

Short communication

Alcohol consumption and breast cancer risk

Peter Boyle and Paolo Boffetta

International Prevention Research Institute, 95 cours Lafayette, 69006 Lyon, France

Corresponding author: Peter Boyle, peter.boyle@i-pri.org

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Introduction

Alcohol consumption has been associated with a variety of different forms of cancer in man for several centuries. The evidence linking alcohol drinking to cancer risk has been reviewed recently [1-3]. There is convincing epidemiological evidence that the consumption of alcoholic beverages increases the risk of cancers of the oral cavity, the pharynx and the larynx, and the risk of squamous cell carcinoma of the oesophagus. The risks tend to increase with the amount of ethanol drunk, in the absence of any clearly defined threshold below which no effect is evident.

Alcohol drinking is also strongly associated with the risk of primary liver cancer; the mechanism, however, might be mainly or solely via the development of liver cirrhosis, implying that light or moderate drinking may have limited influence on liver cancer risk. An increased risk of colorectal cancer has been observed in many cohort and case-control studies, which seems to be linearly correlated with the amount of alcohol consumed and to be independent of the type of beverage.

Evidence regarding an association between alcohol consumption and breast cancer risk has come to the fore during the past 20 years. It therefore seems appropriate to look at some of the key studies and to monitor the evolution of the accumulation of the evidence for association and the public health responses.

Throughout the following text, one drink – whether a glass of beer, a standard glass of wine, or a measure of spirits – will be considered to contain 10 g ethanol.

The early evidence

Nurses Health Study

The Nurses' Health Study in the United States was initially based on 89,538 US nurses aged between 34 and 59, with no history of cancer [4]. These nurses completed an independently validated dietary questionnaire – which included the use of beer, wine, and spirits – in 1980.

During the first 4 years of follow-up, 601 cases of breast cancer were diagnosed among cohort members [4].

Among women who consumed 5 to 14 g alcohol daily (about three to nine drinks per week), the age-adjusted relative risk of breast cancer reported was 1.3 (95% confidence interval (CI), 1.1 to 1.7). Consumption of 15 g alcohol or more per day was associated with a relative risk of 1.6 (95% CI, 1.3 to 2.0) and there was evidence of a highly significant increase in risk with increasing reported alcohol consumption (Mantel extension χ for linear trend = 4.2, $P < 0.0001$). Among women without risk factors for breast cancer who were under 55 years of age, the relative risk associated with consumption of 15 g alcohol or more per day was 2.5 (95% CI, 1.5 to 4.2) [4].

While several previous case-control studies had been reported, the Nurses Health study served to launch research into this association.

Meta-analysis of nutritional case-control studies

Howe and colleagues assembled data from six case-control studies conducted to examine the relationship between diet, nutrition and breast cancer risk [5]. Data from 1,575 cases and 1,974 controls were analysed with respect to alcohol intake.

There appeared to be a highly statistically significant and consistent elevated risk of breast cancer for drinkers of 40 g or more of alcohol per day, for whom the relative risk, as compared with that of nondrinkers, is 1.69 (95% CI, 1.19 to 2.40) [5]. This association was not due to confounding by a number of diet-related factors, including total calories, fat, fibre and vitamin C.

Meta-analysis of published studies

By the early 1990s, the association between alcohol consumption and the risk of breast cancer had been reported fairly consistently in numerous studies. In order to clarify the situation, Longnecker undertook a meta-analysis of 38 epi-

demographic studies that had reported information on alcohol consumption and breast cancer risk [6].

In this meta-analysis, Longnecker reported a risk, relative to nondrinkers, of 1.1 (95% CI, 1.1 to 1.2) for one drink per day, a risk of 1.2 (95% CI, 1.1 to 1.3) for two drinks per day and a risk of 1.4 (95% CI, 1.2 to 1.6) for three or more drinks per day.

Pooled analysis of prospective studies

Smith-Warner and colleagues undertook a pooled analysis of six prospective studies, conducted in four countries, which met *a priori* criteria [7]. Information about 4,035 cases of breast cancer derived from studies of 322,647 women was available.

The pooled multivariate relative risk associated with an increment of 10 g/day (about one drink per day) was 1.09 (95% CI, 1.04 to 1.13) [7].

Collaborative group on hormonal factors in breast cancer

The analyses included 58,515 women with invasive breast cancer and 95,067 controls from 53 studies. Compared with women who reported drinking no alcohol, the relative risk of breast cancer was 1.32 (95% CI, 1.19 to 1.46; $P < 0.00001$) for an intake of 35 to 44 g/day alcohol, and was 1.46 (95% CI, 1.33 to 1.61; $P < 0.00001$) for ≥ 45 g/day alcohol.

The relative risk of breast cancer increased by 7.1% (95% CI, 5.5 to 8.7; $P = 0.0001$) for each additional 10 g/day intake of alcohol; that is, for each extra unit or drink of alcohol consumed on a daily basis. This increase was the same in ever smokers and never smokers (7.1% per 10 g/day alcohol, $P < 0.00001$, in each group) [8].

Public health response

European Code Against Cancer

The second revision of the European Code Against Cancer, to produce the third version, was completed in 2003 [9]. The revision involved 125 European scientists from different disciplines working in 18 subcommittees, and the launch took place on 16 June 2003 at the European Institute of Oncology.

All evidence that had become available since the previous version [10] was evaluated and modifications were made to the Code. In particular, in view of the mounting evidence of an increased risk of breast cancer with moderate consumption of alcohol, it was recommended under Point 5 of the Code that 'If you drink alcohol, whether beer, wine or spirits, moderate your consumption to two drinks per day if you are a man and one drink per day if you are a woman'.

International Agency for Research on Cancer monograph

A global assessment of the association between alcohol consumption and cancer risk had been undertaken by the International Agency for Research on Cancer in 1988 [1].

Owing to a continually growing body of scientific evidence, the impact of alcohol consumption on cancer risk required re-assessment and a Working Group was assembled to evaluate all the evidence, which met in February 2007 [2].

More than 100 epidemiological studies that investigated the association have consistently found that the risk of breast cancer in women is increased by increasing alcohol consumption. The Working Group concluded that daily alcohol consumption of 50 g alcohol is associated with a relative risk of about 1.5 compared with that of nondrinkers. For regular consumption of even 18 g/day alcohol, the risk is significantly increased. The Working Group concluded there was sufficient evidence that alcohol consumption was associated with an increased risk of breast cancer.

Breast cancer burden attributable to alcohol consumption

Boffetta and Hashibe estimated that a total of 389,100 cases of cancer are attributable to alcohol drinking worldwide, representing 3.6% of all cancers (5.2% in men, 1.7% in women) [3]. The corresponding figure for mortality is 232,900 deaths (3.5% of all cancer deaths). This proportion is particularly high among men in Central and Eastern Europe. Among women, breast cancer comprises 60% of alcohol-attributable cancers. Boffetta and Hashibe [3] estimated in Europe in 2002 that 28,300 cases of breast cancer, representing 7.7% of all breast cancers, were attributable to alcohol consumption.

An exercise was conducted to estimate the attributable fraction of breast cancer in France in 2000 [11]. The results indicated that 10.7% of breast cancer cases could be attributed to the use of hormone replacement therapy and oral contraceptives, 10.1% of cases could be attributed to physical inactivity, 9.4% could be attributed to alcohol consumption and 5.4% to changes in reproductive factors since 1930 [11].

Key recent studies

Million Women Study (UK)

A total of 1,280,296 middle-aged women in the United Kingdom enrolled in the Million Women Study were routinely followed for incident cancer [12]. One-quarter of the cohort reported drinking no alcohol; 98% of drinkers consumed fewer than 21 drinks per week, with drinkers consuming an average of 10 g alcohol (one drink) per day.

Low to moderate alcohol consumption in women increases the risk of certain cancers. Every additional drink regularly consumed per day contributes 11 breast cancers per 1,000 women up to age 75 [12].

Women's Health Study (1992 to 2004)

The Women's Health Study (1992 to 2004) followed women who, at baseline, were free of cancer and cardiovascular

disease, and provided detailed dietary information, including alcohol consumption, for the preceding 12 months [13]. During an average of 10 years of follow-up, 1,484 cases of total breast cancer (1,190 invasive and 294 *in situ*) were documented among 38,454 women free of cancer and cardiovascular disease at baseline.

High alcohol consumption was associated with a modest increase in breast cancer risk; the multivariable relative risks for ≥ 30 g/day alcohol versus no alcohol were 1.32 (95% CI, 0.96 to 1.82) for total breast cancer and 1.43 (95% CI, 1.02 to 2.02) for invasive breast cancer.

An increased risk was limited to oestrogen receptor (ER)-positive and progesterone receptor (PR)-positive tumours. The multivariable relative risks for an increment of 10 g/day alcohol were 1.11 (95% CI, 1.03 to 1.20) for OR-positive and PR-positive tumours (804 cases), 1.00 (95% CI, 0.81 to 1.24) for OR-positive and PR-negative tumours (125 cases), and 0.99 (95% CI, 0.82 to 1.20) for OR-negative and PR-negative tumours (167 cases).

National Institutes of Health–AARP Diet and Health Study (1995 to 2003)

The National Institutes of Health–AARP Diet and Health Study (1995 to 2003) consisted of 184,418 postmenopausal women aged 50 to 71 years. During an average of 7 years of follow-up, 5,461 breast cancer cases were identified [14].

Alcohol consumption was significantly positively associated with total breast cancer: even a moderate amount of alcohol (>10 g/day) significantly increased breast cancer risk. In a comparison of >35 g/day versus 0 g/day alcohol, the multivariate relative risks were 1.35 (95% CI, 1.17 to 1.56) for total breast cancer, 1.46 (95% CI, 1.22 to 1.75) for ductal tumours, and 1.52 (95% CI, 0.95 to 2.44) for lobular tumours.

The multivariate relative risks for OR-positive/PR-positive, OR-positive/PR-negative, and OR-negative/PR-negative tumours were 1.46 (95% CI, 1.12 to 1.91) for >35 g/day versus 0 g/day alcohol, 1.13 (95% CI, 0.73 to 1.77) for >20 g/day versus 0 g/day alcohol, and 1.21 (95% CI, 0.79 to 1.84) for >20 g/day versus 0 g/day alcohol, respectively [14].

Summary

The association between alcohol consumption and the risk of breast cancer has been reported fairly consistently in numerous studies. Willett and colleagues reported a significant association in the first prospective study with detailed exposure information [4]. Howe and colleagues demonstrated an association in a meta-analysis of six case–control studies designed to investigate nutrition and cancer [5].

In a meta-analysis of 38 epidemiologic studies, the pooled risk estimates were 1.1 (95% CI, 1.1 to 1.2) for one drink per

day, 1.2 (95% CI, 1.1 to 1.3) for two drinks per day, and 1.4 (95% CI, 1.2 to 1.6) for three or more drinks per day, relative to nondrinkers [6]. A pooled analysis of six prospective studies reported similarly modest increases in risk, with a dose-dependent trend between alcohol consumption and breast cancer risk, after taking into account the major risk factors [7]. In another pooled analysis of 53 epidemiologic studies with 58,515 cases and 95,067 controls, for each additional 10 g/day increase in alcohol intake, an increase in breast cancer risk of 7.1% (standard error, 1.3%) was reported in never smokers [8]. Differences in risk due to alcohol beverage types have not been observed [15]. The association is consistent among both premenopausal and postmenopausal women, although there is evidence emerging that the effect may be greater in (or confined to) ER-positive/PR-positive breast cancer.

The third version of the European Code Against Cancer incorporated the growing body of evidence into Point 5 of the Code, recommending that women limit their alcohol consumption to one drink per day in view of the risk of breast cancer [9]. This level was one-half of the recommended daily limit for men.

On the basis of the growing body of evidence, the International Agency for Research on Cancer convened a Working Group to prepare a Monograph on Alcohol Drinking in February 2007. The Group concluded there was sufficient evidence that the risk of breast cancer was increased by alcohol consumption [2].

Very recent studies, notably from the Million Women Study [12], have strengthened knowledge of the impact of moderate alcohol consumption levels on increasing the risk of breast cancer.

Conclusions

A number of key questions arise when considering the association between alcohol consumption and breast cancer.

Does even moderate consumption of alcohol increase the risk of breast cancer?

There is a large body of evidence consistent with alcohol consumption increasing the risk of breast cancer. There is consistent evidence from large, prospective studies that even moderate alcohol consumption increases the risk of breast cancer.

Does the risk of breast cancer increase with increasing alcohol consumption?

The relative risk of breast cancer associated with alcohol consumption is quite small and it has taken the establishment of large, well-conducted studies to identify the risk. Most studies have confirmed a gradient of increasing risk of breast cancer associated with increasing levels of alcohol consumption, even at moderate levels of consumption.

Is alcohol consumption an important cause of breast cancer?

Even though the increase in risk is quite small, there is a large portion of women who consume moderate amounts of alcohol. In France, 9.4% of breast cancer is attributable to alcohol consumption; and 7.7% of all breast cancers in Europe are attributable to alcohol consumption.

What is the effect of stopping or reducing alcohol consumption on breast cancer risk?

It is unknown at the present time whether the increased risk of breast cancer associated with alcohol consumption stops or is reduced.

Is the mechanism by which alcohol consumption causes breast cancer known?

The mechanism of action whereby alcohol consumption increases the risk of breast cancer is unknown at the present time. The risk is starting to appear, however, stronger in (or confined to) women with ER-positive/PR-positive breast cancer. This could provide the potential to focus attention on the search for a mechanism.

Competing interests

The authors declare that they have no competing interests.

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