |
|--|--|--|---|--|
| | | alcohol drinking (never, <25, ≥25 years) | RR estimates 1.3, 1.3 Trend <i>p</i> value < 0.001 RR for total alcohol drinking 1.3 (95% CI 1.1-1.5) | and endometrial cancer risk and are, in any case, inconsistent with a protective role of alcohol in endometrial carcinogenesis.” |
|--|--|--|---|--|

In another study by the same group (La Vecchia *et al.*, 1986), also in an Italian population in Northern Italy, 206 patients were compared with 206 control subjects. Alcohol consumption was again rated on the basis of number of drinks per day (0, <2, ≥2, <3, ≥3, <4, ≥4). RR estimates were: 1.0, 1.6, 1.6, 3.4, 4.3 (*p* = 0.02). These results suggested a positive relationship between alcohol consumption and endometrial cancer risk, although this was significant only on multivariate analysis.

| | | | | |
|---|--|--|--|--|
| La Vecchia <i>et al.</i> (1986) Milan, Italy | Hospital-based case-control 206 cases, 206 controls | Alcoholic drinks/day (0, <2, ≥2, <3, ≥3, <4, ≥4) | RR estimates (95% CI) 1.6 (0.8-3.18), 1.6 (0.77-3.21), 3.4 (1.03-11.51), 4.3 (1.02-18.43) Trend <i>p</i> value = 0.02 | Relationship between alcohol and endometrial cancer apparently positive, but only significant on multivariate analysis |
|---|--|--|--|--|

No clear association

Six studies reported finding no clear association between alcohol consumption and endometrial cancer risk. Shu *et al.* (1991), in a population-based case-control study of the aetiology of endometrial cancer in 268 patients, found that the odds ratio (OR) for women consuming alcohol was 1.2 compared to those not drinking alcohol, a non-significant association. They therefore concluded that alcohol was not a risk factor for endometrial cancer.

| | | | | |
|---|--|---|-------------------------|--|
| Shu <i>et al.</i> (1991) Shanghai, China | Population-based case-control 268 cases, 268 controls | Whether or not alcohol was consumed (no or yes) | OR 1.2 (95% CI 0.6-2.6) | Alcohol drinking was not related to risk |
|---|--|---|-------------------------|--|

Levi *et al.* (1993) studied the effect of a number of dietary factors, including alcohol intake, on the risk of endometrial cancer. The initial analysis suggested a

significant protective effect of high alcohol consumption (more than one glass per day) (OR 1.59, $p < 0.05$). However, when total energy intake was considered (with an OR of 2.7 in itself), the ORs for low, intermediate and high alcohol consumption were: 1.0, 0.8 and 1.2 ($p = 0.60$). The authors therefore concluded that there was no protective effect of alcohol on endometrial cancer risk, or even a possible adverse effect.

| | | | | |
|---|--|---|--|---|
| Levi <i>et al.</i> (1993) Switzerland, Northern Italy | Hospital-based case-control 274 cases, 572 controls | Millilitres of alcohol per day (tertiles) | OR 0.8, 1.2 Trend p value = 0.60 | Authors feel their results are compatible with the hypothesis that alcohol intake has no, or possibly an adverse, effect on endometrial cancer |
|---|--|---|--|---|

Austin *et al.* (1993) evaluated the effect of cigarette smoking and alcohol use on the risk of endometrial cancer in 103 cases compared with 236 controls. Their analysis was on the basis of type of alcohol consumed (none, beer, red wine, white wine, liquor, any). RRs were: 1.0, 0.4, 0.8, 1.0, 0.6 and 0.6, and there was no dose-response with daily alcohol consumption in grams ($p = 0.31$). Although the authors admitted that their findings were inconclusive, they could find no evidence of a positive association between alcohol consumption and endometrial cancer risk.

| | | | | |
|---------------------------------------|--|--|--|--|
| Austin <i>et al.</i> (1993) USA | Hospital-based case-control 103 cases, 236 controls | Type of alcohol consumed (none, beer, red wine, white wine, liquor, any) | RR (95% CI) 0.4 (1.1-1.2), 0.8 (0.3- 2.5), 1.0 (0.5-2.2), 0.6 (0.2-1.8), 0.6 (0.3-1.3) No dose-response with daily consumption in g ($p = 0.31$) | Risk of endometrial cancer was not associated with type of alcohol consumed or g alcohol consumed per day; no association observed |
|---------------------------------------|--|--|--|--|

Gapstur and colleagues (1993) used data from the Iowa Women's Health Study to examine the relationship between endometrial cancer and alcohol consumption. They found no statistically significant association between endometrial cancer and consumption of beer, wine or liquor. There was no interaction between alcohol and any other endometrial cancer risk factors, including body mass index (BMI) or non-contraceptive oestrogen use.

| | | | | |
|---|--|-----------------------------------|--|--|
| Gapstur <i>et al.</i> (1993) Iowa Women's Health Study (USA) | Follow-up study of 25,170 postmenopausal women from 1986 to 1990 167 incident cases | Grams alcohol per day (0, <4, ≥4) | RR (95% CI) 0.7 (0.5-1.1), 0.9 (0.6-1.3) Trend <i>p</i> value = 0.37) | A causal relationship between alcohol and endometrial cancer is unlikely, based on these results |
|---|--|-----------------------------------|--|--|

The study of Kalandidi *et al.* involved 145 women with histologically confirmed incident cancer of the endometrium. They were compared with 298 controls. The risk of endometrial cancer was found to decrease with number of livebirths, early age at menopause and later age at menarche, but there was no significant association of disease risk with alcohol intake.

| | | | | |
|--|--|---|---|---|
| Kalandidi <i>et al.</i> (1996) Athens, Greece | Hospital-based case-control 145 cases, 298 controls | Whether or not alcohol was consumed (no or yes) | OR (95% CI) 0.72 (0.44-1.37) <i>p</i> = 0.67 | The expected inverse association of endometrial cancer with alcohol drinking is "not evident" |
|--|--|---|---|---|

In a population-based case-control study of women identified from a tumour registry and controls selected randomly from driver's licence lists and Medicare files, Newcomb *et al.* (1997) found that over the whole study population, compared with abstainers, the multivariate relative risk for recent consumption of two or more drinks per day was 1.27 (95% CI 0.78-2.07) and that increasing consumption was not associated with risk of disease. However, when the group was divided into older and younger women, and pre- versus postmenopausal status, the association between alcohol and cancer risk appeared to be inverse for premenopausal women who consumed, on average, at least one drink per day, and a similar trend was observed for women ≤55 years of age.

| | | | | |
|--|---|--|---|--|
| Newcomb <i>et al.</i> (1997) Wisconsin, USA | Population-based case-control 739 cases, 2313 controls | Alcoholic drinks per week (none, any, <1, 1-2, 3-6, 7—13, ≥14, | RR (95% CI) 1.1 (0.86-11.33), 1.2 (0.96-1.56), 0.9 (0.65-1.14), 1.1 | "...endometrial cancer is not positively associated with |
|--|---|--|---|--|

| | | | | |
|---|---|--|---|-----------------|
| | | continuous) | (0.83-1.50), 0.8 (0.55-1.19), 1.3 (0.78-2.07), 1 (0.98-1.02) Trend <i>p</i> value = 0.82 | alcohol intake” |
| Newcomb <i>et al.</i> (1997) Wisconsin, USA | Population-based case-control 739 cases, 2313 controls | Alcoholic drinks per week (none, any, <1, 1-2, 3-6, 7—13, ≥14, continuous) | RR (multivariate analysis) for women ≤55 years, 0.58 (95% CI 0.28- 1.21) and for premenopausal women 0.20 (95% CI 0.06-0.71) | |

Protective effect

Six studies [including the data of Newcomb *et al.* (1997), described above], reported an apparent protective effect of alcohol consumption for endometrial cancer.

The data of Rosenberg *et al.* (1982), on breast cancer and alcoholic beverage consumption, were presented in such a way as to allow re-analysis of one of the control groups, who had endometrial cancer. Gavalier (1983), reporting on this re-analysis, found an apparent inverse relationship between endometrial cancer and alcohol intake, suggesting a possible protective effect of alcoholic beverage consumption in the development of endometrial cancer. Although animal studies have suggested that long-term feeding with alcohol causes ovarian failure and decreased plasma oestradiol concentrations (Van Thiel *et al.*, 1977, 1978; Gavalier *et al.*, 1980), the dose of alcohol required is very high.

| | | | | |
|--|--|-------------------------------|----------------------------|---|
| Rosenberg <i>et al.</i> (1982) (re- analysed by Gavalier (1983) | Hospital-based case-control 334 cases, 2694 controls (non- malignant disorders) | Ever versus never drinkers | OR 0.76 (CI 0.57- 0.95) | Gavalier, re- analysing the data from the original study, believed that the results showed a protective effect of alcohol against endometrial cancer |
|--|--|-------------------------------|----------------------------|---|

Kato *et al.*, in a population-based case-control study of 290 cases, found a slight, but non-significant trend towards a protective effect of alcohol.

| | | | | |
|------------------------------------|---|--|---|---|
| Kato <i>et al.</i> (1989) Japan | Population-based case-control 290 cases, 8920 controls | Frequency of alcohol consumption (never, current, occasional, daily) | 0.7, 0.7, 0.4 (95% CI 0.2-1.4) Daily cf less, 0.5 (95% CI 0.2-1.4) | Slight, but non-significant, trend towards protective effect of alcohol on endometrial cancer |
|------------------------------------|---|--|---|---|

Webster and coworkers (1989), following up the possible mechanism suggested by Gavalier in 1983, postulated that it was conceivable that women consuming alcohol would have lower oestrogen levels, and would therefore be at reduced risk of endometrial cancer compared to women who did not drink. Analysis of their data showed that women who were non-drinkers had a risk of endometrial cancer of 1.83 relative to the risk of women who had consumed an average of 150 g alcohol per week. Women who drank, but less than 150 g alcohol per week, were at an intermediate risk. The “protective” effect of alcohol was particularly marked in obese women and was virtually absent in lean women.

| | | | | |
|-------------------------------------|---|--|--|---|
| Webster <i>et al.</i> (1989) USA | Population-based case-control 351 cases, 2247 controls | Grams alcohol per week (≥ 150 , 50-149, 1-49, 0) | OR (95% CI) 1.11 (0.68-1.81), 1.61 (1.04-2.49), 1.83 (1.11-3.01) | Alcohol may reduce a woman’s risk of endometrial cancer, particularly in obese women, but “this association has virtually no public health significance in terms of potential benefits of alcohol consumption”. |
|-------------------------------------|---|--|--|---|

The study of Swanson *et al.* (1993) is interesting in that it supports the data of Newcomb *et al.* (1997) with regard to the age-dependence of a protective effect: they also found a stronger inverse association among younger women. They were unable to attribute the protective effect of alcohol to any one type of alcohol-containing beverage, but beer appeared to have the most pronounced effect. Although the results suggested an inverse association between moderate alcohol consumption and endometrial cancer risk among young women, support for a causal association was qualified, as the authors feared under- or over-reporting due to their study design.

| | | | | |
|-------------------------------------|--|--|--|---|
| Swanson <i>et al.</i> (1993) USA | Hospital-based case-control 400 cases, 297 controls | Alcoholic drinks per week (0, <1, 1-4, >4) | <55 years, RR 0.8, 0.6, 0.3 (CI 0.1-1.2) ≥55 years, RR 0.8, 1.3, 1.1 (CI 0.5-2.5) Any versus none (all ages), RR 0.8 (0.5-1.3) | Alcohol ingestion is associated with reduced risk of endometrial cancer |
|-------------------------------------|--|--|--|---|

Seventh-Day Adventists do not consume alcohol, tobacco or pork. Mills and colleagues (1994) studied cancer incidence rates in this population compared with a control US white population. Although in women the standardised morbidity ratio (SMR) for cancer overall was generally lower in the Adventists than the controls, for endometrial cancer the SMR was significantly higher. However, this study was unable to correct for the effect of alcohol alone, and therefore any one of the other dietary factors associated with the Adventists' lifestyle could have affected the results. In addition, the two groups compared were geographically distant from each other, with possibly different socioeconomic characteristics.

| | | | | |
|---|--|---|--|---|
| Mills <i>et al.</i> (1994) Seventh-Day Adventists in California, USA | Population-based study, among 34,000 Seventh-Day Adventists compared with comparable white US population | Any alcohol versus no alcohol (Adventists do not consume alcohol) | SMR for uterine cancer among Seventh-Day Adventists 1.91, and for cervical cancer 1.60 | The SMR for endometrial cancer was significantly higher in Adventists |
|---|--|---|--|---|

Conclusions

Thirteen studies to date have reported on the relationship between endometrial cancer and alcohol consumption. Only two of these studies have reported that endometrial cancer incidence is associated with consumption of alcohol; all the others have reported either no definite association, or an inverse association.

An interesting observation reported by Swanson *et al.* (1993) and Newcomb *et al.* (1997) is that if such an inverse association exists, it appears to be more pronounced in younger, or premenopausal, women.

The data reported here are in contrast to many reports of the relationship between breast cancer and alcohol (see CC/98/22 and CC/99/8), where the results appeared to suggest a positive association between breast cancer and alcohol. Both cancers are thought to be oestrogen dependent. The effect of alcohol on sex hormones

is equivocal (see Appendix 1), but several studies have found that alcohol increases sex hormone concentrations. Both endometrial cancer and breast cancer are thought to be oestrogen-dependent, in that longer exposure to oestrogens appears to increase their incidence. However, the study by Mills *et al.* (1994), in a non-drinking Seventh-Day Adventist population, suggests that some of the risk factors may differ; in that study, a lower incidence of breast cancer, but a significantly higher incidence of endometrial cancer, was found.

References

- Armstrong BK, Brown JB, Clarke HT *et al.* (1981) Diet and reproductive hormones: a study of vegetarian and nonvegetarian postmenopausal women. *J Natl Cancer Inst* 67: 761-767.
- Austin H, Drews C, Partridge EE (1993) A case-control study of endometrial cancer in relation to cigarette smoking, serum estrogen levels, and alcohol use. *Am J Obstet Gynecol* 169: 1086-1091.
- Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD, Lannom L, Hoover RN (1993) Reproductive, menstrual and medical risk factors for endometrial cancer: results from a case-control study. *Am J Obstet Gynecol* 167: 1317-1325.
- Gapstur SM, Potter JD, Sellers TA, Kushi LH, Folsom AR (1993) Alcohol consumption and postmenopausal endometrial cancer: results from the Iowa Women's Health Study. *Cancer Causes Control* 4: 323-329.
- Gavaler JS (1983) Protective effect of alcohol against endometrial cancer. *Lancet* ii: 627.
- Kalandidi A, Tzonou A, Lipworth L, Gamatsi I, Filippa D, Trichopoulos D (1996) A case-control study of endometrial cancer in relation to reproductive, somatometric, and life-style variables. *Oncology* 53: 354-359.
- Goldin BR, Adlercreutz H, Gorbach SI *et al.* (1982) Estrogen excretion patterns and plasma levels in vegetarian and omniverous women. *N Engl J Med* 307: 1542-1547.
- Hill HA, Austin H (1996) Nutrition and endometrial cancer. *Cancer Causes Control* 7: 19-32.
- La Vecchia C, Decarli A, Fasoli M, Gentile A (1986) Nutrition and diet in the etiology of endometrial cancer. *Cancer* 57: 1248-1253.
- Levi F, Franceschi S, Negri E, La Vecchia C (1993) Dietary factors and the risk of endometrial cancer. *Cancer* 71: 3575-3581.

Longcope C, Gorbach S, Goldin B *et al.* (1987) The effect of a low fat diet on estrogen metabolism. *J Clin Endocrinol Metab* 64: 1246-1250.

Mills PK, Beeson WL, Phillips RL, Fraser GE (1994) Cancer incidence among California Seventh-Day Adventists, 1976-1982. *Am J Clin Nutr* 59: 1136S-1142S.

Newcomb PA, Trentham-Dietz A, Storer BE (1997) Alcohol consumption in relation to endometrial cancer risk. *Cancer Epidemiol Biomarkers Prevent* 6: 773-778.

Parazzini F, La Vecchia C, Bocciolone L, Franceschi S (1991) The epidemiology of endometrial cancer. *Gynecol Oncol* 41: 1-16.

Parazzini F, La Vecchia C, D'Avanzo B, Moroni S, Chatenoud L, Ricci E (1995) Alcohol and endometrial cancer risk: findings from an Italian case-control study. *Nutr Cancer* 23: 55-62.

Peterson EP (1968) Endometrial carcinoma in young women. *Obstet Gynecol* 31: 702-707.

Rosenberg L, Slone D, Shapiro S, Kaufman DW, Helmrich SP, Miettinen OS, Stolley PD, Levy M, Rosenshein NB, Schottenfeld D, Engle RL (1982) Breast cancer and alcoholic-beverage consumption. *Lancet* i: 267-271.

Shu X-O, Brinton LA, Zheng W, Gao YT, Fan J, Fraumeni JF (1991) A population-based case-control study of endometrial cancer in Shanghai, China. *Int J Cancer* 49: 38-43.

Swanson CA, Wilbanks GD, Twiggs LB, Mortel R, Berman ML, Barrett RJ, Brinton LA (1993) Moderate alcohol consumption and the risk of endometrial cancer. *Epidemiology* 4: 530-536.

Van Leeuwen FE, Rookus MA (1989) The role of exogenous hormones in the epidemiology of breast, ovarian and endometrial cancer. *Eur J Cancer Clin Oncol* 25: 1961-1972.

Webster LA, Weiss NS and the Cancer and Steroid Hormone Study Group (1989) Alcoholic beverage consumption and the risk of endometrial cancer. *Int J Epidemiol* 18: 786-791.

Weiderpass E, Baron JA, Adami H-O *et al.* (1999) Low-potency oestrogen and risk of endometrial cancer: a case-control study. *Lancet* 353: 1824-1828.

Weiss NS, Sayvetz TA (1980) Incidence of endometrial cancer in relation to the use of oral contraceptives. *N Engl J Med* 302: 551-554.

Appendix 1 to Annex to CC/99/27. Alcohol effects on plasma hormone concentrations

Premenopausal women

| Author | DHEAS | Oestrone | Oestradiol | SHBG | Androstenedione |
|---|---------------------------|----------------------------|--|-------------|-------------------------------|
| Reichman <i>et al.</i> (1993) | 7% increase $p < 0.05$ | 21% increase $p < 0.01$ | 27% increase $p < 0.01$ | 4% decrease | |
| Dorgan <i>et al.</i> (1994) | No association | No association | No association | | 27% increase (CI 5.6-53.5) |
| Eriksson <i>et al.</i> (1996) (acetaldehyde) | | | Positive association $r = 0.4, p = 0.026$ | | |
| Muti <i>et al.</i> (1998) | | | 18% increase $p < 0.05$ | | |

Postmenopausal women

| Author | DHEAS | Oestrone | Oestrone sulphate | Oestradiol | SHBG | Prolactin | Testosterone | Androstenedione |
|---|-------|--------------------------------------|-------------------|---|------|-----------|---------------------------------------|---------------------------------------|
| Cauley <i>et al.</i> (1989) | | Decrease ($F = 1.39, p = 0.24$) | | Decrease ($F = 3.59, p = 0.06$) | | | No change ($F = 0.64, p = 0.42$) | No change ($F = 1.67, p = 0.28$) |
| Gavaler <i>et al.</i> (1991) USA Madrid Copenhagen Lisbon | | | | Positive association No association Positive association Positive association (all reported as significant) | | | | |
| London, S. (1991) (n = 325) | | No association | | No association | | | | |
| Gavaler and Love (1992) (n = 128) | | | | 62% increase ($p < 0.01, 2$ -tailed) | | | | |

| Author | DHEAS | Oestrone | Oestrone sulphate | Oestradiol | SHBG | Prolactin | Testosterone | Androstenedione |
|---|--|--|---|---|--|------------------------|--|----------------------------|
| Gavaler and Van Thiel (1992) (same cohort as above) | | | | 62% increase ($r < 0.255$) | | | 15% decrease ($r < 0.175$) | |
| Gavaler <i>et al.</i> (1993) (same cohort as above) | | | | 61% increase | | | 15% decrease | |
| Ginsburg <i>et al.</i> (1995) | | | | | | Increase $p < 0.03$ | | |
| Hankinson <i>et al.</i> (1995) | | No association | 33% increase with ≥ 2 drinks per day $r = 0.17, p = 0.05$ | No association | | No association | | |
| Newcomb <i>et al.</i> (1995) | Pearson correlation coefficient 0.077 | Pearson correlation coefficient 0.018 | | | Pearson correlation coefficient - 0.059 | | Pearson correlation coefficient 0.022 | |
| Ginsburg <i>et al.</i> (1996) | | Decrease in women on HRT $p < 0.05$ | | 228% increase ONLY in women on HRT $p < 0.001$ | | | | |
| Nagata <i>et al.</i> (1997) | 65% increase $p < 0.01$ for trend | | | 110% increase $p < 0.01$ for trend | 17% decrease $p = 0.25$ for trend | | | |
| Madigan <i>et al.</i> (1998) | | 33% increase $p = 0.02$ | 42% increase $p = 0.37$ | 18% increase $p = 0.17$ | 15% decrease $p = 0.45$ | | | 23% increase $p = 0.39$ |

Alcohol effects on urinary hormone concentrations

Premenopausal women

| Author | DHEAS | Oestriol | Oestrone | Oestradiol | Androstenedione |
|-------------------------------|-------|----------------------------|----------------------------|---|-----------------|
| Reichman <i>et al.</i> (1993) | | 29% increase $p < 0.03$ | 15% increase $p < 0.05$ | 32% increase $p < 0.009$ (peri-ovulatory phase) 22% increase $p < 0.02$ (luteal phase) | |

Postmenopausal women

| Author | DHEAS | Oestriol | Oestrone | Oestradiol | Androstenedione |
|--|-------|------------------------------|-------------------------------|-------------------------------|-----------------|
| Trichopoulos <i>et al.</i> (1987) | | -7% decrease (CI -20, +8) | 0% increase (CI -11, +13) | -2% decrease (CI -14, +11) | |
| Katsouyanni <i>et al.</i> (1991) (n = 88) | | 15% (95% CI -5-40) | 20% increase (95% CI 4-38) | 16 (95% CI 2-31) | |

Appendix 2 to Annex to CC/99/27. Studies of alcohol ingestion and endometrial cancer

| Author and location | Study design | Alcohol assessment | Results | Conclusions of authors |
|---|--|--|--|--|
| Positive association | | | | |
| Parazzini <i>et al.</i> (1995) Northern Italy | Hospital-based case-control 726 patients, 2123 controls | Alcoholic drinks/day (0, >0≤1, >1≤2, >2) Duration of alcohol drinking (never, <25, ≥25 years) | RR estimates 1.0, 1.1, 1.3, 1.6, 10.26 Trend <i>p</i> value < 0.001 RR estimates 1, 1.3, 1.3 Trend <i>p</i> value < 0.001 | “These findings suggest a potential link between alcohol drinking and endometrial cancer risk and are, in any case, inconsistent with a protective role of alcohol in endometrial carcinogenesis.” |
| La Vecchia <i>et al.</i> (1996) Milan, Italy | Hospital-based case-control 206 cases, 206 controls | Alcoholic drinks/day (0, <2, ≥2, <3, ≥3, <4, ≥4) | RR estimates 1.0, 1.6, 1.6, 3.4, 4.3 Trend <i>p</i> value = 0.02 | Relationship between alcohol and endometrial cancer apparently positive, but only significant on multivariate analysis |
| No clear association | | | | |
| Shu <i>et al.</i> (1991) Shanghai, China | Population-based case-control 268 cases, 268 controls | Whether or not alcohol was consumed (no or yes) | OR 1.0, 1.2 | Alcohol drinking was not related to risk |
| Levi <i>et al.</i> (1993) Switzerland, Northern Italy | Hospital-based case-control 274 cases, 572 controls | Millilitres of alcohol per day (tertiles) | OR 1.0, 0.8, 1.2 Trend <i>p</i> value = 0.60 | Authors feel their results are compatible with the hypothesis that alcohol intake has no, or possibly an adverse, effect on endometrial cancer |
| Austin <i>et al.</i> (1993) USA | Hospital-based case-control 103 cases, 236 controls | Type of alcohol consumed (none, beer, red wine, white wine, liquor, any) | RR 1.0, 0.4, 0.8, 1.0, 0.6, 0.6 No dose-response with daily consumption in g (<i>p</i> = 0.31) | Risk of endometrial cancer was not associated with type of alcohol consumed or g alcohol consumed per day; no association observed |
| Gapstur <i>et al.</i> (1993) Iowa Women’s Health Study (USA) | Follow-up study of 25,170 postmenopausal women from 1986 to 1990 167 incident cases | Grams alcohol per day (0, <4, ≥4) | RR 1.0, 0.7, 1.0 Trend <i>p</i> value = 0.37) | A causal relationship between alcohol and endometrial cancer is unlikely, based on these results |
| Kalandidi <i>et al.</i> (1996) Athens, Greece | Hospital-based case-control 145 cases, 298 controls | Whether or not alcohol was consumed (no or yes) | OR 1.0, 0.72 <i>p</i> = 0.67 | The expected inverse association of endometrial cancer with |

| | | | | |
|---|--|--|--|---|
| | | | | alcohol drinking is “not evident” |
| Newcomb <i>et al.</i> (1997) Wisconsin, USA | Population-based case-control 739 cases, 2313 controls | Alcoholic drinks per week (none, any, <1, 1-2, 3-6, 7—13, ≥14, continuous) | RR (multivariate analysis) 1.0, 1.1, 1.2, 0.9, 1.1, 0.8, 1.3, 1 Trend <i>p</i> value = 0.82 | “...endometrial cancer is not positively associated with alcohol intake” |
| Protective effect | | | | |
| Rosenberg <i>et al.</i> (1982) (re-analysed by Gavalier (1983)) | Hospital-based case-control 334 cases, 2694 controls (non-malignant disorders) | Ever versus never drinkers | OR 0.76 (CI 0.57-0.95) | Gavalier, re-analysing the data from the original study, believed that the results showed a protective effect of alcohol against endometrial cancer |
| Kato <i>et al.</i> (1989) Japan | Population-based case-control 290 cases, 8920 controls | Frequency of alcohol consumption (never, current, occasional, daily) | 1.0, 0.7, 0.7, 0.4 Daily cf less, 0.5 | Slight, but non-significant, trend towards protective effect of alcohol on endometrial cancer |
| Webster <i>et al.</i> (1989) USA | Population-based case-control 351 cases, 2247 controls | Grams alcohol per week (≥150, 50-149, 1-49, 0) | OR (CI) 1.0 (reference), 1.11 (0.68, 1.81), 1.61 (1.04, 2.49), 1.83 (1.11-3.01) | Alcohol may reduce a woman’s risk of endometrial cancer, particularly in obese women, but “this association has virtually no public health significance in terms of potential benefits of alcohol consumption”. |
| Swanson <i>et al.</i> (1993) USA | Hospital-based case-control 400 cases, 297 controls | Alcoholic drinks per week (0, <1, 1-4, >4) | <55 years, RR 1.0, 0.8, 0.6, 0.3 (CI 0.1-1.2) ≥55 years, RR 1.0, 0.8, 1.3, 1.1 (CI 0.5-2.5) Any versus none (all ages), RR 0.8 (0.5-1.3) | Alcohol ingestion is associated with reduced risk of endometrial cancer |
| Mills <i>et al.</i> (1994) Seventh-Day Adventists in California, USA | Population-based study, among 34,000 Seventh-Day Adventists compared with comparable white US population | Any alcohol versus no alcohol (Adventists do not consume alcohol) | SMR for uterine cancer among Seventh-Day Adventists 1.91, and for cervical cancer 1.60 | The SMR for endometrial cancer was significantly higher in Adventists |
| Newcomb <i>et al.</i> (1997) Wisconsin, USA | Population-based case-control 739 cases, 2313 controls | Alcoholic drinks per week (none, any, <1, 1-2, 3-6, 7—13, ≥14, continuous) | RR (multivariate analysis) for women ≤55 years, 0.58 (95% CI 0.28-1.21) and for premenopausal women 0.20 (95% | |

| | | | |
|--|--|---------------|--|
| | | CI 0.06-0.71) | |
|--|--|---------------|--|