REVIEW OF ALCOHOL: ASSOCIATION WITH BREAST CANCER

A possible association between alcohol consumption and breast cancer has been identified in CC95/4 and CC95/12. In CC95/4, the need for a more detailed review of this topic was identified. This paper reviews and updates the available epidemiological data. A summary of the most recent data is provided in Appendix 1.

Introduction

1. There is an extensive literature available on the epidemiology of breast cancer. Known risk factors for breast cancer include age, ethnic group, family history of the disease, age at birth of first child, menarche and at menopause, history of biopsy for benign breast disease, socio-economic status, obesity and, in premenopausal breast cancer, history of lactation. Other proposed risk factors have been cited, such as parity (in addition to age at birth of first child), use of oral contraceptives and hormone replacement therapy but whether they are involved in the aetiology of breast cancer remain controversial.
2. At a previous meeting, the Committee evaluated studies published to 1995 on a possible association between alcohol consumption and breast cancer (see attached extract of CC/95/4 for details). The studies included an IARC review of 4 large prospective studies and 13 case control studies with respect to alcohol. The studies provided evidence of a consistent dose-response relationship, generally with up to 1.5-2 fold risk. Confounding due to recognised factors was controlled in most of them, but the Working Group did not reach a firm conclusion as to whether a causal association had been established between drinking alcohol and breast cancer. Seven additional prospective studies, 17 new case-control studies and two meta-analyses were also reviewed, together with a formal analysis of the data from six case-control studies which controlled for known dietary confounding factors and an authoritative review of the association between alcohol and breast cancer. An additional qualitative review of the design and conduct of 38 case-control study reports published between 1980 and 1992 was also considered.

3. At its meeting in 1995 (CC/95/4), the Committee agreed that "the adequacy of control for confounding by known and/or alleged risk factors varied in the different accounts. A weak dose-related association was reported in most cohort studies and in some hospital based case-control studies. The results of population based case-control investigations did not generally support an association. A small statistically significant dose-related increase in relative risk was reported in the two meta-analysis reports (RR at 3 drinks/day 1.38 (CI 1.23-1.55)). The Committee noted that small increases in relative risk documented in the epidemiological studies ranged between approximately 1.2 to 3 and were associated with a highly variable consumption of alcohol (ca 1-60 g ethanol/day). It was agreed that clear evidence of causality had not been demonstrated."
4. The Committee concluded "that while there is no decisive evidence that breast cancer is causally related to drinking alcohol, the potential significance, for public health, of even a weak association between alcohol and breast cancer is such that we recommend, in particular, that this matter is kept under review."
5. Relevant extracts of Reports CC/95/4 and CC/95/12 are attached, which include summaries of studies published up to 1995. Appendix 1 summarises studies from 1995 onwards. A copy of a recent review of a pooled analysis of cohort studies is also attached, together with a recent paper by Mezzetti *et al.* suggesting that the risk from alcohol is significantly greater in premenopausal women.

Alcohol consumption and breast cancer rates

Breast cancer accounts for 38% of cancers in women, and for 27% of cancer-related deaths. In the UK, the death rate for breast cancer has shown a steady decrease since 1991, particularly in older age groups. However, the incidence rate continues to rise, particularly in women under the age of 64 years (Appendix 2).

Against this background, consumption of alcohol by persons over the age of 15 years has remained relatively steady over the past 20 years (see Fig. 1). Data for women alone are not available. According to a UK-based report published in 1990[1], women still consume less alcohol on average than men, with the average consumption for women, at 10.6 g/day, being around one-third that for men (31.5 g/day). According to this report, consumption of alcohol is greater in the middle of the age range, from 25 to 40 years, roughly the reproductive age range for women. Working women who

consume alcohol are likely to have a higher alcohol intake than other women consuming alcohol[1].

Studies up to 1995

Reports CC/95/4 and CC/95/12 reviewed studies on the association of breast cancer and alcohol consumption up to May 1995. The data obtained confirmed the multifactorial aetiology of breast cancer, and identified the following as risk factors: age at menarche, age at first birth, parity, body mass index, family history of breast cancer, non-contraceptive oestrogen use, education and total energy intake. There was little evidence of an association between smoking and breast cancer. A weak association between the consumption of alcoholic beverages and breast cancer was found in 4 out of 5 cohort studies, and other studies suggested that heavy drinking was associated with a modest increase in relative risk (RR). The association between age and menopausal status and risk of breast cancer due to the consumption of alcohol was particularly inconclusive.

Two meta-analysis studies[2,3] reported a weak, but dose related response. Of the 38 studies reviewed in 1994 by Longnecker, 15 reported a positive association, three a negative association and the remaining 20 studies reported a non-significant association. The RR (95% confidence interval (CI)) was estimated as:

1 drink/day 1.11 (1.07-1.16)

2 drinks/day 1.24 (1.15-1.34)

3 drinks/day 1.38 (1.23-1.55)

From these data, it was proposed that the population attributable risk in the USA was approximately 4%. Longnecker considered that most of the studies had controlled adequately for potential confounding factors.

Roth[4] reviewed the design of 38 case-control studies, including type of control, type and degree of matching, number of confounders controlled for and statistical power. It was established that type of control (hospital or community) and mix of cases (with respect to menopausal status) were significant confounding variables. Roth concluded that the association between drinking alcoholic beverages and breast cancer was generally weak and that measurement and/or selection bias had occurred in the available case control studies.

Objectives of this paper

The primary objective of this paper is to consider whether studies published between 1995 and 1998 report significant new findings which would lead to a revision of the previous conclusions. The separate associations between alcohol consumption and breast cancer in premenopausal and postmenopausal women, a possible confounding factor referred to by Roth[4], will also be examined, as will any differences in drinking pattern, i.e. lifetime drinking versus drinking at a particular stage of life only. Lastly, the effects of different alcoholic beverages will also be examined.

Methods utilised

Bibliographical databases (Medline and Current Contents) were searched from January 1995 to October 1998 for all publications relating to alcohol consumption and breast cancer in women. Those papers reporting the results of original studies were selected for review, togther with a recent authoratative pooled analysis of six major cohort studies (a copy of which is attached). Each paper was analysed for the type of study, origin of study population, period over which the study was undertaken, number of cases and controls, any matching of controls, details of how alcohol consumption was assessed, potential confounding factors that were considered, the major findings, with particular emphasis on: any association between the risk of breast cancer and ever drinking, the possibility of a dose-effect relationship, any difference between pre- and post-menopausal women, the effect of total duration of drinking and the effect of the type of beverage. Alcohol consumption has been quoted as stated by the authors. Conversion to estimated consumption in grams was not appropriate, due the the inconsistency of the type and extent of information on alcohol consumption provided in the different studies. The numbers of cases and controls indicated, were those available for anlysis of the effects of alcohol, and in some instances were less than the total study population. The statistical analyses performed by the authors were scrutinised, and only those results that were statistically significant (for relative risks and odds ratios, the 95% confidence interval did not include 1.0, for Chi-square and trend analsysis, $P < 0.05$) have been highlighted in this report.

Studies since 1995

Cohort studies

Three cohort studies were identified[5-7]. In the study by van den Brandt *et al.*[5], in 422 breast cancer cases identified from a sub-cohort of the Netherlands Cohort Study, the RR (95% CI) for breast cancer in drinkers versus non-drinkers was:

<5 g alcohol/day	1.30 (0.66-1.75)
5-14 g/day	1.29 (0.89-1.85)
15-29 g/day	1.28 (0.81-2.03)
≥30 g/day	1.72 (0.90-3.28)

The trend was significant (P=0.047), but the overall RR was not (1.31, 95% CI 1.00-1.71).

The authors commented that the association with alcohol was stronger in women with a history of benign breast disease, a family history of breast cancer, or with an early menopause.

Sturgeon *et al.*[6] reported on a large cohort of white women aged 20-79 years, selected from four regions in the USA. Weak but positive associations (no CIs were provided in this study) between mortality ratio (MR) and alcohol consumption were found in two out of three regions relative to the south for younger women [20-49 years: MR 0.98 (W), 1.05 (NE), 1.05 (MW)] and in all three regions for the older group [50-79 years: MR 1.10 (W), 1.28 (NE), 1.15 (MW)]. However, the effects reported could be accounted for by age alone.

Thun *et al.*[7] reported on a cohort of 230,552 women in the USA who reported alcohol and tobacco use in 1982. Cause-specific death rates and rates of death from all causes across categories of baseline alcohol consumption were calculated in the 13,669 subjects who died during the subsequent 9 years. Breast cancer was associated with drinking in women, and the mortality from breast cancer was 30% higher in women reporting at least one drink daily than among non-drinkers (RR 1.3; 95% CI 1.1-1.6). The RR increased with the amount of alcohol consumed (p=0.02 for trend) (<1 drink/day: RR 1.1, 95% CI 0.9-1.3, 1 drink/day: RR 1.2, 95% CI 1.0-1.6: 2-3 drinks/day: RR 1.5 (95% CI 1.2-1.9: ≥4 drinks/day: RR 1.0 (0.7-1.4).

Case control studies

Twenty-two case control studies, published between 1995 and 1998, are reported in Appendix 1[8-29]. Seventeen of these studies have reported a significant positive relationship between alcohol consumption and breast cancer incidence, with relative risks in the range 1.2-2.5. Of the five which found no such relationship[8,17,22,25,26], in that by Freudenheim *et al.*[8] in the USA, a possible association with the intake of hard liquor was suggested, but this did not reach statsitical significance. No significant assocation was evident with the intake of wine or beer, although the RR for ≥ 28 units of beer/month was 1.37 (95% CI 0.83-2.25).

In the study of Haile *et al.*[17], which was of premenopausal women only, there was a non-signficant increase in risk with 3 or more drinks or week (OR 1.8, 95% CI 1.0-3.4).

In a multi-centre European study[22] of post-menopausal women only, there was no association between current alcohol consumption and risk of breast cancer (RR 1.0, 95% CI 0.70-1.430). There was, however, a significant association in ex-drinkers (RR 1.66, 95% CI 1.06-2.62). The authors state that consumption levels in their study were quite low.

Robbins *et al.*[25], looked at regional distribution of established risk factors in an effort to explain the increased incidence of breast cancer in the San Francisco Bay area. Alcohol consumption had a negligible effect on the relative risk of breast cancer in this study, and the results could be explained entirely by regional differences in known risk factors.

In a study of premenopausal women only, Brinton *et al.*[26] found no significant relationship between the consumption of alcohol and the risk of breast cancer (in women <35 yeasr of age consuming ≥7 drinks pr week: RR 1.20, 95% CI 0.9-1.5). A possible interaction in these women between oral contraceptive use and alcohol consumption was not significant (P = 0.20).

The study of Erichsen and Soegaard[9] in Denmark was carried out in a relatively small number of subjects (30), and sought to identify a population of women who would be at high risk of developing breast cancer using two markers of high risk lifestyle: aged >25 years at first birth, and daily alcohol intake of ≥7 g/day. Although the combined selection power of the two markers was significant (odds ratio 4.6; 95% CI 1.2-15.6),

that of alcohol alone was not. The contribution of alcohol to the OR was less than that of age at first birth.

In a cross-national study published in 1996[30] of trends in 66 countries, alcohol consumption did not contribute significantly in a stepwise linear regression model to explain breast cancer mortality rates.

Premenopausal versus postmenopausal women

Ten studies compared alcohol and breast cancer in pre- and postmenopausal women[8,10,11,13-15,24,27,29,31]. Of these, one found that the risk was greater in postmenopausal women[13], five found a higher risk among premenopausal women[11,14,15,27,29] and four, including the pooled analysis of cohort studies, found no difference between the groups[8,10,24,31]. In one of the studies[11], it was suggested that occasional consumption of wine or spirits might actually have a protective effect in postmenopausal women. Hence, there is nor persuasive evidence that either pre- or post-menopausal women are at greater risk from any effects of alcohol on breast cancer.

Postmenopausal

A Swedish study[13] found that alcohol intake did not affect breast cancer risk among women under 50 years of age, but among those over 50 years, ever-drinking conferred an RR of 1.8 (95% CI = 1.2-2.6), and drinking later in life appeared to have a greater effect than drinking earlier in life.

In another Swedish study[11], modest consumption of wine or spirits was associated with a reduced risk of breast cancer in postmenopausal women, but not in premenopausal women (RR for wine: 0.4, 95% CI 0.3-0.7; spirits: 0.6, 95% CI 0.4-0.9).

van den Brandt *et al.*[5], in their study of 1812 postmenopausal women, all aged over 54 years, from the Netherlands Cohort Study, reported a positive association between alcohol and breast cancer in these subjects. However, the overall RR of 1.31 (95% CI 1.00-1.71) failed to reach significance.

In a study of women in Los Angeles[12], all of whom were postmenopausal (age range 55 to 64 years), the ORs (95% CI) for alcohol consumption was significant (e.g. 19-32 g/day, 1.63 (1.14-2.33); 33-45 g/day, 2.45 (1.22-4.93).

In a European multi-centre study of postmenopausal women[22], the overall RR was not significantly increased (1.00, 95% CI 0.70-1.43). The RRs for in the first, second and third tertiles of alcohol intake similarly failed to reach significance (1.00 (0.63-1.59), 0.98 (0.63-1.58) and 1.06 (0.65-1.73), respectively).

Premenopausal

A Japanese study of sake drinking in pre- and postmenopausal women[14] suggested that alcohol intake had a significant effect in premenopausal women only (RR for ≥ 1 unit sake/day 2.03; 95% CI 1.36-3.03), although it was pointed out that older women in Japan tended to drink very little.

Levi *et al.*[15] in a Swiss study on 230 breast cancer cases, found a consistent association between alcohol intake and breast cancer incidence which was significant only in premenopausal women (RR for ≥ 1 drink/day 5.4; 95% CI 2.5-11.9). The difference between pre- and post-menopausal women was significant (P<0.005).

Mezzetti *et al.*[27] found a stronger association between alcohol intake in premenopausal women than in postmenopausal women for both low and high alcohol intakes (population attributable risk (95% CI) in premenopausal women 21.1 (10.9-31.4) *cf* 5.4 (-2.5-13.4) in postmenopausal women). The ORs (95% CI) for >20 g per day were 1.60 (1.23-2.08) in premeopausal women and 1.11 (0.92-1.33) in postmenopausal women.

In their study on Italian subjects, Ferraroni *et al.*[29] found that there the effects of alcohol on risk of breast cancer were significant in premenopausal women (OR 1.25 (95% CI 1.12-1.41) but not in postmenopausal women (OR 1.07 (95% CI 0.92-1.25). This difference between the groups was significant (P=0.032).

In their study of a population of premenopausal women, Haile *et al.*[17] reported that they had found "some evidence" that high alcohol consumption (≥3 drinks per week) increased the incidence of breast cancer [OR = 1.8 for ≥3 drinks/week (95% CI = 1.0-3.4)], but this was not significant.

Viel *et al.*[19] studied a group of premenopausal French women, aged 30-50 years. The consumption of 9 g or more alcohol per day was associated with a significant increase in the risk of breast cancer (RR 2.69, 95% CI 1.40-5.17). Although this association was only with red wine, this was the predomoninant beverage consumed by this group.

Brinton *et al.*[26] found that in women under 35 years, there was a non-significant positive relationship between heavier consumption of alcoholic beverages and incidence of breast cancer for consumption of ≥7 drinks per week (RR 1.20, 95% CI 0.9-1.5).

Menopausal status not significant

Freudenheim *et al*.[8] found that the relationship between alcohol consumption and risk of breast cancer was not significant in either pre- or post-menopausal women. However, the authors do comment that consumption was generally low in their subjects.

A report by Longnecker *et al.*[10] found that in women 40 years of age or older, alcohol consumption before 30 years of age was unrelated to risk, whereas consumption in the previous age interval was clearly related. Among premenopausal women, consumption before age 30 years was related to risk more than was consumption in the previous age interval. Although the authors concluded that overall, the alcohol breast cancer relationship was stronger in postmenopausal than in premenopausal women, this difference was not statistically significant.

In an American study of women aged 20-79 years[24], after adjustment for covariates, there was no difference between pre- and post-menopausal women in the effects of alcohol on the risk of breast cancer.

In the pooled analysis of cohort studies by Smith-Warner *et al*.[31], the adjusted RR for total alcohol intakes of 30 to <60 g per day in all women was 1.41 (95% CI 1.18-1.69). However, there was no difference in RR between pre- and post-menopausal women (P=0.49).

The conclusions of studies in which the issue of whether menopausal status has any impact on the apparent association between alcohol consumption and increased risk of breast cancer has been addressed are very inconsistent. On balance, the evidence is against a greater risk in postmenopausal than premenopausal women. However, there is little convincing evidence that premenopausal women are at greater risk.

Type of alcohol ingested

Ten studies compared intake of alcohol in different forms[5,8,10-12,15,19,24,28,29].

In their cohort study, van den Brandt[5] investigated the effects of beer, wine and liquor separately. These studies did not reveal a signigicant or differential effect of beverage type on risk of breast cancer (RR for beer, 0.93 (95% CI 0.82-1.05); wine, 1.01 (0.99-1.02); liquor, 1.02 (0.99-1.04)).

Freudenheim *et al.*[8] analysed their data on the basis of wine, beer or hard liquor consumption. There was no apparent increase in RR for breast cancer with intake of hard liquor or wine. Although there was increase in RR with intake of at least one beer per day, the effect was weak and non-significant, [1-2 drinks/mo, 0.93 (0.71-1.21); 3-27, 1.02 (0.74-1.41); ≥28, 1.37 (0.83-2.25)]. The authors admitted to a possible measurement bias, as no details were obtained regarding the size of an alcohol portion.

In a study of lifetime alcohol consumption in the USA[10], the data were analysed by type of beverage. The overall risk of breast cancer for alcohol consumption was significant, RR for 13 g/day = 1.31 (95% CI 1.20-1.43). Altough the effects of beer (RR for 13 g/day=1.25 (95% CI 1.13-1.39) and spirits (RR 1.18 (1.07-1.13), considered separately, were significant, those of wine consumption were not (RR 0.93 (0.79-1.08)). The difference in the effect of beverage type was significant (P<0.01).

The study of Ranstam *et al.*[11], in contrast, found no association between beer consumption and breast cancer risk, and occasional consumption of wine and spirits appeared to have a protective effect, at least in postmenopausal women (RR = 0.4, 95% CI = 0.3-0.7 for weekly wine consumption and RR = 0.6, 95% CI = 0.4-0.9 for occasional consumption of spirits, in postmenopausal women).

Longnecker *et al*.[12] investigated the effects of beverage type in 1431 matched pairs of postmenopausal women. Although the risk for spirits studied separately (RR for 13 g/day 1.22 (95% CI 1.04-1.24) was significant, whilst that for wine (1.04 (0.79-1.36)) and beer (0.91 (0.71-1.17)) was not, the risk associated with spirit intake was not significantly different from that associated with the other two beverages.

Levi *et al.*[15] reported a similar association between breast cancer and the consumption of wine, beer and spirits, particularly in premenopausal women, with odds ratios (95% CI) for the highest intake of wine (>4 drinks/day), beer (≥ 0.5 drinks/day and spirits (≥ 1 drink/day) of 2.0 (1.2-3.2), 2.6 (1.4-4.6) and 2.0 (0.9-4.7), respectively.

Viel *et al.*[19], reporting on a population of 154 premenopausal breast cancer patients, found a significant relative risk for consumption of ≥ 9 g alcohol per day, particularly

with red wine (RR for >4 litres per month: 3.96, 95% CI 1.59-9.84), but pointed out that in this French population, red wine was the preferred alcoholic beverage. RR (95% CI) for >1 l of beer per month: 1.93 (0.78-4.80); >2 l fortified wine per month: 1.03 (0.39-2.72); >1 litre of white wine per month: 1.62 (0.46-5.62).

In a study of 1214 women aged between 20 and 79 years, Bowlin *et al.*[24] found that the RR of breast cancer for beer, wine and liquor were very similar ($RR_{adjusted}$ (95% CI): 1.28 (0.72-2.29), 1.32 (1.00-1.72) and 1.30 (0.96-1.75), respectively). The authors concluded that "multivariate analysis for … type of drink and breast cancer risk was similar as in univariate analysis". Whilst this was true of the RRs, the 95% CIs, which previously excluded 1.0, increased to include 1.0.

In an Italian study[28] of 470 breast cancer patients and a similar number of controls, it was concluded that altough alcohol consumption was associated with an increased risk of breast cancer, the type of beverage consumed did not make any obvious difference.

Ferraroni *et al.*[29] compared the effects of a number of beverages on the risk of breast cancer in a group of over 2500 patients with a similar number of controls. The type of beverage did not influence the RR for breast cancer from alcohol consumption. RR (95% CI) for wine: 1.27 (1.06-1.53); beer: 1.44 (1.16-1.79); grappa: 1.57 (1.12-2.19); spirits: 1.51 (1.02-2.22).

The balance of evidence from these studies is that the type of beverage has no effect on any risk of breast cancer from the consumption of alcohol. It appears that it is the alcohol itself that is associated with any increase in risk. However it should be noted that most populations consume a variety of alcoholic beverages, depending on fashion and stage of life, and hence attributing risk to a particular type of beverage can be difficult.

Lifetime versus "stage of life" drinking

Several studies have compared drinking patterns at certain stages of life versus lifetime drinking.

Freudenheim *et al.*[8] investigated the drinking pattern at different periods in the life of the subjects, and concluded that this had no significant effect on risk of breast cancer. ORs (95% CI) for consumption of ≥28 drinks per month: 2 years ago, 0.81 (0.62-1.30); 10 years ago, 0.91 (0.63-1.32); 20 years ago, 0.74 (0.51-1.07; at 16 years of age, 0.72 (0.22-2.40). In all cases, the trend with the amount consumed was not significant

(P≥0.25). There was little evidence for any increase in risk with the total amount consumed in a lifetime. However, these authors had not found any assocition between drinking and risk of breast cancer.

Longnecker *et al.*[12] reported a positive association between average lifetime alcohol intake in breast cancer patients (P for trend <0.01). There was no increase in risk when drinking started in early adulthood (P=0.25). There was some evidence that starting to drink late in life increased the risk (compared OR (95% CI) per 13 g/day for consumption at 40 years (1.14 (1.04-1.24)) with the OR per 13 g/day change from the amount at age 40 years to age at study (1.12 (1.03-1.23)).

Holmberg *et al.*[13] found that in women over the age of 50 years, there was little effect of the duration of drinking. ORs (95% CI) in postmenopausal women for years of use were: ≤10 years, 1.5 (0.9-2.5); 11-20 years, 1.8 (1.1-3.0); >20 years, 1.9 (1.2-3.0). Similarly, the age at first drinking did not significantly alter the risk, with ORs (95% CI) in postmenopausal women for age at first use of alcohol of: ≥28 years, 1.8 (1.2-2.7); 15-27 years, 1.7 (1.0-2.7). There was some indication that starting to drink later in life (>35 years) had a greater impact on the risk of breast cancer than starting at younger ages (OR (95% CI) when starting at 25 years: 1.2 (0.7-2.1); at 35 years: 1.5 (1.1-2.3); 45 years, 1.5 (1.2-2.4) [NB these figures are approximate as they were taken from a graph].

A more detailed study by Levi *et al.*[15] found that the association between alcohol consumption and breast cancer was unrelated to duration [ORs (95% CI) for duration of >20 years, 1.6 (1.0-2.6); 20-29 years, 1.4 (0.9-2.3); ≥30 years, 1.5 (1.0-2.4)]. There was some evidence that starting to drink early in life has a greater efffect than starting later in life. The multivariate ORs were 1.8 (95% CI 1.2-2.8) for women who started to drink before the age of 30 years and 1.4 (95% CI 0.9-2.0) for those who started drinking at ≥30 years.

Swanson *et al.*[23] studied women aged 20-79 years for age at starting drinking and duration of drinking. They found that alcohol consumption patterns in the teens and twenties did not alter the risk of breast cancer (OR (95% CI) for those consuming ≥7 drinks per week in their teens, 1.34 (0.9-.20); for those consuming ≥14 drinks per week in their twenties, 1.29 (0.9-2.0). Consumption in the 30s had a significant effect; OR (95% CI) for ≥14 drinks per week, 1.80 (1.2-2.6), but this was confounded

by the recent pattern of consumption. The age at which drinking started did not have any significant effect on the risk of breast cancer (ORs (95% CI) for age at which drinking started: <17 years, 0.81 (0.6-1.1); 17-19 years, 1.19 (1.0-1.4); ≥20 years, 1.15 (1.0-1.4)). The number of years since drinking began had no effect on the risk of breast cancer.

Bowlin *et al.*[24] reported that the greater the total years of drinking (ORs (95% CI) for >0-<20 years, 1.33 (0.89-1.98); 20-<40 years, 1.48 (1.13-1.93); 40+ years, 1.32 (0.98-1.77)), the greater the risk (P for trend <0.004), but when adjusted for grams per day, neither duration (P=0.54), not total alcohol consumed (P=0.08) were important Intensity of drinking therefore seemed to be of greater significance. Age at which drinking started had no effect (ORs (95% CI) *cf* starting to drink at ≥ 25 years, for age at which drinking started: ≤17 years, 0.79 (0.58-1.08); 18-24 years, 1.01 (0.79-1.29)).

Ferrarini *et al.*[29] found no significant increase in the risk of breast cancer with the duration of drinking; OR (95% CI) for ≥40 years consumption 0.95 (0.8-1.13). In premenopausal women only, the lower the age at first consumption of alcohol the greater the risk (P<0.001).

It is apparent from these studies that very few consistent trends appear. The balance of evidence suggests that age at which drinking started, pattern of consumption in earlier life and the total duration of drinking have no effect on any risk of breast cancer associated with alcohol consumption. There is some degree of agreement that it is the intensity of recent alcohol consumption that determines any increased risk of breast cancer.

Amount of alcohol consumed

Several studies have looked at the risk of breast cancer in relation to the amount consumed. Only those studies in which intake was stratified by more than two levels (other than zero) are considered here.

van den Brandt *et al.*[5] found a higher RR with alcohol consumption of ≥30 g/day (RR (95% CI) <5 g/day, 1.30 (0.66-1.15); 5-14 g/day; 1.29 (0.89-1.85); 15-29 g/day; 1.28 (0.81-2.03); ≥30 g/day; 1.72 (0.90-3.28). Although total and stratified alcohol intake had no signicant effect on the risk of breast cancer, the trend for increasing intake was significant, P=0.05). There were also significant trends for wine (P=0.04) and liquor (P=0.005) consumption, but not with beer consumption (P=0.06).

Thun *et al.*[7] found a weak but significant trend between daily alcohol intake and RR for breast cancer (<1 drink/day: RR 1.1, 95% CI 0.9-1.3, 1 drink/day: RR 1.2, 95% CI 1.0-1.6: 2-3 drinks/day: RR 1.5 (95% CI 1.2-1.9: ≥4 drinks/day: RR 1.0 (0.7-1.4), (P=0.02).

In their study, Freudenheim *et al*[8] found no significant effect on total alcohol consumption and risk of breast cancer. No increase in risk was apparent at any level of alcohol intake (1-2 drinks per month, 3-27 drinks per month or ≥28 drinks per month), e.g. P for trend for consumption 2 years ago=0.93.

Longnecker *et al.*[10] found a highly significant trend between the amount of alcohol consumed and the risk of breast cancer (RRs (95% CI): 1.39 (1.16-1.67) for 1 drink per day, 1.69 (1.36-2.10) for 2 drinks, 2.30 (1.51-3.51) for 3 drinks and 1.75 (1.16-2.64) for 4 or more drinks per day (P for trend <0.0001).

In a second study, Longnecker *et al.*[12] also found a significant relationship between the estimated average lifetime intake of alcohol and risk of breast cancer; ORs (95% CI) compared to abstainers were: for < 6 g/day, 1.01 (0.84-1.22); for 6-11 g/day, 1.21 (0.95-1.55); for 12-18 g/day, 0.94 (0.69-1.29); for 19-32 g/day, 1.63 (1.14-2.33); for 33-45 g/day, 2.45 (1.22-4.93); and for ≥46 g/day, 0.94 (0.46-1.93). The trend was significant (P=0.01). The authors attributed the "odd" result for ≥46 g/day as due to misreporting, confounding factors or selection bias.

Holmberg *et al.*[13] found that although only consumption of >0.75 g alcohol per day was associated with an increased risk of breast cancer, there was no consistent effect of intake above this on risk [OR (95% CI): ≤0.75 g/day, 1.2 (0.8-1.8); 0.76-2.0 g/day, 1.9 (1.2-2.9); ≥2.0 g/day, 1.6 (1.0-2.4)].

Levi *et al.*[15] reported that the multivariate OR (95% CI) for alcohol and breast cancer risk varied with consumption level, being 1.3 (0.8-1.9) for <1 drink per day, 1.8 (1.1-2.9) for 1-2, 1.5 (0.8-2.7) for 2-4 and 2.7 (1.3-5.8) for >4 drinks per day P (for trend <0.01).

Weiss *et al.*[18] reported that the risk of regional/distant tumours of the breast increased with the average lifetime amount of alcohol consumed,with RRs (955 CI) for <1-6.9 drinks per week of 1.15 (0.9-1.4); 7-13.9 drinks per week, 1.21 (0.8-1.8); ≥14 drinks per week, 2.52 (1.6-4.1).

In their multi-centre study, Royo-Bordonada *et al*.[22] reported that there was no evidence for a dose-effect relationship bertween alcohol consumption and risk of breast cancer (RR (95% CI) for tertile of lowest alcohol consumption, 1.00 (0.60-1.67); middle tertile, 1.01 (0.60-1.73); highest tertile, 1.18 (0.69-2.03)), P for trend 0.81.

Swanson *et al*.[23] reported that alcohol consumption of ≥14 drinks per week was associated with an increased RR of regional/distant breast cancer (2.4, 95% CI 1.6-3.8). However, at lower levels of consumption, there was no significant increase in risk, nor was there any indication for a dose-effect (in women <45 years, RR (95% CI) of regional/distant breast cancer for <1 drink per week, 1.24 (0.9-1.6); 1-2.9 drinks/wk, 1.17 (0.9-1.6); 3-6.9 drinks/wk, 0.95 (0.7-1.3); 7-13.9 drinks/wk, 1.32 (0.9-1.9).

Ferraroni *et al*.[29] investigated the relationship between amount of alcohol consumed and risk of breast cancer in pre- and postmenopausal women. There was a significant trend between consumption and risk of breast cancer in the group as a whole and in premenopausal women, but not in postmenopausal women. ORs (95% CI) for consumption of 1-5.07 g per day, 1.21 (1.00-1.47); 5.88-13.40 g/day, 1.23 (1.02-1.50); 13.41-24.55 g/day, 1.19 (0.98-1.45); 24.56-27.60 g/day, 1.21 (0.99-1.47); >27.60 g/day, 1.41 (1.17-1.71), P for trend <0.001. P for trend in premenopausal women, <0.0002; postmenopausal women, 0.62).

In their pooled analysis of cohort studies, Smith-Warner *et al*.[31] address the issue of dose-effect between alcohol consumption and risk of breast cancer. They found that the risk increased linearly with intake below 60 g per day (i.e. >99% of participants), with a pooled multivariate relative risk of 1.09 (95% CI 1.04-1.13) for an increment of 10 g per day alcohol.

Although there is some inconsistency between the studies, the majority report that there is a signifcant relationship between the amount of alcohol consumed and the risk of breast cancer. It should be noted that whilst comparisons of different levels of alcohol intake are possible within studies, differences in the nature of the information and its manner of presentation make it very difficult to make comparisons between studies.

Review

A recent review published in early 1998[31] has analysed the results of six prospective cohort studies, dating from 1989 to 1994. The object of this study was to assess the risk of invasive breast cancer associated with total and beverage-specific alcohol consumption and to evaluate whether dietary and non-dietary factors modify the association. Six prospective studies, from Canada, the Netherlands, Sweden and the United States, were included. The studies included a total of 322,647 women evaluated for up to 11 years, including 4335 participants with a diagnosis of incident invasive breast cancer. The authors chose to use a pooled analysis technique, on the basis that in meta-analyses, the primary sources of data are published results in which alcohol intake has been analysed using different analytical methods and cut-off points, thereby limiting the comparisons that can be made.

For alcohol intakes <60 g/day (reported by >99% of the study population), risk was found to increase linearly with increasing intake, by 3-16% for an increment of 10 g/day of alcohol (around 0.75-1 drink); the pooled multivariate RR for an increment of 10 g/day was 1.09 (95% CI 1.04-1.13). The multivariate-adjusted RR for total alcohol intakes of 30 to less than 60 g/day (about 2-5 drinks) versus non-drinkers was 1.41 (95% CI 1.18-1.69). Limited data suggested that alcohol intakes of ≥60 g/day were not associated with further increased risk (RR 1.31; 95% CI 0.86-1.98; n=30), and the specific type of alcoholic beverage did not strongly influence risk estimates. The association between alcohol intake and breast cancer was not modified by other factors.

The study concluded that alcohol consumption is associated with a linear increase in breast cancer incidence in women over the range of consumption reported by most women. The authors comment that the increase in risk associated with the consumption of ≤30 g/day alcohol of 30-40% is similar to that associated with several reproductive factors and a family history of breast cancer. The authors concluded that among women who consume alcohol regularly, reducing alcohol consumption might be a potential means to reduce breast cancer risk, but noted that moderate alcohol consumption is also associated with reduced risk of cardiovascular disease and overall mortality among women. Hence, the risk-benefit analysis of modifying alcohol consumption is complex.

Three studies[15,24,31] have suggested that the incidence of breast cancer could be significantly reduced by limiting alcohol ingestion. Levi *et al.*[15] estimate that alcohol consumption could account for 8-42% of breast cancer cases. Bowlin *et al.*[24] estimate that 25% of breast cancer among women between 20 and 79 years is attributable to ever drinking alcohol. Smith-Warner *et al.*[31], in their review, conclude that reduction of regular alcohol consumption in women is likely to reduce breast cancer risk. However, these and other authors do emphasise that moderate alcohol consumption is associated with reduced risks of certain other major dieseases, particularly cardiocascular disease.

Conclusions

1. The results of these studies confirm previous observations that there appears to be an association between alcohol intake and increased risk of breast cancer in women.
2. On balance, there was a weak association between the amount of alcohol consumed and the relative risk.
3. The duration of drinking had little or no effect on the relative risk, when corrected for amount of alcohol consumed. Nor did the age at which drinking started.
4. There is no evidence that postmenopausal women are at greater risk from any effects of alcohol on the risk of breast cancer than premenopausal women. There is little convincing evidence that premenopausal women are at greater risk than postmenopausal women.
5. Insufficient data exist to state conclusively whether the type of alcoholic beverage ingested affects the risk, but on the evidence of the studies available, it is the alcohol content itself, rather than any congeners or other ingredients, that is responsible for any association.
6. In summary, studies published over the past 4 years continue to provide evidence for a link between alcohol consumption and increased risk of breast cancer in women (range of RRs 1.2-2.5).

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