LIGHT-TO-MODERATE ALCOHOL CONSUMPTION AND RISK OF BREAST CANCER

1. INTRODUCTION

Over the past fifteen years, the relationship between alcohol consumption and an increased risk of breast cancer in women has been analyzed and studied extensively. Numerous epidemiological studies have shown that moderate-to-high levels of alcohol consumption (>15 grams per day) are positively associated with an increased risk of breast cancer (Longnecker, 1994; Smith-Wamer, et al., 1998). However, the relationship between light-to-moderate alcohol consumption (< 15 grams per day) and an increase in breast cancer risk remains controversial (Zhang, et al., 1999; Kropp, et al., 2001). Epidemiological studies assessing the impact of light-to-moderate alcohol consumptions have produced inconsistent findings, with some studies having reported a positive association (Longnecker, 1994; Brandt, et al., 1995), and others a negative association, or no association at all (Freudenheim, et al., 1995; Kropp, et al., 2001; Zhang, et al., 1999). Comparison of these studies is difficult because of the differences between studies with regard to the dose of alcohol above which an effect is seen, the setting of arbitrary cut-off points for intake categories, the types of alcoholic beverages involved in the association, and the effect modification by other risk factors (Brandt, et al., 1995). Alcohol consumption is a potentially modifiable behavior, a characteristic that accounts for the intense interest in the scientific community to determine any possible association it has with an increasing risk of breast cancer (Smith-Wamer, et al., 1998).

2. EVIDENCE OF POSITIVE ALCOHOL / BREAST CANCER ASSOCIATIONS

In 1994, Longnecker conducted a meta-analysis of 38 epidemiological studies that evaluated the relationship between alcohol consumption and an increased risk of breast cancer. The quality of

the studies included in the analysis were evaluated according to set criteria, and, although the results were adjusted for established risk factors for breast cancer, Longnecker reported that the adjustments did not affect the original odds ratio found for alcohol intake and risk of breast cancer. Longnecker reported a dose-response relation, with a modestly sloping dose-response curve. The risk of breast cancer associated with the intake of 13 grams of alcohol per day was eleven percent greater than for nondrinkers (95% CI: 1.07-1.16). Longnecker used 13 grams of alcohol to signify 'about one drink' (1994, p. 74), and did not report risk ratios for alcohol intakes less than 13 grams. This creates difficulties when attempting to compare this study with later studies that investigate light-to-moderate levels of alcohol consumption, and utilize a different number of grams to signify one drink, e.g., Zhang, et al., (1999).

Although reporting a positive association between alcohol consumption and breast cancer risk, Longnecker (1994) acknowledges that the increase in risk in most studies, including his own, is only moderate, leaving open the possibility that the association is due to confounding by unknown factor/s. Longnecker also tries to put the research into perspective, stating that the proportion of all breast cancers attributable to alcohol consumption, if causal, is about four percent (1994, p. 79). In an article five years later, Longnecker (1999) attributes two percent of breast cancer cases to alcohol consumption, and suggests considering competing risks and causes of death in creating a given risk profile for women that can provide an estimate of the overall benefits and risks of light-to-moderate alcohol consumption.

Longnecker (1994) reported that studies with stronger alcohol consumption and breast cancer risk associations tended to be from countries with high per capita alcohol intakes. For example, studies conducted in Western Europe are more likely to show a stronger association between

alcohol consumption and breast cancer than studies conducted in North America (Longnecker, 1994). Although the reason for this pattern is not known, two studies, one conducted in Switzerland (Levi, et al., 1996) and one conducted in the Netherlands (Brandt, et al., 1995), demonstrate this strong association.

Levi et al. (1996) performed a hospital-based case-control study in the Swiss Canton of Vaud that included 230 cases of breast cancer and 507 controls to assess the prevalence of the association between alcohol consumption and breast cancer. Multivariate odds ratios were calculated for <1 drink per day, 1-2 drinks per day, 2-4 drinks per day and >4 drinks per day. The odds ratios were 1.3 (95% CI: 0.8-1.9), 1.8 (95% CI: 1.1-2.9), 1.5 (95% CI: 0.8-2.7) and 2.7 (95% CI: 1.3-5.8) respectively. In a study outlined below (Ellison, et al., 2001), it was shown that hospital-based case-control studies showed a seven percent greater risk association between breast cancer and alcohol consumption than in cohort studies. Even after accounting for the seven percent, the odds ratios shown here are considerably higher than ones reported in North America (Longnecker, 1994).

Brandt et al. (1995) conducted a cohort study in the Netherlands involving 62,573 postmenopausal women and 422 breast cancer cases. Alcohol consumption data was obtained through a questionnaire, with alcohol intake levels divided into five categories: nondrinkers, and those who drank <5, 5-14, 15-29, or ≥30 grams of alcohol per day. The rate ratios for the alcohol intake categories when compared with the nondrinkers were 1.30, 1.29, 1.28, and 1.72 respectively (p=0.047; no confidence levels given). A positive association between alcohol intake and the risk of breast cancer in postmenopausal women was reported.

In a population-based case-control study of 1,645 women younger than 45 years of age, Swanson et al. (1997) evaluated the effects of alcohol consumption in relation to breast cancer risk during different periods of life. 1,497 controls were frequency matched by geographic area and age, and a lifetime history of alcohol use was acquired from both the cases and the controls. As a lifetime average, risk of breast cancer was found to be slightly higher (risk ratio (RR)=1.10, 95%, CI: 1.10-1.3) for drinkers than for nondrinkers. Risk of breast cancer was increased approximately 70-80% for women who consumed 14 or more 'drinks' of alcohol per week (RR=1.79, 95%, CI: 1.2-2.6.

After a careful analysis of the data that-was presented to determine how the lifetime average was calculated, some anomalies become apparent. Swanson et al. (1997) were assessing alcohol consumption in number of drinks per week, and reported a risk ratio of 1.35 (95%, CI: 1.1-1.7) for a 'usual intake' of less than one drink per week (approximately 11-15 grams of alcohol per week). This corresponded to a 30 percent greater risk of breast cancer if less than one drink was consumed per week (~2 grams per day), a finding that is possible, but very unusual. This finding is especially unusual considering that the study was conducted in the United States of America, and after comparison with the risk ratios reported in the same study for 1-2.9 and 3-6.9 drinks per week. The risk ratios for 1-2.9, 3-6.9, 7-13.9 and ≥14 drinks per week were 1.01 (95%, CI: 0.8-1.2), 1.03 (95%, CI: 0.8-1.3), 1.10 (95%, CI: 0.8-1.5) and 1.79 (95%, CI: 1.2-2.6) respectively. These results are more probable, however they only show a *very* weak association between light-to-moderate alcohol consumption and risk of breast cancer, if at all. The data does support consistent, positive association between moderate-to-high alcohol consumption and increased risk of breast cancer.

Smith-Wamer et al. (1998) conducted a pooled analysis of six large cohort studies to assess the risk of invasive breast cancer associated with total and beverage-specific alcohol consumption. The studies included met predefined criteria in order to allow comparisons to be made and conclusions to be drawn. The studies were conducted in Canada, the Netherlands, Sweden, and the United States. They included a total of 322, 647 women and 4, 335 breast cancer cases. The authors reported a linearly increasing risk of breast cancer incidence with increasing intake of alcohol of less than 60 grams per day. The pooled multivariate relative risk was increased 9 percent per 10 grams per day, i.e. 1.09 (95% CI: 1.04-1.13; *P* for heterogeneity among studies, 0.71). The multivariate-adjusted relative risk for total alcohol intakes of 30-60 grams per day versus nondrinkers was 1.41 (95% CI, 1.18-1.69); women consuming 30 to 60 grams per day of alcohol had a 41% higher risk of invasive breast cancer than nondrinkers.

Smith-Wamer et al. (1998) discussed the limitations of meta-analyses, mainly that the primary sources of data in-the studies included are published results in which alcohol intake has been analyzed using different analytic methods and arbitrarily chosen cutoff points. In order to minimize the effect of this limitation, Smith-Wamer et al. defined strict criteria by which the included studies conformed to, and participants were excluded from the analysis if they met study-specific exclusion conditions. Another limitation of the study is that only recent alcohol consumptions were measured, and therefore lifetime alcohol consumption and consumption during early adulthood could not be examined. On the positive side, conducting a meta-analysis by pooling the data from multiple studies enhances the power to detect associations of smaller magnitudes (Smith-Wamer, et al., 2001).

One important distinction that Smith-Wamer et al. (1998) did not make was the lack of identifiable risk for breast cancer found with an alcohol consumption of less than 15 grams per day in four of the six included studies (Zhang, et al., 1999b). Although initially touted as a study that showed support for a causal relationship between all levels of alcohol consumption and breast cancer (Longnecker, 1999), the evidence now suggests that Smith-Wamer et al.'s findings should be reexamined before being used to support an association between light-to-moderate alcohol consumption and breast cancer.

3. EVIDENCE OF NEGATIVE OR NULL ALCOHOL / BREAST CANCER ASSOCIATIONS

Freudenheim et al. (1995) performed a case-control study investigating the association of lifetime alcohol intake with risk of premenopausal and postmenopausal breast cancer. 740 women from New York diagnosed with breast cancer (301 premenopausal and 439 postmenopausal breast cancer cases) and 810 controls (316 premenopausal and 494 postmenopausal) were extensively interviewed on their lifestyle history, diet history and family history. Little evidence of an association between light-to-moderate alcohol consumption and risk of breast cancer was found, however the participants consumed less than one drink per day on average (0.89). The odds ratio for breast cancer for women who consumed approximately one drink per day was 0.91 (95%, CI: 0.55-1.50). These associations were not confounded by diet or other identified breast cancer risk factors (Freudenheim, et al., 1995).

In a prospective, population-based cohort study, Zhang et al. (1999) assessed the effect of average alcohol consumption on risk of breast cancer for 2, 764 women from 1948 to 1993, and for 2, 284 women from 1971-1993. Of these women, 221 and 66 incidents of breast cancer cases

were found respectively. The long follow-up period in this study permitted an assessment of potential alcohol effects that may require years to appear, and the estimates of average alcohol consumption were derived from multiple examinations (Zhang, et al., 1999). The amount of alcohol consumed was divided up into four groups: nondrinkers, <5.0 grams per day, 5.0-<15.0 grams per day, and ≥15.0 grams per day.

Multivariate-adjusted rate ratios of breast cancer in each category of alcohol consumption were assessed with the two cohorts combined. The results for nondrinkers, <5.0 grams per day, 5.0-<15.0 grams per day, and ≥15.0 grams per day were 1.0, 0.8 (95% CI: 0.6-1.1), 0.7 (95% CI: 0.5-1.1), and 0.7 (95% CI: 0.5-1.1) respectively. No association was found between the light consumption of alcohol and an increase in the risk of breast cancer for either group of women. The small number of women who reported an intake of > 15.0 grams per day had a median intake of 24 grams, leaving the study with not enough statistical power to examine the relation of heavy alcohol consumption and risk of breast cancer (Zhang, et al., 1999). The statistical result for the group with an intake of ≥15.0 grams per day should, therefore, be ignored.

Kropp et al. (2001) conducted a population-based case-control study of 706 German women aged 50 years of age or less to evaluate the effect of low-to-moderate doses of ethanol on breast cancer risk among premenopausal women. The women had been diagnosed with breast cancer in 1992-1995; the study also included 1,381 residence-and age-matched controls. Kropp et al. assessed lifetime alcohol consumption in three age categories - ages 15-20 years, ages 20-30 years, and ages 30-50 years - and for five different types of alcoholic beverages - beer, wine, aperitifs, liquor, and spirits. The interaction of alcohol consumption with other co-variables (such

as education, family history of breast cancer, and number of full-term pregnancies) was investigated using the difference between deviances of the models with and without the interaction terms.

This study produced some findings that support Zhang et al.'s(1999) results of an apparent reduced breast cancer risk for low-to-moderate levels of alcohol consumption. Kropp et al. (2001) were able to conduct a study that not only produced the reduced breast cancer risk at low-to-moderate levels of alcohol consumption, but also had the statistical power to examine high dose relationships between alcohol consumption and breast cancer risk. Kropp et al. found a reduced breast cancer risk of approximately 30 percent for low-to-moderate alcohol consumption levels of 1-5, 6-11, and 12-18 g/day. In multivariate conditional logistic regression analysis, the adjusted odds ratios for breast cancer for these three different alcohol consumption levels were 0.71 (95% CI: 0.54, 0.91), 0.67 (95% CI: 0.50, 0.91), and 0.72 (95% CI: 0.51, 1.05) respectively. However, for an alcohol consumption level of 19-30 g/day an odds ratio around unity was found (1.10; 95% CI: 0.73, 1.65), and an odds ratio of 1.94 (95% CI: 1.18, 3.20) was found for an ethanol intake of greater than 30 g/day. These results produce a J-shaped curve as the dose-response function (Kropp, et al.. 2001).

Kropp et al. (2001) explained their findings by postulating the existence of 'thresholds' through which plausible mechanisms that link chronic alcohol consumption to breast cancer must pass in order to exert a critical effect. The absence of adverse effects on breast cancer risk for low-to-moderate alcohol consumption in Kropp et al.'s study would have therefore been conceivable, as the alcohol consumption had not reached the level necessary to pass through the 'threshold'.

Kropp et al. (2001) also reported that breast cancer risk was increased at a lower consumption level for beer than for wine, although they did not report how much more it was increased, or even if the difference was significant. Kropp et al. then suggested that their results above might be further accounted for by the beneficial role of light-to-moderate levels of wine consumption in counteracting the cancer-promoting function of the alcoholic component in wine. The possible beneficial role of wine consumption on breast cancer is still under investigation, however the statistics on the significance of the difference between the wine and beer consumption level on breast cancer risk must be published or otherwise made available by Kropp et al. (2001) before any correlations can be drawn.

4. EFFECTS OF STUDY ATTRIBUTES

In an interesting meta-analysis assessing whether effect estimates differed according to various study attributes, Ellison et al. (2001) found that most studies demonstrate a monotonic increase in the relative risk of breast cancer with alcohol consumption, with an average 12 grams per day being associated with a 10 percent increase in breast cancer risk compared to nondrinkers (95% CI: 1.00, 1.11). Hospital-based case-control studies showed a 7 percent greater risk association between breast cancer and alcohol consumption than in cohort studies, and the magnitude of the association was 11 percent higher for cohort studies with less than 10 years of follow-up compared to cohort studies with longer follow-up intervals. No differences were found between breast cancer risk and intake of beer, wine, or spirits. The analyses also did not yield differences in the relationship between alcohol and breast cancer occurring before and after menopause.

5. BIOLOGICAL MECHANISMS

The mechanisms by which alcohol ingestion stimulates carcinogenesis are not known, although there is some support for the concept that ethanol is not a carcinogen, but a co-carcinogen and/or a tumor promoter (Seitz, et al., 1998, p.75). The biologic mechanisms of alcohol's effect on breast cancer etiology alone are even more controversial, and are widely discussed but not proven in detail. One of the most prevalent theories is that hormones play a promotional role in breast carcinogenesis, and more specifically that prolonged estrogenic stimulation of the mammary epithelia contributes to the development of breast cancer (Castro, et al., 2001; Sarkar, et al., 2001; Singletary, 1997). Related to this theory is the postulation that increased levels of circulating estradiol in response to estrogen and alcohol intake may lead to an increase in the risk of breast cancer (Purohit, 1998). Fan, et al. (2000) reported findings of a decrease in the action of tumor suppressors as a result of ethanol doses, and proposed this as a possible contributor to alcohol-induced breast cancer. Another model suggests the involvement of alcohol-derived reactive oxygen species in inducing DNA modifications and carcinogenesis (Wright, et al., 1999).

A large quantity of research has been conducted on a possible biological mechanism for alcohol's effect on breast cancer etiology, however no accepted mechanism of action has been established. The lack of a plausible biological mechanism for the breast cancer-enhancing effect of alcohol is responsible for much of the continuing controversy over the association between alcohol intake and risk of breast cancer being found in epidemic logical studies (Singletary, 1997).

6. DATA RELIABILITY

The reliability of the data collected in retrospective, epidemiological studies is always a concern because of the recall and selection bias inherent in the studies. The issue of data reliability is especially important when discussing the relationship between light-to-moderate alcohol consumption and breast cancer risk because of the weakness of both the positive and negative associations found in the epidemiological studies (Freudenheim, et al., 1995).

Giovannucci et al. (1993) conducted two case-control studies of breast cancer risk in relation to alcohol consumption to determine the effect of breast cancer status on response status and recall of alcohol consumption. In one study, alcohol use was ascertained prospectively, and in the other, it was obtained retrospectively. The study was designed so that the entire study population was known, which avoided the need for selection techniques for controls that may produce selection bias (Giovannucci, et al., 1993). The analysis based on the prospective data demonstrated a higher risk of breast cancer among women who drank 30 grams or more of alcohol daily relative to nondrinkers, with an odds ratio of 1.55 (95% CI: 1.01-2.39). The retrospective analysis also yielded a positive association between alcohol intake and breast cancer (odds ratio = 1.42, 95% CI: 0.85-2.40), but it was slightly weaker due to recall bias. Data from this study suggests that population-based case-control studies may not exaggerate an association between breast cancer risk and alcohol consumption (Giovannucci, et al., 1993).

Longnecker et al. (1992) examined the reliability of self-reported alcohol consumption for different age periods of women's lives. 211 women with a mean age of 54 years (± 10) were interviewed over the telephone and asked to report their intake of alcoholic beverages for

different age periods of their lives. Six to twelve months later they were interviewed again and asked the same questions. The correlation coefficients between reports of average daily intake were similar for all specific age periods (16-19 years, r=0.81; 20-29 years, r=0.84; 30-39 years, r=0.75; recent consumption, r=0.77), and the correlation between the two interviews for lifetime average alcohol consumption (grams per day) was 0.87. This data indicates that self-reports of past alcohol consumption are reasonably reliable, although care should always be taken to account for the modest bias that will be evident in any study that relies on self-reported data. Recall bias can never be completely ruled out, especially since the majority of epidemiological studies examining the association between alcohol consumption and breast cancer risk rely on self-reported data collected after diagnosis (Kropp, et al., 2001).

7. CONCLUSION

The association between light-to-moderate alcohol consumption and breast cancer will remain controversial until an accepted mechanism of action is established. The evidence that has been found and interpreted both for and against the existence of the association is on a small enough scale so as to be beyond the resolution of epidemiological studies, due to the possibility that the respective evidence was the result of confounding, other bias', or chance (Longnecker, 1999). The goal of the epidemiological studies undertaken in this area of research is to determine who is at risk, and why. Accurate recommendations regarding light-to-moderate alcohol consumption require precise estimates of the dose-response relation between alcohol intake and risk of breast cancer, a requirement that so far has not been met (Giovannucci, et al

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