COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Committee on Carcinogenicity Statement on Consumption of alcoholic beverages and the risk of breast cancer in women. Consideration of significance to public health (2004).

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Committee on CARCINOGENICITY

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD CONSUMER PRODUCTS AND THE ENVIRONMENT

STATEMENT ON CONSUMPTION OF ALCOHOLIC BEVERAGES AND RISK OF BREAST CANCER IN WOMEN

CONSIDERATION OF SIGNIFICANCE TO PUBLIC HEALTH.

Introduction

Breast Cancer in U.K

1. Breast cancer is the most common cancer in women and the most common cause of cancer mortality in women. Each year there are approximately 41,000 cases (2000 data) registered and 13,000 deaths (2001data) in the U.K [1,2]. The most clearly established risk factors for breast cancer are reproductive[3] (e.g. age at first full term pregnancy, parity, age at menarche and menopause). Other known risk factors for breast cancer include age, ethnic group, family history of the disease, history of benign breast disease, socioeconomic status, use of oral contraceptives and hormone replacement therapy and, in postmenopausal breast cancer, obesity. The reason for the interest in the association between alcohol and breast cancer is that even a small risk, if causally associated with alcohol, may have serious public health implications. In addition, drinking alcoholic beverages maybe one of the few risk factors for breast cancer where intervention might offer some scope for prevention. An extensive literature on the association between alcohol and breast cancer was reviewed by the World Health Organisation's International Agency for Research on Cancer in 1988[4] and by this Committee for the InterDepartmental Working Group on Alcohol in 1995[5] but neither group was able to advise that there is a causal association between drinking alcoholic beverages and breast cancer.

2. A further review was undertaken by the COC in 1999 (**http://www.doh.gov.uk/alcbrst.htm**).[6] The Committee concluded there was sufficient evidence to associate drinking alcoholic beverages with an increased risk of breast cancer but agreed that a systematic review of all the epidemiology studies and further evaluation of potential mechanisms were required before definite conclusions could be reached. The conclusions reached following the 1999 review are summarised in paragraphs 11-14 below. The Department of Health commissioned a systematic review of the epidemiology from the Department of Epidemiology and Public Health at Imperial College, London. The Committee agreed to undertake a further review of all the available information when the report of the systematic review became

available. The Committee was also aware that additional relevant data on alcohol consumption and risk of breast cancer was expected from the Oxford Collaborative Group on Hormonal factors in Breast Cancer and should also be reviewed when available. The draft report of the systematic review undertaken by Imperial College and a copy of the published report by the Oxford Collaborative Group on Hormonal Factors[7] both became available in November 2002 and thus a further review was initiated.

Consumption of alcoholic beverages in the U.K.

3. Estimates of the consumption of alcoholic beverages are generally reported in terms of units of alcohol or grams of ethanol consumed per day. One unit of alcohol is approximately equivalent to half a pint of normal strength beer, lager, or cider, a single measure of spirits, one small glass of ordinary strength (9% by volume) wine or one small glass of port, sherry or other fortified wine. This is approximately equivalent to 8 grams by weight or 1centilitre (10 ml) by volume of pure alcohol (ethanol).[8] One research publication has reported that the average amount of ethanol in a standard drink in the U.K ranges between 8-10 grams with an average of 9.5 grams.[9] This later figure has been used by the Imperial College research group in its systematic review.

4. The Department of Health for England advises that women should drink no more than 2-3 units of alcohol per day (i.e. 16 g – 24g ethanol/day). This daily benchmark applies whether individuals drink every day, once or twice a week, or occasionally. This guidance on sensible drinking was derived from an Interdepartmental Working Group (IDWG) report published in 1995. The IDWG considered all of the evidence relating to potential health benefits to women from drinking 1-2 units per day and the evidence for progressive health risk from consistently drinking 3 or more units per day.[10] Prior to 1995 the sensible drinking message had been expressed in terms of a weekly intake of alcohol units (i.e. less than 14 units/week was unlikely to damage a woman's health). The effect of the change in advice from a weekly limit to a daily benchmark has only recently been investigated in routine surveys which evaluate drinking patterns among women (see paragraph 6 below).

5. There is a lot of information on the consumption of alcoholic beverages regularly obtained as part of the General Household Survey (GHS). (http://www.statistics.gov.uk/ssd/surveys/general_household_survey.asp) and the Health Survey for England (HSfE) (http://www.official-documents.co.uk/document/deps/doh/survey02/summ03.htm) Detailed information can be obtained from these sources and therefore only a very brief review of the main conclusions on drinking patterns amongst women in the U.K. is presented below. (No comment on regional or socio-economic influences on drinking patterns has been included in this statement.) The GHS is a face-to-face interview survey conducted with a sample of 13,200 households across Great Britain and gathers a large amount of information on social, economic and health-related

topics. The GHS has reported annually since 1971 (with breaks in 1997, 1999 and 2000 when the survey was re-developed) The HSfE is an annual survey which has provided information on consumption of alcoholic beverages since 1991. Both surveys have been adapted in recent years to take into account the change to expressing the sensible drinking message in terms of daily benchmark intake of alcohol units. The Committee also had access to an evaluation of the HfSE undertaken by Dr Paola Primatesta and colleagues from University College London.[11]

6. The available information from these surveys provides similar findings. The average consumption of alcoholic beverages (expressed either as weekly or, where available as daily intakes) in women of all ages has increased over the last decade. Thus the weekly average intake from the HSfE was 6.2 units/week in 1993, 7.1 units/week in 1998 and 8.4 units/week in 2002. This trend was most noticeable in women aged 16-24 years where consumption rose from about 8 units/week in 1993/4 to almost 12 in 2001 and 13.3 units/week in 2002. The GHS reported a similar finding for women aged 16-24 across Great Britain with average weekly consumption reported to be 7.3 units in 1992 and 14.1 units in 2002. Primatesta and colleagues reported a strong correlation between mean or median intake and proportion of women exceeding the Sensible Drinking Limit (expressed as 14 units/week). A marked increase in women aged 16-24 years reporting consumption in excess of 14 units/week is noticeable from 1992 to 2002. The GHS reports this increase to be from 17% to 33%. The HSfE reported similar findings (from 20% in 1992 to 33% in 2002). Information on daily consumption of alcoholic beverages collected from 1998 in the GHS documented that the proportion of women aged 16-24 years who had drunk 6 or more units on at least one day in the previous week rose from 24% to 28% between 1998 and 2002. The equivalent proportion among women aged 25-44 years of age was 11% in 1998 rising to 14% in 2001, and 13% in 2002.

7. Thus, overall, the evidence supports the view that consumption of alcoholic beverages among women is increasing with the predominant increase in young women aged 16-24. The evidence suggests that increased consumption among women aged 45 years or more is spread evenly across the week whilst the increase in intakes in younger women, and particularly those aged 16-24 years predominantly occurs on one or two days per week. The GHS survey authors did note that there were too few data on daily consumption patterns to reach any conclusions about long term trends in daily consumption of alcoholic beverages.

Background to COC consideration

COC Statement for the Interdepartmental Working Group on Alcohol (1995)

8. The Committee first considered the epidemiological evidence for an association between alcohol and breast cancer in 1995 at the request of the Interdepartmental Working Group (IDWG) on Sensible Drinking[10]

as part of the review of medical and scientific evidence and its interpretation of the long term effects of drinking alcoholic beverages. The Committee provided a statement to the IDWG on the evidence for alcohol and cancer at all sites and concluded that drinking alcoholic beverages causes a dose-related increase in the risk of squamous carcinomas of the upper aerodigestive tract as a whole, and for cancers of the oral cavity, pharynx, larynx, and oesophagus which was independent of the effect of smoking. There was a substantial amount of information available to members who were able to draw conclusions on dosimetry, duration and frequency of drinking alcoholic beverages and the effect of abstinence and of smoking.[5]

9. A substantial amount of research was available to the Committee on drinking alcoholic beverages and breast cancer in 1995. Members reviewed the 1988 IARC monograph, which provides an evaluation of four large prospective and 13 case-control studies. The Committee also reviewed seven additional prospective studies[12-18], 17 new case control studies[19-35] and two systematic reviews [36,37]. In addition a number of reviews of the available information were also considered.[38-40] The Committee agreed that the adequacy of control for confounding by known and/or alleged risk factors for breast cancer varied in the different accounts. A dose-related association was reported in most cohort studies and in some hospital-based case-control studies. The results of population-based case-control studies did not generally support an association. A statistically significant dose-related increase in relative risk (RR) was reported in the two systematic reviews (RR at 3 drinks/day 1.38 (95% CI 1.23-1.55)). The Committee noted that the small increases in relative risk documented in epidemiological studies ranging between approximately 1.2-3 were associated with highly variable estimates of consumption (*ca* 1-60g ethanol/day). It was agreed that clear evidence of causality had not been demonstrated.[5]

10. The Committee concluded "...that while there is no decisive evidence that breast cancer is causally related to drinking alcoholic beverages, 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 be kept under review."[5] The Interdepartmental Working Group endorsed the COC's conclusions and the recommendation that the relationship between alcohol and breast cancer should be kept under review.[10]

<u>COC review of information published between 1995-1999</u>
http://www.advisorybodies.doh.gov.uk/coc/index.htm*).*

11. The Committee considered review papers prepared by the DH Toxicology Unit at Imperial College on the published epidemiology studies and investigations into potential mechanisms by which drinking alcoholic beverages could increase the risk of breast cancer.[41-43] The epidemiological evidence included three prospective studies[44-46] and a further 22 case-control studies.[47-68] The results were in accordance with the conclusions reached in the 1995 review in that most studies reported a small association between drinking alcoholic beverages and

increased risk of breast cancer with evidence for a dose-response in the majority of studies examined. A pooled analysis of six prospective studies also reported a significant trend between increasing alcohol consumption and increased risk of breast cancer.[69] The Committee agreed that no conclusions on the influence of menopausal status, type of beverage, frequency of drinking could be reached from the available information.

12. The DH Toxicology Unit paper[42] identified sparse evidence for a number of potential mechanisms by which alcohol could induce breast cancer including enhanced metabolism of carcinogens[70-72], increased cellular permeability to potential carcinogens[73], impaired immune responsiveness[74], and abnormal differentiation of mammary tissue.[75] A further published paper presented a hypothesis that alcohol could induce tissue and DNA damage via the formation of reactive oxygen species in breast tissue.[76] However, most of the available studies on mechanism examined the effects of drinking alcoholic beverages on oestrogen metabolism in humans. There was evidence from both cross-sectional and intervention studies that alcohol consumption affected oestrogen metabolism in premenopausal[77,78] and postmenopausal[79-85] women. Some recent research provided evidence that drinking alcoholic beverages affected serum oestradiol concentrations in premenopausal women using oral contraceptives,[86] The Committee considered that the data on effects of drinking alcohol on hormones were complex and asked for a further tabulation of data on plasma and urinary sex hormones following consumption of alcohol. Overall the available data from the 1999 review suggested a plausible mechanistic link between consumption of alcohol and breast cancer involving effects on hormones. The interpretation of these data was particularly complicated and difficult; for example, the influence of confounding effects of other possible breast cancer risk factors such as obesity, use of oral contraceptives and hormone replacement therapy and their potential interaction with drinking alcoholic beverages needed to be considered carefully.

13. The Committee assessed all of the available data using the Bradford-Hill criteria as a guide to consideration of causality. The Committee concluded there was considerable evidence to support an association between drinking alcoholic beverages and risk of breast cancer but the magnitude of the association was small (i.e. the relative risk is modest and, even for heavy drinkers, in most studies does not exceed 3 (i.e. 3 times that of non-drinkers). The Committee also considered that it was difficult to ascertain the nature of the dose-response relationship from the available information. The small magnitude of the association between drinking alcoholic beverages and risk of breast cancer and the complex aetiology (i.e. there are weak associations with a number of other risk factors) of breast cancer are the main reasons for the difficulty in reaching a definite conclusion. The association could be due to systematic biases in the studies or to confounding by other risk factors. The Committee concluded that a rigorous systematic review (including appropriate meta-analyses) was needed in an attempt to identify and evaluate potential biases, confounding and heterogeneity

so that a fuller assessment of causality and the magnitude of the risk associated with drinking alcoholic beverages could be made. It would also be important for any further analyses to provide an estimate of the Population-Attributable Risk (PAR). A systematic review was subsequently commissioned with the Department of Epidemiology and Public Health, Imperial College London.

14. The Committee had also asked its sister committee, the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) to update its 1995 review on the evidence regarding the potential for alcoholic beverages to induce mutagenicity *in-vivo*. The COM considered the available evidence up to November 2000. The COM reaffirmed its 1995 conclusion that consumption of alcoholic beverages does not present any significant concern with respect to mutagenic potential. The statement can be found on the COM internet site. (http://www.advisorybodies.doh.gov.uk/com/index.htm)

Introduction to current review

15. An initial draft report of the systematic review was considered at the November 2002 COC meeting. Further drafts were considered at meetings during 2003. The Department of Health also commissioned a further review of evidence on possible mechanisms by which drinking alcoholic beverages could induce breast cancer from the DH Toxicology Unit at Imperial College. The Committee also received a copy of the published paper from the Oxford Collaborative Group on Hormonal Factors in Breast Cancer just prior to its November 2002 meeting. The Committee agreed that it would be important to compare the approaches used and results reported in the commissioned systematic review study by the Imperial College group with results published by the Oxford Collaborative Group as this might help it to draw conclusions about causality. The Committee also reviewed additional epidemiological studies on the association between drinking alcohol and breast cancer retrieved up to June 2003. The primary objectives of the current COC review were;

a) To evaluate the report of the systematic review undertaken by the Department of Epidemiology and Public Health, Imperial College and the investigations undertaken by the Oxford Collaborative Group study and to consider whether the association between drinking alcoholic beverages and increased risk of breast cancer can be explained by bias or confounding and the extent of heterogeneity in the reported association.

b) To review the available evidence for a mechanistic basis for the observed association between drinking alcoholic beverages and breast cancer.

c) To assess whether the association between drinking alcoholic beverages and risk of breast cancer can be considered causal

d) To evaluate quantitative estimates for population attributable risk (PAR).

Review of New Information

Uncertainties in evaluation

16. Potential uncertainties that might affect the interpretation of results obtained in the two systematic reviews considered by the Committee (i.e from Imperial College and the Oxford Collaborative Group) could include misclassification of cases and controls, misclassification of exposure, misreporting of alcohol consumption, the evaluation of dose-response, and the evaluation of potential effects of confounding factors for breast cancer on estimated risks associated with drinking alcohol. The Committee considered that the different approaches used by the two groups complemented each other. Thus the evaluation of individual subject level data by the Oxford group would allow for a more consistent classification of exposure and adjustment for confounding factors. The evaluation of study quality by the Imperial group would aid in the assessment of the sensitivity of findings to study design.

Systematic review undertaken by Department of Public Health and Epidemiology[87-89](Draft reports reviewed at November 2002 and meetings during 2003). Finalised report submitted to peer reviewed journal and considered by COC at June 2004 meeting.[120]

17. The objectives of the systematic review and subsequent meta-analyses undertaken by Imperial College were to determine the magnitude of any association between drinking alcohol and primary breast cancer, to explore the dose-response relationship, to examine whether any association was related to specific beverages or to consumption of all alcoholic beverages, to explore possible heterogeneity, bias and confounding and to estimate the population attributable risk. All publications, in any language, between January 1st 1966 and 31st December 2003 were eligible for inclusion. The results from studies were examined after data on study design and methods had been abstracted and reviewed independently by two members of the team. Duplicate reports of the same study were carefully evaluated to include only a single and the most complete dataset. A simple scoring scheme was used: suboptimal design (1), good design but insufficient control for confounding (2), good design and adequate control of confounding (3). Meta-analyses were undertaken for least, at-least-age, and multivariate-adjusted odds ratios (where possible) separately for all reports, those scoring 2 or 3 and, finally those scoring 3. Dose response modelling used standardised exposures (converted to grams/day (g/day)), the mid-point estimates for consumption, and a linear model with a variable intercept and meta-analysis of dose-response using a random effects model. The authors assumed that an average drink in the U.K. contained approximately 9.5g ethanol and used this as a conversion factor in reporting their analysis of risk of breast cancer associated with drinking alcoholic beverages.

18. A total of 298 papers were identified. Data from 111were considered appropriate for inclusion in the review. These related to 98 unique studies. The number of studies that provided data that could be included in the ever versus never analysis was 89 and was based on 75,728 cases. Using all these studies and least adjusted odds ratios, a statistically significant risk associated with drinking alcohol of 1.11 (95% CI 1.06-1.17) was reported. Combining least adjusted odds ratios estimates from studies scoring 2 or 3, the risk associated with drinking was 1.12 (95% CI 1.06-1.18). The odds ratio for studies with a score of 3 and multivariate adjustment was 1.22 (95% CI 1.09-1.37). The use of a linear dose-response model with a variable intercept allowed for the presence of drinkers/exdrinkers in the referent group and also avoided the assumption that if a linear dose-response relationship existed then it would be linear through the origin. It was reported that when the adjusted dose-response slopes from studies of good design only (multivariate adjustment for confounders with a score of 3) were combined, the odds ratio was found to be 1.10 (95% CI 1.05-1.15) associated with drinking an extra 1g of ethanol (in alcoholic beverages) per day amongst drinkers. The Imperial research group reported that a woman drinking on average two drinks per day (assuming each drink contains 9.5 g ethanol) has a lifetime risk of breast cancer estimated to be 10% (95% CI 5-15%) higher than a woman who drinks an average of one drink per day. The relative risk can also be expressed in terms of units of alcohol consumed (where, as noted in paragraph 3 above each unit contains 8 g of ethanol). This is important since intakes in the U.K. are usually expressed in terms of unit of alcohol consumed. Thus a woman consuming on average two units per day has a lifetime risk of breast cancer estimated to be 8% (95%CI 4%-12%) higher than a woman who drinks on average one unit per day. There was no evidence for stronger or weaker associations with any particular type of beverage.

19. The Imperial research group found considerable unexplained statistical heterogeneity between the studies they reviewed. Thus meta regression with random effects was used to investigate heterogeneity. The following study characteristics were included: data collected before or after disease onset, hospital or community controls, pre and post menopausal participants and country of study population. It was noted that there was a significant difference in relative risk between case-control studies using hospital or community controls, but the association between drinking alcohol and breast cancer was still statistically significant in studies using either of these control groups. Otherwise none of the variables included in the meta regression significantly reduced heterogeneity between studies. Funnel plots were used to investigate the possibility of publication bias, and they did not indicate that this had been a problem. Bias and confounding could not be dismissed as an explanation of the results, but the study methods minimised their impact as far as possible.

20. A Population Attributable Risk (PAR) for the U.K had been calculated using Cancer Statistics for 1999 and information on drinking patterns

derived from the Health Survey for England from 1993 and 1998. Assuming causality and that 1 unit of alcohol contains 8 g ethanol, the PAR calculated from the best quality studies was 6.0% (95% CI 3.2%-8.8%) (i.e the fraction of breast cancer cases that could be prevented if drinking was reduced to a very light level (i.e below 1 unit per week). Using 2000 cancer registration data for the U.K, this would suggest approximately 2430 cases each year (95% CI 1290-3560) could be prevented.

COC Comments on draft and final reports of systematic review undertaken by Imperial College

21. The Committee considered that the work had been thoroughly undertaken and was the largest and most comprehensive systematic review available.

22. The scoring system allowed examination of study quality and, further analyses had been undertaken to examine for bias and confounding. The Committee noted that the majority of analyses reported statistically significant positive associations. The investigators had acknowledged that the definition of non-drinker, use of mid point estimates of alcohol consumption and aggregate (study) data instead of individual data had limited the evaluation. Members noted there were limited data available on assessment of the influence of menopausal status and agreed no conclusions could be drawn on this aspect. The Committee agreed that the evaluation of dose-response was difficult, particularly at higher levels of drinker where there were comparatively fewer data available. Members accepted the rationale for adopting a linear model with a variable intercept .

23. It was noted that the available mechanistic data supported the possibility of a threshold for carcinogenesis. The Committee considered that the estimate of Population Attributable Risk (PAR) was potentially one of the most important outcomes of the systematic review with regard to presentation of the public health significance of the analyses. Members noted that there was no significant alteration in PAR when non-drinkers were excluded. The Committee concluded that the PAR estimate based on best studies and most adjusted model using intake data for England and cancer registration data for the UK represented an acceptable analysis. They recommended that the PAR estimate could be used in the consideration of policy options.

<u>Publication by Oxford Collaborative Group on Hormonal Factors in Breast Cancer.[7](Report reviewed at November 2002 meeting)</u>

24. The Oxford Collaborative Group has collated individual subject data from epidemiology studies where the relationship between breast cancer and hormonal, reproductive and other factors (including alcohol consumption) had been investigated. Case-control studies were eligible if they included at least 100 women with incident invasive breast cancer and recorded appropriate information on the potential risk factors for breast cancer. Cohort studies were included using a nested

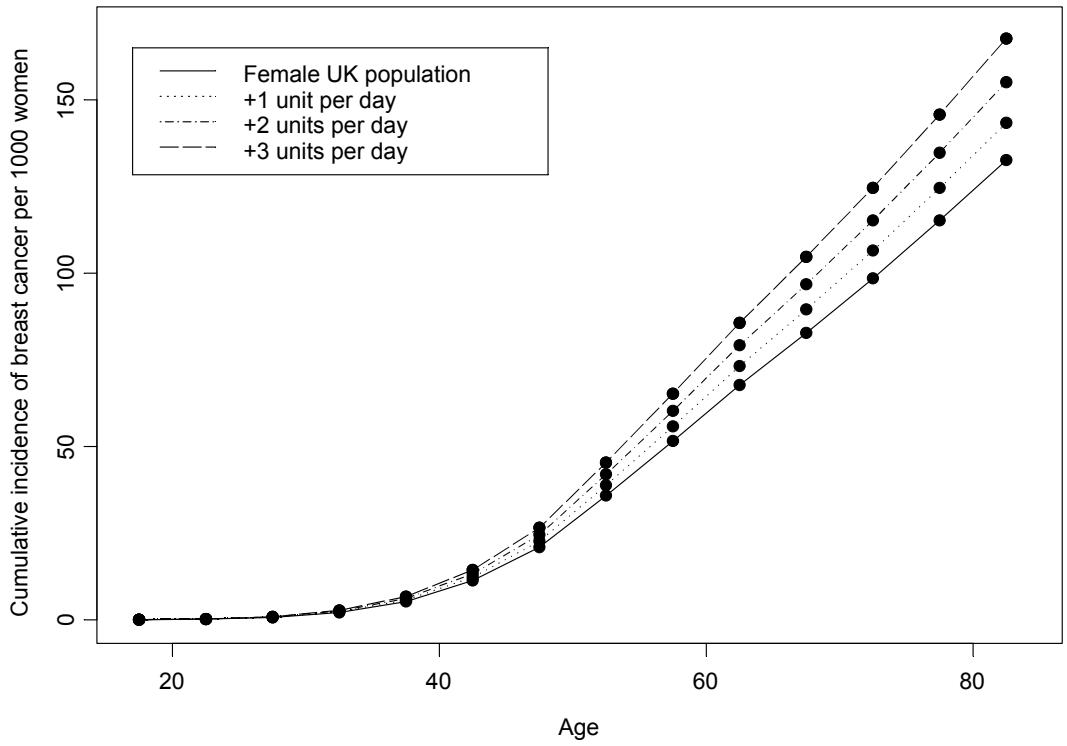
case-control design, in which four controls were selected at random, matched on follow-up to age of diagnosis and, where appropriate broad geographical regions. There were 53 studies (two unpublished) that contributed data on alcohol and tobacco usage. There were a total of 58,515 cases where individual data were obtained and 95,067 controls. Relative risks of breast cancer were estimated after stratifying for age, study centre, parity, and where appropriate, women's age when their first child was born, and by tobacco use. A relative risk of breast cancer of 1.32 (95%CI 1.19-1.45) was reported for an intake of alcoholic beverages equivalent to 35-44 g ethanol per day (i.e. approximately 4-5 drinks/day) compared to non-drinkers. The relative risk of breast cancer increased by 7.1% (95% CI 5.5%-8.7%) for each additional 10 g/day intake of ethanol in alcoholic beverages. The authors estimated that approximately 4% of breast cancers in developed countries were attributable to drinking alcoholic beverages.

25. The Committee noted that the Oxford Collaborative Group had access to individual data from 58,515 women, including some from unpublished studies. They had been able to determine median intakes of alcohol. The dose response data reported suggested some evidence for a threshold below a median intake of 8 g/day. Overall it was felt that the Imperial College group had examined significantly more cases that the Oxford Collaborative group.

Discussion of Oxford Collaborative Group research and Imperial College review (March 2003 - June 2004 meetings)

26. The Committee noted the percentage of non-drinkers was 36% in the Oxford Collaborative study and 28.6% in the Imperial College report. The estimate of PAR reported by the Oxford Collaborative Group was 4 % compared to 6% by the Imperial research team. The Committee considered that this difference between the two studies was minor and probably resulted from different proportions of non-drinkers included in the respective calculations. Members considered that the approach used to determine cumulative incidence of breast cancer with age per 100 women at 2, 4 and 6 drinks per day was a useful way to present risks (see figure 5 of the Oxford Collaborative Group report[7]) and suggested the Imperial research group undertake a similar analysis based on their data. Taken together, the results of the two systematic reviews considered by the Committee (i.e. the Imperial research group report commissioned by the Committee and the published Oxford Collaborative Group paper) indicate that the association between drinking alcohol and risk of breast cancer is very unlikely to be due to chance.

27. Following the November 2003 meeting, the Imperial research group provided the figure given below which reports the cumulative incidence of breast cancer per 1000 women for each additional unit of alcohol drunk per day.[120] The solid curve shows the cumulative incidence for the female population in the U.K. (where the average consumption of alcohol is 1 unit per day). The dotted curves show the estimated



cumulative incidence if women drank an extra 1,2, or 3 units per day, where a unit of alcohol contains 8 g ethanol. Studies included in the systematic review undertaken by Imperial College do not permit an assessment of breast cancer in non-drinking women in the U.K.

28. The estimated cumulative incidence of breast cancer for women aged 60 and 80 assuming daily consumption of alcohol throughout the majority of a life has been tabulated below.

Cumulative Incidence per 1000 women

	Current consumption	+1 unit per day	+2 units per day	+3 units per day
Age 60	60	65	70	75
Age 80	125	134	145	157

Additional published epidemiology studies retrieved after November 2002

29. The Committee reviewed a number of additional epidemiological papers at the March 2003 meeting retrieved after the November 2002 meeting.[90-96] The Committee noted new evidence from the Nurses Health Study I cohort that self reported diagnosis of Benign Breast Disease (BBD) might potentially be a useful marker for breast cancer and noted the dose-response relationship between BBD and alcohol intake. [93] This association might be explored in further research. Members noted the recent studies of receptor status in the association between drinking alcohol and breast cancer and agreed no conclusions could be drawn from the conflicting data. Members commented on one small case-control study which suggested an elevated risk of breast cancer in African-American women who drank alcohol and noted the claim that there was increased mortality in African-American women following diagnosis of breast cancer which might be attributable to

drinking alcohol or represent a particular susceptibility of African-American women.[91] The Committee asked for additional literature review work on this topic to be undertaken.

30. Some additional papers were submitted to the 26 June 2003 COC meeting.[97-100] The information available, which included a review of all relevant studies published up to April 2001 suggested that there is no association between drinking alcohol and increased mortality from breast cancer following diagnosis.[101,102] A further review of the claimed variation in risk of breast cancer between different ethnic groups revealed that any association is unlikely to be due to consumption of alcohol. It was noted that, for women, alcohol consumption by ethnic minority groups in the U.K is lower than the estimate for the whole population.[103,104] One small study found that heavy drinking of alcohol did not modify the risk of early onset breast cancer in young women.[98] Two studies reported on the potential role of genetic polymoprhisms of metabolising enzymes but the results suggested that any modifying effect on alcohol induced breast cancer was minimal.[99,100]

Further paper from DH Toxicology Unit on mechanisms[105]

31. The DH Toxicology Unit noted in its paper that alcohol may not be carcinogenic to the breast *per se*, but may facilitate carcinogenesis through a variety of mechanisms. Several pathways have been proposed, including effects on the permeability of cell membranes in the breast, induced hepatic metabolism of carcinogens by ethanol-inducible enzymes, inhibition of DNA repair mechanisms, effects on hormone metabolism and interactions of alcohol with other host and environmental factors. The paper has been published on the COC internet site (http://www.doh.gov.uk/coc/index.htm)

32. The Committee was aided in its deliberations by expert advice from Professor H S Jacobs (Emeritus Professor of Reproductive Endocrinology, University College Medical School, London) who attended the November 2002 meeting of the COC. The DH Toxicology Unit report highlighted evidence to support the view that alcohol induced hyperinsulinaemia and increased Insulin-like Growth Factors (IGFs) which subsequently induced an increase in breast tissue density through increased cell division.[105-108] It was noted that there were additional studies to support an association between drinking alcohol and effects on oestrogen metabolism.[109] There were considerably less convincing data for a number of suggestions such as alcohol induced suppression of melatonin excretion products and aromatisation of androgens to oestrogens. The Committee agreed that it would be appropriate to focus the review on the effects of alcohol on oestrogens, hyperinsulinaemia and effects on IGFs. The evidence supporting other proposed mechanisms was preliminary and no conclusions could be drawn.

33. Evidence to support the association of alcohol with increased oestrogen levels has been documented in a number of studies[110,111] not previously reviewed by COC. The Committee considered a cross

sectional study by Verkassalo PK et al[112] and agreed that sufficient numbers of premenopausal (n= 636) and postmenopausal (n = 456) women had been included. The results were inconsistent with the data previously reviewed by the committee in 1999 and suggested an effect of cigarette smoking, but not drinking alcohol, on levels of oestrogens. These results were not consistent with the available epidemiological data on breast cancer. The COC reviewed a study by Dorgan JF et al [113]in postmenopausal women and agreed that a satisfactory crossover design had been used for this intervention study, although there were some reservations about potential compliance of study participants. It was noted that there was some evidence for a small increase in oestrone sulphate and dehydroepiandrosterone sulphate (DEHA sulphate) following the consumption of 15 g or 30 g ethanol/day over an eight week period. There was no effect on oestradiol levels (free or bound) in this study. Members agreed the data supported a small effect of drinking alcohol on adrenal output of hormones. This study suggested the effect of drinking alcohol on hormone levels was milder than that suggested by the cross sectional studies previously reviewed by the COC in 1999.

34. The Committee agreed that the weight of evidence available suggested that drinking alcohol produced a number of biochemical effects in the liver which resulted in changes to oestrogen metabolism and IGF levels which, over a prolonged period of time, i.e. decades, could induce breast cancer. Both of these suggested mechanisms would potentially have a threshold with regard to induction of breast cancer.

Consideration of Causality

35. The Committee had previously considered the available evidence in accordance with the Bradford-Hill criteria[114] during its review in 1999. The Committee agreed it would be appropriate to undertake a further review using these criteria as an aid in the assessment of the potential causation of breast cancer by drinking alcoholic beverages as there were new epidemiological and mechanistic data available. An assessment of the evidence has been tabulated below.

Criterion	**Evidence regarding alcohol and breast cancer**	**Comments**
Strength	Limited	The RR* in alcohol drinkers is modest and, even for heavy drinkers, in most studies rarely exceeds 3 (i.e. risk in drinkers is 3 times that of non-drinkers). However the RR for most other identified breast cancer risk factors also rarely exceed this value.
Consistency	Yes.	Literature largely points towards a small positive association but there is still unexplained heterogeneity. The systematic review by Longnecker MP[37] also reported significant heterogeneity. The pooled analysis of prospective studies published by Smith-Warner SA et al[69] found evidence of heterogeneity in results for pre menopausal women but not postmenopausal women Heterogeneity was only partly explained in the systematic review report from the Imperial College group.[87-89] However the approach used by the Oxford collaborative group which used individual data from the same cases, gave substantially similar results to the Imperial College group.[7]
Specificity	Not relevant.	Cancer risk attributed to alcohol is not specific to breast cancer (e.g. prolonged alcohol consumption can induce cancers of the head and neck and oesophagus and liver).

Temporality	Yes	Association demonstrated in prospective studies where alcohol consumption can be studied before the occurrence of disease.
Biological gradient	Yes	There is evidence for a monotonic dose-response curve in the submitted systematic reviews from Imperial College and in the Oxford Collaborative group analysis.
Plausibility	Yes	Evidence for effect of alcohol consumption and elevations in blood levels of oestrogen metabolites documented.[77-86,110-112] Raised oestradiol is a risk factor for breast cancer.[5] The evidence therefore suggests a plausible mechanism Further studies have also suggested that an effect of drinking alcoholic beverages could affect liver biochemistry and hence could affect insulin levels and Insulin dependent Growth Factors (IGFs) and thus induce increased cell numbers in in breast tissue.
Coherence	Limited	Evidence for an increased risk of breast cancer in alcoholics[115] and for a relatively low rate of breast cancer incidence among populations abstaining from alcohol (e.g. Mormons).[116]
Experiment	Limited.	Evidence from one limited study where ICR mice were given ethanol via the drinking water (at 10% or 15%) for 25 months.[117] No evidence that alcohol is carcinogenic in a large number of carcinogenicity studies including some conducted to acceptable standards .[5] Some evidence that alcohol affects breast tissue differentiation in animals.[118]
Analogy	Yes	Other causes of significantly increased oestradiol levels in exposed populations are suggested risk factors for breast cancer (e.g. use of oral contraceptives and HRT).[5] IGFs may be involved in development and progression of breast cancer.[107,108]

*RR = Relative risk

36. There was evidence to satisfy most of the criteria**.** The Committee agreed that, overall, there was no consistent evidence that alcohol is carcinogenic from experimental studies in animals. The isolated finding of mammary tumours in ICR mice[117] given extremely high doses of ethanol in the drinking water in excess of the Maximum Tolerated Dose level had not been demonstrated in other studies in rats and mice which also used high doses of ethanol. The Committee was aware of some preliminary findings which suggested that *in-utero* exposure to ethanol in rats may be associated with increased mammary tumourigenesis, but agreed that no conclusions could be based on the preliminary results of this work. [119] The Committee considered that the criterion of specificity was not relevant to the assessment of breast cancer risk.

37. The Committee agreed that the available evidence indicated there is a modest association between drinking alcohol and increased risk of breast cancer which was consistently demonstrated. The small magnitude of the association between drinking alcoholic beverages and risk of breast cancer and the complex aetiology of breast cancer (i.e. there are weak associations with a number of other risk factors) are the main reasons for the difficulty in reaching a definite conclusion. However the most recent review of mechanisms provided evidence for a number of plausible mechanisms which focused on a potential effect of drinking alcohol on liver function. Overall, the Committee considered it was prudent to assume a causal association exists.

Significance to Public Health

38. The Committee agreed that if, for practical purposes, a causal association is assumed, then it was important to consider the magnitude of the association between drinking alcohol and breast

cancer in terms of potential impact on public health. The Population Attributable Risk (PAR) is an estimate of the proportion of cancer cases which might be prevented if the levels of alcohol consumption were reduced to very light levels of drinking (below 1 unit/week). The calculation of PAR from epidemiological data requires information on the rate of breast cancer in the population, the estimate of relative risk, and data on intake of alcoholic beverages. There are some uncertainties in all of these and, hence in the estimate of PAR produced. The estimate of PAR from the Imperial College group which takes some of the uncertainties into account in the estimate of relative risk is 6.0% (95% CI 3.2%-8.8%). Based on the 2000 data for breast cancer registration in the U.K this would indicate that approximately 2430 cases/year (95% CI 1290-3560) may be attributable to drinking alcoholic beverages.

39. The estimate of PAR from the Oxford Collaborative Group was slightly lower. The Committee agreed that it would be prudent to base its evaluation on the calculations proposed by Imperial College since these were based on intake data for England and could be readily applied to the U.K. The Committee noted that the systematic review undertaken by the Imperial College group had reported inconclusive results for the effect of Hormone Replacement Therapy on risk of breast cancer associated with drinking alcohol. The Oxford Collaborative group had reported that stratification for use of oral contraceptives and HRT had not affected the estimation of risk of breast cancer associated with drinking of alcoholic beverages. The Committee felt that the potential for oral contraceptive and HRT use to influence the association between drinking alcohol and risk of breast cancer had not been researched in detail and recommended further epidemiological studies to assess any potential interactions.

40. The Committee agreed with the reported assessment of cumulative risk submitted by the Imperial College group and noted that lifetime drinking of an extra 3 units of alcohol per day above the national average for the female population of 1 unit/day would result in an additional 15 cases of breast cancer/1000 women at 60 years of age. An extra 32 cases of breast cancer/1000 women would occur at 80 years of age at this increased level of drinking. This needs to be compared to background rates of 60 cases of breast cancer/1000 women at 60 years of age and 125 cases of breast cancer/1000 women at 80 years of age where the average intake of alcohol is 1 unit per day. The Committee agreed there was a progressive increase in the risk of breast cancer associated with increasing amounts of alcoholic beverages drunk and duration of drinking. A review of the sensible drinking message would have to balance the increasing risk of breast cancer against the benefit attributed to drinking alcoholic beverages of reduced mortality due from coronary heart disease. Such an evaluation would be outside the terms of reference of the COC.

41. The Committee noted the evidence for increasing consumption of alcoholic beverages by women in the U.K, and particularly amongst younger women and was concerned that if the increased intake of

alcoholic beverages reported amongst this group were maintained over most of their lifetime then it would result in an increase in the number of alcohol-related breast cancer cases. The surveys of alcohol consumption reported to the Committee specifically reported drinking in various age groups. The youngest age group studied included women aged 16-24 years. It was therefore important to raise awareness of the potential risks associated with drinking alcoholic beverages particularly amongst young women.

Conclusions of current review

42. The Committee reached the following conclusions based on an evaluation of all the data available up to the end of June 2003 and a finalised report of a systematic review undertaken by Imperial College submitted to the June 2004 COC meeting.

a. Taken together, the results of the two systematic reviews considered by the Committee (i.e. the Imperial College research group report, commissioned by the Committee, and the published Oxford Collaborative Group paper) indicate that the association between drinking alcohol and risk of breast cancer is very unlikely to be due to chance **(paragraph 26)**.

b. From the Imperial College review, the best estimate for the relative risk of breast cancer associated with each additional gram of ethanol consumed was1.01 (95% CI 1.005-1.015). This means that a woman drinking an average of two units of alcohol (each unit containing 8 g ethanol) per day has a lifetime risk estimated to be 8% higher compared to a woman who drinks an average of one unit of alcohol per day, There was no evidence for variation in the association with any specific type of alcoholic drink **(paragraph 18).**

c. The Population Attributable Risk (i.e. percentage of breast cancers which could be prevented if drinking were reduced to a very low level of less than 1 unit/week) using U.K cancer registry data and intake data from the Health Survey for England is 6% (95% CI 3.2%-8.8%). This equates to approximately 2430 cases of breast cancer per year (95% CI 1290-3560) **(paragraph 20).**

d. The assessment of cumulative risks suggests that lifetime drinking of an extra 3 units of alcohol per day would result in an additional 15 cases of breast cancer/1000 women at 60 years of age and an extra 32 cases of breast cancer/1000 women at 80 years of age compared to current rates of 60 cases of breast cancer/1000 women at 60 years and 125 cases of breast cancer/1000 women at 80 years where the average intake is 1 unit per day (**paragraphs 28 and 40**).

e. The Committee agreed that the weight of evidence available suggested that drinking alcohol produced a number of biochemical effects in the liver which resulted in changes to oestrogen metabolism and IGF

levels, which over a prolonged period of time, i.e decades, could induce breast cancer. Both of these suggested mechanisms would potentially have a threshold with regard to induction of breast cancer. **(paragraph 34).**

f. The Committee concluded it prudent to assume that drinking alcoholic beverages may cause breast cancer in women. **(paragraph 37).**

g. The Committee agreed that more research into the potential for interaction between use of oral contraceptives and use of Hormone Replacement therapy and the induction of breast cancer by drinking alcoholic beverages was appropriate. **(paragraph 39).**

h. The Committee was concerned to note that if the increased consumption of alcoholic beverages by young women were maintained over most of their life-time then it would result in an increase in the number of alcohol-related breast cancer cases in the future. It is therefore important to raise awareness of the potential risk of breast cancer in women associated with drinking alcoholic beverages. **(paragraph 41).**

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Glossary of terms/phrases used in statement.

Aetiology:	The study of causation**.**
Benign Breast Disease:	A proliferation of breast tissue which is not malignant. However some forms are indicative of an elevated risk of Breast Cancer.
Breast Cancer:	A malignant tumour of breast tissue, usually arising from ductal or lobular epithelial cells. The great majority of breast cancers occur in women. Breast cancer is rare in men.
Causal Association:	Describes the relationship between two factors which are associated where it can be established that one of the factors causes the other, i.e smoking cigarettes and lung cancer.
Collaborative Group On Hormonal Factors in Breast Cancer:	A large international collaborative group of researchers. The secretariat is based at the Cancer Research UK Epidemiology Unit, Gibson Building, Radcliffe infirmary, Oxford OX2 6HE. The group had access to raw data from 65 epidemiology studies in its evaluation of the association between drinking alcoholic beverages and increased risk of breast cancer.
Epidemiology studies:	Epidemiology is the study of the distribution and determinants of diseases in human populations. All of the studies included in the COC review of the association between drinking alcoholic beverages and increased risk of breast cancer are called Analytical studies. Very briefly, the basic outline of the types of studies included in this review are; A. Case-control studies where drinking patterns are gathered from individuals with breast cancer and compared to patterns in control individuals who don't have breast cancer. B. Cohort studies where information on drinking patterns is gathered from individuals who are then followed for a period of time (often decades) until the occurrence of breast cancer or death.

General Household Survey (GHS):	The GHS is conducted on a yearly basis by the Social Survey Department of the Office for National Statistics (ONS). It has chartered the changes in British households and society since 1971. Questions about drinking habits were included every other year from 1978-1998 and every year from 2000 onwards. Questions regarding maximum daily amount drunk last week and weekly drinking habits have been included every year have been included since 1998.
Heterogeneity:	A variation in an estimate which exceeds the expected.
Hormone Replacement Therapy: (HRT)	HRT consists of oestrogen given continuously to women during the menopause to manage symptoms associated with loss of ovarian function. Cyclical progestogen is given to women who have not had a hysterectomy. HRT may also help to prevent osteoporosis.
IGFs	Insulin-like Growth Factors.
International Agency for Research on Cancer (IARC):	The International Agency for Research on Cancer (IARC) is part of the World Health organisation. IARC's mission is to co-ordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships.
Interdepartmental Working Group on Alcohol (IDWG):	The IDWG was established in 1994 and consisted of a group of officials. Its remit was to review current medical and scientific evidence and its interpretation on the long term effects of drinking alcohol and, to consider whether the sensible drinking message should be reviewed in the light of this, also taking into account Government policies on the short term effects of drinking

	alcohol and any other factors considered relevant by this group. The IDWG produced a report entitled “Sensible Drinking” in December 1995.
Mechanisms (by which alcohol could induce breast cancer):	A term describing the effects of alcohol drinking on biochemistry and physiology which could, if sustained over a period of time, ultimately lead to induction of breast cancer. Evidence regarding mechanisms can come from a variety of sources including studies in cell culture (in-vitro), studies in animals, and investigations in human epidemiology or volunteer studies. A proposed mechanism for induction of cancer cannot be verified through statistical evaluation of cancer data and requires scientific judgement to assess plausibility.
Menarche:	The beginning of menstruation
Menopause:	The cessation of menstruation, occurring usually around the age of 50y. Pre-menopausal (before menopause). Post-menopausal (after menopause).
Meta-Analysis:	A meta-analysis study is a specialised statistical analysis which combines the results of individual studies producing a quantitative summary across all studies of the effect of interest. This type of study can provide valuable information to help in estimating the strength and consistency of the association between drinking alcohol and breast cancer.
Meta-Regression:	A statistical analysis which aims to investigate how the size of an effect varies with characteristics of the studies in a meta-analysis
Oral contraceptive:	A compound, usually hormonal, taken usually by the oral route in order to block ovulation and prevent pregnancy. Most oral contraceptives available in the U.K contain both an oestrogen and a progestogen.

Parity:	Condition of a women with respect to having borne viable offspring.
Random Effects	A statistical model which assumes that an underlying strength of association can vary between studies.
Recommended level of drinking :	The recommended number of units of alcohol which can be consumed without long term adverse effects. This has been set as daily benchmarks which are appropriate for regular and irregular drinkers. For women this is 2-3 units/day. Drinking in excess of 3 units/day accrues progressive health risks.
Risk factors for breast cancer:	The aetiology (see above definition) of breast cancer is complex. An association has been demonstrated for many different factors including heredity, reproductive, hormonal, and lifestyle factors. A role for environmental factors can be deduced from geographical variation in rates of breast cancer and changes in rates among migrants toward those of the host country. Thus drinking alcohol is one of several risk factors for breast cancer.
World Health Organisation:	The World Health Organisation, the United Nations specialised agency for health, was established on 7 April 1948. WHO's objective, as set out in its Constitution, is the attainment by all peoples of the highest possible level of health. Health is defined in WHO's Constitution as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. The WHO has established agencies to assist in its work. One of which is IARC (see above for definition).

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Committee on Carcinogenicity (Non-technical Summary) 2004. Consumption of alcoholic beverages and the risk of breast cancer in women

This statement is available here:
http://webarchive.nationalarchives.gov.uk/20140506122027/http://www.iacoc.org.uk/statements/alco04nontech.pdf

Committee on CARCINOGENICITY

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)

NON-TECHNICAL SUMMARY

CONSUMPTION OF ALCOHOLIC BEVERAGES AND RISK OF BREAST CANCER IN WOMEN

1. The COC has evaluated all the available published research up to June 2003 on the association between drinking alcohol and breast cancer. The COC also commissioned some specialist research to aid in reaching conclusions.[1] Breast cancer is a complex disease. Information on the range of causes has been considered in detail in the full statement. Further information can be obtained from the Cancer Research UK internet site (**http://www.cancerresearchuk.org/aboutcancer/specificcancers/breastcancer**)

2. The conclusions given below update and replace the previous review by the COC in 1999 which is available on the internet. (**http://www.advisorybodies.doh.gov.uk/coc/index.htm**

3. The Committee concluded it prudent to assume that drinking alcoholic beverages may result in breast cancer in women.

4. The new research[1] estimates that a woman drinking an average of two units of alcohol per day* has a lifetime risk of developing breast cancer 8% higher than a woman who drinks an average of one unit of alcohol per day. The risk of breast cancer further increases with each additional drink consumed per day. There was no evidence for variation in the association with any specific type of alcoholic drink.

5. The research also concludes that approximately 6% (between 3.2% and 8.8%) of breast cancers reported in the U.K. each year could be prevented if drinking was reduced to a very low level (i.e. less than 1 unit/week). This approximates to between 1290 and 3560 cases of breast cancer out of a total of approximately 41,000 new cases registered each year.

6. The risk of breast cancer associated with drinking alcohol increased with the amount of alcohol consumed. Thus, if a women increased her drinking from the U.K average level of 1 unit per day by an extra 1, 2,

†This non-technical summary is intended for the lay reader. Please refer to COC statement (http://www.advisorybodies.doh.gov.uk/coc/statements.htm) for full details of COC evaluation and conclusions.

or 3 units a day then the incidence of additional cases of breast cancer expected at 60 years and 80 years can be calculated;

The following table summarises the results.

Cumulative Incidence per 1000 women

	Current consumption	+1 unit per day	+2 units per day	+3 units per day
Age 60	60	65	70	75
Age 80	125	134	145	157

7. It is not known precisely how drinking alcohol can lead to breast cancer. The most likely explanation is that drinking alcohol can produce biochemical effects in the liver (such as changes to oestrogen metabolism and effects on growth factors) which if drinking alcohol is prolonged (i.e. over decades) could lead to breast cancer.

8. There is not enough information available to assess whether drinking alcohol can interact with the use of oral contraceptives or hormone replacement therapy by women to increase further the risk of breast cancer. More research on these aspects is required.

9. The Committee was concerned that recent evidence** demonstrated that the consumption of alcohol is increasing mainly in young women. If the increased consumption of alcohol is maintained over most of their lifetime, then the number of alcohol-related breast cancer cases may be even higher in these women than reported in paragraph 5 above. The Committee concluded that it was important to raise awareness of the potential risks of drinking alcoholic beverages, particularly amongst young women.

November 2004

References

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* A standard 'unit' of alcohol contains 8grams of ethanol, the amount usually found in half a pint of normal strength beer, or cider, a single measure of spirits, or one small glass of ordinary wine. In recent years

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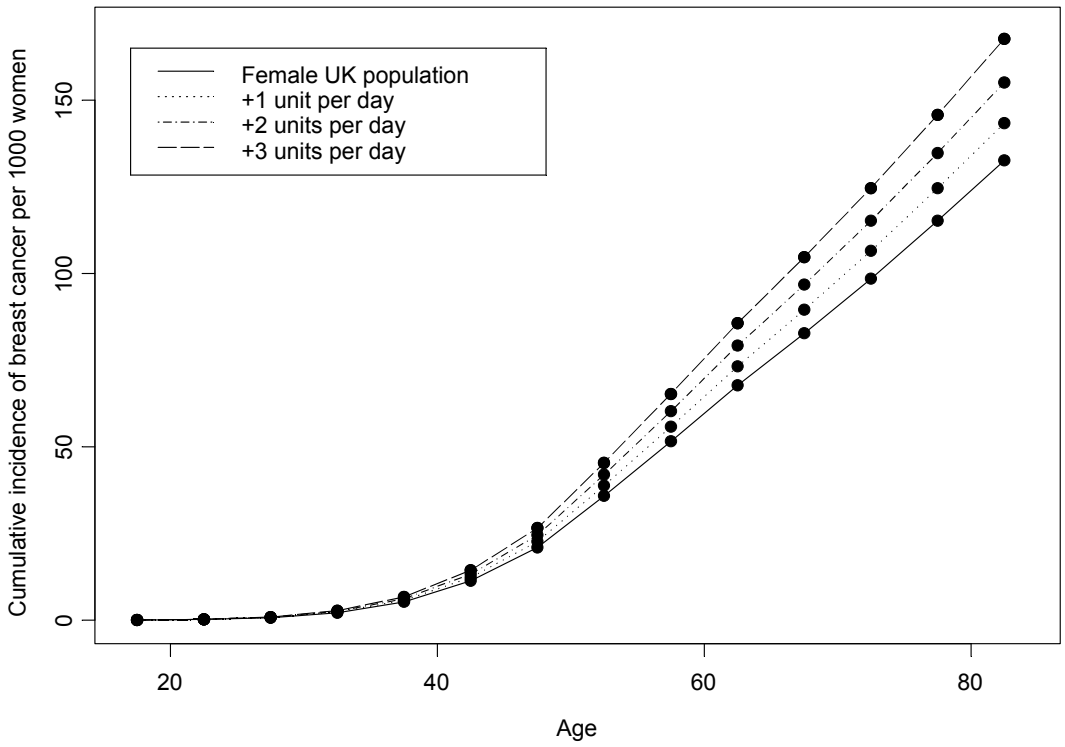
the average amount of alcohol in some drinks has increased and maybe up to 10grams ethanol.
**There is a lot of information on the consumption of alcoholic beverages regularly obtained as part of the General Household Survey (GHS). (http://www.statistics.gov.uk/lib2001/index.html) and the Health SurveyforEngland(HSfE) (http://www.doh.gov.uk/public/summary1.htm) Detailed information can be obtained from these sources. These studies examined alcohol in a variety of age groups. The youngest age group was 16-24 y.

Graph of cumulative incidence of breast cancer and effect of drinking additional units of alcohol.

The bold line indicates cumulative incidence at current average intakes



of alcohol (1 unit/day). The dotted lines show the effect of increasing intakes by additional 1,2, or 3 units per day.

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Consumption of Alcohol and Female Breast Cancer Risk

Extract from IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 96: Alchol Consumption and Ethyl Carbamate
Pages 418-479

Full document is available here:
http://monographs.iarc.fr/ENG/Monographs/vol96/mono96.pdf

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Secretariat
October 2014

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Consumption of Alcohol and Female Breast Cancer Risk

Extract from IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 100E: Personal Habits and Indoor Combustions

Pages 394-397, 446-449, 472 and Tables 2.36, 2.37, 2.38, 2.39, 2.40, 2.41, 2.42 2.43, 2.44, and 2.45

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