CC/2014/19

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

Consumption of Alcohol and Female Breast Cancer Risk

1. As part of the strategy proposed to consider the role of alcohol consumption and cancer risk, it was suggested that the COC review the epidemiological data on alcohol consumption and cancer. In 2007 (published IARC 2010), IARC reviewed the epidemiological evidence on the possible association between alcoholic beverage consumption and cancer at 27 anatomical sites (cancers of the oral cavity and the pharynx, larynx, oesophagus, liver, breast stomach, colon and/or rectum, pancreas, lung, urinary bladder, endometrium, ovary, uterine cervix, prostate, kidney, lymphatic and haematopoietic system, testis, brain, thyroid, melanoma and other female cancers (vulva and vagina)). They re-affirmed their previous conclusion (IARC, 1988) that cancers of the upper digestive tract (oral cavity, pharynx, larynx, and oesophagus) and the liver are causally related to the consumption of alcoholic beverages. In addition, IARC considered that there was now sufficient evidence to conclude that cancer of the colo-rectum and female breast are causally related to the consumption of alcoholic beverages (IARC, 2010). Following another IARC review in 2009 (IARC 2012), IARC reaffirmed their position for the aforementioned cancers and also reported an association between alcohol consumption and cancer of the pancreas, although they were unable to reach a conclusion on whether this was causal.

Female Breast Cancer Statistics for the UK

2. Breast cancer is the most common cancer among women in the UK, accounting for 30% of all new cases of cancer in females (Cancer Research UK, accessed 2014). In 2011, there were 49,936 new cases of female breast cancer with a crude incidence rate of 155 new breast cancer cases for every 100,000 females in the UK. Female breast cancer incidence is strongly related to age, with the highest incidence rates overall being in older women. In the UK between 2009 and 2011, an average of 80% of breast cancer cases were diagnosed in the over 50s, and around a quarter (24%) were diagnosed in women aged 75 and over. Age-specific incidence rates rise steeply from around age 30-34, level off for women in their 50s, then rise further to age 65-69. Rates drop slightly for women aged 70-74 and then increase steadily to reach an overall peak in the 85+ age group. The peaks and troughs of incidence for women aged 50 and over may partly be explained by the impact the NHS breast screening programme for women in the 50-69 age group and those aged 70. In 2010, in the UK, the lifetime risk of developing breast cancer was 1 in 8 for women.

3. Breast cancer is the 2nd most common cause of cancer death among women in the UK, accounting for 15% of female deaths from cancer. In 2011, in the UK, there were 11,684 deaths from breast cancer in women, with a crude mortality rate of around 36 breast cancer deaths for every 100,000 females in the UK. Female breast cancer mortality is strongly related to age. In the UK between 2009 and 2011, 46%

and 75% of breast cancer deaths were in women aged 75 years and over or aged 60 years and over, respectively.

Female Breast Cancer Risk Factors

4. Around 27% of female breast cancers in the UK are linked to lifestyle factors (Parkin, 2011). Both IARC and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) have evaluated the effect of exposure to tobacco, alcohol, infections, radiation, occupational exposures and medications as well as diet, overweight and obesity, and physical exercise on breast cancer risk and categorised them as outlined in Table A. Other risk factors for breast cancer include age, endogenous oestrogen hormones, reproductive factors, family history and genetic factors, breast density, benign breast disease, in situ breast carcinoma, previous cancer, other occupational exposures.

Table A. IARC and WCRF/AICR Evaluations of Breast Cancer Risk Factors (Cancer Research UK)

Increases risk ('sufficient' or 'convincing' evidence)	**May increase risk ('limited' or 'probable' evidence)**	**Decreases risk ('sufficient' or 'convincing' evidence)**	**May decrease risk ('limited' or 'probable' evidence)**
• Alcoholic beverages • Diethylstilbestrol • Oestrogen-progestogen contraceptives • Oestrogen-progestogen menopausal therapy • X radiation and Gamma radiation • Body fatness[a] • Adult attained height[a]	• Digoxin • Oestrogen menopausal therapy (hormone replacement therapy) • Ethylene oxide • Shift-work involving circadian disruption • Tobacco smoking • Adult attained height[b] • Greater birth weight[b] • Abdominal fatness[a] • Adult weight gain[a] • Total dietary fat[a]	• Breastfeeding	• Body fatness[b] • Physical activity

[a] Post-menopausal breast cancer only. [b] Pre-menopausal breast cancer only.

Mechanism of action of alcoholic beverages and breast cancer

5. Alcohol consumption may cause cancer through a number of different mechanisms, including mutagenesis via its mutagenic metabolite acetaldehyde, by inducing oxidative damage and CYP2E1 (which is responsible for metabolism of alcohol to acetaldehyde) or by affecting folate and one-carbon metabolism pathways. More specifically for breast cancer, it may act via perturbation of oestrogen

metabolism and response. In their statement on mutagenicity and alcohol in 2000 (http://cot.food.gov.uk/sites/default/files/cot/cotcomcocrep2000.pdf), COM commented on a paper (Wright et al 1999) which outlined 'the reactive oxygen species hypothesis of alcohol induced breast cancer'. It was concluded that whilst there was evidence that ethanol and its metabolites induced the formation of free radicals *in vitro*, the evidence *in vivo* was conflicting. Overall it was concluded that there was insufficient evidence to support the hypothesis with respect to breast cancer. The COM has recently reviewed studies on alcohol and mutagenicity since 2000 and agreed that there was convincing evidence across the in vitro and animal studies to conclude that acetaldehyde is a mutagen. There is some evidence that alcohol itself is also a mutagen although the data available was of varying quality and in vivo data was lacking. Studies looking at human alcoholic beverage consumption and mutagenic endpoints, such as DNA adduct and micronuclei, were generally of poor quality and that no conclusions could be drawn. The COM is currently considering the role of alcohol-induced oxidative damage to DNA.

COC Statement on Alcohol and Breast Cancer (2004)

6. The COC evaluated all the available published research up to June 2003 on the association between drinking alcohol and breast cancer. The COC also commissioned specialised research to aid reaching their conclusions. The COC statement and non-technical summary were published in November 2004 and are attached as Annex A and B. The Committee concluded it prudent to assume that drinking alcoholic beverages may result in breast cancer in women. The research considered by the Committee concluded that approximately 6% (between 3.2% and 8.8%) of breast cancers reported in the UK each year could be prevented if drinking was reduced to a very low level (i.e. less than 1 unit/week). The evidence suggested that the risk of breast cancer associated with drinking alcoholic beverages increases with duration of consumption of alcohol.

Updated review of Alcohol consumption and Female Breast Cancer

7. In the evaluation of the carcinogenicity of alcohol (IARC monograph 96, 2010 (Annex C and IARC monograph 100e, 2012 Annex D), IARC state that alcohol causes breast cancer and classifies it as a group 1 definite carcinogen. Literature for the current review was obtained following a PubMed search and the search terms included alcohol, ethanol, drinking, consumption and breast cancer. Studies published since January 2008 to September 2014 were included in the retrieval to ensure all studies published on this topic since the last IARC review to date were considered.

8. Each cohort and case-control study was assessed for quality using a modified scoring scheme similar to the Newcastle-Ottawa star scoring scheme. Pooled or meta-analyses were not scored. Information on alcohol consumption was extracted from all the relevant studies. Alcohol consumption categories varied between studies. For comparative purposes and to obtain a uniform variable for alcohol consumption, where possible, we calculated alcohol intake in terms of grams of ethanol/day. Information on adjustment factors used in the individual studies e.g. smoking, body mass index (BMI), obesity and caffeine intake were also extracted from the papers.

Meta- and combined analyses of alcohol consumption and breast cancer risk and breast cancer mortality and secondary events

9. Five meta-analyses and 2 combined analyses have been performed since the last IARC review. Three studies (Brennan et al., 2010; Trentham-Dietz et al., 2014; and Seitz et al., 2012) reported an increased risk, one Chinese study (Li et al. 2011) reported a decreased risk and another Chinese study (Gao et al. 2014) observed no association between breast cancer risk and alcohol consumption. In the studies examining the association between alcohol consumption and breast cancer mortality, Reding et al. (2008) observed a decreased risk of breast cancer mortality among drinkers. Overall Gou et al. (2013) observed no association between alcohol consumption and breast cancer mortality. However, they did report a non-statistically significant increased dose response relationship of alcohol consumption with breast cancer mortality and recurrence.

Alcohol Consumption and Breast Cancer Risk (Table 1)

10. Seitz et al. (2012) reviewed the role played by alcohol consumption (light and heavy drinking) and breast cancer risk. They also performed a meta-analysis of data on light alcohol drinking and breast cancer risk using data from 113 studies (70 case-control and 43 cohort studies). Criteria set for inclusion in the meta-analysis were a) case-control or cohort studies published as original articles; b) studies that reported findings as ORs, RRs or hazard ratio (HRs) for light drinkers versus non-drinkers; c) studies that reported CI or standard errors of the risk estimates or sufficient data to calculate them. For the purposes of the analysis, light drinking was defined as ≤1 drink/day (≤12.5g ethanol/day). Although the reference category was non-drinker, the paper noted that 16% of the estimates included occasional drinkers in the reference category. A pooled RR was estimated of breast cancer for light drinkers versus non-drinkers using random-effects models and adjusted for age, family history, parity, menopausal status, oral contraceptive/hormonal replacement therapy use. There were 44,552 cases (40,899 incident cases and 3,653 deaths) in the non-drinkers category and 77,539 cases (76,303 cases and 1,236 deaths) in the light drinkers' category. They reported a modest but significant association between light drinking and breast cancer risk with a pooled RR of 1.04 (95% CI 1.02 - 1.07). Substantial heterogeneity was observed among the single study estimates (I^2 = 64%).

11. Trentham-Dietz et al. (2014) performed a combined analysis of five US population based case-control studies, known collectively as the Collaborative Breast Cancer Study to investigate whether risk factors of breast cancer such as alcohol consumption differ depending on women's age or menopausal status. Information on alcohol intake was obtained by interview. Alcohol intake was defined as the average of the sum of drinks of beer, wine, liquor per week during the 5 years prior to the reference date. ORs and 95% CI were calculated using logistic regression and were adjusted for age, state of residence, study period, family history of breast cancer, BMI, alcohol status, age at menarche, parity, age at first pregnancy, oral contraceptive (OC) use, and smoking status. Their analysis on the effect of alcohol consumption on breast cancer risk consisted of 18,895 cases and 23,028 controls. The reference category was never drinkers. The results indicated

that consumption of increasing amounts of alcohol was associated with increased breast cancer risk (see table B).

Table B. Trentham-Dietz et al. (2014) Analysis of effect of alcohol consumption on breast cancer risk	
	All Women OR (95% CI)
Never drinkers (reference category)	1.00
Former drinker	1.16 (95% CI 1.07 – 1.27)
< 7 drinks/week (<10g/day)	1.11 (95% CI 1.04 – 1.19)
7–13 drinkers/week (10 - 20 g/day)	1.25 (95% CI 1.15 – 1.37)
≥14 drinkers/week (>20 g/day),	1.65 (95% CI 1.40 – 1.83)

12. They also observed that alcohol intake and breast cancer risk was significantly modified by age and menopausal status. They found that increasing consumption of alcohol was associated with greater risk of breast cancer for all women of all ages and menopausal status, although odds ratio estimates were not statistically significant for some age categories among pre-menopausal women (see table C).

Table C. Trentham-Dietz et al. (2014) Analysis of effect of age and menopausal status on breast cancer risk from alcohol		
	Pre-menopausal Women OR (95%CI)	Post-menopausal Women OR (95%CI)
<40 years	1.11 (1.01–1.22)	-
aged 40–44 years	0.99 (0.95–1.04)	-
aged 45–49 years	1.04 (0.95–1.14)	-
aged ≥50 years	1.17 (1.05–1.30)	-
aged <55 years	-	1.11 (1.04–1.20)
aged 55–59 years	-	1.14 (1.07–1.22)
aged 60–64 years	-	1.11 (1.04–1.17)
aged 65–69 years	-	1.13 (1.07–1.20)
aged ≥70 years	-	1.25 (1.15–1.36)

13. Brennan et al. (2010) conducted a systematic review and meta-analysis of cohort and case-control studies to determine the effect of dietary patterns including alcohol drinking patterns on breast cancer risk. Specifically, four studies examining drinking pattern and breast cancer risk were analysed, with a total sample of 2,645 cases and 63,538 controls. Multivariable-adjusted odds ratios (ORs) comparing highest and lowest categories of drinking pattern scores were combined using random effects meta-analyses. When intake of alcohol in the highest category was compared with intake in the lowest category, an increase in breast cancer risk was observed (OR = 1.21, 95% Confidence Interval (CI) 1.04 – 1.41). There was no evidence of heterogeneity between the studies (I^2 = 15%, P = 0.32).

14. Gao et al. (2014) conducted a systematic review and meta-analysis of 39 cohort and case-control studies to determine the effect of tea consumption, physical activity and alcohol consumption on breast cancer risk among Chinese females. Specifically for alcohol consumption, two cohort studies and twenty-four case-control studies on alcohol were included in the meta-analysis, involving 13,204 cases and 87,248 controls. Pooled ORs and 95% CI were calculated using random effects modelling.

The paper did not provide any information on the amount or frequency of alcohol consumption or whether the results were adjusted for confounders. For all studies combined, they found no significant association between alcohol drinking and breast cancer risk (OR = 0.85 (95%CI 0.72-1.02); I^2=63.8%, *P*<0.001; N=26). Similar results were obtained when they analysed the cohort studies (OR = 0.73 (95% CI 0.29 - 1.85); I^2 = 26%; N = 2) and case-control studies (OR = 0.86 (0.72 -1.03); I^2 = 66%; N = 24).

15. Li et al. (2011) carried out a systematic review on both cohort and case-control studies and a meta-analysis on case-control studies investigating the association between alcohol consumption and cancer risk including breast cancer in the Chinese population. 4 case-control studies were identified that examined the association between alcohol consumption and breast cancer. The sample size consisted of 1655 cases and 2175 controls for inclusion in their analysis. The authors noted the complexity of the definition of drinker and non-drinker. For the purposes of their meta-analysis, ORs and Relative Risks (RRs) were pooled. Participants who described drinking the smallest amount and those who never drank were classified as "non-drinkers" and the rest of subjects were classified as the "drinkers" category. Significant heterogeneity was found (p≤0.10, I^2>50%) between the studies and therefore the meta-analysis was performed using the random effects model. Comparing non-drinkers with drinkers, they reported that alcohol consumption was associated with a decreased pooled OR of 0.76 (99% CI, 0.60–0.97, p = 0.0001).

Alcohol consumption and breast cancer mortality and recurrence (Table 2)

16. Gou et al (2013) carried out a systematic review and meta-analysis of cohort studies investigating the association between alcohol consumption and breast cancer survival and mortality. 25 cohort studies were identified for inclusion in the analysis and represented a number of countries including 14 USA studies, 3 Danish studies, two German studies and the remainder from Canada, Australia, UK, France, Italy and Sweden. Information on alcohol consumption was obtained pre-diagnosis in 14 studies and post diagnosis in 10 studies. One study contained information on both alcohol consumption pre and post diagnosis. The total sample size for all included cohort studies was 719,555, the number of breast cancer deaths was 10,912 and breast cancer recurrence was 2,027. The median follow-up ranged from 2.9 years to 18 years. HR and the related 95% CI were calculated using the random-effects model. Their analysis found that pooling all data from highest versus lowest comparisons, alcohol consumption was not associated with a significantly increased breast cancer mortality (HR = 1.06, 95% CI 0.97-1.17, I^2=31%) and recurrence (HR = 1.21, 95% CI 0.95-1.53, I^2=0%). They also observed that pre-diagnosis and post-diagnosis alcohol consumption was not associated with increased breast cancer mortality (HR = 1.05, 95% CI 0.93-1.19, I^2=36% for pre diagnosis alcohol consumption and a HR = 1.08, 95% CI 0.94-1.25, I^2=30% for post diagnosis consumption) and recurrence (HR = 1.24, 95% CI 0.89-1.73, I^2=31% for pre-diagnosis consumption and HR = 1.17, 95% CI 0.80-1.73, I^2=0% for post-diagnosis consumption). They also examined the relationship of different alcohol consumption (<10 g/d, >10 g/d, <15 g/d, >15 g/d, <20 g/d and >20 g/d) with breast cancer mortality and recurrence. The data indicated a non-significant dose-response relationship between alcohol consumption and breast cancer mortality with effect size and heterogeneity of 0.94 (95% CI 0.88-1.01) I^2=10% for < 10 g/d, 1.03 (95%

CI 0.97-1.10) I^2 =51% for >10 g/d, 0.95 (95% CI 0.90-1.01) I^2=9% for < 15 g/d, 1.08 (95% CI 0.98-1.18) I^2=36% for > 15 g/d,0.96 (95% CI 0.92-1.01) I^2=14% for <20 g/d and 1.14 (1.02 1.27) I^2=49% for >20 g/d of alcohol. The data also indicated a non-significant dose-response relationship between alcohol consumption and breast cancer recurrence of 0.98 (0.88 - 1.11) for <10 g/d, 1.09 (95% CI 0.94 - 1.26) for >10 g/d, 1.00 (95% CI 0.91 - 1.10) for < 15 g/d, 1.04 (95% CI 0.83 - 1.30) for > 15 g/d, 1.00 (95% CI 0.91 - 1.10) for <20 g/d and for 1.04 (95% CI 0.83 - 1.30) for >20 g/d of alcohol.

17. In a combined analysis of two US population based case-control studies on breast cancer, Reding et al. (2008) investigated the effect of pre-diagnostic alcohol consumption on the risk of death (overall and breast cancer mortality) in 1,286 women with invasive breast cancer diagnosed before 45 years of age. Information on alcohol consumption (number of drinks, frequency (times per day/week/month) and type (beer/wine/liquor) of alcohol use from the time alcohol use began until their diagnosis of breast cancer) was obtained by in-person interviews. One drink was defined as either 12 oz of beer, 1.5 oz of liquor, or 4 oz of wine. Average weekly alcohol consumption was computed for the period spanning 7 years to 2 years prior to diagnosis, referred to in the paper as the 5 years prior to diagnosis. The weekly average number of drinks consumed over the 5-year period was calculated by taking the total number of drinks consumed during the period and divided by 260, the total number of weeks in the 5-year period. Average weekly alcohol consumption was categorized as never or none during this period, >0 to <3, 3 to <7 and 7 or more drinks per week (equivalent to >0 to <4g, 4g -<10 g, >10g ethanol/day respectively); and referred to as non-drinkers, light, moderate, and heavy drinkers, respectively. A woman who had consumed less than 12 alcoholic beverages in her lifetime or less than one drink per month for 6 months or more was considered a never drinker. The lifetime average weekly intake of alcohol was determined by calculating the average amount of alcohol consumed per week from age 15 until diagnosis. The reference category was non-drinker. Estimates of the relative risk of dying (HR) were calculated using Cox proportional hazards models and were adjusted for age, diagnosis year and mammogram history (defined as ever having a mammogram). They observed a 30% reduction in the risk of dying from breast cancer (OR = 0.7 (95% CI, 0.5–0.9) in women who reported alcohol consumption in the five year period before diagnosis compared to women who reported no alcohol consumption during the same time period. When they examined the effect of the average number of drinks consumed, the reduction in risk of dying did not vary substantively (OR = 0.7 (95% CI, 0.6–0.95) light drinkers; OR = 0.6 (95% CI, 0.4–0.8) for moderate drinkers OR = 0.7 (95% CI, 0.5–0.9) for heavy drinkers compared to non-drinkers. Similar patterns of risk in relation to average lifetime alcohol consumption were also observed (ORs = 0.6 (95%CI 0.5 - 0.8), 0.7 (95%CI 0.5 - 1.0) and 0.6 (95%CI 0.5 0.9) for light drinkers, moderate drinkers and heavy drinkers compared to never drinkers (OR= 1.0). They also examined the effect of alcohol beverage type on risk of dying from breast cancer. They observed that a reduction in risk of dying with recent alcohol consumption was limited to wine consumption (RR= 0.7 (95% CI, 0.6–0.9). They observed no association with beer or liquor consumption.

Summary of meta-analysis and combined analysis studies

18. The meta-analysis of 113 studies by Seitz et al. (2012) and the combined analysis of 5 large population case-control studies of Trentham-Dietz et al. (2014) offer further evidence of the role increasing alcohol consumption plays in breast cancer risk. Seitz et al. specifically addressed the issue of light drinking (<10g/day) while Trentham-Dietz et al. (2014) examined the dose response element. These two studies conducted analysis on specific alcohol intakes and adjusted for relevant confounding factors. While Brennan et al. (2010) found an increased risk of breast cancer with alcohol drinking, their study focused on dietary patterns rather than specific levels of consumption of alcohol.

19. Gao et al. (2014) offers a more comprehensive analysis of the available data on alcohol consumption and breast cancer risk in the Chinese population compared to study by Li et al. (2011). All four case-control studies in Li et al. were included by Gao et al. in their analysis. It is noted that the results of Gao et al. (2014) and Li et al. (2011) are not in agreement with Seitz et al. (2012) or Trentham-Dietz et al. (2014). However, differences in inclusion/exclusion criteria such as selection of only Chinese populations by Gao et al. (2014) and Li et al. (2011) may have led to this discrepancy. The relevance of their findings to the UK population should also be considered.

20. For the mortality meta-analysis, we note that although Gou et al. (2013) observed no association between alcohol consumption and breast cancer mortality, they did note that the data was trending towards an association with increasing doses (significant at >20g/d). The results differed between the Gou et al. (2013) and Reding et al. (2008), but consideration should be given to the differences in the type and number of studies included in their analyses (39 cohort studies with a total sample size of over 700,000 women in Gou et al. (2013) in comparison to a combined analysis of 2 population case-control studies with a total sample size of 1286 women in Reding et al. (2008)). It should also be noted that Gou et al. (2013) included the Reding et al. analysis in their meta-analysis.

Cohort studies

21. The cohort studies have been divided into two categories: a) those examining breast cancer risk (7 studies) and b) those examining breast cancer mortality (8 studies). Within each section, the studies are reported by geographically region (UK, European, US and others regions) and within each region in order of their Newcastle-Ottawa (NO) score, beginning with the highest scoring studies.

Cohort studies examining alcohol consumption and breast cancer risk (Table 3)

22. Couto et al. (2013) investigated whether adherence to a Mediterranean dietary pattern influenced breast cancer risk in a cohort of 49,258 Swedish women enrolled in the Swedish Women's lifestyle and Health WLH) cohort study. Information on the role played by the alcohol component of the diet was extracted from the paper for the purpose of this review. Information on alcohol consumption of participants was

obtained using a food frequency questionnaire. Relative risks and 95% CI were estimated using Cox regression analysis and were adjusted for a number of potential confounders including history of breast cancer in mother and/or sister(s), personal history of benign breast disease, smoking status, BMI, height, age at first birth and total number of children, educational level, age at menarche, total energy intake, consumption of beverages, potatoes, sweets and eggs. They observed no statistically significant association between the alcohol component of the Mediterranean diet score and breast cancer risk in all women and in pre-menopausal and post-menopausal women. The RRs for breast cancer associated with an increment in daily intake of alcohol of 5 g were 1.04 (95% CI 0.99–1.09), 1.03 (95% CI 0.98–1.09), 1.05 (95% CI 0.98–1.13) in all women, and pre-menopausal and post-menopausal women, respectively.

23. Horn-Ross et al. (2012) investigated the association between alcohol consumption and breast cancer risk and whether and when the cessation of hormone therapy (HT) modified the effects in the US California Teachers Study (CTS) cohort of 40,680 women. Information such as frequency of consumption of specific beverages, quantity and serving size of alcohol consumption was collected using a self-administered questionnaire and daily intake in grams of alcohol was calculated for each woman. The exposure categories were non-drinkers (during the past year), <20 g/day, and ≥20 g/d. RRs and 95% CI were estimated using Cox regression models and adjusted for age at first full-term, a family history of breast cancer in a first degree relative, BMI, and average long-term physical inactivity. After follow-up, 660 were diagnosed with invasive breast cancer (530 cases (80%) had oestrogen receptor positive (ER+) tumours and 94 cases (14%) had ER negative (ER-) tumours). Information on ER status was not available on the remainder. They found that alcohol consumption of <20 g/d at follow-up was not associated with breast cancer risk overall (RR=1.01, 95% CI: 0.85 – 1.20) but alcohol consumption of ≥20 g/d was associated with an overall increased risk of breast cancer (RR=1.26, 95% CI: 1.02–1.56). When they stratified by time since HT cessation, they found that alcohol consumption of <20 g/d at follow-up was not associated with breast cancer risk with the exception of an increase in risk among current HT users (RR=1.60, 95% CI: 1.13–2.26). When they stratified by time since HT cessation and alcohol consumption of ≥20 g/d, the increased risk was limited to women who were current HT users (RR=2.11, 95% CI: 1.41–315 compared to non-drinkers who never used HT) with a statistically non-significant elevation observed among women who never used HT (RR=1.52, 95% CI: 0.94–2.47).They observed that women who consumed ≥20 g/day of alcohol and were current HT users were at significantly increased risk of ER+ breast cancer (RR=2.03, 95% CI: 1.16–3.55 and RR=4.09, 95% CI: 2.29–7.30 for oestrogen only therapy (ET) and oestrogen-progesterone therapy (EPT) users, respectively) compared to women who never used HT and did not consume alcohol. They observed no increase in risk for alcohol consumption of ≥20 g/d among those who had ceased using HT (RR=1.20, 95% CI: 0.78–1.84). Alcohol consumption of ≥20 g/d among never HT users was slightly lower (RR=1.61, 95% CI: 0.93–2.77). They observed no increase in risk in ER- breast cancer (RR=0.65, 95% CI: 0.17–2.45) for alcohol of ≥20 g/d among current HT users compared to non-drinkers who never used HT) but the data was of limited statistical power due to the small sample size of ER- breast cancers.

24. Park et al. (2014) examined the association between alcohol consumption and post-menopausal breast cancer risk in a multi-ethnic Hawaiian/Californian population cohort of largely never, lightly or moderately drinking women. 85,089 women were included in the analysis. Information on alcohol consumption was obtained using a self-administered quantitative food frequency questionnaire (QFFQ) and included details on average consumption of various beverage types over nine categories of frequency and portion sizes. Alcohol intake was categorised into six groups: non-drinkers (0), 0.1–4.9, 5–9.9, 10–14.9, 15.0–29.9 and ≥30 g/day. Non-drinker was the reference category. HRs and 95% CI of breast cancer risk were estimated using proportional hazards regression and adjusted for ethnicity, age at cohort entry, family history of breast cancer, age at first live birth, age at menarche, age and type of menopause, number of children, HRT, smoking status, education, physical activity, BMI and energy intake. For all women combined, they observed an increase in breast cancer risk for women consuming ≥ 5g of alcohol a day compared to non-drinkers with the highest consumption group of ≥ 30g/day having a HR of 1.53 (95% CI 1.32-1.77) and the multivariate HR for 10g increase was 1.04 (95% CI 1.02- 1.06). An increased risk with higher alcohol consumption was found in African Americans (HR for 10 g increase = 1.04; 95% CI: 1.01–1.07), Japanese Americans (HR = 1.08; 95% CI: 1.01–1.15), Latinas (HR = 1.05; 95% CI 1.00–1.11), whites (HR = 1.04; 95% CI: 1.02–1.07), but not in Native Hawaiians (HR = 0.98; 95% CI: 0.91–1.05). When they examined the data by beverage type, they observed significant associations for wine (HR for 10 g increase = 1.11; 95% CI: 1.06–1.15), red wine (HR = 1.08; 95% CI: 0.98–1.18) and hard liquor (HR = 1.04; 95% CI: 1.01–1.07), but no association was observed for beer (HR = 1.02; 95% CI: 0.98–1.06). They also conducted separate analyses based on oestrogen receptor (ER) and progesterone receptor (PR) status (ER+/PR+, ER+/PR- and ER-/PR- cases; there were too few ER-/PR+ cases for analysis) and found an association with increasing alcohol consumption and breast cancer risk across the ER/PR status. For the ER+/PR+ status, they observed increasing HRs for breast cancer with increasing alcohol intake (OR = 0.92 (95% CI 0.81–1.04) for 0.1-4.9 g/day; 1.14 (95% CI 0.91–1.42) for 5.0 -9.9 g/day; 1.35 (95% CI 1.13–1.61) for 10-14.9 g/day and 1.61(95% CI 1.30–2.00) for ≥30 g/day) compared to a non-drinker.

25. Liu et al. (2013) investigated the association between alcohol consumption before first pregnancy and the risk of either breast cancer or benign breast disease (BBD) in a cohort of 91,005 women in the US Nurses' Health Study II. Information on the total number of drinks of alcohol (none or <1 per month, 1–3 per month, 1 per week, 2–4 per week, 5–6 per week, 7–13 per week, 14–24 per week, 25–39 per week, and 40+ per week) consumed between ages 18 and 22 years was obtained using a high school food-frequency questionnaire (HS-FFQ). One drink was defined as 1 bottle or can of beer, a 4-ounce glass of wine, or a shot of liquor, with ethanol estimates of 12.8 g for regular beer, 11.3 g for light beer, 11.0 g for wine, and 14.0 g for liquor. Total alcohol consumption was expressed in grams of ethanol per day. Alcohol consumption between ages 18 and 22 years was categorized into 4 groups: no consumption (none), any consumption up to 5 g of ethanol/day (0.1–4.9 g/day), between 5 and 15 g/day (5.0–14.9 g/day), and 15+ g/day. Non-drinkers were the reference category. Cox proportional hazards models were used to estimate HRs and 95% CI, adjusted for age in months, total energy intake, age at menarche, menopausal status, average body size between ages 5 and 10 years, family history of breast cancer in mother or sister(s), current and duration of OC use, current

alcohol consumption, and parity and age at first birth. A total of 91,005 women were eligible and over the 10-years of follow-up, 1609 breast cancer cases and 970 cases of proliferative BBD were identified. They observed that cumulative average alcohol consumption between menarche and first pregnancy was associated with increased risk for breast cancer (RR = 1.13 per 10g/day intake; 95% CI = 1.03 to 1.24) as was alcohol intake after first pregnancy (RR = 1.11 per 10g/day intake; 95% CI = 0.99 to 1.24). When they analysed the association between cumulative average alcohol consumption before first pregnancy and breast cancer risk according to the length of the menarche to first pregnancy interval, the risk estimates for alcohol intake before first pregnancy were stronger among women with 10 years or more between these two reproductive events as compared with women with a duration of less than 10 years ($P_{interaction}$ = 0.01). A 10-g increase in cumulative daily alcohol consumption before first pregnancy was associated with a relative risk of 1.21 (95% CI = 1.08 to 1.36) among women with a duration of 10 years or more. Analysing the data stratified by ER/PR status, they observed that cumulative drinking before first pregnancy was related to risks of ER^+/PR^+ tumours (RR = 1.18 per 10g/day intake; 95% CI = 1.03 to 1.34) compared with the risks for ER^+/PR^- tumours (RR = 0.86; 95% CI = 0.60 to 1.22) and ER^-/PR^- tumours (RR = 0.84; 95% CI = 0.60 to 1.16). They observed an increasing trend in the risk of proliferative BBD with a 10-g increase in cumulative alcohol consumed between menarche and first pregnancy after adjustment for cumulative drinking after first pregnancy (RR = 1.16, 95% CI = 1.02 - 1.32). The association between alcohol consumption before first pregnancy and proliferative BBD appeared to be restricted to women with longer durations between menarche and first pregnancy. The relative risk per 10g/day drinking was 1.06 (95% CI = 0.85 to 1.31) among women with less than 10 years between menarche and first pregnancy. The relative risk per 10g/day was 1.20 (95% CI = 1.03 to 1.40) among women with duration of 10 or more years the relative risk.

26. Chen et al. (2011) examined the association between alcohol consumption during adult life and breast cancer risk in a prospective observational study of 105,986 women enrolled in the Nurses' Health Study in the US. Subjects were followed from 1980 until 2008. Information on alcohol consumption was collected on eight separate occasions throughout the study period when participants completed a semi-quantitative food frequency questionnaire. Consumption of beer, wine, and spirits was ascertained as separate items. Alcohol consumption in grams per day was calculated as the sum of the daily number of drinks multiplied by the average alcohol content per type of alcoholic beverage (12.8 g of alcohol per 12-oz serving of beer, 11.0 g per 4-oz serving of wine, and 14.0 g per standard serving of liquor). Cumulative average alcohol intake was calculated by averaging alcohol use over time beginning in 1980. For analyses of current alcohol use, alcohol intake was updated at each alcohol questionnaire without accounting for prior use. Never-drinkers were the reference category. HR and multivariate adjusted RRs and 95% CI were computed using Cox proportional hazards models and adjusted for menopausal status, age at menarche, parity, age at first birth, BMI, family history of breast cancer in a first-degree relative, breastfeeding, cigarette smoking, and self-report of benign breast disease. For cumulative alcohol intake, they observed a modest but significant association between alcohol consumption at 5.0 - 9.9 g alcohol/day with breast cancer risk (multivariate RR = 1.15 (95% CI, 1.06-1.24) and a greater risk of breast cancer (RR = 1.51; 95% CI, 1.35-1.70) for women who consumed at least 30 g of alcohol daily on average compared with women who

never consumed alcohol. They also examined whether the associations varied by type of alcohol and found little difference between beverage type (RR = 1.12 (95% CI, 1.07-1.18) per 10 g per day for wine, RR = 1.09 (95% CI, 1.03-1.15) per 10 g per day for beer; and RR = 1.09 (95% CI, 1.05-1.13) per 10 g per day for liquor. When they examined frequency of drinking and binge drinking and excluded cumulative alcohol consumption from the model, they observed a strong association between both parameters and breast cancer risk. For frequency, they observed a RR of 1.20 (95% CI 1.11 – 1.30) for women who consumed alcohol on 5-7 days and for binge drinking they reported a RR of 1.33 (95% CI 1.11 – 1.59) for women consuming ≥6 drinks in 1 day compared with not drinking. When cumulative alcohol consumption was added to the model, only a weak association was observed for binge drinking and no association was observed for frequency of consumption of alcohol and breast cancer risk. They also examined the effect of different periods of life (18 to 40 years and > 40 years) and found that alcohol consumption at both these time periods was strongly associated with breast cancer risk. For ages 18-40 years and compared to non-drinkers, they observed increasing risk of breast cancer with increasing consumption of alcohol (RR = 1.06 (95% CI 0.97-1.14) for 0.1-4.9 g/day, 1.13 (95% CI 1.02-1.26) for 5.0-9.9 g/day, 1.25 (95% CI 1.09-1.43) for 10.0-19.9 g/day, 1.33 (95% CI 0.97-1.82) for ≥20g/day and 1.16 (95% CI 1.08-1.25) per 10-g increase in consumption per day). When the data was stratified by oestrogen receptor and progesterone receptor status, they found alcohol consumption was more strongly associated with risk of ER+ and/or PR+ tumours. When they stratified the data by histology subtypes, they observed similar risks with alcohol intake for ductal and lobular cancers of the breast.

27. Hartz and He (2013) investigated the role played by established and potential risk factors of breast cancer risk in a large cohort of 147,202 post-menopausal US women (aged 50 – 79 years) participating in the Women's Health Initiative (WHI) study. Information on alcohol servings per week was obtained using a self-administered questionnaire. Non-drinker was the reference category. HRs and 95% CI were estimated using Cox proportional hazard regression to test the association between the risk factors and breast cancer incidence and adjusted for age and race. They observed a 13% increased risk of breast cancer among those women who consumed alcohol > 1 per week (OR = 1.13, 95% CI 1.05 – 1.20) compared to a non-drinker.

28. In a prospective population-based Japanese Miyagi Cohort study, Kawai et al. (2011) investigated the association of alcohol consumption and breast cancer risk. A total of 19,227 women aged 40-64 years were followed from 1990-2003. Information on alcohol intake was obtained using a food frequency questionnaire and participants provided details on whether they were never, past, or current drinkers. Never drinkers were defined as women who had never or hardly ever drunk alcohol. Past drinkers were defined as those who had quit drinking before the baseline survey. Drinkers were asked to state the age at which they had started drinking (never, < 25 years, 25 -35 years, >35 years), frequency of drinking (never, occasional, 1–2 times per week, 3–4 times per week, 5–7 times per week) (although not stated explicitly it assumed that this is in days per week), the types of alcoholic beverages consumed, and the volume drunk on each occasion (never, <11.5 g, ≥11.5 to<23.0 g, ≥23 g). The amount of alcohol consumed per day was calculated by multiplying the total amount of alcohol drunk on each occasion by the frequency of

drinking and standardised to daily consumption (never, <5.0 g/day, ≥5.0 to <15.0 g/day and ≥15.0 g/day). Cox proportional-hazard regression model was used to estimate HRs and 95% CIs for the incidence of breast cancer according to category of exposure variable and to adjust for age (continuous variable), body mass index, smoking, occupation, walking, educational level, age at menarche, parity number, family history of breast cancer, age at menopause, and use of exogenous female hormones and/or OC use. Never drinkers served as a reference group. In their multivariate analyses, they observed a non-statistically significant less than unity HR of 0.39 (95% CI 0.14–1.08) for past drinkers and a HR of 1.00 (95% CI 0.74–1.35) for current drinkers compared to never drinkers. In their analyses of frequency of alcohol consumption, women who were current frequent drinkers at 5–7 times per week appeared to have a decreased risk (HR = 0.66, 95% CI: 0.29–1.53) compared to never drinkers, but this was not significant. No significant association was observed between age of first exposure or amount of alcohol consumed per occasion and breast cancer risk. When they examined the risk associated with amount of alcohol consumed per day, they found that women who consumed ≥5.0 to <15.0 g/day had a non-significantly increased risk (HR = 1.21, 95% CI 0.71 – 2.07) however, no indication for such increased risk was observed among women who consumed >15.0 g/day (HR = 0.90, 95% CI 0.41–1.91) compared to never drinkers. In terms of menopausal status, the HRs and 95% CIs for breast cancer risk among current drinkers compared with never drinkers was 1.05 (0.70–1.56) for premenopausal women and 1.06 (0.66–1.71) for postmenopausal women.

Summary of cohort studies on breast cancer risk

29. The results of Horn-Ross et al. (2012), Park et al. (2014) and Chen et al. (2011) are in line with previously published cohort data such as the UK Million Women's study (Allen et al. 2009). Considering data for all women participating in these studies, Horn-Ross et al. with a NO score of 8, reported an increased risk of breast cancer (RR = 1.26, 95% CI 1.02 -1.56) at an alcohol consumption level of ≥ 20g/d. Similar results were obtained by Park et al. (2014) and Chen et al. (2011). Both of these studies scored a NO of 7, and observed an increase in risk in breast cancer with increasing alcohol consumption (HR = 1.53, 95% CI 1.32-1.77 and 1.51, 95% CI 1.35 – 1.70 at ≥30g/day in Park et al. and Chen et al., respectively). A number of studies considered the menopausal status of women in their studies. The European study by Couto et al. (2013) and a Japanese study by Kawai et al. (2011) did not observe any difference in risk between pre-menopausal women and post-menopausal women. An US study by Hartz & He (2012) observed an 13 % increased risk of breast cancer in post-menopausal women consuming > 1 drink/week.

Cohort studies examining alcohol consumption and breast cancer mortality and secondary events (Table 4)

30. Vrieling et al. (2012) investigated the association between pre-diagnostic alcohol intake and breast cancer recurrence, breast cancer-specific mortality and overall mortality in a German prospective cohort study of 2,522 post-menopausal breast cancer patients aged 50-74 years. Information on alcohol intake was obtained using a food frequency questionnaire. Details were collected on frequency of consumption (times per day, week, month or year) and quantity of each beverage type consumed.

Alcohol intake was calculated based on the average glass volume and ethanol content for each type of alcoholic beverage. They divided alcohol consumption into four categories based on an estimated 12 g of alcohol (<0.5, ≥0.5 to <6.0, ≥6.0 to <12.0, ≥12.0 g/day). The lowest category was defined as the reference category. HRs and 95 % CI were estimated using Cox proportional hazards models and adjusted for the following variables depending on the model; age, study centre, tumour size, nodal status , primary metastasis status, tumour grade, joint oestrogen/progesterone receptor (ER/PR) status, radiotherapy, HRT use at diagnosis, mode of detection. When they examined the association between alcohol consumption and breast cancer specific mortality, they found that women consuming ≥ 0.5 to <6 g/day and ≥12 g/day of alcohol had a significantly higher risk of breast cancer-specific mortality compared with women drinking <0.5 g/day of alcohol (HR = 1.51, 95 % CI: 1.04, 2.21 and HR = 1.74, 95 % CI: 1.13, 2.67, respectively). They did not find any significant association for women drinking ≥ 6 to <12 g/day of alcohol (HR = 0.92, 95 % CI: 0.56, 1.53) and breast cancer-specific mortality compared with women drinking <0.5 g/day of alcohol. When the data analysis was restricted to stage I –IIIa patients, they no longer observed a significant association between consumption of ≥12g/day and breast cancer-specific mortality compared to women consuming < 0.5g/day (HR = 1.31, 95%CI 0.76 – 2.26). They did not find an association between alcohol consumption and breast cancer recurrence among stage I-IIIa breast cancer patients at any level of alcohol consumption (HR = 1.00 for intakes of <0.5 g/day, HR = 1.03 (95% CI 0.74 - 1.44) for intakes of ≥0.5 to <6.0 g/day, HR = 0.86 (95% CI 0.54 - 1.36) for intakes of ≥6.0 to <12.0, and a HR = 1.08 (95% CI 0.73 - 1.58) for intakes ≥12.0 g/day. They did not observe any effect modification in the data when the results were stratified by tumour grade, ER status, BMI, HRT use and smoking status. When they examined the effect of beverage type on breast-cancer specific mortality, no association was observed for women consuming ≥ 12 g/day of wine or beer and breast cancer-specific mortality compared to those consuming <0.5 g/day (HR = 1.39, 95% CI 0.88- 2.19 for wine and HR = 1.57, 95% CI 0.77 - 3.16 for beer).

31. Holm et al. (2013) investigated the association between pre-diagnostic alcohol consumption and breast cancer outcomes measured as breast cancer recurrence and breast cancer specific mortality among 1,052 women diagnosed with breast cancer in a prospective Danish cohort of 29,875 women. Information on alcohol intake was obtained using three different exposure parameters: 1) baseline intake of alcohol measured both as a linear and as a categorical variable (<1 unit/day, 1<unit<2/day, >2 units/day: one unit defined as 10 g ethanol) obtained from a food frequency questionnaire, 2) cumulative intake calculated as total intake from year 20 until one year before baseline, calculated in drink years (one unit of alcohol/day in one year) and 3) historical intake or recorded cumulative intake in the age groups of twenties, thirties, forties and fifties obtained from a lifestyle questionnaire. The alcohol intake categories were ≤1 unit/day (reference category and equivalent to ≤ 8g ethanol/day); <1 - ≤2 units/day (equivalent to <8 - ≤16 g ethanol/day) and >2 unit/day equivalent to > 16g ethanol/day). HRs and 95% CI for breast cancer outcomes (recurrence and mortality) were estimated using Cox proportional hazard models and adjusted for clinical prognostic factors such as tumour size, lymph node status, receptor status and grade and other confounders such as BMI, smoking, menopausal status, hormone replacement therapy (HRT) use, education level, physical activity and total folate intake. When they analysed the data for breast

cancer recurrence, they found an association between pre-diagnostic alcohol intake with a higher risk of recurrence of breast cancer. There was a dose-dependent increase in risk with increasing consumption with a statistically significant increase at the highest category with HRs of 1.31(95% CI 0.81 – 2.11) for <1 - ≤2 units/day and 1.65 (95% CI 1.02–2.67) for >2 unit/d compared with the reference category. They also found that cumulated alcohol intake was associated with higher recurrence risk in the highest intake category (>40 drinking years, HR = 2.02 (95% CI 1.06–3.85)) compared with the lowest (0-10 drinking years).When they examined intake of alcohol during four different periods of life (twenties, thirties, forties and from age 50 until one year before study entry), except for 'intake in twenties' all measures of lifetime alcohol intake were non-significantly associated with higher recurrence risk. For breast cancer mortality, they observed a non-statistically significant higher risk with increasing baseline intake of alcohol (HR = 1.06 (95% CI 0.66 – 1.72) for <1 - ≤2 units/ day, 1.10 (95% CI 0.67 – 1.82) for > 2 units/day) compared to the reference category. Similar to the results obtained for recurrence, all measures of lifetime alcohol intake were non-significantly associated with higher breast cancer mortality except for intake in twenties. The linear estimate of cumulated alcohol intake showed a non-significant higher mortality by higher number of drinking years (HR = 1.03; 95% CI 0.97–1.10). They did not find any association between cumulative alcohol intake assessed as number of drinking years and breast cancer mortality.

32. Harris et al. (2012) investigated whether an association exists between alcohol intake and breast cancer survival in a 3146 women in the Swedish Mammography Cohort. Information on diet including alcohol intake was obtained using a food frequency questionnaire. Alcohol intake was calculated by multiplying the reported frequency of consumption by age-specific drinks sizes and was categorised into the following: non-drinker, <3.4 g/day, 3.4 – 9.9 g/day and ≥ 10g/day. HRs and 95% CI for death from breast cancer were estimated using Cox proportional hazard models with time since diagnosis in months as the timescale and adjusted for adjusted for age, energy intake, education level, marital status, menopausal status at diagnosis, BMI, calendar year of diagnosis, disease stage, grade, radiation treatment, and chemotherapy and/or hormonal treatment. During follow-up there were 385 breast cancer deaths among the 3146 breast cancer cases. They observed an increased but not significant association between alcohol intake and breast cancer-specific mortality. They found that women who consumed 10 or more g per day of alcohol had a covariate-adjusted HR of breast cancer death of 1.09 (95% CI 0.66–1.81) and a covariate and clinical-characteristics adjusted HR of 1.36 (95% CI 0.82–2.26) compared with non-drinkers.

33. Newcomb et al. (2013) investigated the role of pre-diagnosis and post-diagnosis alcohol intake on breast cancer survival in a US multisite population-based cohort of 22,890 women with incident invasive breast cancer. Information on alcohol consumption was obtained by interview and included details on lifetime alcohol consumption, quantity and frequency of consumption of beer, wine and spirits. For dose-response analyses, total alcohol consumption and intake by beverage type were categorised into drinks/week: 0, 1-2, 3-6, 7-9 and ≥ 10 drinks/week and 0, 1-2, 3-6, ≥7 drink/week, respectively. HRs and 95% CIs for associations with survival across categories of alcohol consumption were estimated using proportional hazards regression and adjusted for age at diagnosis, stage of disease at diagnosis, state of residence at diagnosis, study phase, family history of breast cancer, age at first birth,

menopausal status, HT use, BMI, smoking status, education, and mammography. They did not observe a linear association between pre-diagnostic increasing alcohol intake and breast cancer survival. In moderate drinkers (3-6 drinks/week) they observed decreased breast cancer mortality compared to non-drinkers (HR = 0.85 (95% CI = 0.75 – 0.95)), but no association for heavier consumption of ≥10 drinks/week (HR = 0.89 (0.77 – 1.04)). Breast cancer survival was similar in women who drank alcohol post diagnosis as compared to non-drinkers with no association observed between weekly alcohol intake and breast cancer mortality. No beverage specific associations were observed. When they examined the association between the change in alcohol consumption before and after breast cancer diagnosis and death from breast cancer, there was no association with more frequent consumption of alcohol post-diagnosis and breast cancer-specific survival compared to a never drinker (HR = 0.96 (95% CI = 0.63 - 1.46) for < 1 drink/wk change, 1.33 (95% CI = 0.87 - 2.05) for ≥ 1 drink/wk decrease and 1.13 (95% CI = 0.70 - 1.80) for ≥ 1 drink/wk increase. When they stratified their analysis by breast cancer subtype, similar results were obtained across both ductal and lobular breast cancer subtypes.

34. Breslow et al. (2010) examined the association between quantity and frequency of alcohol consumption and cancer-specific mortality including breast cancer using pooled data from the National Health Interview Survey (NHIS) cohort in the US. The cohort consisted of 323,354 participants (2,716,472 person-year follow-up). There were 8,362 deaths from all cancers and 677 female breast cancer deaths. Lifetime alcohol drinking status was assessed. Participants were categorised into the following groups: 1) never drinkers (not consumed alcohol in the past year or if they had also consumed fewer than 12 drinks over the course of their lifetime), 2) lifetime infrequent drinkers (if they had consumed 12 or more drinks in their lifetime but fewer than 12 drinks in any previous year), 3) former drinkers (if they had consumed 12 or more drinks in their lifetime and 12 or more drinks in any previous year but no drinks in the past year) and 4) current drinkers (had consumed 1 or more drinks in the past year). For current drinkers, data was also obtained on frequency (average number of drinking days per week classified as <1, 1–2, or ≥3 days per week) and quantity (number of drinks consumed, on average, on drinking days classified as 1, 2, or ≥ 3 drinks per day) of alcohol consumption. Total alcohol consumption (quantity multiplied by frequency) was also examined and characterized as light (≤ 3 drinks per week equivalent to ≤4 g ethanol/day), moderate (>3–7 drinks per week equivalent to >4 - 10 g ethanol/day), or heavier (>7 drinks per week equivalent to >10g ethanol/day). Cox proportional hazards regression models were used to derive RRs and were adjusted for sex, race/ethnicity, education, region, marital status, smoking status, and BMI. From their analysis, they observed that former drinkers had a 26% increased risk of breast cancer mortality in comparison to never drinkers. However, lifetime infrequent drinkers were not at increased risk of breast cancer mortality. They also did not observe an increased risk of breast cancer mortality among moderate (RR = 1.02, (95% CI 0.66 – 1.57) or heavier current drinkers (RR = 1.09, (95% CI 0.68 – 1.76) compared with never drinkers. They observed a decreased risk in breast cancer mortality among current light drinkers (RR= 0.75, (95% CI 0.57 – 0.98) compared with never drinkers. They did not observe a significant association of quantity of alcohol consumed on drinking days with risk of breast cancer mortality (RR = 0.84 (95% CI 0.57 - 1.23) for 2 drinks consumed on average on drinking days and RR = 0.72 (95% CI 0.45 - 1.16) for 3 or more drinks consumed on average on drinking days) compared to the referent group of 1 drink

consumed, on average, on drinking days. When they examined the effect of frequency of consumption, there was a trend in the data of increased breast cancer mortality risk among women who drank more frequently (RR = 1.00 (95% CI 0.67 - 1.50) for those drinking 1-2 days per week and RR = 1.44 (95% CI 0.96 - 2.17) for those drinking ≥ 3 days per week) compared to the referent category of <1 drink/week (RR = 1.00).

35. Kwan et al. (2010) investigated the effect of alcohol consumption on breast cancer outcomes (recurrence, overall death, death from breast cancer, and death from causes other than breast cancer) in the Life After Cancer Epidemiology (LACE), a prospective US cohort study of 1,897 early-stage breast cancer survivors. Results on breast cancer recurrence and breast cancer deaths are only reported here. Potential effect modifications by factors such as menopausal status, obesity and ER status were also considered. Information on alcohol intake was obtained using a food frequency questionnaire with participants providing details of frequency of beer, wine and spirit consumption over the past year and associated portion size. They calculated the servings per week of wine, beer, and liquor by multiplying portion size by frequency of consumption and standardized to weekly consumption. For all alcohol, servings per day in ounces (oz) was converted to grams (g) per day of alcohol (one standard drink in the United States = 13.7 g [0.6 oz] of pure ethanol) and categorized as none (≤ 0.5 g/d, the lowest category of intake, non-drinkers), 0.6 to 5.0 g/d (occasional drinkers), and ≥6 g/d (regular drinkers). However, in the analyses performed, the cutoffs used were 0-≤ 0.5, >0.5-<6 and ≥6 g/d, respectively. Most of the analyses presented in the paper compared the lowest group with others combined or the highest group with others combined. When they considered beverage type, only data on wine consumption was categorised (none, ≤ 1 serving, or ≥ 2 servings per week). For beer and liquor, the data was examined as either “none” or “any” consumption due to low intake in the cohort. Non-drinkers were the referent category. HRs and 95% CIs were computed using the delayed-entry Cox proportional hazards model based on time since cohort enrolment until event and adjusted for age at diagnosis, race, BMI at 1 year pre-diagnosis, menopausal status, smoking status, total folate intake, stage of disease, hormone receptor status, definitive surgery, tamoxifen use, adjuvant treatment, and positive lymph nodes. During follow-up, there were a total of 293 breast cancer recurrences, 273 deaths (154 which were attributed to breast cancer). They observed a dose dependent increase in breast cancer recurrence with increasing alcohol consumption. Compared with non-drinkers, women consuming ≥ 6 grams of alcohol per day had an increased risk of breast cancer recurrence (HR = 1.35, 95% CI 1.00 - 1.83) and death from breast cancer (HR= 1.51, 95% CI 1.00 – 2.29). Similarly, drinking at least two servings of wine per week was associated with an increased risk of breast cancer recurrence (HR = 1.33, 95% CI 0.97-1.81) and breast cancer death (HR = 1.37, 95% CI 0.88 – 2.14). They found no clear association for consumption of beer or spirits and breast cancer outcomes. When the data was stratified based on menopausal status and BMI, they found that in both post-menopausal women and overweight and obese women consumption of 6 or more grams of alcohol per day was associated with an increased risk of recurrence (HR = 1.51 (95% CI 1.05 - 2.19) for postmenopausal women and HR = 1.60 (95% CI 1.08 - 2.38) for overweight/obese women)). They also had an increased risk of breast cancer death (HR = 1.72 (95% CI, 1.05 - 2.81) for post-menopausal women and HR = 1.61 (95% CI 0.94 - 2.76) for overweight/obese women) compared to non-drinkers. They

observed a positive dose-response of increasing risk of both outcomes with increasing alcohol consumption. For pre-menopausal women and normal weight women, they observed no apparent associations with alcohol intake and breast ancer recurrence and breast cancer death. They noted that the number of women with ER-negative tumours was small in their sample. However, they observed no difference in risk of breast cancer recurrence or breast cancer mortality by ER status for alcohol intake.

36. Kwan et al. (2013) investigated the role of post-diagnosis alcohol consumption and breast cancer recurrence and total mortality using data from 9,329 US breast cancer survivors in the After Breast Cancer Pooling Project (ABCPP). Potential effect modifications by factors such as menopausal status, obesity and ER status were also considered. Information on alcohol consumption was assessed using food frequency questionnaires. Servings per day in oz were converted to grams (g) per day of alcohol (one standard drink in the United States is commonly 12.0-14.0 g of pure alcohol depending on the alcohol by volume of the drink) and categorised as non-drinker (<0.36 g/day), occasional drinkers (0.36 - <6.0 g/day) and regular drinkers (≥ 6.0 g/day). Higher consumption categories were also created to examine dose response relationships among regular drinkers (6.0 - <12.0 g/day, 12.0 - <24.0 g/day, and ≥ 24.0 g/d). HRs and 95% CI for breast cancer outcomes (recurrence and mortality) were estimated using Cox proportional hazard models and adjusted for age at diagnosis, stage of disease, race/ethnicity, education, menopausal status around diagnosis, hormone receptor status, surgery, treatment (radiation therapy, chemotherapy, HT), smoking, physical activity, pre-diagnosis BMI, and comorbidity. Non-drinkers were the reference category. When they examined breast cancer recurrence, they found that neither occasional nor regular consumption of alcohol was associated with any increase in risk of breast cancer recurrence (HR=0.99; 95% CI: 0.87- 1.12 for occasional drinkers, HR =1.03, (95% CI 0.86 - 1.24) for 6-<12 g/day; HR =1.12 (95% CI 0.93 - 1.34) for 12-<24 g/day; HR =1.04 (95% CI 0.84 - 1.31) for ≥24 g/day), and there was no relationship with amount of alcohol consumed. For breast cancer mortality, no significant associations were found for any amount of alcohol intake. When they examined the role of potential modifiers on the risk of breast cancer recurrence, they observed significant effect by menopausal status (p for interaction=0.027) and ER status (p for interaction=0.012) but not pre-diagnosis BMI (p for interaction = 0.94). They observed that increasing consumption of alcohol post-diagnosis among post-menopausal women was associated with an increased risk of recurrence. The increased risk associated with regular consumption (≥6.0 g/day) was statistically significant (HR=1.19, (95% CI 1.01 - 1.40)). In contrast, occasional drinking (0.36-<0.6 g/day) post-diagnosis among premenopausal women was associated with a decreased risk of recurrence (HR=0.75; 95% CI: 0.59 - 0.94) with no apparent dose-response relationship. When they stratified their data by ER status, they observed some effect modification for risk of recurrence of breast cancer. While they found no association among ER+ women, occasional alcohol consumption (0.36 -<6.0 g/day) in ER- women was associated with decreased risk of recurrence (HR = 0.70, 95% CI 0.53-0.92) but not with regular consumption (≥6.0 g/day) (HR = 1.03, 95% CI 0.78 – 1.36).

37. Flatt et al. (2010) examined the roles of alcohol and obesity as predictors of additional breast cancer events and all-cause mortality in a cohort of 3088 breast cancer survivors who participated in the US Women Healthy Eating and Living

(WHEL) study. Information on alcohol intake was assessed using a food frequency questionnaire and 24-hour recalls and data was collected on quantity, frequency of various alcoholic beverage types and total alcohol consumption. In their assessment and in order to be conservative, the higher of the two estimates (food frequency or 24-hour recall) was used and converted to grams of alcohol consumed with 10g of alcohol equivalent to 10 oz of beer, 3.5 oz of wine, or a 1-oz shot of 80-proof alcohol in a mixed drink. Women who consumed no alcohol or less than 10 g per month (equivalent to < 0.5 g ethanol/day) were classified as “Non- or Minimal drinkers”. The primary study outcomes were invasive breast cancer recurrence, new primary breast cancer or death due to any cause. HRs and 95% CI were estimated using Cox proportional hazard models and adjusted for a number of confounders including stage, grade, time from diagnosis to study entry, ethnicity, education, physical activity, parity, BMI and smoking status. In their multivariate analysis, they found higher alcohol intake was not associated with risk for additional breast cancer events (HR = 0.91, 95% CI 0.71 - 1.18). However, compared to non/minimal drinkers, moderate/heavy drinkers (>300g/month equivalent to 10g ethanol/day) had a decreased risk for all-cause mortality (HR= 0.69; 95% C.I. 0.49-0.97), and for breast cancer mortality (HR = 0.70, 95% C.I. 0.48-1.02).

Summary of cohort studies on breast cancer mortality

38. Three European studies offer some evidence of a role played by alcohol in breast cancer mortality. Data from the German cohort (NO score of 9) of Vrieling et al. (2012) reported an increased risk of breast cancer mortality with increasing levels of pre-diagnosis alcohol consumption up to ≥ 16g/day. Similar results were obtained by Holm et al. (2013) in a Danish cohort (up to ≥ 12g/day) and Harris et al. (2012) in a Swedish cohort (up to ≥ 10g/day). The data from the US was more conflicting and varied depending on the exposure parameters considered in the study (frequency of consumption, quantity of consumption, lifetime drinker, past drinker, pre-diagnosis consumption or post-diagnosis consumption). Kwan et al. (2010) observed an increase in breast cancer mortality with increasing quantity of alcohol consumption. However, Breslow et al. (2010) did not observe an association with alcohol quantity but did observe an increase in mortality with frequency of consumption. Kwan et al. (2013) observed no association between post-diagnosis alcohol consumption and breast cancer mortality. Similarly, Newcomb et al. (2013) found no association for either pre-diagnosis or post-diagnosis consumption and breast cancer mortality.

Case-Control Studies

39. The case-control studies have also been divided into two categories: a) those examining breast cancer risk (12 studies) and b) those examining breast cancer mortality (1 study). Within each section, the studies are reported by geographically region (UK, European, US and others regions) and within each region in order of their Newcastle-Ottawa (NO) score, beginning with the highest scoring studies.

Case-Control studies examining alcohol consumption and breast cancer risk (Table 5)

40. Pieta et al. (2012) investigated the role of lifestyle factors including alcohol consumption and their effect on breast and ovarian cancer risk in a Polish case-control study of 1,484 women (1,144 controls, 138 breast cancer cases and 202 ovarian cancer cases). The participants were aged between 18 - 80 years. Only results pertaining to breast cancer are described here. Information on alcohol consumption was obtained using a questionnaire and included details on frequency of consumption. ORs and 95% CI were calculated but no information was provided on adjustment factors. They observed an increase in breast cancer risk with alcohol consumption. They found that the consumption of 20-25g of pure ethanol sporadically once a month was associated with a 1.2 fold higher risk of breast cancer development (results presented in text and not tabulated).

41. Gledo et al. (2012) examined the role played by a number of lifestyle factors including alcohol consumption on breast cancer risk in a case-control study of 200 women (100 cases) in Bosnia and Herzegovina. Information on alcohol consumption such as quantity and frequency of consumption was obtained using a questionnaire. ORs and 95%CI were calculated using multivariate correlation analysis and adjusted for confounders (no specific details provided). For women that consumed alcohol there was a non-significant increase in the risk of breast cancer (OR = 1.73, 95% CI 0.40-7.50).

42. Wu et al. (2012) investigated the association between lifetime alcohol intake and breast cancer in a US population-based case-control study of 4,231 Asian American women (2,229 cases and 2,002 matched controls). Information on lifetime alcohol intake such as frequency, quantity, duration, timing and beverage type was assessed using two separate measures (quantitative food frequency questionnaire and lifetime history assessment). Daily alcohol consumption in grams was estimated by multiplying the number of drinks of each specific type of alcohol consumed per week by the appropriate number of grams of ethanol per drink, and then summing across the type of alcohol and dividing by seven. ORs and 95% CI were calculated using conditional logistic regression models with matched sets defined jointly by age and specific Asian ethnicity and were adjusted for birthplace and years of residence in the United States among non-US born, education, interviewer, age at menarche, parity, current BMI, years of regular recreational physical activity, total calories, intake of soy, green tea and black tea, menopausal status, age at menopause, and family history of breast cancer. They did not find any association between current alcohol consumption and breast cancer risk in all subjects combined compared to non-drinkers (OR = 0.87, 95% CI 0.74 – 1.03). However, risk patterns differed by ethnicity and nativity. They observed ORs for breast cancer risk among current drinkers < 1.0 for Chinese (US and non-US born) and non-US born Filipinos and found no association for non-US born Japanese. However, they reported elevated breast cancer risk for Japanese (US born) women with an adjusted OR per 5 g alcohol of 1.32 (95% CI 1.01 -1.73) and a non-significantly elevated association with current intake of US born Filipino women (adjusted OR per 5 g 2.11 (95% CI 0.78 – 5.71). They did not find a significant association between lifetime alcohol consumption and breast cancer risk in Chinese (US born and non-US born) and in non-US born Filipinos. In contrast, an increasing risk of breast cancer was observed

with increasing lifetime alcohol intake among US born Filipinos and non-US born Japanese women with adjusted OR per 5 g of alcohol of 1.23 (95% CI 0.86 – 1.77) and 1.90 (95% CI 0.65 – 5.49), respectively. For US born Japanese women, breast cancer risk increased with increasing alcohol amount (OR per 5g = 1.24 (95% CI 1.01 - 1.53) and with increasing duration of consumption (OR per 10 years = 1.18 (95% CI 1.01 -1.38). When they examined the risk patterns by ethnicity, they observed adjusted ORs of 1.21 (95% CI 1.02 -21.43) for Japanese, 0.95 (95% CI 0.79 – 1.14) for Chinese and 0.85 (95% CI 0.68 -1.07) for Filipino per 5 g/day. When they examined risk patterns by nativity, they found that US born women had an adjusted OR per 5 g/day of alcohol intake of 1.21 (95% CI 1.00 - 1.45) and non-US born women had an OR of 0.91 (95% CI 0.80 – 1.04). They also stratified the data by smoking status, folate and soya intake, BMI and menopausal status. They observed an increased risk associated with lifetime alcohol intake among Japanese who were ever smokers but not Japanese women who were non-smokers. None of the other factors modified the alcohol/breast cancer association. Stratifying the data by ER/PR status, they observed that the alcohol/breast cancer associations were significant among ER+, PR+ and PR- , but not ER- tumours. Combined ER/PR status analysis revealed that increased risks were found among Japanese American women with ER+/PR+ and ER+/PR- tumours. The risk associated with 10 + years of drinking was 1.56 for ER+/PR+ and 3.43 for ER+/PR- tumours (95% CI values not given).

43. Chandran et al. (2013) investigated the association between recent and lifetime alcohol consumption and breast cancer risk in a sample of African-American (AA) (803 controls and 889 cases) women participating in the US case-control Women Circle of Health Study (WCHS) . Information on alcohol consumption was obtained using data from a food frequency questionnaire. Details included frequency and portion sizes of beverages (wine, beer and spirits) consumed during the 12 months prior to diagnosis. Alcohol intake was calculated as grams (g) of ethanol based on the assumption that there are 14 g of ethanol in a 12 oz can of beer, 1 shot or 1.5 oz of liquor or mixed drink, or 5 oz of wine and expressed in total g per week. The sum of consumption of all the alcoholic beverages was used to estimate total recent alcohol consumption for each participant. Lifetime alcohol consumption and drinking during different life periods was also assessed under the following categories: under 20 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, 60 years and over. Total recent alcohol intake and consumption of individual beverages were categorised as non-drinker or drinker. Drinkers were further divided into the following consumption categories <14 g per week (< 1 drink per week or 2g/day), 14–<28 g per week (1–<2 drinks per week or 2-<8 g/day) and ≥28 g per week (≥2 drinks per week or ≥ 4g/day). Multivariable logistic regression analyses were used to compute ORs and 95% CI and adjusted for adjusted for age, ethnicity, country of origin, education, age at menarche, age at menopause, menopausal status, parity, age at first birth, breastfeeding, family history of breast cancer, history of benign breast disease, HRT use, OC use, BMI, total energy intake and physical activity.

44. In general, Chandran et al. found that alcohol intake was very low among the study participants. They observed no association between recent alcohol intake and breast cancer risk compared to non-drinkers (OR = 0.95, 95%CI 0.77-1.17) or for increasing levels of consumption (OR = 0.95; 95% CI: 0.65–1.39, comparing >28 g per week vs <14 g per week). There was also no evidence of an association

between drinking beer or wine and breast cancer risk (OR = 0.77, 95%CI 0.41 -1.45 and 1.16 95%CI 0.71-1.88 for ≥28g per week), respectively, compared to those consuming <14g/week. They did observe a statistically non-significant increase in breast cancer risk when they compared those consuming ≥28g/week of mixed spirit drinks with those consuming <14g/week (OR = 1.53, 95% CI 0.84-2.79). While they did not observe an association between ever drinkers and breast cancer risk (OR = 0.98, 95% CI 0.78-1.19) compared to never drinkers, the results suggest a decreased breast cancer risk for women in the highest category of lifetime drinking compared to non-drinkers (OR = 0.77, 95% CI 0.58-1.03). They also observed inverse statistically significant associations among women who drank alcohol when they were either < 20 years of age or <60 years of age compared to non-drinkers in these age intervals (OR = 0.65, 95%CI 0.47-0.89 and OR= 0.42, 95%CI 0.17-1.01), respectively. No association was observed between alcohol consumption during any other age interval and breast cancer risk. When they stratified the results based on menopausal status at time of diagnosis, they observed an OR for premenopausal women of 1.21 (95%CI 0.90-1.62) and an OR for postmenopausal women of 0.78 (95%CI 0.57-1.07) for recent alcohol intake, with no evidence of an association for increasing consumption in either group. They did note that there was an inverse association between drinking under 20 years and breast cancer risk for both pre- and post-menopausal women (OR = 0.60, 95% CI 0.38-0.94 and 0.64, 95% CI 0.41-0.99), respectively. When they examined recent and lifetime alcohol intake and ER and PR status, similar inverse associations were observed for bothER+/PR+ and ER-/PR- breast cancer subtypes. Similarly, an inverse association with drinking under 20 years of age was found for both ER+/PR+ and ER-/PR- tumours, with borderline significance found among women with hormone receptor-positive cancers (OR = 0.64, 95% CI 0.41 – 0.99).

45. Llanos et al. (2012) investigated the associations between alcohol consumption and breast cancer in an African American case-control study of 97 cases and 102 controls. They also examined the effect modification of weekly alcohol consumption by anthropometric measures including waist circumference, waist-to-hip ratio (WHR), and BMI. ORs and 95% CI were estimated and adjusted for age, education, age at menarche, and parity. They observed an inverse association between alcohol consumption and breast cancer risk among women with low waist circumferences and alcohol intakes of 1-6 drinks/week equivalent to 1.5-8.5g/day and ≥7 drinks/week equivalent to ≥10g/day (ORs =0.44 (95% CI 0.15 - 1.26) and 0.47 (0.07 - 3.28), respectively). They observed a decreased breast cancer risk among women consuming moderate amounts of alcohol (1- 6 drinks) and who had low WHR and low BMI (OR = 0.23, 95% CI 0.07- 0.79 and 0.53, 95%CI 0.18 - 1.54), respectively. Conversely, high waist circumference, high WHR and alcohol consumption of ≥7 drinks was associated with increased risk of breast cancer (OR = 4.22 (95% CI 0.39 - 46.15) and 1.62 (95% CI 0.23 - 11.26)), respectively.

46. Ronco et al. (2011) conducted a case-control study of 1,098 participants (460 cases and 638 controls) from Uruguay investigating the association and interaction between benzo[a]pyrene, alcohol and breast cancer risk. Information on alcohol intake such as age when drinking commenced, age at cessation of drinking, number of glasses per day or week and type of alcoholic beverage consumed were obtained. Never drinkers were the reference category. ORs and 95% CI were estimated using unconditional multiple logistic regression and adjusted for age, residence, urban/rural

status, education, family history of breast cancer among first-degree relatives, BMI, menopausal status, age at menarche, parity, mate drinking, and total energy intake. They observed an increased risk of breast cancer among ever drinkers (OR 1.63, 95 % CI 1.19-2.23) compared with never drinkers. For specific beverage types, they observed an increased risk of breast cancer for wine (OR = 1.43, 95% CI 1.02-2.00), beer (OR=1.62, 95% CI 0.76-3.46) and hard spirits (OR=1.92, 95% CI 0.80-4.63) compared to never drinkers. Also, they reported that total consumption (OR = 1.55, 95% CI 0.96-2.51 for 1-21.6 g/day; OR = 1.67, 95% CI 1.14-2.46 for 22g/day), duration (OR = 1.46, 95% CI 0.95-2.23 for 1-32 years of drinking; OR = 1.83, 95% CI 1.18 - 2.82 for 33+ years of drinking), and cumulative exposure to alcohol (OR = 1.58, 95 % CI 1.03-2.42 for cumulative 1-87; OR = 1.68, 95 % CI 1.09-2.57 for cumulative 88+) were directly associated with risk of breast cancer compared to never drinkers.

47. Beasley et al. (2010) investigated the association between alcohol consumption, folate intake and breast cancer risk in a Mexican population-based case control study of 1000 incident breast cancer cases and 1074 controls. Information on alcohol consumption including frequency and past drinking habits (if they ever drank alcohol, the age when they first began drinking, and if they ever drank more than one drink per month for at least one year) was obtained using a food frequency questionnaire (FFQ) and in-person interview. Consumption of alcohol was calculated assuming 13.9g per 12oz of beer, 15.4g per 5oz of wine, and 9.3g per 1oz of liquor. Never drinkers were defined as those having intakes of 0 grams of alcohol per day and were the reference category. ORs and corresponding 95% CI for recent and lifetime alcohol use were estimated using conditional logistic regression models, matched by age category, health care system, and region and adjusted for BMI, family history of breast cancer, age at first pregnancy, number of births, lactation, total energy, physical activity, education, age at menarche, menopausal status, OC use, smoking, fibrocystic disease, and past HT use. Compared with never drinkers, they did not find an increased risk of breast cancer among current drinkers (OR = 0.98, 95%CI 0.76 – 1.27), however, women reporting ever drinking had a greater risk of breast cancer (OR = 1.25, 95% CI = 0.99-1.58 for ever drinkers and OR = 1.74, 95% CI 1.27–2.39 for ever drink >1 drink per month for ≥ 1 year). Compared to never drinkers, although no dose-response was observed, the risk of breast cancer was increased in those consuming >0–2 g/day (OR = 1.19 (95% CI 0.90–1.58) and 1.20 (95% CI 0.85–1.70) for those consuming ≥2 g/day. They did observe some interaction in the association between ever consuming any alcohol and breast cancer stratified by folate intake. They found that women in the lowest tertile of folate intake (mean=197 µg/day) had a higher odds of breast cancer (OR = 1.99, 95% CI = 1.26–3.16) compared to women with the highest tertile of folate intake (mean=532 µg/day) (OR = 1.12, 95% CI = 0.69–1.83).

48. Sanchez-Zamorano et al. (2011) examined the role played by common lifestyle factors including alcohol consumption on breast cancer risk in a population-based case-control study of Mexican women, including 1,000 breast cancer cases and 1074 controls, the same study group as assessed by Beasley et al (2010) in paragraph 47. Information on alcohol consumption was obtained using a food frequency questionnaire and alcohol intake was categorised as 1) non-drinker, 2) < 1 g/day and 3) ≥ 1 g/day. The reference category was alcohol consumption at ≥ 1 g/day. Conditional logistic regression models were used to estimate the association

between alcohol intake and the risk of breast cancer in pre- and post-menopausal women and were adjusted for age category, health care system, socioeconomic status, breast feeding, age at menarche, age at menopause, BMI, family history of breast cancer in first-degree relatives, personal history of diabetes, waist-to-hip ratio (WHR), height, daily intake of folate and total calories. In both pre- and post-menopausal women, they observed that never drinking was associated with a decreased breast cancer risk compared to those consuming ≥ 1 g/day of alcohol (OR = 0.79, 95% CI 0.40-1.00 for pre-menopausal women and OR = 0.56, 95% CI 0.35-0.91 for post-menopausal women).

49. Islam et al. (2013) examined the association between alcohol consumption and breast cancer risk in a case-control study of pre- and post-menopausal Japanese women including 1,754 breast cancer cases and 3,508 controls. They also investigated the combined effects of folic acid and alcohol consumption and breast cancer risk. Effects of alcohol stratified on breast cancer receptor status (oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2)) were also examined. Information on alcohol intake was obtained using a self-reported questionnaire. Daily alcohol consumption was determined as a product of the frequency of alcohol consumption and the average amount of ethanol consumed in grams on each occasion. Daily alcohol consumption in grams was determined by adding the pure alcohol amount in the average daily consumption of beverages consumed (Japanese sake (rice wine), shochu (distilled spirit), beer, wine, and whiskey) The following conversions were used in the calculations: 1 cup of Japanese sake (180 ml) = 23 g of ethanol, one drink of shochu (108 ml) = 23 g ethanol, one large bottle of beer (633 ml) = 23 g of ethanol, one glass of wine (80 ml) = 10 g of ethanol, and one shot of whiskey (28.5 ml) = 11.5 g of ethanol. Drinking consumption was classified into four categories: non-drinker, 1 to <5, 5 to <23, and ≥23 g/day. ORs and 95% CI were estimated using conditional logistic models and adjusted for age, smoking habit, BMI, drinking habit, daily physical activity of any intensity, family history of breast cancer, total energy intake, age at menarche, parity, and referral pattern to the hospital. Compared to non-drinkers, they observed a positive association between alcohol intake and breast cancer risk (OR = 1.10 (95% CI, 0.94–1.29) for 1-≤5 g/day, 1.23 (95% CI, 1.02–1.48) for 5-≤23 g/day and 1.39 (95% CI, 1.07–1.80) for ≥ 23g day). When they stratified their analyses by menopausal status, they observed a stronger association with alcohol intake among post-menopausal women (OR = 1.24 (95% CI, 0.97–1.57) for 1-≤5 g/day, 1.40 (95% CI, 1.05–1.85) for 5-≤23 g/day and 1.69 (95% CI, 1.14–2.51) for ≥ 23g day) compared to non-drinking post-menopausal women. In contrast, no association was observed among pre-menopausal women. They also examined the associations between alcohol intake and breast cancer risk, stratified by tumour receptor status. They did not observe any trend across the various tumour subtypes among pre-menopausal women. However, they found that the ORs were higher than unity among post-menopausal women consuming ≥ 23g/day of alcohol compared to non-drinkers across most subtypes and was statistically significant for the tumour subtypes ER-/PR-/HER2+ (OR = 2.99, 95%CI 1.08-8.26) and ER-/PR-/HER2- (OR=3.72, 95% CI 1.30-10.67).

50. Zhang and Holman (2012) investigated the role played by low to moderate alcohol intake on breast cancer risk in a hospital-based case-control study of 2,018 women (1009 cases and 1009 controls) from the Zhejiang province of China.

Information on alcohol intake such as frequency, quantity, and beverage type was obtained using a food frequency questionnaire (FFQ). Daily alcohol intake was calculated using the frequency and quantity variables derived from the FFQ. It was assumed that there was 10g of ethanol per 285 mls of beer, per 100 mls of wine and per 30 mls of liquor. Never drinkers/abstainers were the reference category. ORs and 95% CI were estimated using unconditional logistic regression and adjusted for age, education, BMI, OC use, HRT, breast cancer in first-degree relatives, total energy intake, folate intake, tea drinking and menopausal status. When they examined the association between breast cancer risk and alcohol consumption, the adjusted ORs in current drinkers were 0.63 (95% CI 0.52-0.76), 0.66 (95% CI 0.53–0.84) and 0.55 (0.38–0.78) for all women, pre-menopausal and post-menopausal women compared to abstainers. When the data was stratified based on beverage type, they observed a significant inverse association in all women and pre-menopausal women who drank wine only (OR = 0.40, 95% CI 0.26 - 0.60 and 0.30, 95% CI 0.17-0.52, respectively) and post-menopausal women who consumed beer only (OR = 0.34, 95% CI 0.15–0.75). Compared with non- drinkers, those who consumed alcohol <5 g per day had a reduced risk of breast cancer with adjusted ORs (95% CIs) of 0.56 (0.45 – 0.69), 0.41 (0.27–0.62) and 0.62 (0.48–0.79) for all women, post-menopausal and pre-menopausal women, respectively. There was a significant increased risk of breast cancer in all women (OR = 2.33, 95% CI 1.26-4.31) with daily alcohol intake ≥ 30 g and non-statistically significant increased risk in pre-menopausal women and post-menopausal women (OR = 2.28, 95% CI 1.00 - 5.20 and OR = 2.29, 95% CI 0.89-5.87) compared to abstainers. They also examined the association between alcohol intake and breast cancer risk with hormone receptor sub-types. They observed an inverse association between daily alcohol intake of <15 g and breast cancer risk across all subtypes defined by ER and PR status, compared with non-drinkers. They did note that daily alcohol intake of ≥15 g was associated with a non-significant increase in breast cancer risk for all tumour receptor subtypes. They also examined the effect of alcohol intake on breast cancer risk by joint tumour receptor status. Relative to non-drinkers, an inverse effect was associated with alcohol intake <15 g for tumours with ER+/PR+ but not ER-/PR- status and this effect was more pronounced in post-menopausal women. When they examined intake of ≥ 15 g of alcohol intake among post-menopausal women with ER+/PR- or ER-/PR+ status, they observed a significant association between intake and breast cancer risk compared to non-drinkers (OR = 4.27, 95% CI 1.57 -11.65).

51. Gao et al. (2013) examined the relationship between alcohol drinking and breast cancer risk in Chinese women (669 cases and 682 controls), in a case-control study. Information on alcohol consumption status was obtained using an in-person interview. Never drinkers were the reference category. ORs and 95% CI were estimated using unconditional logistic regression analysis and adjusted for age, menopausal status, education levels, occupation, BMI and mean family income. They reported an increased risk of breast cancer was associated with alcohol consumption (OR = 1.86, 95%CI 1.02 – 3.39).

52. Wang et al. (2013) investigated the role played by individual lifestyle factors including alcohol consumption and their effects jointly with stress on breast cancer risk in a Taiwanese hospital-based case-control study of 471 women (157 cases and 314 controls). Information on alcohol consumption was obtained from a structured questionnaire about personal habits. Alcohol consumption was measured as

average alcohol consumption (times per day or week) and amount of alcohol ingested. Total alcohol intake was 11.0 g of ethanol per 120 mls of wine, 14.0 g for 45 mls of spirit, 12.8 g for 360 mls of regular beer or 11.3 g for 360 mls of a light beer. Alcohol consumption was categorised as 'no' if a participant's alcohol consumption was less than the above criterion every day and 'yes' otherwise. ORs and 95% CI were estimated using conditional multiple logistic regression analysis and adjusted for education level, age at menarche and past HT. They did not observe any significant association between alcohol consumption and breast cancer risk (OR = 1.50 (95% CI 0.74 – 3.03). However, when they considered both stress and alcohol consumption jointly, they found that those of high perceived stress consuming high amounts of alcohol had a significantly higher OR of breast cancer risk (OR = 2.91, 95% CI 1.23 – 6.86) compared to those with low perceived stress and who abstained from excessive alcohol consumption.

Summary of case-control studies on breast cancer risk

53. Twelve case-control studies investigating the association between alcohol intake and breast cancer risk have been published since the last IARC review (2012). The two available European studies did not achieve high scores in the NO scale for quality. Although both studies did observe increased breast cancer risk with alcohol consumption, they had a number of methodological limitations (no dose response data, lack of information on adjustment for potential confounding factors and small sample size). It should be noted that the three US case-control studies considered specific ethnic populations (African-American and Asian-American). The relevance of these ethnicities to the UK population requires consideration. Similar increased risk of breast cancer was associated with alcohol consumption in the three South American studies (Ronco et al. (2011); Beasley et al., (2010) and Sanchez-Zamorano et al., (2011)), the Japanese study of Islam et al. (2013) and in the Chinese study of Zhang and Hollman (2012) when alcohol consumption was considered in terms of g/day.

Case-control studies examining alcohol consumption and breast cancer mortality and secondary events (Table 6)

54. Weaver et al. (2013) investigated both total alcohol intake and intensity (drinks per drinking day) over different time periods of life and association with mortality in 1,097 women (pre-menopausal and post-menopausal) diagnosed with breast cancer who participated in the US Western New York Exposures and Breast Cancer (WEB) population-based case-control study. Information on alcohol consumption was obtained using the cognitive lifetime drinking history (CLDH) survey, administered by trained interviewer and details were collected on type, intensity, and volume of alcohol consumed. Abstainers were defined as those who did not have 12 or more drinks during any one year of their lives. Alcohol consumption was assessed in three categories a) drinking status (ever or never) for lifetime, and current or non-current drinkers for the 30 days, and 12 months prior to interview; b) volume of alcohol consumed compared to abstainers during the lifetime, in the period ten to 20 years prior to diagnosis, in the period two to ten years prior to diagnosis, and in the period between menarche and first birth (time of interview for nulliparous women); and c) intensity (number of drinks per drinking day with a drink defined as 12 ounces of beer, five ounces of wine, or 1.5 ounces of liquor) during the lifetime, in the period

ten to 20 years prior to diagnosis, in the period two to ten years prior to diagnosis, and in the period between menarche and first birth (time of interview for nulliparous women). Intensity was categorised into the following: abstainers, 1 drink or less, 2–3 drinks, and 4 or more drinks per day (equivalent to 8 g/day or less, 16-24 g/day and >28 g/day). Abstainer or non-drinker was the reference category. HRs and 95% CI were estimated for all-cause and breast cancer mortality using Cox proportional hazards models and adjusted for smoking status, tumour stage, age, education level, calories, BMI, and race.

55. For both pre- and post-menopausal women, they observed no association between breast cancer specific mortality and drinking status in the past 30 days, past 12 months or over a lifetime. They also observed no association between total alcohol intake and death from breast cancer in pre- and post-menopausal women in any of the categories analysed (total lifetime alcohol intake, total alcohol intake from menarche to age of first birth, total alcohol intake 10-20 years prior to diagnosis and total alcohol intake 2-10 years prior to diagnosis). Drinking intensity was not associated with breast cancer-specific mortality in pre-menopausal women. When they examined intensity of alcohol consumption in post-menopausal women, compared to abstainers, women consuming 4 or more drinks per drinking day over their lifetime or ten to 20 years prior to diagnosis or two to ten years prior to diagnosis, had increased breast cancer-specific mortality (HR = 2.68 (95% CI 0.94 – 7.67), 2.45 (95% CI 0.80 – 7.57) and 1.86 (95% CI 0.51 – 6.79) respectively. Compared to abstainers, they did observe a decrease in HR for breast cancer-specific mortality among post-menopausal women who consumed 1 drink or less per drinking day between menarche and age of first birth (HR = 0.27, 95% 0.09 – 0.77).

Summary of case-control studies on breast cancer mortality

56. Only one case-control study by Weaver et al. (2013) was identified in the literature, published since 2009. For a number of exposure parameters including total lifetime alcohol intake, no association between alcohol consumption and breast cancer mortality was observed. However, when they examined drinking intensity (binge drinking), they reported increased breast cancer mortality in post-menopausal women consuming 4 or more drinks/d over their lifetime or 10-20 years prior to diagnosis or 2-10 years prior to diagnosis. They did not observe the same association in pre-menopausal women.

Nested Case-Control Studies (Table 7)

57. Bissonauth et al. (2009) investigated the role played by alcohol consumption, coffee drinking and total energy expenditure on breast cancer risk in a nested case-control study from a cohort of French-Canadian women. A total of 560 women were included in the analysis (280 breast cancer cases who were non-gene carriers of mutated BRCA gene and 280 controls who were non-gene carriers of mutated BRCA). Information on alcohol consumption such as frequency, quantity and beverage type was collected using a food frequency questionnaire. ORs and associated 95% CI of BRCA-unrelated breast cancer were estimated using conditional logistic regression and adjusted for age, education, physical activity, smoking, coffee consumption and total energy. Consumption of ≤1.9 g ethanol per

day was the reference category. They observed an increasing risk of breast cancer with increasing consumption of alcohol (OR = 1.30, 95% CI (0.86 – 2.08) for those consuming >1.9-<9.0 g/day and OR = 1.55, 95% CI (1.02 – 2.37) for those consuming > 9.0 g/day compared to reference category. They reported a similar association between beer, wine and spirits and breast cancer risk. The ORs were 1.34 (95% CI 1.28-2.11) for more than two bottles of beer per week, OR = 1.16 (95% CI 1.08 – 2.58) for > 10 oz. of wine per week and OR = 1.09 (95% CI 1.02 - 2.08) for > 6 oz. of spirit per week, respectively.

Types of alcoholic beverage

58. There was generally consistent evidence from both cohort and case-control studies that the risk does not vary significantly by beverage type (Bissonauth et al., 2009; Chen et al., 2011; Newcomb et al., 2013; Vrieling et al., 2012; Ronco et al., 2011). This is in line with previous observations from IARC. However, cohort studies by Park et al. (2014) and Kabat et al. (2011) did show that intake of wine and liquor but not beer showed positive associations with breast cancer and ER+ breast cancer at certain intakes of alcohol, respectively. Zhang and Holman (2011) also observed differences in breast cancer risk across alcohol beverage types depending on the menopausal status of the women. Kwan et al. (2010) observed an increased risk of breast cancer recurrence with wine consumption but not with beer or liquor consumption. Chandran et al. (2013) observed an increased risk of breast cancer with certain intakes of mixed spirits but not with beer or wine consumption. Li et al. (2010) also observed some variations with beer, wine and spirit consumption and the risk of ductal and lobular breast cancer risk, but none of the differences were statistically significant.

Histological subtype

59. Ductal carcinomas account for roughly 90% of invasive breast cancers and lobular carcinomas account for 10% invasive breast cancers in the UK (Cancer Research UK). Four US cohort studies (Chen et al., 2011; Li et al., 2010; Kabat et al., 2010 and Kotsopoulos et al., 2010) have examined the association with consumption of alcoholic beverages by histological breast cancer subtype. Similar associations were reported for ductal and lobular subtypes in the studies of Kotsopoulos et al. (2010) and Chen et al. (2011). Slightly stronger positive associations for alcohol intake and lobular tumours compared with ductal tumours were found by Li et al., 2010. Kabat et al. (2010) did not find any association between alcohol intake at any level of consumption and the risk of breast ductal carcinoma in situ (DCIS). For breast cancer mortality, Newcomb et al. (2013) observed similar results for ductal and lobular breast cancer subtypes and alcohol consumption. McLaughlin et al. (2014) investigated the association between alcohol consumption and secondary breast cancer occurrence and reported an increasing risk of secondary breast cancer with increasing post-diagnosis alcohol consumption in DCIS survivors.

Cohort studies of consumption of alcohol consumption and breast cancer risk by histology status (Table 8)

Chen et al. (2011) is described elsewhere in this paper (see paragraph 28).

60. Li et al. (2010) examined the association between alcohol intake and risk of different post-menopausal breast cancer subtypes defined by histology and hormone receptor status among 87,724 women in the Women's Health Initiative Observational prospective cohort study. Information on alcohol intake such as drinking status and frequency was obtained using self-assessment and frequency of alcohol consumption among current drinkers was categorised into six groups based on the number of drinks consumed per week (<0.5, 0.5-0.9, 1.0-3.9, 4.0-6.9, 7.0-13.9, >14.0) equivalent to <0.5, 0.7-1.3, 1.4 - 5.5, 5.7- 9.8, 10 - 19.9, ≥ 20g ethanol/day, respectively. Never drinkers were the reference category. HRs and 95% CI were estimated using Cox proportional regression models and adjusted for age, race, and/or ethnicity, education, BMI, use of menopausal HT, smoking status, Gail model scores of 5-year breast cancer risk and number of screening mammograms received in the past five years.

61. Li et al. (2010) observed an increase in all invasive breast cancer risk with increased alcohol intake (HR of 1.02 (95% CI 0.87 - 1.18) per <0.5 drinks per week, 1.05 (95% CI 0.85 - 1.28) per 0.5–0.9 drinks per week, 1.10 (95% CI 0.94 - 1.30) per 1.0–3.9 drinks per week, 1.12 (95% CI 0.91 - 1.36) per 4.0–6.9 drinks per week, 1.27 (95% CI 1.05 - 1.53) per 7.0–13.9 drinks per week, and 1.24 (95% CI 1.00 - 1.55) per ≥14.0 drinks per week. They reported that the number of drinks consumed per day was more strongly associated with the risk of invasive lobular breast cancer than ductal breast cancer. Compared to never drinkers, women consuming ≥ 14 drinks per week had a statistically significant increased risk of lobular carcinoma (HR = 2.13, 95% CI 1.36-3.33) but not a statistically significantly increased risk of ductal carcinoma (HR = 1.06, 95% CI 1.00-1.13). When they examined the data for specific beverage consumption, they observed differences between invasive ductal and lobular carcinoma risks. For current beer, wine and spirit drinkers, they observed HRs of 1.14 (95% CI 0.92 – 1.43), 1.04 (95% CI 0.86 – 1.26) and 1.05 (95% CI 0.84 – 1.29) for ductal carcinomas and HRs of 1.70 (95% CI 1.13 – 2.54), 1.58 (95% CI 1.11 – 2.25) and 1.68 (95% CI 1.14 – 2.47) for lobular carcinomas, respectively.

62. Alcohol consumption was positively associated with the risk of both ER+PR+ and ER+PR- breast cancers (risk per drink per day consumed among current drinkers HR 1.08, 95% CI 1.02 – 1.15 and 1.12, 95% CI 1.00-1.25, respectively. They did not find any significant association with ER-PR- breast cancer, although the results suggested an inverse trend (risk per drink per day among current drinkers HR = 0.85, 95% CI 0.65 – 1.05). They also examined the association between alcohol intake and risk of lobular and ductal carcinoma, stratifying the data for ER+PR+ tumours. They found that the association between number of drinks consumed per day among current drinkers and risk of lobular carcinoma was stronger than the risk of ER+PR+ ductal carcinoma (HR = 1.16, 95% CI 1.06 – 1.26 and 1.05, 95% CI 0.97 – 1.14), respectively. They also reported that women who consumed ≥ 7.0 drinks/week had an increased risk of ER+PR+ lobular carcinoma (HR = 1.82, 95% CI 1.18 – 2.81) but not a statistically significant increased risk of ER+PR+ ductal carcinoma (HR = 1.14, 95% CI 0.87 – 1.50).

63. Kabat et al. (2010) assessed the association between adult alcohol consumption and invasive DCIS in a US cohort of 63,822 post-menopausal women. Information on alcohol intake was obtained using both a food frequency questionnaire and a health habits questionnaire. Alcohol frequency was categorised into the following number of servings per unit time: never or less than once per month, 1-3 per month, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 2-3 per day, 4-5 per day, and 6+ per day. A medium serving was defined as a 12-oz. can or bottle of beer, a 6-oz. glass of wine, or 1 shot (1.5 oz.) of hard liquor. Frequency of total alcohol intake was also categorised into non-drinker, past drinker, <1 drink/month, <1 drink/week, 1 to <7 drinks/week, and 7+ drinks/week. They also examined the intakes of various beverages (beer, wine, and hard liquor). Non-drinkers were the reference category. Cox proportional hazards models were used to estimate HRs and 95% CI for associations of alcohol consumption and risk of DCIS and adjusted for age, age at menarche, age at first full-term pregnancy, parity, age at menopause, BMI, waist circumference, use of OC, use of HT, history of breast biopsy, mammogram in the past 2 years, family history of breast cancer in a first-degree relative, physical activity, pack-years of smoking, education, ethnicity, and treatment arm assignment in each of the three clinical trials. They did not find any association between alcohol intake at any level of consumption and the risk of DCIS. Similarly, alcohol intake showed no association with risk of either high-grade or low-grade DCIS. When the data was stratified by HT use, BMI, family history of breast cancer, dietary folate and methionine intake, no significant association or trends were observed between alcohol intake and DCIS.

64. Kotsopoulos et al. (2010) examined the association between risk factors including alcohol consumption on the risk of two invasive breast cancer subtypes, ductal and lobular carcinoma among post-menopausal women from the Nurse's Health Study cohort. Information on alcohol intake was obtained using a food frequency questionnaire. Alcohol intake was expressed in g/day and categorised as 0, <5, 5 - <15 and ≥ 15 g/day. Non-drinker was the reference category. RRs and 95% CI were estimated using Cox proportional hazard regression analysis and adjusted for age, age at menopause, age at menarche, menopausal status, parity, age at first birth, nulliparous or parous, parity and post-menopausal hormone status and use, BMI, and BMI at age 18. Their results suggest a positive association between increasing alcohol intake and the risk of lobular subtype of breast cancer (ORs = 1.30 (95% CI 1.05 - 1.59) for <5 g/day, 1.34 (95% CI 1.08 - 1.67) for 5 - <15 g/day and 1.75 (95%CI 1.36 - 2.24) for ≥15 g/day) compared to non-drinkers. A similar trend was also observed for the ductal subtype (ORs = 1.15 (95% CI 1.06 - 1.24) for <5 g/day, 1.22 (95% CI 1.12 - 1.32) for 5 - <15 g/day and 1.31 (95% CI 1.19 - 1.45) for ≥15 g/day). When they restricted the analyses to oestrogen receptor-positive and progesterone receptor-positive (ER+/PR+) tumours, similar results were observed. A positive association between increasing alcohol intake and the risk of lobular subtype of ER+/PR+ breast cancer (ORs = 1.11 (95% CI 0.80 - 1.55) for <5 g/day, 1.52 (95% CI 1.10 - 2.10) for 5 - <15 g/day and 2.28 (95%CI 1.60 - 3.24) for ≥15 g/day). Although they did observe an association for ER+/PR+ ductal subtype, it was not as strong as for the lobular subtype (ORs = 1.16 (95% CI 1.03 – 1.31) for <5 g/day, 1.40 (95% CI 1.23 - 1.58) for 5 - <15 g/day and 1.37 (95%CI 1.17-1.61) for ≥15 g/day) compared to non-drinkers.

Cohort studies of consumption of alcohol consumption and breast cancer mortality and secondary events by histology status (Table 9)

Newcomb et al. (2013) is described elsewhere in this paper (see paragraph 33).

65. McLaughlin et al. (2014) examined the association of BMI, physical activity, and alcohol intake with the risk of a second *in situ* or invasive breast cancer diagnosis in the large, population-based Wisconsin In Situ Cohort (WISC) of DCIS survivors. The study sample consisted of 1,925 women with a first primary DCIS diagnosis. Information on alcohol consumption such as quantity of specific beverages consumed per day, week, or month at one-year pre-diagnosis was obtained by interview. Cox proportional hazards regression was used to estimate the HRs and 95% CI and adjusted for age at diagnosis, menopausal status, method of detection, surgical treatment type, radiation therapy, tamoxifen use, year of diagnosis, tumour size, tumour grade, BMI and physical activity. Over the follow-up time period, 162 second breast cancer events were observed, they observed an increasing linear trend in risk of any second breast cancer diagnosis with increasing post-diagnosis alcohol intake (HRs = 1.28 (0.59–2.78) for >0–<2 drinks/wk (->0-<2.85g/day), 1.76 (0.64–4.80) for 2–<7 drinks/wk (2.85g-<10g/day) and 2.59 (0.61–11) for 7+ drinks/wk (10+g/day)) compared to non-drinkers. However, when alcohol consumption was measured continuously per 1 drink/wk, the increased risk of any second breast cancer diagnosis with increasing alcohol intake was not statistically significant in either the pre- or post-diagnosis analysis (pre-diagnosis HR = 1.02; 95% CI, 0.99–1.05; post-diagnosis HR = 1.03; 95% CI, 0.94–1.11). Stratifying the data to consider only invasive second breast cancer diagnoses, they observed an increasing trend of risk of invasive breast cancer, although this was not statistically significant, with increasing post-diagnosis alcohol intake (HRs = 1.38 (95% CI 0.37–5.47) for >0–<2 drinks/wk, 1.40 (95% CI 0.14–4.35) for 2–<7 drinks/wk and 1.74 (95% CI 0.17–9.68) for 7+ drinks/wk) compared to non-drinkers. No such trend was observed with pre-diagnosis alcohol intake.

Tumour receptor status

66. The association between alcohol consumption and breast cancer risk by oestrogen receptor (ER) and progesterone receptor (PR) status has been examined in 9 cohort studies and 4 case-control studies. Four cohort studies (Chen et al., 2011; Liu et al., 2013; Park et al., 2014; Li et al., 2010) and one case-control study (Wu et al., 2012) found ER+ tumours were more likely to show a positive association with alcohol intake than ER- tumours. One case-control studies investigating breast cancer risk (Chandran et al. 2013) and two cohort studies investigating alcohol consumption and breast cancer mortality observed similar associations for ER+ and ER – tumours (Vrieling et al., 2012 and Kwan et al., 2010). Kwan et al. (2013) found no association between alcohol intake and breast cancer mortality but observed an association between occasional drinking and ER- type breast cancer mortality. Results from two case-control studies (Zhang and Holman (2012) and Islam et al. (2013)) varied depending on menopausal status and alcohol intake. Two other cohort studies (Horn-Ross et al., 2012 and Kabat et al., 2011) found a positive association between alcohol consumption and ER+ breast cancer risk but no comparative data was provided with ER- breast cancer.

Cohort studies of consumption of alcohol consumption and breast cancer risk by receptor status (Table 10)

67. The cohort studies of Horn-Ross et al., (paragraph 23), Park et al., 2014 (paragraph 24), Lui et al., 2013 (paragraph 25), Li et al., 2010 (paragraph 61 & 62) and Chen et al 2011 (paragraph 28) all examine the relationship between alcoholic beverages and breast cancer risk by receptor.

68. Triple-negative breast cancer (TNBC) tumours accounts for approximately 15%-25% of all breast cancer cases. TNBC is characterised by the absence of the ER, PR and lack of overexpression of the human epidermal growth factor receptor (HER2). Using data from the Women's Health Initiative, Kabat et al. (2011) investigated the association of alcohol consumption and smoking with the risk of TNBC and ER+ breast cancer. The study sample size was 148,030 women, among whom 300 had TNBC and 2,479 had ER+ breast cancer. Information on alcohol consumption was obtained using two questionnaires (a health habits questionnaire and a food frequency questionnaire (FFQ)). Details collected included lifetime consumption, current drinking status, intake of specific alcohol beverages, frequency (never or less than once per month, 1–3 per month, 1 per week, 2–4 per week, 5–6 per week, 1 per day, 2–3 per day, 4–5 per day, and 6+ per day) and serving size. A medium serving was defined as a 12 oz can or bottle of beer, 6 oz glass of wine, or 1 shot (1.5 oz) of hard liquor. Using the information from the questionnaires, two variables to describe frequency of total alcohol intake were described in the paper: a categorical variable (non-drinker, past drinker, <1 drink per month, <1 drink per week (1.4g/day), 1–<7 drinks per week(1.4-<10g/day), and ≥7 drinks per week (≥10g/day)) and a continuous variable (alcoholic drinks per week). Non-drinkers were the reference category. Cox proportional hazards models were used to estimate HRs and 95% CI for the associations between smoking-related variables and alcohol intake and risk of TNBC and ER+ breast cancer. Adjustments were made in the analysis for age, age at menarche, age at first full-term pregnancy, parity, age at menopause, BMI, waist circumference, use of oral contraceptives, use of hormone therapy, history of breast biopsy, family history of breast cancer in a first-degree relative, mammogram in past two years, physical activity, education, ethnicity, and study arm assignment in each of the clinical trials or the observational study.

69. Although no trend was observed in the data, they did observe a decreased risk of TNBC among alcohol drinkers compared to non-drinkers (HRs = 0.47 (95% CI 0.29–0.78) for <1 drink/month; 0.78 (95% CI 0.53–1.16) for <1 drink/week; 0.68 (95% CI 0.46–1.02) for 1–6 drinks/week and 0.57 (95% CI 0.34–0.95) for ≥7 drinks/week). Considering specific beverage types, intake of beer, wine, and liquor were not associated with TNBC. For ER+ breast cancer, women consuming ≥7 drinks per week had a significantly increased risk of ER+ breast cancer (HR 1.26, 95% CI 1.06–1.50) compared to non-drinkers. When the data was stratified by beverage type, no association was observed for beer but intake of wine and liquor showed small but statistically significant positive associations with ER+ breast cancer at ≥ 3 servings/week (HR = 1.16, 95% CI 1.02 -1.32 and 1.36, 95% CI 1.17 – 1.58), respectively.

Cohort studies of consumption of alcohol consumption and breast cancer mortality and secondary events by receptor status (Table 11)

70. Three cohort studies examined alcohol consumption and breast cancer breast cancer mortality and secondary events by receptor status but have been described elsewhere in this paper (Vrieling et al., 2013 (paragraph 30); Kwan et al., 2010 (paragraph 35); Kwan et al., 2013 (paragraph 36)).

Case-control studies of consumption of alcohol consumption and breast cancer risk by receptor status (Table 12)

71. Four case-control studies examined alcohol consumption and breast cancer risk by receptor status but have been described elsewhere in this paper (Wu et al., 2012 (paragraph 42); Chandran et al., 2013 (paragraph 43 & 44); Islam et al., 2013 (paragraph 49); and Zhang and Holman, 2012 (paragraph 50)).

Polymorphisms and genetic susceptibility

72. In humans, the majority of ingested alcohol is eliminated via metabolic degradation in the liver. Ethanol is first metabolized into acetaldehyde through several enzymatic and non-enzymatic mechanisms. IARC 96 provides a detailed description of the enzymes involved in ethanol metabolism in humans (http://monographs.iarc.fr/ENG/Monographs/vol96/mono96.pdf page 1083-1098). In brief, the main enzymatic pathways involve alcohol dehydrogenase (ADH), the P450 CYP2E1 and catalase. Acetaldehyde is subsequently oxidized into acetate through several enzymatic pathways, with the majority being metabolised in the liver by aldehyde dehydrogenase (ALDH). The ADH enzyme *"ADH1B* is polymorphic, with an amino acid transition from arginine (Arg) to histidine (His) at codon 47 (Arg47His) in exon 3, bestowing the super-active "fast" metabolic character on ethanol. Approximately 40-times greater maximum velocity has been identified for the ADH1B fast His than for the less active Arg/Arg form. *The superactive ADH1B*2 allele is highly prevalent among East Asians (54–96%; Goedde et al., 1992), but relatively rare among Caucasians (1–23%). Individuals with the ADH1B*1/*1 genotype code less active ADH, which is a risk factor for excessive alcohol consumption in both East Asians and Caucasians (Zintzaras et al., 2006; Matsuo et al., 2007)"* (IARC monograph 100e). *"ADH1C is a major gene polymorphism among Caucasians (Bosron & Li, 1986). The homodimer encoded by the ADH1C*1 allele catalyses the production of acetaldehyde from ethanol at a rate 2.5 times faster than the homodimer encoded by the ADH1C*2 allele (Bosron & Li, 1986)"* (IARC monograph 100e).

Cohort studies of consumption of alcohol consumption and breast cancer risk by genetic polymorphisms and susceptibility (Table 13)

73. LeCarpentier et al. (2011) examined the effect of alcohol consumption on breast cancer risk in a French cohort of 1,337 women including 863 BRCA1 mutation carriers and 474 BRCA2 mutation carriers. Details of alcohol consumption such as number of glasses per week were recorded and categorised as 0, 1-5, 6-10, and >10 at the age of 20 and at the time of interview. HRs and 95% CI were estimated using

Cox proportional hazard regression models and adjusted for parity, menopausal status, gene and number of years of smoking interruption. When the analyses were stratified by tobacco use (never smokers and ever smokers), they observed no increased risk of breast cancer with alcohol consumption in current drinkers compared to never-drinkers. For all women, they reported an HR = 1.10, 95% CI 0.76 – 1.61 for never smokers and an HR = 0.89, 95% CI 0.53 – 1.52 for ever smokers. For those carrying the BRCA1 mutation, they observed an HR = 1.02, 95% CI 0.65 – 1.60 for never smokers and an HR = 0.90, 95% CI 0.49 – 1.68 for ever smokers. Similarly no associations were observed for all women and BRCA1 carriers with increasing dose of alcohol and breast cancer risk. However, the HR was higher among BRCA2 carriers who were current drinkers compared to never drinkers (HR =1.21, 95% CI 0.68 – 2.15).

Case-Control studies of consumption of alcohol consumption and breast cancer risk by genetic polymorphisms and susceptibility (Table 14)

74. McCarty et al. (2012) assessed the modifying effects of ADH1B, ADH1C and CYP2E1 on the association between alcohol intake and breast cancer incidence. This case-control study consisted of 2,111 women (1,041 breast cancer cases and 1,070 controls) enrolled in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. Information on alcohol intake was obtained using a food frequency questionnaire such as frequency and serving size of beer, wine and spirits. RRs and 95% CI were estimated using Cox proportional hazard ratios, adjusted for age, race, ethnicity, age at menarche, parity, age of first live birth, family history of breast cancer, and personal history of benign breast disease. Compared to non-drinkers, they observed an increase in breast cancer risk with increasing alcohol consumption, with HR of 1.31 (95% CI 1.01 – 1.71) for women consuming >0 – 0.99 drinks/day (>0-9.99g/day), 1.54 (95% CI 1.04 – 2.28) for women consuming 1.00 – 1.99 drinks/day (10g-19.9g/day), 1.75 (95% CI 1.02 – 3.00) for women consuming 2.00-2.99 drinks/day (20-29.8 g/day) and 2.00 (95% CI 1.11 – 3.61) for women consuming 3 or more drinks/day (>30g/day). Stratifying by ADH1B genotype, they observed for the GG genotype statistically significant associations between all levels of alcohol intake and breast cancer risk (HR = 1.29 (95% CI 0.97 – 1.72) for women consuming >0 – 0.99 drinks/day, 1.66 (95% CI 1.09 – 2.52) for women consuming 1.00 – 1.99 drinks/day, 1.88 (95% CI 1.07 – 3,29) for women consuming 2.00-2.99 drinks/day and 2.22 (95% CI 1.19 – 4.13) for women consuming 3 or more drinks/day. However for the GA and AA genotypes, no associations between alcohol intake and breast cancer risk were observed with some indications of a decreased risk at higher levels of alcohol consumption compared to non-drinkers. When they examined the data stratifying by ADH1C genotypes, they found the association between alcohol intake at all levels and breast cancer risk was similar across all genotypes. For CYP2E1, small sample size of CT and TT genotypes made interpretation of the results difficult.

75. A number of genes associated with hereditary susceptibility to breast cancer have been identified and include *BRCA1*, *BRCA2*, *TP53*, *PTEN/MMAC1*, and *STK11.* Germline mutations in *BRCA1* are associated with early-onset breast cancer, ovarian cancer and mutations in *BRCA2* are associated with multiple cases of breast cancer in families, and are also associated with male breast cancer,

ovarian cancer, prostate cancer, melanoma, and pancreatic cancer, and fallopian tube cancer.

76. Dennis et al. (2010) investigated the role played by alcohol on breast cancer risk in 3,850 women with either the BRCA1 or BRCA2 mutation in a case control study. Information on alcohol consumption such as current drinking status, quantity and beverage type were obtained using a self-administered questionnaire. Non drinkers were the reference category in the study. ORs and 95% CI were estimated using conditional logistic regression analysis and adjusted for ethnicity, menopausal status, oral contraceptive use, HRT use, smoking, oophorectomy, BMI and parity.

77. Among women with a *BRCA1*-mutation, the odds ratio for breast cancer associated with current alcohol consumption was 0.82 (95% CI 0.70–0.96), and a significant trend of decreasing risk of breast cancer with increasing drinks per week was observed (OR = 0.77, 95% CI 0.67–0.94 for 0-3 drinks/week (0- 4.3 g/day), 0.98, 95% CI 0.73–1.32 for 4-9 drinks/week (5.7-12.9g/day), 0.55, 95% CI 0.33–0.91 for ≥ 10 drinks/week (≥ 14g/day), p-trend = 0.03) compared to a non-drinker. The association was not appreciably modified by age at diagnosis or BMI.
Among *BRCA1* carriers, consumers of wine exclusively had a reduced risk of breast cancer compared to non-drinkers (OR = 0.64, 95% CI 0.47–0.87), whereas women who did not consume wine exclusively had a risk of breast cancer that was similar to that of non-drinkers (OR = 0.89, 95% CI 0.70–1.12). A significant decreasing trend in the risk of breast cancer was seen with increasing weekly alcohol consumption for consumers of wine exclusively, but not for the other subgroups of types of alcohol consumed.

78. Among women with a *BRCA2*-mutation, the odds ratio associated with current alcohol consumption was estimated to be 1.00 (95% CI 0.71–1.41). The association between the number of drinks consumed per week and breast cancer risk was not significant (OR = 0.97, 95% CI 0.67 – 1.41 for 0-3 drinks/week, 1.04 95% CI 0.67 – 1.63 for 4-9 drinks/week, 1.16, 95% CI 0.55 – 2.45 for ≥ 10 drinks/week, p-trend = 0.72), nor was it modified by restricting to pairs in which both the case and control consumed alcohol, by age at diagnosis, or by BMI. Among women with a *BRCA2* mutation, the odds ratios for breast cancer associated with exclusive and non-exclusive wine consumption compared to no alcohol consumption were 1.01 (95% CI 0.61–1.69) and 0.88 (95% CI 0.53–1.48), respectively.

Nested Case-Control studies of consumption of alcohol consumption and breast cancer risk by genetic polymorphisms and susceptibility (Table 15)

79. Benzon Larsen et al. (2010) examined the modifying effect of various alcohol dehydrogenase (ADH) enzyme polymorphisms on breast cancer risk in a Danish case-control study of 809 post-menopausal women. Information on alcohol intake such as frequency, beverage type and drinking patterns were obtained using both food frequency questionnaires and lifestyle questionnaires. Incident rate ratios (IRRs) were determined using conditional logistic regression analysis and adjusted for parity, age of first birth, length of school education, duration of HRT use and BMI. They observed that the variant allele carriers of ADH1B $Arg^{48}His$ were at a lower risk of breast cancer (IRR = 0.78, 95% CI 0.48-1.26) than the homozygous wild type allele carriers. Homozygous variant allele carriers of ADH1C $Arg^{272}Gln$ were at a

1.27 (95% CI 0.94 – 1.73) higher risk and heterozygous carriers were at a 1.09 (95% CI 0.87 – 1.36) higher risk of breast cancer than homozygous wild-type allele carriers although none of the associations were of statistical significance. They also reported that for both heterozygous and homozygous carriers of the variant allele of ADH1C $Arg^{272}Gln$, alcohol intake was associated with a 1.12 fold (95% CI 1.01 – 1.24) and 1.19 fold (95% CI 1.01 -1.39) higher risk per 10 g of alcohol consumed per day. Alcohol intake was not associated with breast cancer among the homozygous wild type carriers.

Studies involving other breast cancer risk factors including alcoholic beverages and breast cancer risk

Cohort Studies investigating other breast cancer risk factors and alcohol consumption (Table 16).

80. Benign breast disease (BBD), in particular certain histopathological types, is a risk factor for increased breast cancer risk (Hartmann et al., 2005). Both Berkey et al. (2010) and Liu et al. (2012) investigated the association between alcohol intake during adolescence and BBD.

81. Using data from the Growing Up Today Study (GUTS), a prospective cohort of 9057 girls from 50 states in the US, Berkey et al. (2010) investigated whether drinking during adolescence is associated with BBD in young women. Information on alcohol intake (including typical alcohol consumption, frequency of drinking, quantity consumed at each occasion and frequency of binge drinking) was obtained by interview in the 2003 survey when participants were 16 -23 years of age. In 2005 and 2007, information was obtained about BDD status of 6877 females. ORs and 95% CI were calculated using logistic regression and adjusted for age and BMI. There were 67 biopsy-confirmed BBD cases and 6752 non-cases for analyses. Compared with non-case BDD females, BDD cases were older, drank more frequently, consumed more at each drinking occasion and average daily consumption was more than twice as high as non-cases. Cases also reported more episodes of binge drinking. In their analyses, alcohol intake was associated with higher BDD risk (OR = 1.50 per drink/day, 95% CI 1.19- 1.90). Analyses stratified by BMI quartiles showed that the elevated risk persisted within BMI subgroups (OR = 1.61 per drink/day for most lean and OR = 1.51 for the heaviest females). They observed a dose-dependent increase in risk of BDD with increasing frequency of alcohol consumption (OR = 1.00 (referent) for never to less than weekly; 1.57 (95% CI 0.80–3.09) for 1–2 days per week; 3.01 (95% CI 1.27–7.14) for 3–5 days per week and 5.50 (95% CI 1.23–24.53) for 6–7 days per week). Analyses stratified by age found elevated BBD risk with higher consumption at ages 19 (OR = 1.76 per drink/day, 95% CI 1.19 – 2.60) and 21 + (OR = 1.51 per drink/day, 95% CI 1.02 – 2.26). A non-significant elevated risk was also observed at other ages (aged 16-17 (OR = 1.52 (95% CI 0.51- 4.53), aged 18 (OR = 1.45 (95% CI 0.59 – 3.52) and aged 20 years (OR = 1.10 (95% CI 0.0.53 – 2.30)).

82. Liu et al. (2012) investigated the association between alcohol intake during adolescence and BBD risk using data from 22,117 women in the US Nurses' Health Study II. 659 cases of BDD were confirmed between 1991-2001. Information on the

total number of drinks of alcohol (none or <1 per month, 1–3 per month, 1 per week, 2–4 per week, 5–6 per week, 7–13 per week, 14–24 per week, 25–39 per week, and 40+ per week) consumed between ages 18 and 22 years was obtained using a high school food-frequency questionnaire (HS-FFQ). One drink was defined as 1 bottle or can of beer, a 4-ounce glass of wine, or a shot of liquor, with ethanol estimates of 12.8 g for regular beer, 11.3 g for light beer, 11.0 g for wine, and 14.0 g for liquor. Total alcohol consumption was expressed in grams of ethanol per day. Alcohol consumption between ages 18 and 22 years was categorized into 4 groups: no consumption (none), any consumption up to 5 g of ethanol/day (0.1–4.9 g/day), between 5 and 15 g/day (5.0–14.9 g/day), and 15+ g/day. Non-drinkers were the reference category. Cox proportional hazards models were used to estimate HRs and 95% CIs, adjusted for age in months, total energy intake, age at menarche, menopausal status, average body size between ages 5 and 10 years, family history of breast cancer in mother or sister(s), current and duration of OC use, current alcohol consumption, and parity and age at first birth. Over the 10-year follow up, 659 incident cases of proliferative BBD were identified. They reported that alcohol consumption was significantly associated with an increased RR of proliferative BBD (HR = 1.15 per 10 g/day equivalent to ~ 1 drink per day, 95% CI, 1.03–1.28). Compared with non-drinkers, the HRs were 1.11 (95% CI, 0.89–1.38) for those who consumed <5 g/day, 1.36 (95% CI, 1.09–1.69) for those who consumed 5.0–14.9 g/day, and 1.35 (95% CI, 1.01–1.81) for those consuming ≥ 15 g/day (*P* for trend = 0.03).

83. Mammographic density (MD) is a strong risk factor for breast cancer. In a meta-analysis of over 40 studies to assess this association, McCormack et al. (2006) reported that the majority of studies found a 2- to 6- fold increased risk of breast cancer for highest to lowest density categories.

84. In a cross-sectional multicentre Spanish population-based study, Cabanes et al. (2011) investigated the association between MD, alcohol consumption and tobacco use. A total of 3,568 women took part in the study. Information on alcohol intake was obtained by interview. Data on current and lifetime alcohol consumption history, age of alcohol initiation, frequency and quantity of alcohol consumption was collected. They estimated that the standard servings of red wine (125 ml), white wine (125 ml), beer (200 ml), sherry (50 ml), hard cider (125 ml), spirits (30 ml), and brandy, gin, rum, whiskey, and vodka (40 ml), contained 13.25, 12.63, 6.15, 3.06, 7.80, 7.40, and 14.25 g of ethanol, respectively. ORs and 95% CI were calculated using ordinal logistic models with random centre-specific intercepts and adjusted for a number of confounding factors including age at mammography, BMI, and screening program, plus number of live births, current smoker status, current alcohol status and HRT use.

85. Cabanas et al. (2011) found a positive association between alcohol consumption and MD. Current alcohol drinking consumption increased the odds of high MD by 13% (OR = 1.13; 95% CI 0.99–1.28) and consuming 10g grams or more of alcohol daily compared to a non-drinker (OR = 1.18 (95% CI 0.99–1.41, P for trend = 0.045). Among drinkers, older age of initiation of alcohol consumption was only slightly associated with a higher probability of being in high MD categories (OR = 1.28, 95 CI 0.92 – 1.79). In contrast, women who started drinking before menarche had a lower probability of being in higher density categories than did other women who also

consumed alcohol. When they stratified their analysis by menopausal state, they found that alcohol consumption was not associated with MD and the dose–response curve was almost flat for pre and peri-menopausal women. They did observe an association with increasing age of initiation of alcohol consumption and MD, though the number of women in the older age groups was small. Among postmenopausal women, in contrast, alcohol consumption increased the odds of being in high MD categories by 15% compared to non-drinkers (OR = 1.15; 95% CI 1.00–1.32).There was a dose-dependent increase in the likelihood of being in a high MD group with increasing daily alcohol consumption compared to a non-drinker (OR = 1.10 (95%CI 0.94 – 1.29) for those consuming 0 to <10 g of alcohol daily and an OR = 1.26 (95% CI 1.03 – 1.53). In comparison with a non-drinker, drinking more than 10 g of alcohol/day increased the probability of having MD by 26% (OR = 1.26; 95% CI 1.03–1.53). They examined the interaction of alcohol consumption and tobacco use with respect to their influence on MD and reported the interaction approached statistical significance in a likelihood ratio test (P = 0.075). They found that for women who drank more than 10 g of alcohol/day, their odds of being in high MD categories decreased by 17% for every increase of 10 cigarettes/day (P = 0.037) compared to women that did not drink. In women who drank less than 10 g/day, however, the increased number of daily cigarettes showed no association with lower MD (P = 0.976).

86. Cabanas et al. (2011) also stratified the data on the alcohol consumption by smoking status (current and non-current smokers). They observed a positive association between increased daily grams of alcohol and high MD among non-current smokers (women who drank more than 10 g of alcohol/day versus non-drinkers OR = 1.25; 95% CI 1.02–1.53; P for trend 0.029). They also found that older age of alcohol initiation increased the probability of being in higher MD groups (> 40 years old at initiation vs ≤ 18 years old at initiation, OR = 1.33 (95% CI 0.91 – 1.95) while starting to drink alcohol before menarche decreased the odds of being in high MD categories by 50% (OR = 0.50; 95% CI 0.29–0.85). Among current smokers, they did not observe an association between drinking alcohol, increased alcohol consumption or age of initiation into alcohol drinking and MD.

Combined analysis of studies involving other breast cancer risk factors including alcohol consumption (Table 17)

87. Conroy et al. (2012) performed a combined analysis of three case control studies from different populations (Japan, Hawaii, California and Japan to investigate whether the association of mammographic density with breast cancer varies by alcohol intake. Alcohol intake was estimated from self-administered questionnaires in the Hawaii and Japan studies and recorded as ever vs. never during face-to-face interviews in the California population. For the combined analysis, intake was classified as ever vs. never (≥1 vs. <1 drink/month) and the ever drinkers were divided into ≤1 and >1 drink/day in Hawaii and Japan studies. A number of methodologies were used to consider the data. The relationship between alcohol intake and mammographic density in the controls was determined using general linear models. ORs and 95% CI were estimated using unconditional logistic regression models adjusted for age at mammogram, menopausal status, HRT use, family history of breast cancer, and location/ethnicity. A further interaction term between mammographic density and alcohol intake was included in the models to

assess effect modification by alcohol intake. Never drinkers were the reference category in the analysis. The authors noted that alcohol consumption in their study population was low; less than 50% of participants were classified as ever drinkers and only 10% of women in Hawaii and Japan consumed > 1 drink/day. Whey they examined alcohol drinking as a dichotomous variable for the total study population, alcohol consumption was not associated with breast cancer (OR = 1.03; 95% CI 0.87 – 1.22). Subgroup analysis found an association between alcohol consumption and breast cancer risk in the Japanese study (OR = 1.58; 95% CI 1.05 – 2.39). However, in the subgroup of 200 Hawaii/Japan women consuming >1drink/day, the OR was 1.23 (95% CI 0.86 – 1.76). Their analysis did not demonstrate a significant interaction between ever drinking and mammographic density ($P_{interaction}$ = 0.28) with similar breast cancer risk estimates obtained for ever and never drinkers at the highest mammographic density tertile (OR = 1.61 (95% CI 1.18 – 2.19) for never drinkers and OR = 2.05 (95% CI 1.47 – 2.86) for ever drinkers. The interaction between alcohol consumption and mammographic density was borderline significant ($P_{interaction}$ = 0.046) in women from Hawaii and Japan consuming > 1 drink/day. They observed ORs of 3.65 (95% CI 1.30 – 10.3) and 6.58 (95% CI 2.28 – 19.0) for 2nd and 3rd mammographic density subgroups as compared to never drinkers

Overall Summary

88. IARC has previously reported that alcohol consumption is causally associated with breast cancer. Further conclusions could be drawn from the new studies presented in this update review of the literature published since 2009. Taking the evidence provided in the large meta-analysis of 113 studies by Seitz et al. (2012), a modest but significant increase risk of breast cancer (4%) was associated with light drinking (up to 1 drink/day). Also consideration should be given to the data presented in three US cohort studies (Horn-Ross et al. (2012), Park et al. (2014) and Chen et al. (2011)) on alcohol consumption and breast cancer risk. Three European studies offer some evidence of a role played by alcohol in breast cancer mortality (Vrieling et al. (2012), Holm et al. (2013) and Harris et al. (2012)). The results from the case-control studies and breast cancer risk are population specific and therefore the relevance of these studies to UK population requires careful consideration.

89. Fewer studies have explored whether the relationship between alcohol and breast cancer varies by type of breast cancer (ductal or lobular) or receptor status but the number of publications in these areas are on the increase. To date, there are conflicting data for alcohol consumption and ductal and lobular breast carcinoma. The cohort study of Li et al. (2010), with an NO score of 8, did observe a statistically significant increase in lobular breast cancer risk but no such increased risk was observed for ductal breast cancer risk with increasing alcohol consumption. For ER status, there is increasing evidence to indicate a stronger association between alcohol consumption and ER+ tumours. Risks are also increased for ER- tumours but the association is not as strong.

90. It should be noted that there are some limitations in terms of disease ascertainment, exposure assessment methods and lack of adjustment for confounders in some of the studies, reflecting their lower star quality rating. When

interpreting the results presented here, the relevance of the study population to the UK population should also be considered.

Questions for the Committee

1) What are the views of the Committee on the recently available epidemiological studies (case-control, cohort, pooled and meta-analysis) on alcohol exposure and breast cancer risk?
2) Do the studies reviewed here add further weight to the existing view that alcohol consumption is causally associated with breast cancer risk?
3) Do the new studies alter the previous COC statement from 2004? If so, how?
4) The Committee intends to calculate the burden of cancer attributable to alcohol consumption in due course. From the data presented here and in the IARC monographs 96 and 100e, can members highlight the relevant studies to take this work forward?

PHE Toxicology Unit/COC Secretariat
October 2014

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Table 1. Meta-analysis and combined analysis studies examining Alcohol Consumption and breast cancer risk							
Reference, location, name of study	**Description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls, n**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Seitz et al. (2012) 113 Studies	Meta-analysis 44,552 cases (40,899 incident cases and 3653 deaths) in the non-drinkers category and 77539 cases (76,303 cases and 1236 deaths) in the light drinkers category	Varied	**Drinking status** Non-drinker Light Drinker (≤ 1drink/day)	 44,552 77,539	 1.0 1.04 (1.02 -1.07)	Adjusted for age, family history, parity, menopausal status, oral contraceptive/hormonal replacement therapy use	Light drinking was defined as ≤ 1 drink/day (≤12.5g ethanol/day).
Trentham-Dietz et al. (2014) Five consecutive phases of a case–control study collectively called the US Collaborative Breast Cancer Study	Combined analysis case-control studies Total 23,959 cases 28,304 controls	Varied	**Drinking status (drinks/week)** **All women** Never drinkers Former drinker < 7 7–13 ≥14 **Women aged 18-39 years** Never drinkers <3 3-6 7–13 14-20 21-27 28-34 ≥ 35 **Women aged 40-49 years** Never drinkers <3 3-6 7–13 14-20 21-27 28-34 ≥ 35	 N= 18,895 10.2% 9.4% 63.0% 9.6% 6.0% 1,324/ 2,038 4,315/ 5,241	 1.00 (ref), 1.16 (1.07–1.27) 1.11 (1.04–1.19) 1.25 (1.15–1.37) 1.65 (1.48–1.83) 1.0 1.09 0.86–1.38 1.22 0.93–1.60 1.25 0.89–1.76 0.91 0.48–1.71 2.54 1.08–5.97 1.35 0.37–4.93 2.17 0.77–6.09 1.0 1.04 0.92–1.18 1.10 0.95–1.28 1.13 0.94–1.35 1.19 0.89–1.57 1.66 0.99–2.77 1.31 0.64–2.66 0.94 0.53–1.68	Adjusted for age, state of residence, study period, family history of breast cancer, BMI, alcohol status, age at menarche, parity, age at first pregnancy, oral contraceptive (OC) use, and smoking status	< 7 drinks/week equivalent to <10g/day; 7–13 drinkers/week equivalent to 10 - 20 g/day; ≥14 drinkers/week equivalent to >20 g ethanol/day

Table 1 continued. Meta-analysis and combined analysis studies examining Alcohol Consumption and breast cancer risk							
Reference, location, name of study	**Description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls, n**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Brennan et al. (2010) Studies included Terry et al., 2001 DeStefani et al. 2009 Nkondjock and Ghadirian, 2005 Ronco et al., 2006	Meta-analysis of 4 studies (one cohort and three case-control studies 2645 cases, 63538 controls	Drinking patterns were described	***Drinking Status*** Lowest Intake Highest intake		 1.00 1.21 (1.04 -1.41)	Not stated	Reference category was lowest category drinkers
Gao et al 2014	Meta-analysis of 26 studies (2 cohort studies and 24 case-control studies), 13,204 cases 87,248 controls	Varied	**Drinking status** All studies (n= 26) Non-drinker Drinker Case-control studies (n = 24) Non-drinker Drinker Cohort studies (n = 2) Non-drinker Drinker	 13,114/ 87,089 12,312/ 14,301 802/72788	 1.00 0.85(0.72,1.02) 1.00 0.86(0.72, 1.03) 1.0 0.73 (0.29, 1.85)	Not stated	Did not provide any information on the amount or frequency of alcohol consumption or whether the results were adjusted for confounders.
Li et al. (2011) Studies included Huang et al, 2006; Jin, 2006; Wang et al, 2008 Zhang, 2007	Meta-analysis of 4 case-control studies Chinese population 1655 cases 2175 controls	Varied	***Drinking status*** Non-drinkers Drinkers p value	 1379/1806 266/359	 1.0 (ref) 0.76 (0.60–0.97) 0.0001	Not stated	99% CI Drinking the smallest amount and those who never drank were classified as “non-drinkers” and the rest of subjects were classified as the “drinkers” category

Table 2. Meta-analysis and combined analysis of studies examining alcohol consumption and breast cancer mortality and secondary events, published since 2009

Reference, location, name of study	Description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases/ controls, n	Pooled odds ratio and confidence intervals (95% CI)[a]	Adjustment factors	Comments
Gou et al (2013) Beasley et al., 2011, Breslow et al., 2011, Fuchs et al., 1995; Flatt et al., 2010 Hebert et al., 1989; Holmes et al., 1999; Kwan et al., 2010; Kwan et al., 2013, McDonald et al., 2002; Newcomb et al., 2013; Reding et al., 2008; Saxe et al., 1999; Thun et al., 1997; Zhang et al., 1995 Ewertz et al., 1991; Hellmann et al., 2010; Holm et al., 2013 Jain et al., 2000 Vrieling et al., 2012) Borugian et al., 2004; Rohan et al., 1993 Barnett et al., 2008, Franceschi et al., 2009, Allemani et al., 2011 Harris et al., 2012	25 cohort studies Total sample size = 719,555 Breast cancer death =10,912 Breast cancer recurrence = 2,027 The median follow-up ranged from 2.9 years to 18 years.	Information on alcohol consumption was obtained pre-diagnosis in 14 studies and post diagnosis in 10 studies. One study contained information on both alcohol consumption pre and post diagnosis.	**Drinking Status** Alcohol Consumption Lowest Category Highest Category Pre-diagnostic Alcohol Consumption Lowest Category Highest Category Post-diagnostic Alcohol Consumption Lowest Category Highest Category Dose Response < 10 g/d >10 g/d < 15 g/d > 15 g/d <20 g/d >20 g/d Alcohol Consumption Lowest Category Highest Category Pre-diagnostic Alcohol Consumption Lowest Category Highest Category Post-diagnostic Alcohol Consumption Lowest Category Highest Category Dose Response < 10 g/d >10 g/d < 15 g/d > 15 g/d <20 g/d >20 g/d		Breast cancer Mortality 1.00 (Ref) 1.06(0.97-1.17) 1.00 (Ref) 1.05 (0.93-1.19) 1.00 (Ref) 1.08 (0.94-1.25) 0.94 (0.88-1.01) 1.03 (0.97-1.10) 0.95 (0.90-1.01) 1.08 (0.98-1.18) 0.96 (0.92-1.01) 1.14 (1.02 1.27) Breast cancer Recurrence 1.00 (Ref) 1.21 (0.95-1.53) 1.0 1.24 (0.89-1.73) 1.00 1.17 (0.80-1.73) 0.98 (0.88 -1.11) 1.09 (0.94-1.26) 1.00 (0.91 -1.10) 1.04 (0.83 -1.30) 1.00 (0.91 -1.10) 1.04 (0.83 -1.30)	Not stated	Reference category was lowest level of alcohol consumption

Table 2. Meta-analysis and combined analysis of studies examining alcohol consumption and breast cancer mortality and secondary events, published since 2009

Reference, location, name of study	Description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases/ controls, n	Pooled odds ratio and confidence intervals (95% CI)[a]	Adjustment factors	Comments
Reding et al. (2008) Two population-based case-control Brinton et al., 1995 Darling et al., 1994	1,286 women with invasive breast cancer	Varied	**<u>Drinking Status</u>** **5 Years Prior to Diagnosis** Non-drinkers Drinkers >0 to <3 3 to <7 ≥7 Wine Consumption *Wine drinkers* Non-wine drinkers Wine drinkers >0 to <3 wines 3 to <7 wines ≥7 wines *Beer drinkers* Non-beer drinkers Beer drinkers >0 to <3 3 to <7 ≥7 *Liquor drinker* Non-liquor drinkers Liquor drinkers >0 to <3 3 to <7 ≥7 **Over Lifetime consumption** Never Drinkers Ever Drinkers >0 to <3 3 to <7 ≥7	Mortality 106/216 701/254 370/144 150/42 181/68 307/147 615/217 430/160 100/32 85/25 503/207 412/156 309/116 55/18 48/22 353 /145 567/219 460/176 53/25 54/18 160/83 756/280 432/152 178/74 146/54	 1.0 (ref) 0.7 (0.5 -0.9) 0.7 (0.6 -1.0) 0.6 (0.4-0.8) 0.7 (0.5- 0.9) 1.0 0.7 (0.6 - 0.9) 0.8 (0.6 -1.1) 0.7 (0.5 - 1.1) 0.7 (0.5 - 1.1) 1.0 (ref) 0.9 (0.7 - 1.1) 0.9 (0.7 - 1.1) 0.8 (0.5 - 1.2) 1.0 (0.6 - 1.5) 1.0 (ref) 0.9 (0.7 - 1.1) 0.9 (0.7 - 1.1) 1.1 (0.6 - 1.5) 0.8 (0.5 - 1.2) 1.0 (ref) 0.7 (0.5 - 0.8) 0.6 (0.5 0.8) 0.7 (0.5 - 1.0) 0.6 (0.5 - 0.9)	Multivariate adjusted for age, diagnosis year and mammogram history (defined as ever having a mammogram). Following factors were assessed for their potential Confounding or modifying effects: mammogram history, smoking history, BMI, education, income race and oral contraceptive use.	A woman who had consumed less than 12 alcoholic beverages in her lifetime or less than one drink per month for 6 months or more was considered a never drinker. Reference category was non drinker

Table 3. Cohort studies examining the effect of alcohol consumption on breast cancer risk, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Couto et al 2013 Swedish Women's lifestyle and Health (WLH) cohort study	Cohort of 49,258 Swedish women 30-49 years at recruitment 1278 breast cancer diagnosed 16 years follow up	Food frequency questionnaire	**<u>Drinking Status</u>** **Incremental intake of 5g alcohol/day** All women Non-drinker Drinker **Pre-menopausal women** Non-drinker Drinker ***Post-menopausal women*** Non-drinker Drinker		 1.00 (ref) 1.04 (0.99-1.09) 1.00 (ref) 1.03 (0.98-1.09) 1.00 (ref) 1.05 (0.98-1.13)	Adjusted for history of breast cancer in mother and/or sister(s), personal history of benign breast disease, smoking status, BMI, height, age at first birth and total number of children, educational level, age at menarche, total energy intake, consumption of beverages, potatoes, sweets and eggs	Non-drinker was the reference category	7 stars

Table 3. Cohort studies examining the effect of alcohol consumption on breast cancer risk, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Horn- Ross et al. (2012) US California Teachers Study (CTS) cohort	Cohort of 40,680 women. 660 women diagnosed with invasive breast cancer 530 cases (80%) had oestrogen receptor positive (ER+) tumours. 94 cases (14%) had ER negative (ER-) tumours). 10 year follow-up	Self-administered questionnaire	**Drinking Status** **Alcohol (g/d)** **All women** non-drinker <20 ≥20 Never used HT non-drinker <20 ≥20 Past HT use non-drinker <20 ≥20 Stopped HT ≥5 yrs non-drinker <20 ≥20 Stopped HT 3–4 yrs non-drinker <20 ≥20 Stopped HT <3 yrs non-drinker <20 ≥20 Current HT use non-drinker <20 ≥20	 233 293 134 50 40 25 117 145 58 65 82 30 31 36 15 17 26 11 58 98 50	 1.0 1.01 (0.85–1.20) 1.26 (1.02–1.56) 1.0 0.78 (0.51–1.18) 1.52 (0.94–2.47) 1.05 (0.75–1.47) 1.03 (0.74–1.43) 1.10 (0.75–1.62) 1.02 (0.70–1.48) 1.16 (0.81–1.66) 1.11 (0.70–1.76) 1.20 (0.76–1.89) 0.91 (0.59–1.40) 1.04 (0.58–1.86) 0.84 (0.49–1.47) 0.93 (0.57–1.49) 1.06 (0.55–2.04) 1.34 (0.91–1.97) 1.60 (1.13–2.26) 2.11 (1.41–3.15)	Adjusted for age at first full-term, a family history of breast cancer in a first degree relative, BMI, and average long-term physical inactivity.	Non-drinkers were the reference category HT = Hormone therapy	8 stars

Table 3. Cohort studies examining the effect of alcohol consumption on breast cancer risk, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Park et al 2014 Multi-ethnic Hawaiian/Californian population	Cohort of 85,089 women 3885 invasive breast cancer cases Follow-up12.4 years	Self-administered quantitative food frequency questionnaire (QFFQ)	**Drinking status** **Alcohol intake (g/day)** Non-drinkers 0.1–4.9 5–9.9 10–14.9 15.0–29.9 ≥30 P trend 10g/day increment	 2342 802 207 126 181 227	 1.00 (ref) 0.98(0.91-1.07) 1.23 (1.06-1.42) 1.21 (1.00-1.45) 1.12 (0.95-1.31) 1.53 (1.32-1.77) <0.001 1.04 (1.02 -1.06)	Adjusted for ethnicity, age at entry, family history of breast cancer, age at first live birth, age at menarche, age and type of menopause, no. of children, HRT, smoking status, education, physical activity, BMI and energy intake.	Non-drinker was the reference category	7 stars

Table 3. Cohort studies examining the effect of alcohol consumption on breast cancer risk, published since 2009

Reference, location, year of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases	Pooled odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Rating for Quality
Liu et al 2013 US Nurses' Health Study II	Total cohort of 91,005 women 10 + years of follow-up 1609 breast cancer cases 970 cases of proliferative BBD.	High school food-frequency questionnaire (HS-FFQ)	**Drinking status** **Cumulative average alcohol intake between menarche and first full term pregnancy (g/day)** 0 g 0.1–4.9 g/day 5.0–14.9 g/day ≥15 g/day Per 10-unit increase P trend **Cumulative average alcohol intake after first full term pregnancy (g/day)** 0 g 0.1–4.9 g/day 5.0–14.9 g/day ≥15 g/day Per 10-unit increase P trend	 323 914 307 65 1609 199 693 197 46 1135	 1.00 (ref) 1.08 (0.94 -1.23) 1.11 (0.94 -1.32) 1.41 (1.07 – 1.86) 1.13 (1.03 -1.24) 0.01 1.00 (ref) 1.09 (0.93 -1.28) 1.17 (0.95 -1.43) 1.30 (0.93 -1.83) 1.11 (0.99 – 1.24) 0.06	Adjusted for age in months, total energy intake, age at menarche, menopausal status, average body size between ages 5 and 10 years, family history of breast cancer in mother or sister(s), current and duration of OC use, and parity and age at first birth.	Non-drinkers were the reference category	7 stars

Table 3. Cohort studies examining the effect of alcohol consumption on breast cancer risk, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Liu et al 2013 Continued	Total cohort of 91,005 women 10 + years of follow-up 1609 breast cancer cases 970 cases of proliferative BBD.	High school food-frequency questionnaire (HS-FFQ)	**Cumulative average alcohol consumption between Menarche to first birth <10 years** 0 g 0.1–4.9 g/day 5.0–14.9 g/day ≥15 g/day Per 10-unit increase P trend **Cumulative average alcohol consumption between Menarche to first birth ≥10 years** 0 g 0.1–4.9 g/day 5.0–14.9 g/day ≥15 g/day Per 10-unit increase P trend	 190 290 63 7 550 133 624 244 58 1059	 1.00 (ref) 1.11 (0.90 to 1.27) 0.94 (0.68 to 1.29) 0.64 (0.30 to 1.39) 0.87 (0.69 to 1.10) 0.25 1.00 (ref) 1.06 (0.84 to 1.32) 1.16 (0.90 to 1.50) 1.66 (1.17 to 2.36) 1.21 (1.08 to 1.36) <.01	Adjusted for age in months, total energy intake, age at menarche, menopausal status, average body size between ages 5 and 10 years, family history of breast cancer in mother or sister(s), current and duration of OC use, and parity and age at first birth.	Non-drinkers were the reference category	7 stars

Table 3. Cohort studies examining the effect of alcohol consumption on breast cancer risk, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Chen et al 2011 Prospective observational US Nurses' Health Study	105,986 women followed from 1980-2008	Semi-quantitative food frequency questionnaire.	**Drinking status** **Alcohol Intake, g/d** **Baseline intake 1980** 0 0.1-4.9 5.0-9.9 10.0-19.9 20.0-29.9 ≥30 RR per 10-g increase **P trend** **Current Intake** 0 0.1-4.9 5.0-9.9 10.0-19.9 20.0-29.9 ≥30 RR per 10-g increase P trend **Cumulative intake** 0 0.1-4.9 5.0-9.9 10.0-19.9 20.0-29.9 ≥30 RR per 10-g increase P trend	 1776 2016 723 1020 246 413 476 6194 2475 1930 692 863 208 350 6518 1669 3143 1063 1091 362 362 7690	 1.00 (Ref) 1.07 (1.00-1.14) 1.15 (1.06-1.26) 1.15 (1.06-1.24) 1.28 (1.12-1.47) 1.50 (1.34-1.67) 1.09 (1.07-1.11) <0.001 1.00 (Ref) 1.04 (0.98-1.11) 1.11 (1.01-1.20) 1.11 (1.03-1.21) 1.21 (1.05-1.40) 1.34 (1.19-1.50) 1.07 (1.05-1.10) <0.001 1.00 (Ref) 1.06 (0.99-1.12) 1.15 (1.06-1.24) 1.22 (1.13-1.32) 1.20 (1.07-1.35) 1.51 (1.35-1.70) 1.10 (1.07-1.12) <0.001	Adjusted for menopausal status, age at menarche, parity, age at first birth, BMI, family history of breast cancer in a first-degree relative, breastfeeding, cigarette smoking, and self-report of benign breast disease	Never drinkers were the reference category	7 stars

Table 3. Cohort studies examining the effect of alcohol consumption on breast cancer risk, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Chen et al. continued	105,986 women followed from 1980-2008	Semi-quantitative food frequency questionnaire.	**Drinking status Days Alcohol Consumed in Typical Week** 0 1-2 3-4 5-7 P for trend **Largest No. of Alcoholic Drinks Consumed in 1 Day in Typical Month** 0 1-2 3-5 ≥6 P trend **Cumulative Alcohol Intake, g/d** 0 0.1-4.9 5.0-9.9 10.0-19.9 ≥20 RR per 10-g increase P for trend **Cumulative Alcohol Intake, g/d** 0 0.1-4.9 5.0-9.9 10.0-19.9 ≥20 RR per 10-g increase P for trend	 2382 1441 500 961 5284 1736 2559 905 131 5331 816 3028 748 322 42 976 2162 704 690 424 	 1 [Ref] 1.05 (0.99-1.13) 1.05 (0.95-1.16) 1.20 (1.11-1.30) <.001 1 [Ref] 1.08 (1.02-1.16) 1.16 (1.07-1.27) 1.33 (1.11-1.59) <.001 ***Breast Cancer 18-40 years*** 1 [Ref] 1.06 (0.97-1.14) 1.13 (1.02-1.26) 1.25 (1.09-1.43) 1.33 (0.97-1.82) 1.16 (1.08-1.25) <.001 ***Breast Cancer >40 years*** 1 [Ref] 1.03 (0.95-1.11) 1.09 (0.99-1.20) 1.20 (1.09-1.33) 1.23 (1.09-1.39) 1.08 (1.05-1.12) <.001	Adjusted for menopausal status, age at menarche, parity, age at first birth, BMI, family history of breast cancer in a first-degree relative, breastfeeding, cigarette smoking, and self-report of benign breast disease	Never drinkers were the reference category	7 stars

Table 3. Cohort studies examining the effect of alcohol consumption on breast cancer risk, published since 2009

Reference, location, year of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases	Pooled odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Rating for Quality
Hartz and He (2013) US Women's Health Initiative (WHI) study	Cohort of 147,202 post-menopausal US women (aged 50 – 79 years) Follow-up 8 years	A self-administered questionnaire	**Drinking Status** None <1/month <1/week >1/week Any alcohol / week		 1.00 1.04 (0.95- 1.14) 1.06 (0.98- 1.14) 1.13 (1.05-1.20) 1.06 (1.03 -1.09)	Age and Race	Reference category was a non-drinker	5 stars
Kawai et al., (2011) Japanese Miyagi Cohort study	Cohort of 19,227 women aged 40-64 years 241 breast cancer cases Follow-up 13 years	Food frequency questionnaire and drinking status	**Drinking Status** **Alcohol Drinking Frequency** Never Past Current **Occasional** 1-2 per week 3-4 per week 5-7 per week **Age upon starting to drink** Never Current <25 25-35 >35 **Amount per occasion** Never Current <11.5 g ≥11.5 - <23.0 g ≥23 g **Amount per day** Never Current <5.0 g ≥5.0 - <15.0 g ≥15.0 g	 171 4 66 19 12 6 171 23 19 13 171 40 17 8 171 40 15 7	 1.00 0.39 (0.14–1.08) 1.00 0.74–1.35) 1.23 (0.76–1.99) 1.18 (0.65–2.14) 0.66 (0.29–1.53) 1.00 0.92 (0.58–1.46) 1.05 (0.65–1.70) 0.96 (0.54–1.70) 1.00 1.14 (0.80–1.62) 0.98 (0.59–1.63) 0.95 (0.46–1.99) 1.00 1.03 0.72–1.47 1.21 0.71–2.07 0.90 0.41–1.98	Adjusted for age, body mass index, smoking, occupation, walking, educational level, age at menarche, parity number, family history of breast cancer, age at menopause and use of exogenous female hormones and/or OC	Never drinkers served as a reference group.	7 stars

Table 4. Cohort studies examining the effect of alcohol consumption on breast cancer mortality and secondary events, published since 2009

Reference, location, year of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases	Pooled odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Rating for Quality
Vrieling et al 2012 German cohort	Cohort of 2,522 post-menopausal breast cancer patients aged 50-74 years 235 breast cancer deaths Enrolled between 2002 and 2005, followed until end of 2009, mean follow-up = 5.5 years	Self-administered food frequency questionnaire	**Drinking Status** **Total alcohol intake (g/day)** <0.5 ≥0.5–<6.0 ≥6.0–<12.0 ≥12.0 **Total alcohol intake (g/day)** <0.5 ≥0.5–<6.0 ≥6.0–<12.0 ≥12.0 **Total alcohol intake (g/day)** <0.5 ≥0.5–<6.0 ≥6.0–<12.0 ≥12.0	*Total no. subjects/ no.of recurrences* 489/61 830/97 342/29 474/52 *Total no. subjects/no.death* 569/50 952/88 397/31 538/54 *Total no. subjects/ no. deaths* 507/31 858/59 351/13 488/28	**Breast cancer recurrence among stage I-IIIa patients** 1.00 (Ref) 1.03 (0.74 -1.44) 0.86 (0.54 -1.36) 1.08 (0.73 -1.58) **Overall Breast cancer mortality** 1.00 (Ref) 1.51 (1.04 -2.21) 0.92 (0.56 -1.53) 1.74 (1.13 -2.67) **Breast cancer mortality among stage I-IIIa patients** 1.0 (ref) 1.29 (0.82 -2.04) 0.73 (0.37 -1.44) 1.31 (0.76 -2.26)	Adjusted for age at diagnosis and study centre, and adjusted for tumour size, nodal status, metastases, tumour grade, ERPR status, radiotherapy, HRT use at diagnosis, mode of detection;	The lowest alcohol intake category was the reference category	9 stars

Table 4. Cohort studies examining the effect of alcohol consumption on breast cancer mortality and secondary events, published since 2009

Reference, location, year of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases	Pooled odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Rating for Quality
Holm et al 2013 Danish "Diet, Cancer and Health" cohort	Prospective Danish cohort of 29,875 women 1,052 women diagnosed with breast cancer Aged 50-64 years Enrolled between 1994-1997. Followed until 2008	Lifestyle questionnaire		N, With outcome (all)	**Recurrence of breast cancer**	Adjusted for clinical prognostic factors such as tumour size, lymph node status, receptor status and grade and other confounders such as BMI, smoking, menopausal status, hormone replacement therapy (HRT) use, education level, physical activity and total folate intake.	≤ 1 unit/day was the reference category	7 stars
			Baseline intake					
			Linear estimate3,*	110 (1028)	1.06 (0.94–1.19)			
			≤1 unit/day**	38 (451)	1.00 (ref)			
			<1unit - ≤2/day	32 (292)	1.31 (0.81–2.11)			
			>2 units/day	37 (285)	1.65 (1.02-2.67)			
			Lifetime intake					
			Twenties	110(729)	0.98 (0.67–1.44)			
			Thirties	110(859)	1.09 (0.90–1.32)			
			Forties	110(922)	1.08 (0.92–1.27)			
			Fifties to current	110(942)	1.07 (0.91–1.26)			
			Drinking years (dy)					
			Linear estimate	110(976)	1.05 (1.00–1.11)			
			0–10 dy	15 (164)	1.00 (ref)			
			>10–40 dy	53(556)	1.34 (0.74–2.42)			
			>40 dy	26 (256)	2.02 (1.06–3.85)			
					Breast cancer Mortality			
			Baseline intake					
			Linear estimate	106(1028	1.06 (0.94–1.19)			
			≤1 unit/day	42 (451)	1.00 (ref)			
			<1unit≤2/day	31(292)	1.06 (0.66–1.72)			
			>2 units/day	29(285)	1.10 (0.67–1.82)			
			Lifetime intake					
			Twenties	106(729)	0.80 (0.51–1.25)			
			Thirties	106(859)	1.02 (0.81–1.28)			
			Forties	106(922)	1.15 (0.99–1.34)			
			Fifties to current	106(942)	1.03 (0.87–1.23)			
			Drinking years (dy)					
			Linear estimate	106(976)	1.03 (0.97–1.10)			
			0–10 dy	19 (164)	1.00 (ref)			
			>10–40 dy	45 (556)	0.93 (0.53–1.63)			
			>40 dy	34 (256)	1.27 (0.69–2.33)			

Table 4. Cohort studies examining the effect of alcohol consumption on breast cancer mortality and secondary events, published since 2009

Reference, location, year of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases	Pooled odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Rating for Quality
Harris et al. (2012) Swedish Mammography Cohort	Cohort of 3146 breast cancer patients 385 breast cancer deaths Follow-up 21 years	Food frequency questionnaire	**Alcohol intake** (g per day) non-drinker <3.4 g/day 3.4 – 9.9 g/day ≥ 10g/day P trend non-drinker <3.4 g/day 3.4 – 9.9 g/day ≥ 10g/day P trend	Breast cancer deaths 139 149 85 18 139 149 85 18	Age adjusted model 1.00 0.85 (0.68-1.08) 0.79 (0.60-1.05) 0.85 (0.51-1.39) 0.26 Covariate-adjusted model 1.00 0.93 (0.73 -1.18) 0.94 (0.70 -1.25) 1.09 (0.66 -1.81) 0.87	Adjusted for age, energy intake, education level, marital status, menopausal status at diagnosis, BMI, calendar year of diagnosis, disease stage, grade, radiation treatment, and chemotherapy and/or hormonal treatment.	Non-drinkers were the reference category	7 stars

Table 4. Cohort studies examining the effect of alcohol consumption on breast cancer mortality and secondary events, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Newcomb et al 2013 US multi-site population-based cohort	22,890 women with incident invasive breast cancer 3,484 breast cancer deaths Follow-up 11.3 years	Information on alcohol consumption was obtained by interview	**Drinking Status** **Pre-diagnostic Alcohol Consumption** **Total** 0 1-2 3-6 7-9 ≥ 10 **Wine** 0 1-2 3-6 ≥ 7 **Beer** 0 1-2 3-6 ≥ 7 **Spirits** 0 1-2 3-6 ≥ 7	**Total** 726 1,769 487 228 274 1,474 1,692 176 142 2,076 1,092 163 153 1,358 1,740 207 179	1.0 (Ref) 0.93 (0.85 -1.02) 0.85 (0.75- 0.95) 0.88 (0.75- 1.02) 0.89 (0.77 -1.04) 1.0 (Ref) 0.98(0.91 - 1.06) 0.85(0.72 - 1.01) 1.11(0.93 - 1.34) 1.0 (Ref) 0.94 (0.87 -1.02) 0.90 (0.76 -1.06) 0.96 (0.81 -1.14) 1.0 (Ref) 0.92(0.85 -1.00) 0.91(0.78 -1.06) 0.86(0.73 -1.02)	Adjusted for age at diagnosis, stage of disease at diagnosis, state of residence at diagnosis, study phase, family history of breast cancer, age at first birth, menopausal status, HT use, BMI, smoking status, education, and mammography.	Non-drinkers were the reference category	9 stars

Table 4. Cohort studies examining the effect of alcohol consumption on breast cancer mortality and secondary events, published since 2009

Reference, location, year of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases	Pooled odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Rating for Quality
Newcomb et al 2013 continued US multi-site population-based cohort	22,890 women with incident invasive breast cancer 3,484 breast cancer deaths Follow-up 11.3 years	Information on alcohol consumption was obtained by interview	**Post-diagnostic Alcohol Consumption** **Total** 0 1-2 3-6 7-9 ≥ 10 **Wine** 0 1-2 3-6 ≥ 7 **Beer** 0 1-2 3-6 ≥ 7 **Spirits** 0 1-2 3-6 ≥ 7 **Change in Alcohol intake Before and After Diagnosis** Never drinker < 1 drink/wk change ≥ 1 drink/wk decrease ≥ 1 drink/wk increase HR per 1 drink/wk change	 **Total** 69 122 39 21 25 **Wine** 100 128 27 21 **Beer** 157 102 10 7 **Spirits** 146 94 20 16 31 110 82 53	 1.00 (ref) 0.88 (0.61 -1.27) 0.80 (0.49 -1.32) 1.01 (0.55 -1.87) 0.83 (0.45 -1.54) 1.00 (Ref) 1.00 (0.70 -1.42) 1.00 (0.58 -1.72) 1.45 (0.77 -2.73) 1.00 (Ref) 1.26 (0.88 -1.79) 1.04 (0.49 -2.22) 0.94 0.37 -2.39) 1.00 (ref) 0.74 (0.53 -1.03) 0.78 (0.45 -1.36) 0.83 (0.43 -1.62) 1.00 (Ref) 0.96 (0.63 -1.46) 1.33 (0.87 -2.05) 1.13 (0.70 -1.80) 0.99 (0.97 -1.01)	Adjusted for age at diagnosis, stage of disease at diagnosis, state of residence at diagnosis, study phase, family history of breast cancer, age at first birth, menopausal status, HT use, BMI, smoking status, education, and mammography.	Non-drinkers were the reference category	9 stars

Table 4. Cohort studies examining the effect of alcohol consumption on breast cancer mortality and secondary events, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Breslow et al., 2011 US National Health Interview Survey (NHIS) cohort	Cohort consisted of 323,354 participants (2,716,472 person-year follow-up). 8,362 deaths from all cancers 677 female breast cancer deaths.	Lifetime drinking was obtained through interview	**Drinking status** Never drinker Former drinker Lifetime infrequent drinker **Current drinker** Light Moderate Heavier P-trend **Quantity of drinks consumed, on average, on drinking days** Q = 1 Q = 2 Q ≥ 3 P-trend **Frequency (average no of drinking days per week** F < 1 F= 1–2 F ≥ 3 P-trend	 228 98 146 128 46 31 103 65 37 80 61 64	 1.0 (ref) 1.26 (0.93 - 1.70) 0.90 (0.70 -1.17) 0.75 (0.57 - 0.98) 1.02 (0.66 - 1.57) 1.09 (0.68 - 1.76) 0.43 1.00 0.84 (0.57-1.23) 0.72 (0.45, 1.16) 0.13 1.00 1.00 (0.67 - 1.50) 1.44 (0.96 - 2.17) 0.06	Adjusted for sex, race/ethnicity, education, region, marital status, smoking status, and BMI	The referent group was never drinkers	8 stars

Table 4. Cohort studies examining the effect of alcohol consumption on breast cancer mortality and secondary events, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Kwan et al 2010 US Life After Cancer Epidemiology (LACE) cohort .	Cohort of 1,897 early-stage breast cancer survivors Follow-up 293 breast cancer recurrences 154 breast cancer deaths Follow-up 7.4 years	Self-administered Food frequency questionnaire	**Drinking status** **All women** **Total alcohol, g/d** None **< 6** **≥ 6** **Pre-menopausal women, g/d** None **< 6** **≥ 6** **Post-menopausal women, g/d** None **< 6** **≥ 6** **All Women** **Wine servings/ wk** None ≤ 1 ≥ 2 **All Women** **Total alcohol, g/d** None **< 6** **≥ 6** **Pre-menopausal women, g/d** None **< 6** **≥ 6** **Post-menopausal Women, g/d** None **< 6** **≥ 6** **Wine servings / week** **None** **≤ 1** **≥ 2**	**No. of events /No. of subjects/** 126/939 68/480 74/478 51/404 175/1230 142/1030 64/473 61/390 69/939 36/480 39/478 22/404 101/1230 78/1030 35/473 30/390	**Breast Cancer recurrence** 1.00 (Ref) 1.05 (0.78-1.42) 1.35 (1.00- 1.83) 1.00 (Ref) 1.01 (0.52 -1.96) 1.25 (0.61 -2.54) 1.00 (Ref) 1.12 (0.76 -1.64) 1.51 (1.05 -2.19) 1.00 (ref) 1.01 (0.75-1.36) 1.33 (0.97-1.81) **Breast Cancer Mortality** 1.00 (Ref) 1.13 (0.74 -1.70) 1.51 (1.00 -2.29) 1.00 (Ref) 1.27 (0.47- 3.38 0.77 (0.20 -2.90) 1.00 (Ref) 1.25 (0.76- 2.07) 1.72 (1.05 -2.81) 1.00 (ref) 1.12 (0.75-1.68) 1.37 (0.88 -2.14)	Adjusted for age at diagnosis, race, BMI at 1 year pre-diagnosis, menopausal status, smoking status, total folate intake, stage of disease, hormone receptor status, definitive surgery, tamoxifen use, adjuvant treatment, and positive lymph nodes	Non-drinkers were the referent category.	7 stars

Table 4. Cohort studies examining the effect of alcohol consumption on breast cancer mortality and secondary events, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**

Kwan et al 2013
 	
US After Breast Cancer Pooling Project (ABCPP)
	Cohort of 9,329 breast cancer survivors
	
	1646 breast cancer recurrences
	
	1543 deaths
	
	Follow-up 10.3 years
		Self-administered food frequency questionnaire	**Drinking Status**
			
			All women
			Total Alcohol intake
			<0.36 g/day
			0.36-<6 g/day
			6-<12 g/day
			12-<24 g/day
			≥24 g/day
			P trend
			
			Pre-menopausal women
			Total Alcohol intake
			<0.36 g/day
			0.36-<6 g/day
			6-<12 g/day
			P trend
			
			Post-menopausal women
			Total Alcohol intake
			<0.36 g/day
			0.36-<6 g/day
			6-<12 g/day
			P trend
			
			All women
			Total Alcohol intake
			<0.36 g/day
			0.36-<6 g/day
			6-<12 g/day
			12-<24 g/day
			≥24 g/day
			P trend
				
				624/3829
				454/2816
				160/1002
				156/928
				93/576
				
				188/838
				133/749
				126/622
				
				389/2765
				287/1928
				262/1763
				
				402/3900
				276/2875
				102/1009
				85/942
				46/580
					Breast cancer recurrence
					
					1.00 (Ref)
					0.99 (0.87-1.12)
					1.03 (0.86-1.24)
					1.12 (0.93-1.34)
					1.04 (0.841.31)
					0.32
					
					1.00 (Ref)
					0.75 (0.59-0.94)
					0.91 (0.72-1.16)
					0.30
					
					1.00 (Ref)
					1.10 (0.94-1.29)
					1.19 (1.01-1.40)
					0.04
					
					Breast cancer mortality
					
					1.00 (Ref)
					0.94 (0.80 -1.10)
					1.06 (0.85 -1.33)
					0.93 (0.73 -1.18)
					0.80 (0.59 -1.09)
					0.29
						Adjusted for age at diagnosis, stage of disease, race/ ethnicity, education, menopausal status around diagnosis, hormone receptor status, surgery, treatment (radiation therapy, chemotherapy, HT), smoking, physical activity, pre-diagnosis BMI, and comorbidity.	The following terminology was used in the studies to classify the drinking status of the women
							Non-drinker (reference category) = <0.36 g/day;
							occasional drinker = 0.36-<6 g/day;
							regular low drinker = 6-<12 g/day;
							regular medium drinker = 12-<24 g/day;
							regular high drinker = ≥24 g/day
								7 stars

Table 4. Cohort studies examining the effect of alcohol consumption on breast cancer mortality and secondary events, published since 2009

Reference, location, year of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases	Pooled odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Rating for Quality
Flatt et al. (2010) US Women Healthy Eating and Living (WHEL) study	Cohort of 3088 breast cancer survivors 518 breast cancer recurrences 315 deaths (83% were breast cancer related) Follow-up 7.3 yrs	Food frequency questionnaire and 24-hour recalls	**Drinking Status** **Alcohol Intake** Minimal intake (< 10 g/month) Light intake (10 -290 g/ month) Moderate/heavy intake (> 300 g/mo) Minimal intake (< 10 g/month) Light intake (10 -290 g/month) Moderate/heavy intake (> 300 g/month)	 213 205 100 139 124 52	**Additional Breast Cancer Events** 1.00 0.89 (0.73, 1.08) 0.91 (0.71, 1.18) **Mortality** 1.00 0.81 (0.63-1.04) 0.69 (0.49, 0.97)	Adjusted for a number of confounders including stage, grade, time from diagnosis to study entry, ethnicity, education, physical activity, parity, BMI and smoking status.	Women who consumed no alcohol or less than 10 g per month were classified as “Non- or Minimal drinkers.	7 stars

Table 5. Case-Control studies examining the effect of alcohol consumption on breast cancer risk, published since 2009								
Reference location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Relative Risk confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
Pieta et al 2012 Polish case-control study of 1,484 women, aged 18-80 years	138 breast cancer cases	1,144 controls	Self-administer questionnaire	Drinking status 0g 20-25g/month	 1.00 1.20	Not stated in paper	No data tabulated in the paper, only text	4 stars
Gledo et al. (2012) Case-control study of 200 women in Bosnia and Herzegovina	100 cases	100 controls	Questionnaire (no specific details on type)	**Drinking status** Non-drinker Drinker	 1.00 (ref) 1.73 (0.40-7.50)	Not stated in paper		3 stars
Wu et al 2012 Population-based case-control study of 4,231 Asian American women	2,229 cases	2,002 matched controls	Quantitative food frequency questionnaire and lifetime history assessment.	**Drinking status** Non drinker Drinker By 5 g/day Non drinker Drinker By 5 g/day Non drinker Drinker By 5 g/day Non drinker Drinker By 5 g/day Non drinker Drinker By 5 g/day	**Japanese** 1.00 (ref) 1.17 (0.99 -1.39) 1.21 (1.02-1.43) **Chinese** 1.00 (ref) 0.83 (0.70 to 0.99) 0.95 (0.79-1.14) **Filipino** 1.00 (ref) 0.84 (0.68 to 1.03) 0.85 (0.68-1.07) **US Born** 1.0 (ref) 1.16 (0.97 to 1.39) 1.21 (1.00-1.45) **Non-US Born** 1.00 (ref) 0.82 (0.73 to 0.93) 0.91 (0.80-1.04)	Adjusted for birthplace and years of residence in the United States among non-US born, education, interviewer, age at menarche, parity, current BMI, years of regular recreational physical activity, total calories, intake of soy, green tea and black tea, menopausal status, age at menopause, and family history of breast cancer.	Non-drinkers were the reference category	7 stars

Table 5. Case-Control studies examining the effect of alcohol consumption on breast cancer risk, published since 2009								
Reference location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Relative Risk confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
Chandran et al 2013 US African-American (AA) women participating in the Women Circle of Health Study (WCHS) case-control study	803 cases	889 controls	Food frequency questionnaire	**Drinking Status** **Total ethanol from recent alcohol intake** Non-Drinker Drinker <14 g/wk 14-<28 g/wk ≥28g/wk **BEER** Non Beer -drinker Beer Drinker <14 g/wk 14-<28 g/wk ≥28g/wk **WINE** Non-wine drinker Wine Drinker <14 g/wk 14-<28 g/wk ≥28g/wk **SPIRIT** Non- Spirit drinker Spirit Drinker <14 g/wk 14-<28 g/wk ≥28g/wk **Lifetime alcohol intake** Never Ever Non drinker ≤3510 drinkers ≥3510 drinks	 1.00 (Ref) 0.95 (0.77-1.17) 1.00 (Ref) 0.98 0.63–1.53 0.95 0.65–1.39 1.00 (Ref) 0.81 0.62–1.06 1.00 (Ref) 1.67 0.79–3.57 0.79 0.41–1.49 1.00 (Ref) 0.94 0.75–1.19 1.00 (Ref) 0.85 0.53–1.38 1.10 0.67–1.80 1.00 (Ref) 1.06 0.83–1.36 1.00 (Ref) 1.50 0.73–3.08 1.53 0.84–2.79 1.00 (Ref) 0.96 (0.78-1.19) 1.00 (Ref) 1.11 (0.85-1.45) 0.77 (0.58-1.03)	Adjusted for adjusted for age, ethnicity, country of origin, education, age at menarche, age at menopause, menopausal status, parity, age at first birth, breastfeeding, family history of breast cancer, history of benign breast disease, HRT use, OC use, BMI, total energy intake and physical activity	Non-drinkers or those consuming <14g/wk were the reference category	6 stars

Table 5. Case-Control studies examining the effect of alcohol consumption on breast cancer risk, published since 2009								
Reference location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Relative Risk confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
Chandran et al 2013 continued	803 cases	889 controls	Food frequency questionnaire	**Drinking status** **Drinking during < 20 years** No Yes **Drinking during 20-29 years** No Yes **Drinking during 30-39 years** No Yes **Drinking during 40-49 years** No Yes **Drinking during 50-59 years** No Yes **Drinking during ≥ 60 years** No Yes	 1.00 (Ref) 0.65 (0.47-0.89) 1.00 (Ref) 0.94 (0.75-1.19) 1.00 (Ref) 0.91 (0.72-1.15) 1.00 (Ref) 0.99 (0.76-1.30) 1.00 (Ref) 1.00 (0.69-1.45) 1.00 (Ref) 0.42 (0.17-1.01)	Adjusted for adjusted for age, ethnicity, country of origin, education, age at menarche, age at menopause, menopausal status, parity, age at first birth, breastfeeding, family history of breast cancer, history of benign breast disease, HRT use, OC use, BMI, total energy intake and physical activity	Non-drinkers or those consuming <14g/wk were the reference category	6 stars

Table 5. Case-Control studies examining the effect of alcohol consumption on breast cancer risk, published since 2009								
Reference location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Relative Risk confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
Chandran et al 2013 continued	803 cases	889 controls	Food frequency questionnaire	**Drinking status** **Pre-menopausal** **Recent alcohol intake** Non-drinker Drinker <14 g/wk 14–<28g/wk ≥28 g/wk P for linear trend **Lifetime alcohol intake** Never Ever Non drinker ≤3510 drinkers ≥3510 drinks **Drinking at <20 yrs** No Yes **Post-menopausal women** **Recent alcohol intake** Non-drinker Drinker <14 g/wk 14–<28g/wk ≥28 g/wk P for linear trend **Lifetime alcohol intake** Never Ever Non drinker ≤3510 drinkers ≥3510 drinks **Drinking at <20 yrs** No Yes	 1.00 (Ref) 1.21(0.90–1.62) 1.00 (Ref) 0.81 (0.45–1.48) 1.18 (0.71–1.95) 0.23 1.00 (Ref) 0.90 (0.66–1.24) 1.00 (Ref) 1.00 (0.69–1.46) 0.74 (0.47–1.17) 1.00 (Ref) 0.60 (0.38–0.94) 1.00 (Ref) 0.78 (0.57–1.07) 1.00 (Ref) 1.14 (0.55–2.36) 0.73 (0.39–1.35) 0.69 1.00 (Ref) 1.07 (0.79–1.46) 1.00 (Ref) 1.33 (0.89–2.00) 0.82 (0.55–1.22) 1.00 (Ref) 0.74 (0.46–1.20)	Adjusted for adjusted for age, ethnicity, country of origin, education, age at menarche, age at menopause, menopausal status, parity, age at first birth, breastfeeding, family history of breast cancer, history of benign breast disease, HRT use, OC use, BMI, total energy intake and physical activity	Non-drinkers or those consuming <14g/wk were the reference category Pre-menopausal women (n=871) Post-menopausal women (n=821)	6 stars

Table 5. Case-Control studies examining the effect of alcohol consumption on breast cancer risk, published since 2009								
Reference location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Relative Risk confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
Llanos et al 2012 African American case-control study	97 cases	102 controls	Assessment measure not specified	**Drinking status Total alcohol consumed/wk** **Low waist circumference, <98.5 cm (n = 51)** <1 drink 1–6 drink/wk ≥7 drink/wk **High waist circumference, ≥98.5 cm (n = 46)** <1 drink 1–6 drink/wk ≥7 drinks/wk **Low Waist Hip Ratio (WHR), <0.85 (n = 46)** <1 drink 1–6 drink/wk ≥7 drinks/wk **High WHR, ≥0.85 (n = 51)** <1 drink 1–6 drink/wk ≥7 drinks/wk **Low BMI, <30.0 kg/m2 (n = 44)** <1 drink 1–6 drink/wk ≥7 drinks/wk **High BMI, ≥30.0 kg/m2 (n = 53)** <1 drink 1–6 drink/wk ≥7 drinks/wk	 1.00 (ref) 0.44 (0.15-1.26) 0.47 (0.07-3.28) 1.00 (ref) 0.84 (0.27-2.59) 4.22 (0.39-46.15) 1.00 (ref) 0.23 (0.07, 0.79) 1.07 (0.13, 8.46) 1.00 (ref) 1.46 (0.49, 4.35) 1.62 (0.23, 11.26) 1.00 (ref) 0.53 (0.18, 1.54) 0.36 (0.06, 2.25) 1.00 (ref) 0.70 (0.23, 2.14) –	Adjusted for age, education, age at menarche, and parity	Consumption of <1 drink/week was the reference category	5 stars

Table 5. Case-Control studies examining the effect of alcohol consumption on breast cancer risk, published since 2009								
Reference location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Relative Risk confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
Ronco et al 2011 Case-control study of 1,098 participants Uruguay	460 cases	638 controls	Information on alcohol intake such as age when drinking commenced, age when quit drinking, number of glasses per day or week and type of alcoholic beverage consumed were obtained by interview	**Drinking status** **Beer** Abstainers Drinkers **Wine** Abstainers Drinkers **Hard liquor** Abstainers Drinkers **Total alcohol (mls)** Never 1-27 28+ P-value for trend **Years of drinking** None 1-32 33+ P-value for trend **Cumulative** None 1-87 88+ P-value for trend	 1.0 (ref) 1.62 (0.76-3.46) 1.0 (ref) 1.43 (1.02-2.00) 1.00 (Ref) 1.92 (0.80-4.63) 1.0 (ref) 1.55 (0.96-2.51) 1.67 (1.14-2.46) 0.005 1.0 (ref) 1.46 (0.95-2.23) 1.83 (1.18-2.82) 0.004 1.0 (ref) 1.58 (1.03-2.42) 1.68 (1.09-2.57) 0.006	Adjusted for age, residence, urban/rural status, education, family history of breast cancer among first-degree relatives, BMI, menopausal status, age at menarche, parity, mate drinking, and total energy intake	Never drinkers were the reference category	7 stars

Table 5. Case-Control studies examining the effect of alcohol consumption on breast cancer risk, published since 2009								
Reference location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Relative Risk confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
Beasley et al. 2010 Population based Mexico	1000 incident breast cancer cases	1074 controls	Food frequency questionnaire obtained using a food frequency questionnaire (FFQ) and in-person interview	**Recent Alcohol Intake** **Current Drinker** No Yes **Alcohol Use** Non-drinker >0–2 g/day ≥2 g/day **Lifetime Alcohol Use** **Ever drank alcohol** No Yes **Ever drink >1 drink per month for ≥ 1 year** No Yes **Age (yr) at first alcohol use** Non-drinker >=26 21–25 18–20 <18 **Age (yr) at first alcohol use, among drinkers** >=26 21–25 18–20 <18	 1.0 0.98 (0.76–1.27) 1.00 1.19 (0.90–1.58) 1.20 (0.85–1.70) 1.00 1.25(0.99–1.58) 1.00 1.74 (1.27–2.39) 1.00 1.22 (0.88–1.70) 1.24 (0.86–1.77) 1.41 (1.02–1.96) 0.92 (0.61–1.39) 1.00 0.87 (0.56–1.35) 1.04 (0.69–1.58) 0.71 (0.44–1.15)	Matched by age category, health care system, and region and adjusted for in previous BMI, family history of breast cancer, age at first pregnancy, number of births, lactation, total energy, physical activity, education, age at menarche, menopausal status, oral contraceptive use, smoking, fibrocystic disease, and past hormone therapy use.	Never drinkers were the reference category	6 stars

Table 5. Case-Control studies examining the effect of alcohol consumption on breast cancer risk, published since 2009								
Reference location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Relative Risk confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
Sanchez-Zamorano et al 2011 Population-based case-control study of Mexican women,	1,000 breast cancer cases	1074 controls	Self-administered Food Frequency questionnaire	**Drinking Status** Alcohol Consumption/day **Pre-menopausal** Never < 1 g/day ≥ 1 g/day Trend test **Post-menopausal** Never < 1 g/day ≥ 1 g/day Trend test	 0.79 (0.40 -1.00) 1.06 (0.69–1.64) 1.00 0.023 0.56 (0.35–0.91) 0.81 (0.51–1.28) 1.00 0.010	Adjusted for age category, health care system, socio-economic status, breast feeding, age at menarche, age at menopause, BMI, family history of breast cancer in first-degree relatives, personal history of diabetes, waist-to-hip ratio (WHR), height, daily intake of folate and total calories.	Women drinking ≥ 1 g/day were the reference category group	6 stars
Islam et al 2013 Case-control study of pre- and post-menopausal Japanese women	1754 breast cancer cases	3508 controls	Self-reported questionnaire	Drinking status *All women* *Alcohol (g/day)* Non drinkers 1-≤5 g/d 5-≤23g/d ≥23g/d P trend *Pre-menopausal* *ALcohol (g/day)* Non drinkers 1-≤5 g/d 5-≤23g/d ≥23g/d P trend *Post-menopausal women* *Alcohol (g/day)* Non drinkers 1-≤5 g/d 5-≤23g/d ≥23g/d P trend	 1.00 (ref) 1.10 (0.94–1.29) 1.23 (1.02–1.48) 1.39 (1.07–1.80 0.002 1.00 (ref) 0.98 (0.79–1.23) 1.07 (0.82–1.39) 1.19 (0.83–1.39) 0.38 1.00 (ref) 1.24 (0.97–1.57) 1.40 (1.05–1.85) 1.69 (1.14–2.51) 0.001	Adjusted for age, smoking habit, BMI, drinking habit, daily physical activity of any intensity, family history of breast cancer, total energy intake, age at menarche, parity, and referral pattern to our hospital	Non-drinkers were the reference category	6 stars

Table 5. Case-Control studies examining the effect of alcohol consumption on breast cancer risk, published since 2009								
Reference location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Relative Risk confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
Zhang and Holman 2012 Hospital-based case-control study of 2,018 women from the Zhejiang province of China.	1009 cases	1009 controls	Self-administer Food Frequency questionnaire	**Alcohol consumption** ***All women*** Abstainers Ex-drinkers Current drinkers ***Pre-menopausal women*** Abstainers Ex-drinkers Current drinkers ***Post-menopausal women*** Abstainers Ex-drinkers Current drinkers **Type of alcohol consumed** **All women** Abstainers Beer only Wine only Liquor only **Pre-menopausal women** Abstainers Beer only Wine only Liquor only **Post-menopausal women** Abstainers Beer only Wine only Liquor only	 1.00 (Ref) 1.34 (0.56-3.22) 0.63 (0.52–0.76) 1.00 (Ref) 2.44 (0.71–8.39) 0.66 (0.53–0.84) 1.00 (Ref) 0.68 (0.17–2.67) 0.55 (0.38–0.78) 1.00 (ref) 0.65 (0.47–0.90) 0.40 (0.26–0.60) 0.81 (0.47–1.39) 1.00 (ref) 0.73 (0.51-1.06) 0.30 (0.17–0.52) 0.73 (0.37–1.47) 1.00 (ref) 0.34 (0.15–0.75) 0.61 (0.32–1.16) 0.88 (0.36–2.16)	Adjusted for age, education, BMI, OC use, HRT, breast cancer in first-degree relatives, total energy intake, folate intake, tea drinking and menopausal status	Never drinkers/ abstainers were the reference category.	6 stars

Table 5. Case-Control studies examining the effect of alcohol consumption on breast cancer risk, published since 2009								
Reference location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Relative Risk confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
Zhang and Holman 2012 **Continued** Hospital-based case-control study of 2,018 women from the Zhejiang province of China.	1009 cases	1009 controls	Self-administer Food Frequency questionnaire	***Drinking status*** ***Ethanol intake (g per day)*** **All women** None >0–<5 5–<10 10–<20 20–<30 ≥30 **Pre-menopausal women** None >0–<5 5–<10 10–<20 20–<30 ≥30 **Post-menopausal women** None >0–<5 5–<10 10–<20 20–<30 ≥30	 1.00 (ref) 0.56 (0.45–0.69) 0.58 (0.35–0.98) 0.89 (0.39–2.03) 0.86 (0.54–1.37) 2.33 (1.26–4.31) 1.00 (ref) 0.62 (0.48–0.79) 0.62 (0.33–1.17) 0.85 (0.31–2.34) 0.86 (0.49–1.50) 2.28 (1.00–5.20) 1.00 (ref) 0.41 (0.27–0.62) 0.49 (0.19–1.24) 0.97 (0.23–4.06) 0.97 (0.42–2.26) 2.29 (0.89–5.87)	Adjusted for age, education, BMI, OC use, HRT, breast cancer in first-degree relatives, total energy intake, folate intake, tea drinking and menopausal status	Never drinkers/ abstainers were the reference category.	6 stars
Gao et al 2013 **Chinese case-control study**	669 cases	682 controls	In-person interview	**Drinking Status** Never Current + ever	 1.00 (Ref) 1.86 (1.02-3.39)	Adjusted for age, menopausal status, education levels, occupation, BMI and mean family income	Never drinkers were the reference category	6 stars
Wang et al 2012 Hospital-based case-control study of 471 women in Taiwan	157 cases	314 controls	Structured questionnaire on personal habits including alcohol intake.	**Drinking Status** Non-drinker Drinker	 1.00 1.50 (0.74-3.03)	Adjusted for education level, age at menarche and past hormonal therapy	Non-drinker was the reference category	4 stars

Table 6. Case-Control studies examining the effect of alcohol consumption on Breast cancer morality and secondary events, published since 2009									
Reference location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Relative Risk confidence intervals (95% CI)**	**Relative Risk confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Quality**
Weaver et al 2013 Cases only study taken from a population-based case-control study US Western New York Exposures and Breast Cancer (WEB)	1097 Cases with breast cancer		Cognitive lifetime drinking history (CLDH) survey, administered by trained interviewer and details were collected on type, intensity, and volume of alcohol consumed	**Drinking Status** **Total lifetime alcohol intake** None Low High **Total alcohol intake, menarche to age at first birth (time of interview for nulliparous women)** None Low High **Total alcohol intake, 10–20 years prior to diagnosis** None Low High **Total alcohol intake, 2–10 years prior to diagnosis** None Low High	Pre-menopausal women 1.00 (Ref) 0.71 (0.25, 2.06) 0.65 (0.22, 1.92) 1.00 (Ref) 0.67 (0.23, 1.92) 0.70 (0.24, 2.10) 1.00 Ref 0.68 (0.23, 1.99) 0.68 (0.23, 2.02) 1.00 (Ref) 0.57(0.19, 1.67) 0.87 (0.29, 2.62)	Post-menopausal women 1.00 (Ref) 0.65 (0.32, 1.34) 0.88 (0.42, 1.84) 1.00 (Ref) 0.92 (0.47, 1.82) 0.50 (0.22, 1.12) 1.00 (Ref) 0.65 (0.32, 1.32) 0.89 (0.42, 1.87) 1.00 (Ref) 0.77 (0.39, 1.56) 0.69 (0.32, 1.48)	Adjusted for smoking status, tumour stage, age, education level, calories, BMI, and race	Abstainer or non-drinker was the reference category. Abstainers were defined as those who did not have 12 or more drinks during any one year of their lives. Low and high alcohol intake defined by menopause-specific cutpoints: for lifetime 1,242.9 and 1,197.6 oz., for menarche to first birth 510.4 and 110.7 oz., for 10–20 years prior to diagnosis 372.8 and 196.3 oz., for 2–10 years prior to diagnosis 183.0 and 118.8 oz. for premenopausal and postmenopausal women, respectively	5 stars

Table 6. Case-Control studies examining the effect of alcohol consumption on Breast cancer morality and secondary events, published since 2009									
Reference location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Relative Risk confidence intervals (95% CI)**	**Relative Risk confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Quality**
Weaver et al 2013 Cont Cases only study taken from a population-based case-control study US Western New York Exposures and Breast Cancer (WEB)	1097 Cases with breast cancer		Cognitive lifetime drinking history (CLDH) survey, administered by trained interviewer and details were collected on type, intensity, and volume of alcohol consumed	**<u>Drinking Status</u>** **Drinks per drinking day, lifetime** 0 1 or less 2–3 4 or more *p* for trend **Drinks per drinking day, menarche to age at first birth**[a] 0 1 or less 2–3 4 or more *p* for trend **Drinks per drinking day, 10–20 years prior to diagnosis** 0 1 or less 2–3 4 or more *p* for trend **2–10 years prior to diagnosis** 0 1 or less 2–3 4 or more *p* for trend	 1.00 (Ref) 0.98 (0.33, 2.87) 0.32 (0.10, 1.02) 0.27 (0.06, 1.17) 0.06 1.00 (Ref) 1.67 (0.60, 4.97) 1.00 (0.39, 2.54) 0.79 (0.25, 2.54) 0.65 1.00 (Ref) 1.47 (0.54, 4.01) 0.71 (0.25, 1.97) 0.44 (0.12, 1.65) 0.25 1.00 (Ref) 0.91 (0.33, 2.48) 0.69 (0.26, 1.89) 1.86 (0.51, 6.79) 0.21	 1.00 (Ref) 0.73 (0.35, 1.52) 0.70 (0.31, 1.60) 2.68 (0.94, 7.67) 0.02 1.00 (Ref) 0.27 (0.09, 0.77) 0.58 (0.30, 1.12) 0.65 (0.22, 1.95) 0.06 1.00 (Ref) 0.79 (0.36, 1.73) 1.51 (0.76, 3.00) 2.45 (0.80, 7.57) 0.22 1.00 (Ref) 1.03 (0.51, 2.07) 1.37 (0.67, 2.80) 1.86 (0.51, 6.79) 0.71	Adjusted for smoking status, tumour stage, age, education level, calories, BMI, and race	Abstainer or non-drinker was the reference category. Abstainers were defined as those who did not have 12 or more drinks during any one year of their lives. [a] time of interview for nulliparous women	5 stars

Table 7. Nested Case-Control studies examining the effect of alcohol consumption on breast cancer risk								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Relative Risk confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
Bissonauth et al 2009	280 breast cancer cases with non-gene carriers of mutated BRCA gene	280 controls with non-gene carriers of mutated BRCA	Self-administered Food Frequency questionnaire	Drinking Status ≤1.9 g/day >1.9-<9.0 > 9.0 g/day	 1.0 (Ref) 1.30 (0.86 – 2.08) 1.55 (1.02-2.37)	Adjusted for age, education, physical activity, smoking, coffee consumption and total energy	Consumption of ≤1.9 g ethanol per day was the reference category	7 stars

Table 8. Cohort studies of consumption of alcohol consumption and breast cancer risk by histology subtype								
Reference, study location, period	**Cohort description**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)**	**Relative risk (95% CI)**	**Adjustment factors**	**Comments**	**Star rating for quality**
Li et al 2010 US Women's Health Initiative Observational prospective cohort	Cohort of 87,724 post-menopausal women Enrolled between Oct 1993 and Dec 1998, followed until Sept 2005 2944 breast cancer cases	Self-administer questionnaire	**Drinking status**	Ductal **(n = 1805)**	Lobular **(n = 720)**	Adjusted for age, race, and/or ethnicity, education, BMI, use of menopausal HT, smoking status, Gail model scores of 5-year breast cancer risk and number of screening mammograms received in the past five years.	Never drinkers were the reference category	8 stars
			Never drinker	1.00 (ref)	1.00(ref)			
			Former drinker	0.94 (0.77- 1.15)	1.25 (0.86 -1.82)			
			Current drinker (drinks/wk)	0.99 (0.83 -1.18)	1.50 (1.08 -2.09)			
			>0.5	0.93 (0.77 -1.13)	1.35 (0.95 -1.93)			
			0.5–0.9	0.99 (0.76 -1.28)	1.46 (0.93 -2.28)			
			1.0–3.9	1.00 (0.81 -1.22)	1.52 (1.05 -2.19)			
			4.0–6.9	1.06 (0.82 -1.35)	1.55 (1.01 -2.39)			
			7.0–13.9	1.21 (0.96 -1.52)	1.87 (1.25 -2.79)			
			≥14.0	1.04 (0.78 -1.39)	2.13 (1.36 -3.33)			
			Risk per drink/day current drinkers	1.06 (1.00 -1.13)	1.13 (1.05 -1.23)			
			P for trend current drinkers	0.055	0.002			
			All invasive cancer ***By beverage type***					
			Beer					
			Never drinker	1.00 (ref)	1.00 (ref)			
			Current drinker	1.14 (0.92- 1.43)	1.70 (1.13 -2.54)			
			<1 drink per day	1.12 (0.90 -1.41)	1.62 (1.08 -2.43)			
			≥1 drink per day	1.65 (1.04 -2.60)	3.55 (1.85 -6.82)			
			Wine					
			Never drinker	1.00 (ref)	1.00 (ref)			
			Current drinker	1.04 (0.86 -1.26)	1.58 (1.11 -2.25)			
			<1 drink per day	1.04 (0.86 -1.26)	1.55 (1.09 -1.21)			
			≥1 drink per day	1.05 (0.81 -1.36)	1.87 (1.22 -2.87)			
			Liquor					
			Never drinker	1.00 (ref)	1.00 (ref)			
			Current drinker	1.05 (0.84 -1.29)	1.68 (1.14 -2.47)			
			<1 drink per day	1.02 (0.82 -1.26)	1.59 (1.07 -2.35)			
			≥1 drink per day	1.28 (0.94 -1.72)	2.46 (1.51 -4.00)			

Table 8. Cohort studies of consumption of alcohol consumption and breast cancer risk by histology subtype							
Reference, study location, period	**Cohort description**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)** **Ductal**	**Adjustment factors**	**Comments**	**Star rating for quality**
Kabat et al 2010 US Women's Health Initiative Clinical trial	Cohort of of 63,822 post-menopausal women (DCIS n = 489) High-grade DCIS (n = 122) Low-/medium-grade DCIS (n = 367) Follow up 8 years	Food frequency questionnaire and a health habits questionnaire	**Alcohol frequency (servings/wk)** 0 >0 to < 1 1 - <3 3 - <7 7 - <14 ≥14 P-trend **Alcohol frequency (servings/wk)** 0 >0 to <3 ≥3 P-trend **Alcohol frequency (servings/wk)** 0 >0 to <3 ≥3 P-trend	 1.00 (ref) 0.91 (0.71-1.15) 0.85 (0.64-1.13) 0.84 (0.62-1.15) 0.84 (0.58-1.23) 0.87 (0.50-1.51) 0.44 1.00 (ref) 1.08 (0.72-1.62) 0.74 (0.43-1.27) 0.20 1.00 (ref) 0.82 (0.65-1.05) 0.88 (0.66-1.17) 0.65	Adjusted age, age at menarche, age at first full-term pregnancy, parity, age at menopause, BMI, waist circumference, use of oral contraceptives, use of hormone therapy, history of breast biopsy, mammogram in the past 2 years, family history of breast cancer in a first-degree relative, physical activity, pack-years of smoking, education, ethnicity, and treatment arm assignment in each of the three clinical trials	Non-drinker was the reference category	7 stars

Table 8. Cohort studies of consumption of alcohol consumption and breast cancer risk by histology subtype								
Reference, study location, period	**Cohort description**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)** **ER +**	**Relative risk (95% CI)** **ER -**	**Adjustment factors**	**Comments**	**Star rating for quality**
Chen et al 2011 Prospective observational US Nurses' Health Study	105,986 women followed from 1980-2008	Semi-quantitative food frequency questionnaire.	**Drinking Status** Alcohol (gms/day) 0 0.1-4.9 5.0 -9.9 10-19.9 20-29.9 ≥30 P for trend	**Ductal** 1.00 (Ref) 1.06 (0.99-1.13) 1.13 (1.04-1.24) 1.22 (1.12-1.33) 1.25 (1.10-1.42) 1.49 (1.30-1.70) <0.0001	**Lobular** 1.0 (ref) 1.10 (0.90-1.33) 1.33 (1.04-1.71) 1.36 (1.15-2.24) 1.61 (1.15-2.24) 1.81 (1.26-2.60) <0.0001	Adjusted for menopausal status, age at menarche, parity, age at first birth, BMI, family history of breast cancer in a first-degree relative, breastfeeding, cigarette smoking, and self-report of benign breast disease	Never drinkers were the reference category	7 stars
Kotsopoulos et al 2010 US Nurse's Health Study cohort	107,759 women in cohort by end of follow-up 6226 invasive breast cancers (4655 ducyal, 659 lobular) Follow-up 30 years	Food frequency question-naire	**Drinking status** **Alcohol intake (g/day)** 0 <5 5 - <15 ≥15 **Alcohol intake, continuous,** RR (P trend) **Alcohol intake (g/day)** 0 <5 5 - <15 ≥15 **Alcohol intake, continuous,** RR (P trend)	**Ductal** 1.00 (ref) 1.15 (1.06-1.24) 1.22 (1.12-1.32) 1.31 (1.19-1.45 1.04 (<0.001) **Ductal ER+/PR+** 1.00 (ref) 1.16 (1.03-1.31) 1.40 (1.23-1.58) 1.37 (1.17-1.61) 1.05 (<0.001)	**Lobular** 1.00 (ref) 1.30 (1.05-1.59) 1.34 (1.08-1.67) 1.75 (1.36-2.24) 1.07 (<0.001) **Lobular ER+/PR+** 1.00 (ref) 1.11 (0.80-1.55) 1.52 (1.10-2.10) 2.28 (1.60-3.24) 1.12 (<0.001)	*A*djusted for age, age at menopause, age at menarche, menopausal status, parity, age at first birth, nulliparous or parous, parity and post-menopausal hormone status and use, BMI, and BMI at age 18	Non-drinker was the reference category	6 stars

Table 9. Cohort studies of consumption of alcohol consumption and breast cancer mortality and secondary events by histology subtype								
Reference, study location, period	**Cohort description**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)**	**Relative risk (95% CI)**	**Adjustment factors**	**Comments**	**Star rating for quality**
Newcomb et al 2013 US multi-site population-based cohort	22,890 women with incident invasive breast cancer 3,484 breast cancer deaths Follow-up 11.3 years	Information on alcohol consumption was obtained by interview	**Drinking Status** **Pre-diagnostic Alcohol Consumption** **Total** 0 1-2 3-6 7-9 ≥ 10 **Wine** 0 1-2 3-6 ≥ 7 **Beer** 0 1-2 3-6 ≥ 7 **Spirits** 0 1-2 3-6 ≥ 7	**Ductal** 1.00 (Ref) 0.94 (0.85 -1.04) 0.86 (0.75 -0.98) 0.86 (0.72 -1.02) 0.86 (0.73 -1.02) 1.00 (Ref) 1.00 (0.92 -1.10) 0.89 (0.74 -1.07) 1.16 (0.94 -1.42) 1.00 (Ref) 0.93 (0.85 -1.02) 0.82 (0.68 -0.99) 0.92 (0.76 -1.12) 1.00 (Ref) 0.91 (0.83 -1.00) 0.90 (0.76 -1.06) 0.82 (0.68 -0.99)	**Lobular** 1.00(ref) 0.93 (0.67- 1.28) 0.97 (0.62 -1.51) 1.23 (0.74 -2.05) 0.90 (0.53 -1.52) 1.00(Ref) 1.00 (0.75 -1.34) 0.79 (0.44 -1.43) 1.34 (0.73 -2.48) 1.00(Ref) 0.96 (0.71 -1.29) 2.74 (1.60 -4.71) 0.90 (0.46 -1.74) 1.00 (Ref) 0.89 (0.66-1.20) 0.72 (0.41 -1.25) 1.08 (0.60 -1.96)	Adjusted for age at diagnosis, stage of disease at diagnosis, state of residence at diagnosis, study phase, family history of breast cancer, age at first birth, menopausal status, HT use, BMI, smoking status, education, and mammography.	Non-drinkers were the reference category	9 stars

Table 9. Cohort studies of consumption of alcohol consumption and breast cancer mortality and secondary events by histology subtype							
Reference, study location, period	**Cohort description**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)**	**Adjustment factors**	**Comments**	**Star rating for quality**
McLaughlin et al 2014 Population-based cohort Wisconsin In Situ Cohort (WISC) of DCIS survivors	Cohort consisted of 1,925 women with a first primary DCIS diagnosis At end of follow up, 162 second breast cancer events	Interview	**Drinking status** Total alcohol (drinks/wk) **Pre-diagnostic intake** No alcohol >0–<2 2–<7 7+ Continuous per drink/wk Ptrend **Post-diagnostic intake** No alcohol >0–<2 2–<7 7+ Continuous per drink/wk P trend **Pre-diagnostic intake** No alcohol >0–<2 2–<7 7+ Continuous per drink/wk P trend **Post -diagnostic intake** No alcohol >0–<2 2–<7 7+ Continuous per drink/wk P trend	**All second breast cancer diagnoses** 1.00 (Ref.) 0.98 (0.62–1.53) 0.91 (0.54–1.53) 1.04 (0.58–1.88) 1.02 (0.99–1.05) 0.88 **All second breast cancer diagnoses** (N = 1,903) 1.00 (Ref.) 1.28 (0.59–2.78) 1.76 (0.64–4.80) 2.59 (0.61–11.0) 1.03 (0.94–1.11) 0.02 **Invasive second breast cancer diagnoses** (N = 1,925) 1.00 (Ref.) 0.95 (0.43–2.08) 1.23 (0.52–2.90) 1.21 (0.45–3.22) 1.04 (0.99–1.09) 0.18 **Invasive second breast cancer diagnoses (N = 1,903)** 1.00 (Ref.) 1.38 (0.37–5.47) 1.40 (0.14–4.35) 1.74 (0.17–9.68) 1.05 (0.90–1.23) 0.15	Adjusted for age at diagnosis, menopausal status, method of detection, surgical treatment type, radiation therapy, tamoxifen use, year of diagnosis, tumour size, tumour grade, BMI and physical activity.	Non-drinker was the reference category	7

Table 10. Cohort studies of consumption of alcohol consumption and breast cancer risk by receptor status								
Reference, study location, period	**Cohort description**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)** **ER +**	**Relative risk (95% CI)** **ER -**	**Adjustment factors**	**Comments**	**Star rating for quality**
Horn-Ross et al 2012 California Teachers Study (CTS)	Cohort of 40,680 women After follow-up, 660 invasive breast cancer cases 530 cases (80%) had oestrogen receptor positive (ER+) tumours 94 cases (14%) had ER negative (ER-) tumours)	Self-administered questionnaire	**Drinking status** **Alcohol (g/d)** **HT use Never** non-drinker <20 ≥20 **HT use Past** non-drinker <20 ≥20 **HT use Current ET** non-drinker <20 ≥20 **HT use Current EPT** non-drinker <20 ≥20	**ER+ Breast cancer tumours** 1.0 0.89(0.56-1.40) 1.61(0.93-2.77) 1.05(0.72-1.54) 1.04(0.71-1.51) 1.20 (0.78-1.84) 1.05(0.61–1.79) 1.51(0.97–2.37) 2.03(1.16–3.55) 1.91(1.01–3.59) 2.00(1.16–3.45) 4.09(2.29–7.30)		Adjusted for age at first full-term, a family history of breast cancer in a first degree relative, BMI, and average long-term physical inactivity	Non-drinker was the reference category	8 stars

Table 10. Cohort studies of consumption of alcohol consumption and breast cancer risk by receptor status

Reference, study location, period	Cohort description	Exposure assessment	Exposure categories	Relative risk (95% CI) ER +	Relative risk (95% CI) ER -	Adjustment factors	Comments	Star rating for quality
Park et al 2014 Multi-ethnic Hawaiian/Californian population 1993–2007	Cohort of 85,089 women 3885 invasive breast cancer cases Follow-up12.4 years	Self-administered quantitative food frequency questionnaire (QFFQ)	**Drinking status** **Alcohol intake (g/day)** Non-drinkers 0.1–4.9 5–9.9 10–14.9 15.0–29.9 ≥30 P trend 10g/day increment Non-drinkers 0.1–4.9 5–9.9 10–14.9 15.0–29.9 ≥30 P trend 10g/day increment	**ER+PR+** 1.00 (ref) 0.92 (0.81–1.04) 1.14 (0.91–1.42) 1.35 (1.13–1.61) 1.61 (1.30–2.00) <0.001 1.06 (1.03–1.08) **ER+/PR-** 1.00 (ref) 1.27 (0.98–1.65) 1.89 (1.24–2.89) 1.11 (0.72–1.72) 1.72 (1.06–2.79) 0.054 1.06 (1.01–1.11)	**ER-PR-** 1.00 (ref) 1.18 (0.94–1.47) 1.57 (1.08–2.27) 1.24 (0.87–1.75) 1.58 (1.04–2.38) 0.025 1.04 (0.99–1.09)	Adjusted for ethnicity, age at entry, family history of breast cancer, age at first live birth, age at menarche, age and type of menopause, no. of children, HRT, smoking status, education, physical activity, BMI and energy intake.	Non-drinker was the reference category	7 stars
Liu et al 2013 US Nurses' Health Study II	Total cohort of 91,005 women 10 + years of follow-up 1609 breast cancer cases 970 cases of proliferative BBD.	High school food-frequency questionnaire (HS-FFQ)	**Drinking status** **Total alcohol intake (g/day)[a]** 0 g/d 0.1–4.9 g/d 5.0–14.9 g/d ≥15 g/d Per 10-unit increase P trend 0 g/d 0.1–4.9 g/d 5.0–14.9 g/d ≥15 g/d Per 10-unit increase P trend	**ER+/PR+** 1.00 (ref) 1.20 (0.97-1.49) 1.33 (1.02- 1.74) 1.67 (1.11 -2.51) 1.18 (1.03 -1.34) 0.01 **ER+/PR−** 1.00 (ref) 1.01 (0.58 -1.76) 0.86 (0.42 -1.74) 0.60 (0.17 -2.07) 0.86 (0.60 -1.22) 0.39	**ER-/PR-** 1.00(ref) 0.80 (0.54 -1.17) 0.87 (0.54 -1.39) 0.76 (0.33 -1.71) 0.84 (0.60 -1.16) 0.28	Adjusted for age in months, total energy intake, age at menarche, menopausal status, average body size between ages 5 and 10 years, family history of breast cancer in mother or sister(s), current and duration of OC use, and parity and age at first birth.	Non-drinkers were the reference category [a] Cumulative average alcohol consumption between menarche and first full term pregnancy	7 stars

Table 10. Cohort studies of consumption of alcohol consumption and breast cancer risk by receptor status

Reference, study location, period	Cohort description	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments	Star rating for quality
Li et al 2010 Women's Health Initiative Observational prospective cohort	Cohort of 87,724 post-menopausal women Enrolled between Oct 1993 and Dec 1998, followed until Sept 2005 2944 breast cancer cases	Self-administered questionnaire	**Drinking status** Never drinker Former drinker Current drinker (drinks/wk) >0.5 0.5–0.9 1.0–3.9 4.0–6.9 7.0–13.9 ≥14.0 Risk per drink/day current drinkers P for trend current drinkers **All invasive cancer** ***By beverage type*** Beer Never drinker Current drinker <1 drink per day ≥1 drink per day Wine Never drinker Current drinker <1 drink per day ≥1 drink per day Liquor Never drinker Current drinker <1 drink per day ≥1 drink per day	All invasive Breast cancer 1.00 (ref) 0.98 (0.83 to 1.15) 1.08 (0.94 to 1.25) 1.02 (0.87 to 1.18) 1.05 (0.85 to 1.28) 1.10 (0.94 to 1.30) 1.12 (0.91 to 1.36) 1.27 (1.05 to 1.53) 1.24 (1.00 to 1.55) 1.07 (1.02 to 1.12) 0.004 1.00 (ref) 1.23 (1.03 to 1.47) 1.20 (1.00 to 1.44) 1.90 (1.34 to 2.70) 1.00 (ref) 1.11 (0.95 to 1.29) 1.10 (0.95 to 1.29) 1.15 (0.94 to 1.41) 1.00 (ref) 1.14 (0.96 to 1.36) 1.11 (0.93 to 1.32) 1.45 (1.14 to 1.83)	Adjusted for age, race, and/or ethnicity, education, BMI, use of menopausal HT, smoking status, Gail model scores of 5-year breast cancer risk and number of screening mammograms received in the past five years.	Never drinkers were the reference category	8 stars

Table 10. Cohort studies of consumption of alcohol consumption and breast cancer risk by receptor status

Reference, study location, period	Cohort description	Exposure assessment	Exposure categories	Relative risk (95% CI) ER +	Relative risk (95% CI) ER -	Adjustment factors	Comments	Star rating for quality
Li et al 2010 continued Women's Health Initiative Observational prospective cohort	Cohort of 87,724 post-menopausal women Enrolled between Oct 1993 and Dec 1998, followed until Sept 2005 2944 breast cancer cases	Self- administered questionnaire	**Drinking status**	**ER+PR+ cancers (n = 1803)**	**ER-PR− cancers (n = 359)**	Adjusted for age, race, and/or ethnicity, education, BMI, use of menopausal HT, smoking status, Gail model scores of 5-year breast cancer risk and number of screening mammograms received in the past five years.	Never drinkers were the reference category	8 stars
			Never drinker	1.00 (ref)	1.00 (ref)			
			Former drinker	0.96 (0.78-1.19)	1.11 (0.73 -1.70)			
			Current drinker (drinks/wk)	1.07 (0.89 -1.28)	0.94 (0.64 -1.37)			
			0.5	1.00 (0.82 -1.22)	0.88 (0.58 -1.34)			
			0.5–0.9	1.00 (0.77 -1.30)	1.26 (0.74 -2.15)			
			1.0–3.9	1.08 (0.88 -1.33)	0.98 (0.63 -1.53)			
			4.0–6.9	1.08 (0.84 -1.40)	1.02 (0.58 -1.79)			
			7.0–13.9	1.32 (1.04 -1.66)	0.91 (0.52 -1.59)			
			≥14.0	1.27 (0.96 -1.68)	0.46 (0.19 -1.12)			
			Risk per drink/day current drinkers	1.08 (1.02 -1.15)	0.85 (0.68 -1.05)			
			P for trend current drinkers	0.009	0.12			

Table 10. Cohort studies of consumption of alcohol consumption and breast cancer risk by receptor status							
Reference, study location, period	**Cohort description**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)** **ER +**	**Adjustment factors**	**Comments**	**Star rating for quality**
Li et al 2010 continued Women's Health Initiative Observational prospective cohort	Cohort of 87,724 post-menopausal women Enrolled between Oct 1993 and Dec 1998, followed until Sept 2005 2944 breast cancer cases	Self- administered questionnaire	**Drinking status** Never drinker Former drinker Current drinker (drinks/wk) <0.5 0.5–0.9 1.0–3.9 4.0–6.9 7.0–13.9 ≥14.0 Risk per drink/day current drinkers P for trend **Intake drinks/wk** <6.9 ≥7.0 Risk per drink/day current drinkers P for trend	**ER+PR− cancers (n = 373)** 1.00 (ref) 0.92 (0.57 -1.49) 1.11 (0.74 -1.69) 0.98 (0.63 -1.54) 0.90 (0.49 -1.67) 1.21 (0.77 -1.92) 1.46 (0.86 -2.48) 1.21 (0.71 -2.05) 1.45 (0.80 -2.63) 1.12 (1.00 -1.25) 0.060 **Invasive ER+PR+ ductal cancers (n = 1105)** 1.00 (ref) 0.86 (0.66 -1.11) 0.95 (0.76 -1.19) 0.92 (0.73 -1.15) 1.14 (0.87 -1.50) 1.05 (0.97 -1.14) 0.194 **Invasive ER+PR+ lobular cancers (n = 497)** 1.00 (ref) 1.17 (0.76 -1.80) 1.39 (0.95 -2.03) 1.32 (0.90 -1.94) 1.82 (1.18 -2.81) 1.16 (1.06 -1.26) 0.001	Adjusted for age, race, and/or ethnicity, education, BMI, use of menopausal HT, smoking status, Gail model scores of 5-year breast cancer risk and number of screening mammograms received in the past five years.	Never drinkers were the reference category	8 stars

Table 10. Cohort studies of consumption of alcohol consumption and breast cancer risk by receptor status								
Reference, study location, period	**Cohort description**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)** **ER +**	**Relative risk (95% CI)** **ER -**	**Adjustment factors**	**Comments**	**Star rating for quality**
Kabat et al 2011 Women's Health Initiative	Cohort of 148,030 women, 300 Triple Negative Breast cancer (TNBC) cases 2,479 ER+ breast cancer cases	Health habits questionnaire and a food frequency questionnaire	**Drinking status** ***Alcohol intake at baseline*** Never drank Past drinker <1 drink/m <1 drink/wk 1-6drinks/wk ≥7 drinks/wk **Beer intake at baseline** 0 <3 drinks/k ≥3 drinks/ wk P for trend **Wine intake at baseline** 0 <3 drinks/k ≥3 drinks/ wk P for trend **Liquor intake at baseline** 0 <3 drinks/k ≥3 drinks/ wk P for trend	**ER +** (N = 2,479) 1.00 (ref) 0.99 (0.84-1.57) 0.87 (0.73-1.05) 0.98 (0.83-1.14) 1.00 (0.86-1.17) 1.26 (1.06-1.50) 1.0 (ref) 1.04 (0.94-1.15) 1.01 (0.73-1.38) 0.51 1.00 (ref) 1.00 (0.91-1.09) 1.16 (1.02-1.32) 0.08 1.00 (Ref) 0.95 (0.86-1.05) 1.36 (1.17-1.58) 0.02	**TNBC** TNBC (N = 300) Alcohol intake at baseline 1.00 (ref) 0.72 (0.48-1.08) 0.47 (0.29–0.78) 0.78 (0.53–1.16) 0.68 (0.46–1.02) 0.57 (0.34–0.95) 1.00 (ref) 0.93 (0.68–1.27) 1.60 (0.79–3.26) 0.74 1.00 (ref) 0.95 (0.73–1.22) 0.75 (0.48–1.17) 0.25 1.00 (ref) 1.07 (0.81–1.43) 0.84 (0.47–1.52) 0.93	Adjusted for age, age at menarche, age at first full-term pregnancy, parity, age at menopause, BMI, waist circumference, use of oral contraceptives, use of hormone therapy, history of breast biopsy, family history of breast cancer in a first-degree relative, mammogram in past two years, physical activity, education, ethnicity, and study arm assignment in each of the clinical trials or the observational study	Non-drinkers were the reference category.	7 stars

Table 10. Cohort studies of consumption of alcohol consumption and breast cancer by receptor status								
Reference, study location, period	**Cohort description**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)** **ER +**	**Relative risk (95% CI)** **ER -**	**Adjustment factors**	**Comments**	**Star rating for quality**
Chen et al 2011 Prospective observational US Nurses' Health Study	105,986 women followed from 1980-2008	Semi-quantitative food frequency questionnaire.	Drinking Status **Alcohol Intake, g/d** 0 0.1-4.9 5.0-9.9 10.0-19.9 20.0-29.9 ≥30 **P trend** **Alcohol Intake, g/d** 0 0.1-4.9 5.0-9.9 10.0-19.9 20.0-29.9 ≥30 **P trend**	ER+/PR+ 1.0 (ref) 1.03 (0.94-1.12) 1.20 (1.02-1.47) 1.14 (1.02-1.28) 1.27 (1.14-1.42) 1.58 (1.34-1.86) <0. 001 **ER+/PR-** 1.0 (ref) 1.15 (0.97-1.36) 1.07 (0.85-1.34) 1.19 (0.95-1.48) 1.39 (1.03-1.88) 1.35 (0.96-1.89) 0.04	ER-/PR+ 1.0 (ref) 1.30 (0.86-1.97) 1.49 (0.89-2.50) 1.30 (0.76-2.23) 1.45 (0.67-3.17) 2.59 (1.33-5.07) 0.02 **ER-/PR-** 1.0 (ref) 1.14 (0.97-1.34) 1.25 (1.01-1.54) 1.17 (0.94-1.46) 1.05 (0.75-1.49) 1.24 (0.87-1.76) 0.23	Adjusted for menopausal status, age at menarche, parity, age at first birth, BMI, family history of breast cancer in a first-degree relative, breastfeeding, cigarette smoking, and self-report of benign breast disease	Never drinkers were the reference category	7 stars

Table 11. Cohort studies of consumption of alcohol consumption and breast cancer mortality and secondary events by receptor status								
Reference, study location, period	**Cohort description**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)** **ER +**	**Relative risk (95% CI)** **ER -**	**Adjustment factors**	**Comments**	**Star rating for quality**
Vrieling et al 2012 MARIE cohort, Germany, 2001–2009	Cohort of 2,522 breast cancer post-menopausal patients aged 50-74 years 235 breast cancer deaths Enrolled between 2002 and 2005, followed until end of 2009, mean follow-up = 5.5 years	Self-administered food frequency questionnaire	**Drinking Status** **Alcohol intake (g/day)** <0.5 ≥0.5–<6.0 ≥6.0–<12.0 ≥12.0	**ER +** 1.00 1.40 (0.84 -2.33) 1.01 (0.53 -1.94) 1.60 (0.92 -2.79)	**ER-** 1.00 1.82 (0.91 -3.66) 1.26 (0.50 -3.17) 1.99 (0.90 -4.37)	Adjusted for age at diagnosis and study centre, and adjusted for tumour size, nodal status, metastases, tumour grade, ERPR status, radiotherapy, HRT use at diagnosis, mode of detection;	The lowest alcohol intake category was the reference category	9 stars
Kwan et al 2010 US Life After Cancer Epidemiology (LACE) cohort .	Cohort of 1,897 early-stage breast cancer survivors Follow-up 293 breast cancer recurrences 154 breast cancer deaths Follow-up 7.4 years	Self-administered food frequency questionnaire	**Drinking Status** **All women** **Total alcohol, g/d** None **< 6** **≥ 6** **Total alcohol, g/d** None **< 6** **≥ 6**	Breast Cancer recurrence **ER+ tumours** 1.00(Ref) 1.00 (0.71-1.40) 1.23 (0.89-1.72) Breast Cancer Mortality **ER+ tumours** 1.00(Ref) 1.04 (0.65-1.68) 1.48 (0.94-2.32)	Breast Cancer recurrence **ER- tumours** 1.00(Ref) 1.29 (0.66 -2.54) 2.00 (0.96 -4.14) Breast Cancer Mortality **ER- tumours** 1.00(Ref) 1.38 (0.5 -3.33) 1.62 (0.57 -4.58)	Adjusted for age at diagnosis, race, BMI at 1 year pre-diagnosis, menopausal status, smoking status, total folate intake, stage of disease, hormone receptor status, definitive surgery, tamoxifen use, adjuvant treatment, and positive lymph nodes	Non-drinkers were the referent category.	7 stars

Table 11. Cohort studies of consumption of alcohol consumption and breast cancer mortality and secondary events by receptor status

Reference, study location, period	Cohort description	Exposure assessment	Exposure categories	Relative risk (95% CI) ER +	Relative risk (95% CI) ER -	Adjustment factors	Comments	Star rating for quality

Kwan et al 2013
 	
US After Breast Cancer Pooling Project (ABCPP)
	Cohort of 9,329 breast cancer survivors
	
	1646 breast cancer recurrences
	
	1543 deaths
	
	Follow-up 10.3 years
		Self-administered food frequency questionnaire	**Drinking Status**
			
			All women
			Total Alcohol intake (g/day)
			
			<0.36 g/day
			0.36-<6 g/d
			6-<12 g/day
			P trend
				Breast cancer recurrence
				
				ER+ tumours
				
				1.00 (ref)
				1.09(0.94-1.26)
				1.08 (0.92-1.26)
				0.31
					Breast cancer recurrence
					
					ER- tumours
					
					1.00 (ref)
					0.70 (0.53-0.92)
					1.03 (0.78-1.36)
					0. 76
						Adjusted for age at diagnosis, stage of disease, race/ ethnicity, education, menopausal status around diagnosis, hormone receptor status, surgery, treatment (radiation therapy, chemotherapy, HT), smoking, physical activity, pre-diagnosis BMI, and comorbidity.	The following terminology was used in the studies to classify the drinking status of the women
							Non-drinker (reference category) = <0.36 g/day;
							occasional drinker = 0.36-<6 g/day;
							regular low drinker = 6-<12 g/day;
							regular medium drinker = 12-<24 g/day;
							regular high drinker = ≥24 g/day
								7 stars

Table 12. Case Control studies of consumption of alcohol consumption and breast cancer risk by receptor status									
Reference, study location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)** **ER +**	**Relative risk (95% CI)** **ER -**	**Adjustment factors**	**Comments**	**Star rating for Quality**
Wu et al 2012 Population-based case-control study of 4,231 Asian American women (Japanee only subset analysis of ER/PR receptor	2,229 cases	2,002 matched controls	Quantitative food frequency questionnaire and lifetime history assessment.	**Drinking status** **Alcohol Consumption** None Former Current **Years of drinking** No > 0 to ≤ 10 > 10 **Amount of alcohol per day (g/day)** No > 0 to ≤ 5. > 5 **Alcohol Consumption** None Former Current **Years of drinking** No > 0 to ≤ 10 > 10 **Amount of alcohol per day (g/day)** No > 0 to ≤ 5. > 5	**ER+/PR+ tumours** 1.00 1.17 1.68 1.00 1.35 1.56 1.00 1.33 1.72 **ER+/PR- tumours** 1.00 1.47 2.76 1.00 1.20 3.43 1.00 2.22 2.06	**ER-/PR- tumours** 1.00 1.98 0.84 1.00 1.73 0.87 1.00 1.38 1.12	Adjusted for birthplace and years of residence in the United States among non-US born, education, interviewer, age at menarche, parity, current BMI, years of regular recreational physical activity, total calories, intake of soy, green tea and black tea, menopausal status, age at menopause, and family history of breast cancer.	Non-drinkers were the reference category. No confidence intervals given in paper.	7 stars

Table 12. Case Control studies of consumption of alcohol consumption and breast cancer risk by receptor status									
Reference, study location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)** **ER +**	**Relative risk (95% CI)** **ER -**	**Adjustment factors**	**Comments**	**Star rating for Quality**
Islam et al 2013 Case-control study of pre- and post-menopausal Japanese women	1754 breast cancer cases	3508 controls	Self-reported questionnaire	**Drinking status** **Drinking alcohol (g/day)** Pre-menopausal women Non drinkers 1-≤5 g/d 5-≤23g/d ≥23g/d P trend Post-menopausal women Non drinkers 1-≤5 g/d 5-≤23g/d ≥23g/d P trend Pre-menopausal women Non drinkers 1-≤5 g/d 5-≤23g/d ≥23g/d P trend Post-menopausal women Non drinkers 1-≤5 g/d 5-≤23g/d ≥23g/d P trend	**ER+** 1.00 (ref) 0.97 (0.73–1.29) 1.06 (0.76–1.47) 1.36 (0.89–2.08) 0.27 1.00 (ref) 1.48 (1.09–2.00) 1.30 (0.89–1.92) 1.42 (0.82–2.47) 0.03 **ER + and/or PR +/HER2 +** 1.00 (ref) 0.84 (0.39–1.80) 1.61 (0.78–3.32) 0.84 (0.24–3.32) 0.59 1.00 (ref) 1.02 (0.46–2.27) 1.12 (0.42–2.99) 2.00 (0.60–6.75) 0.39	**ER−** 1.00 (ref) 0.73 (0.42–1.29) 1.64 (0.97–2.78) 0.50 (0.15–1.68) 0.77 1.00 (ref) 0.75 (0.45–1.23) 0.94 (0.53–1.64) 1.98 (1.07–3.68) 0.27 **ER – /PR – /HER2 +** 1.00 (ref) 0.70 (0.23–2.19) 1.92 (0.75–4.94) 0.52 (0.64–4.24) 0.72 1.00 (ref) 0.87 (0.38–2.04) 1.00 (0.38–2.63) 2.99 (1.08–8.26) 0.18	Adjusted for adjusted for age, ethnicity, country of origin, education, age at menarche, age at menopause, menopausal status, parity, age at first birth, breastfeeding, family history of breast cancer, history of benign breast disease, HRT use, OC use, BMI, total energy intake and physical activity	Non-drinkers were the reference category	6 stars

Table 12. Case Control studies of consumption of alcohol consumption and breast cancer risk by receptor status									
Reference, study location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)** **ER +**	**Relative risk (95% CI)** **ER -**	**Adjustment factors**	**Comments**	**Star rating for Quality**
Islam et al 2013 Continued Case-control study of pre- and post-menopausal Japanese women	1754 breast cancer cases	3508 controls	Self-reported questionnaire	**Drinking status** **Drinking alcohol (g/day)** Pre-menopausal women Non drinkers 1-≤5 g/d 5-≤23g/d ≥23g/d P trend Post-menopausal women Non drinkers 1-≤5 g/d 5-≤23g/d ≥23g/d P trend	**ER + and/or PR +/HER2 –** 1.00 (ref) 0.96 (0.67–1.40) 0.92 (0.59–1.43) 1.60 (0.94–2.64) 0.34 1.00 (ref) 1.43 (0.97–2.11) 0.94 (0.54–1.65) 1.59 (0.78–3.24) 0.23	**ER – /PR – /HER2 -** 1.00 (ref) 0.47 (0.10–2.18) 2.47 (0.81–7.49) 1.39 (0.17-11.50) 0.29 1.00 (ref) 0.61 (0.21–1.79) 1.25 (0.46–3.38) 3.72 (1.30-10.67) 0.09	Adjusted for adjusted for age, ethnicity, country of origin, education, age at menarche, age at menopause, menopausal status, parity, age at first birth, breastfeeding, family history of breast cancer, history of benign breast disease, HRT use, OC use, BMI, total energy intake and physical activity	Non-drinkers were the reference category	6 stars

Table 12. Case Control studies of consumption of alcohol consumption and breast cancer risk by receptor status									
Reference, study location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)** **ER +**	**Relative risk (95% CI)** **ER -**	**Adjustment factors**	**Comments**	**Star rating for Quality**
Zhang and Holman 2012 Hospital-based case-control study of 2,018 women from the Zhejiang province of China.	1009 cases	1009 controls	Self-administer Food Frequency question-naire	***Drinking Status Ethanol intake (g per day)*** **All women** None >0–<15 ≥15 None >0–<15 ≥15 **Pre-menopausal women** None >0–<15 ≥15 None >0–<15 ≥15 **Post-menopausal women** None >0–<15 ≥15 None >0–<15 ≥15	 **ER+/PR+ tumours** 1.00 0.55 (0.41-0.73) 0.89 (0.51-1.56) **ER+/PR− tumours** 1.00 (Ref) 1.06 (0.68–1.64) 2.82 (1.47–5.42) **ER+/PR+ tumours** 1.00 (ref) 0.58 (0.42–0.81) 0.99 (0.51–1.89) **ER+/PR− tumours** 1.00 (Ref) 1.08 (0.64–1.81) 1.96 (0.80–4.79) **ER+/PR+ tumours** 1.00 (ref) 0.45 (0.25–0.81) 0.76 (0.23–2.51) **ER+/PR− tumours** 1.00(Ref) 0.98 (0.43–2.25) 4.27 (1.57–11.65)	 **ER-/PR- Tumours** 1.00 (ref) 0.46 (0.33–0.64) 1.42 (0.84–2.41) **ER−/PR+ tumours** 1.00 (Ref) 1.06 (0.68–1.64) 2.82 (1.47–5.42) **ER-/PR-Tumours** 1.00 (ref) 0.49 (0.32–0.74) 1.34 (0.67–2.69) **ER−/PR+ tumours** 1.00 (Ref) 1.08 (0.64–1.81) 1.96 (0.80–4.79) **ER-/PR-Tumours** 1.00 (ref) 0.36 (0.20–0.64) 1.62 (0.69–3.81) **ER−/PR+ tumours** 1.00 (Ref) 0.98 (0.43–2.25) 4.27 (1.57–11.65)	Adjusted for age, education, BMI, OC use, HRT, breast cancer in first-degree relatives, total energy intake, folate intake, tea drinking and menopausal status	Never drinkers/ Abstainer were the reference category.	6 stars

Table 13. Cohort studies of consumption of alcohol consumption and breast cancer risk by genetic polymorphisms and susceptibility								
Reference, study location, period	**Cohort description**	**Exposure assessment**	**Exposure categories**	**Cases**	**Relative risk (95% CI)**	**Adjustment factors**	**Comments**	**Star rating for Quality**
Le Carpentier et al 2011 French cohort	1,337 women including 863 BRCA1 mutation carriers and 474 BRCA2 mutation carriers	Details of alcohol consumption such as number of glasses per week were recorded and categorised as 0, 1-5, 6-10, and >10 at the age of 20 and at the time of interview	**Drinking status** **Never Smokers** **Alcohol consumption** Never use Current use **Alcohol consumption at age 20 years (glasses/wk)** Never use 1–5 6–10 >10 **Ever Smokers** **Alcohol consumption** Never use Current use **Alcohol consumption at age 20 years (glasses/wk)** Never use 1–5 6–10 >10	 62 139 137 29 24 9 27 146 93 29 36 12	**Breast Cancer Risk** 11 1.00 1.10 (0.76–1.61) 1.00 0.82 (0.50–1.34) 1.02 (0.56–1.87) 1.26 (0.53–2.96) 1.00 0.89 (0.53–1.52) 1.00 0.74 (0.44–1.26) 1.18 (0.72–1.93) 0.89 (0.40–1.96)	Adjusted for parity, menopausal status, gene and number of years of smoking interrupti-on	Never-drinkers were the reference category	5 stars

Table 13. Cohort studies of consumption of alcohol consumption and breast cancer risk by genetic polymorphisms and susceptibility								
Reference, study location, period	**Cohort description**	**Exposure assessment**	**Exposure categories**	**Cases**	**Relative risk (95% CI)**	**Adjustment factors**	**Comments**	**Star rating for Quality**
Le Carpentier et al 2011 Continued French cohort	1,337 women including 863 BRCA1 mutation carriers and 474 BRCA2 mutation carriers	Details of alcohol consumption such as number of glasses per week were recorded and categorised as 0, 1-5, 6-10, and >10 at the age of 20 and at the time of interview	**Drinking Staus** **Never Smokers** **Alcohol consumption** Never use Current use **Alcohol consumption at age 20 years (glasses/wk)** Never use 1–5 6–10 >10 **Ever Smokers** **Alcohol consumption** Never use Current use **Alcohol consumption at age 20 years (glasses/wk)** Never use 1–5 6–10 >10	 38 92 86 21 16 6 18 89 63 16 19 7	**Breast Cancer Risk BRCA1 carriers** 1.00 1.02 (0.65–1.60) 1.00 0.79 (0.43–1.46) 0.89 (0.44–1.80) 1.16 (0.42–3.19) 1.00 0.90 (0.49–1.68) 1.00 0.70 (0.35–1.38) 1.10 (0.59–2.03) 0.78 (0.31–1.96)	Adjusted for parity, menopausal status, gene and number of years of smoking interruption	Never-drinkers were the reference category	5 stars

Table 14. Case-Control studies of consumption of alcohol consumption and breast cancer by genetic polymorphisms and susceptibility								
Reference, study location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)**	**Adjustment factors**	**Comments**	**Star rating for Quality**
McCarty et al 2012 Case-control study of 2,111 women enrolled in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial	1,041 breast cancer cases	1,070 controls	Food Frequency questionnaire	**Daily alcohol intake or alcohol metabolism genotype** **Daily servings of alcohol** None >0–0.99 1.00–1.99 2.00–2.99 3.00+ **Alcohol servings/day (quintile)** 0–<0.001 0.001–<0.032 0.032–<0.111 0.111–<0.672 0.672+ **ADH1B genotype GG** None >0–0.99 1.00–1.99 2.00–2.99 3.00+ **GA or AA** None >0–0.99 1.00–1.99 2.00–2.99 3.00+	 1.00 1.31 (1.01, 1.71) 1.54 (1.04, 2.28) 1.75 (1.02, 3.00) 2.00 (1.11, 3.61) 1.00 1.27 (0.94, 1.71) 1.38 (1.01, 1.89) 1.31 (0.95, 1.82) 1.74 (1.22, 2.47) 1.00 1.29 (0.97, 1.72) 1.66 (1.09, 2.52) 1.88 (1.07, 3.29) 2.22 (1.19, 4.13) 1.00 0.90 (0.33, 2.46) 0.51 (0.06, 4.55) 0.30 (0.01, 8.77) 0.00	Adjusted for age, race, ethnicity, age at menarche, parity, age of first live birth, family history of breast cancer, and personal history of benign breast disease	Non-drinkers were the reference category	6 stars

Table 14. Case-Control studies of consumption of alcohol consumption and breast cancer by genetic polymorphisms and susceptibility								
Reference, study location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)**	**Adjustment factors**	**Comments**	**Star rating for Quality**
McCarty et al 2012 Continued Case-control study of 2,111 women enrolled in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial	1,041 breast cancer cases	1,070 controls	Food Frequency questionnaire	**ADH1C genotype GG** None >0–0.99 1.00–1.99 2.00–2.99 3.00+ **GA** None >0–0.99 1.00–1.99 2.00–2.99 3.00+ **AA** None >0–0.99 1.00–1.99 2.00–2.99 3.00+ **CYP2E1 genotype CC** None >0–0.99 1.00–1.99 2.00–2.99 3.00+ **CT or TT** None >0–0.99 1.00–1.99 2.00–2.99 3.00+	 1.00 1.68 (0.81, 3.49) 1.11 (0.36, 3.41) 1.69 (0.42, 6.75) 2.14 (0.31, 14.91) 1.00 1.03 (0.66, 1.58) 1.29 (0.71, 2.36) 1.59 (0.61, 4.14) 1.01 (0.43, 2.41) 1.00 1.59 (1.03, 2.46) 1.80 (0.87, 3.72) 1.87 (0.80, 4.36) 4.13 (1.19, 14.26) 1.00 1.29 (0.98, 1.70) 1.70 (1.13, 2.57) 1.61 (0.91, 2.85) 1.96 (1.06, 3.65) 1.00 0.86 (0.20, 3.74) 0.05 (0, 0.95) 5.28 (0.64, 43.41) 0.46 (0.01, 15.71)	Adjusted for age, race, ethnicity, age at menarche, parity, age of first live birth, family history of breast cancer, and personal history of benign breast disease	Non-drinkers were the reference category	6 stars

Table 14. Case-Control studies of consumption of alcohol consumption and breast cancer by genetic polymorphisms and susceptibility								
Reference, study location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)**	**Adjustment factors**	**Comments**	**Star rating for Quality**
Dennis et al 2010 Case control study of 3,850 women with either the BRCA1 or BRCA2 mutation	1925 cases 1480 pairs *BRCA1* mutations 445 pairs with *BRCA2* mutation	1925 controls	Self-administered questionnaire.	**Drinking status Number of Alcoholic Drinks Consumed per Week** **All types** None 0–3 4–9 ≥10 p-trend **Exclusive wine consumers** None 0–3 4–9 ≥10 p-trend **Wine and other alcohol types** None 0–3 4–9 ≥10 p-trend **Other alcohol types** None 0–3 4–9 ≥10 p-trend	 **BRCA1 (n = 1480 pairs)** 1.00 0.77 (0.67–0.94) 0.98 (0.73–1.32) 0.55 (0.33–0.91) 0.03 **BRCA1 (n = 895 pairs*)** 1.00 0.62 (0.45–0.87) 0.82 (0.41–1.67) 0.39 (0.11–1.45) 0.01 1.00 1.05 (0.78–1.42) 1.10 (0.61–1.96) 0.64 (0.21–1.99) 0.79 1.00 0.62 (0.43–0.91) 1.07 (0.40–2.85) 0.70 (0.13–3.75) 0.08	Adjusted for ethnicity, menopausal status, oral contraceptive use, HRT use, smoking, oophorectomy, BMI and parity.	None drinkers were the reference category in the study * informat-iion on type of alcohol consumed	6 stars

Table 14. Case-Control studies of consumption of alcohol consumption and breast cancer by genetic polymorphisms and susceptibility								
Reference, study location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)**	**Adjustment factors**	**Comments**	**Star rating for Quality**
Dennis et al 2010 Continued Case control study of 3,850 women with either the BRCA1 or BRCA2 mutation	1925 cases 1480 pairs *BRCA1* mutations 445 pairs with *BRCA2* mutation	1925 controls	Self-administered questionnaire.	**All types** None 0–3 4–9 ≥10 p-trend **Exclusive wine consumers** None 0–3 4–9 ≥10 p-trend **Wine and other alcohol types** None 0–3 4–9 ≥10 p-trend **Other alcohol types** None 0–3 4–9 ≥10 p-trend	**BRCA2 (n = 445 pairs)** 1.00 0.97 (0.67–1.41) 1.04 (0.67–1.63) 1.16 (0.55–2.45) 0.72 **BRCA2 (n = 246 pairs*)** 1.00 1.09 (0.60–1.95) 1.12 (0.49–2.60) 0.50 (0.08–3.02) 0.92 1.00 0.90 (0.44–1.82) 0.81 (0.34–1.93) 1.38 (0.31–6.15) 0.68 1.00 1.19 (0.41–3.45) 0.54 (0.12–2.34) N/A 0.79	Adjusted for ethnicity, menopausal status, oral contraceptive use, HRT use, smoking, oophorectomy, BMI and parity.	None drinkers were the reference category in the study * informat-iion on type of alcohol consumed	6 stars

Table 15. Nested Case-Control studies of consumption of alcohol consumption and breast cancer risk by genetic polymorphisms and susceptibility								
Reference, study location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Relative risk (95% CI)**	**Adjustment factors**	**Comments**	**Star rating for Quality**
Benzon-Larsen et al 2010 Danish case-control study of 1618 women	809 post-menopausal breast cancer cases	809 controls	Food frequency questionnaires and lifestyle questionnaires	**IRR for breast cancer in relation to genotypes per 10 g alcohol/day** ***ADH1B Arg^{48}His*** GG AA + AG ***ADH1C Arg^{272}Gln*** CC CT TT CT + TT	 740/728 28/40 276/295 359/356 133/117 492/473	 1.08 (1.01–1.16) 1.10 (0.79–1.54) 0.99 (0.89–1.11) 1.12 (1.01–1.24) 1.19 (1.01–1.39) 1.14 (1.04–1.24)	Adjusted for parity, age of first birth, length of school education, duration of HRT use and BMI. Incident rate ratios (IRRs)	6 stars

Table 16. Cohort Studies investigating other breast cancer risk factors and alcohol consumption

Reference, study location, period	Cohort description	Exposure assessment	Exposure categories	Cases	Relative risk (95% CI)	Adjustment factors	Comments	Star rating for quality
Berkey et al 2010 Growing Up Today Study (GUTS), prospective cohort from 50 US states 1996-2007	9057 girls At follow-up in 2005 and 2007 67 BBD cases 6752 non-cases	Interview	**Drinking status Alcohol intake, days/week** Never to less than weekly 1–2 d/wk 3–5 d/wk 6–7 d/wk Drinks/occasion Drinks/day Past-yr Binge drinking: continuous, per binge Past-yr binge drinking 12 or more binges vs none **Age when alcohol intake was reported** 16-17 yrs 18 yrs 19 yrs 20 yrs 21 + yrs		 1.00 (ref) 1.57 (0.80–3.09) 3.01 (1.27–7.14) 5.50 (1.23–24.53) 1.06 (0.92-1.21) 1.50 (1.19 – 1.90) 1.04 (0.99 – 1.10) 1.50 (0.78 – 2.86) 1.52 (0.51- 4.50) 1.45 (0.59 – 3.52) 1.76 (1.19 – 2.60) 1.10 (0.53 – 2.30 1.51 (1.02 – 2.26)	Adjusted for age and BMI	Never to less than weekly was reference category	9 stars

Table 16. Cohort Studies investigating other breast cancer risk factors and alcoholic beverages								
Reference, study location, period	**Cohort description**	**Exposure assessment**	**Exposure categories**	**Cases**	**Relative risk (95% CI)**	**Adjustment factors**	**Comments**	**Star rating for quality**
Liu et al 2013 US Nurses' Health Study II	Total cohort of 91,005 women 10 + years of follow-up 970 cases of proliferative BBD.	High school food-frequency questionnaire (HS-FFQ)	**Drinking status** **Cumulative average alcohol intake between menarche and first full term pregnancy (g/day)** 0 g 0.1–4.9 g/day 5.0–14.9 g/day ≥15 g/day Per 10-unit increase P trend **Cumulative average alcohol intake after first full term pregnancy (g/day)** 0 g 0.1–4.9 g/day 5.0–14.9 g/day ≥15 g/day Per 10-unit increase P trend **Menarche to first birth <10 years** 0 g 0.1–4.9 g/day 5.0–14.9 g/day ≥15 g/day Per 10-unit increase P trend **Menarche to first birth ≥10 years** 0 g 0.1–4.9 g/day 5.0–14.9 g/day ≥15 g/day Per 10-unit increase P trend	 179 549 204 38 970 149 527 122 22 820 106 216 67 10 399 73 333 137 28 571	 1.00(ref) 1.22 (1.02-1.46) 1.31 (1.06 -1.62) 1.40 (0.97 – 2.01) 1.15 (1.02 – 1.29) 0.1 1.00(ref) 1.26 (1.04 -1.51) 1.19 (0.93 -1.52) 1.07 (0.67 – 1.72) 1.01 (0.87 – 1.17 0.93 1.00 (referent) 1.21 (0.94 to 1.57) 1.29 (0.92 to 1.81) 1.12 (0.57 to 2.19) 1.06 (0.85 to 1.31) 0.61 1.00 (ref) 1.10 (0.81 to 1.48) 1.24 (0.88 to 1.75) 1.46 (0.90 to 2.38) 1.20 (1.03 to 1.40) 0.02	Adjusted for age in months, total energy intake, age at menarche, menopausal status, average body size between ages 5 and 10 years, family history of breast cancer in mother or sister(s), current and duration of OC use, and parity and age at first birth.	Non-drinkers were the reference category	7 stars

Table 16. Cohort Studies investigating other breast cancer risk factors and alcoholic beverages

Reference, study location, period	Cohort description	Exposure assessment	Exposure categories	Cases	Relative risk (95% CI)	Adjustment factors	Comments	Star rating for quality
Liu et al 2012 US Nurses' Health Study II	22,117 women in the cohort 659 BDD cases during follow-up 1991-2001	High school food-frequency questionnaire (HS-FFQ	**Drinking status** **Alcohol intake, g/da** None 0.1–4.9 5.0–14.9 ≥15 P for trend Per 10 g/day increase	**No. of BDD cases** 155 193 236 75	 1.00 (ref) 1.11 (0.89–1.38) 1.36 (1.09–1.69) 1.35 (1.01–1.81) 0.03 1.15 (1.03–1.28)	Adjusted for age in months, total energy intake, age at menarche, menopausal status, average body size between ages 5 and 10 years, family history of breast cancer in mother or sister(s), current and duration of OC use, current alcohol consumption, and parity and age at first birth	Non-drinkers were the reference category.	6 stars

Table 16. Cohort Studies investigating other breast cancer risk factors and alcoholic beverages

Reference, study location, period	Cohort description	Exposure assessment	Exposure categories	Cases	Relative risk (95% CI)	Adjustment factors	Comments	Star rating for quality
Cabanas et al 2011 cross-sectional multicentre Spanish population-based study,	3,568 women in the cohort 45-68 years Mammographic density was assessed using the Boyd semi-quantitative scale of 6 categories A =0% B= <10% C=10-25% D=25-50% E= 50-75% F=>75%	Interview using structured questionnaire	**Alcohol drinking (All Women)** **Current Drinker** No Yes **Daily g alcohol** 0 (non-drinker) 0 -< 10 g 10 g or more **Lifetime alcohol use** Never Ex-drinker Current **Age of alcohol initiation** ≤18 years old 19–24 25–40 >40 years old Before/at 18 years old After 18 years old After menarche Before/at menarche Before/at first pregn. After first pregnancy	 1477 2072 1477 1460 613 1312 165 2072 603 540 508 146 1194 603 1734 68 1060 463	 1.00 1.13 (0.99–1.28) 1.00 1.11 (0.97–1.27) 1.18 (0.99–1.41) 1.00 0.98 (0.73–1.32) 1.13 (0.99–1.28) 1.00 1.10 (0.89–1.37) 1.14 (0.92–1.42) 1.28 (0.92–1.79) 1.00 0.88 (0.73–1.05) 1.00 0.66 (0.42–1.03) 1.00 1.11 (0.90–1.36)	Adjusted for a number of confounding factors including age at mammography, BMI, and screening program, plus number of live births, current smoker status, current alcohol status and HRT use	Non-drinker was the reference category	8 stars

Table 16. Cohort Studies investigating other breast cancer risk factors and alcoholic beverages

Reference, study location, period	Cohort description	Exposure assessment	Exposure categories	Cases	Relative risk (95% I)	Adjustment factors	Comments	Star rating for quality
Cabanas et al 2011 Continued	3,568 women in the cohort 45-68 years Mammographic density was assessed using the Boyd semi-quantitative scale of 6 categories A =0% B= <10% C=10-25% D=25-50% E= 50-75% F=>75%	Interview using structured questionnaire	**Pre- or peri menopausal (Women)** **Current Drinker** No Yes **Daily g alcohol** 0 (non-drinker) 0 -< 10 g 10 g or more **Lifetime alcohol use** Never Ex-drinker Current **Age of alcohol initiation** ≤18 years old 19–24 25–40 >40 years old Before/at 18 yr After 18 yrs After menarche Before/at menarche Before/at first pregnancy After first pregnancy	 301 499 301 373 126 263 38 499 225 123 101 21 245 225 451 20 300 100	 1.00 1.04 (0.79-1.36) 1.00 1.07 (0.80–1.42) 0.95 (0.65–1.40) 1.00 0.65 (0.35–1.23) 0.98 (0.74–1.30) 1.00 1.03 (0.69–1.55) 1.03 (0.67–1.57) 2.57 (1.06–6.26) 1.00 0.91 (0.65–1.26) 1.00 0.49 (0.21–1.14) 1.00 1.04 (0.68–1.59)	Adjusted for a number of confounding factors including age at mammography, BMI, and screening program, plus number of live births, current smoker status, current alcohol status and HRT use	Non-drinker was the reference category	**8 stars**

Table 16. Cohort Studies investigating other breast cancer risk factors and alcoholic beverages

Reference, study location, period	Cohort description	Exposure assessment	Exposure categories	Cases	Relative risk (95% CI)	Adjustment factors	Comments	Star rating for quality
Cabanas et al 2011 Continued	3,568 women in the cohort 45-68 years Mammographic density was assessed using the Boyd semi-quantitative scale of 6 categories A =0% B= <10% C=10-25% D=25-50% E= 50-75% F=>75%	Interview using structured questionnaire	**Post-menopausal Women** **Current Drinker** No Yes **Daily g alcohol** 0 (non-drinker) 0 -< 10 g 10 g or more **Lifetime alcohol use** Never Ex-drinker Current **Age of alcohol initiation** ≤18 years old 19–24 25–40 >40 years old Before/at 18 Yr After 18 years After menarche Before/at menarche Before/at first pregn. After first pregnancy	 1174 1573 1174 1087 486 1047 127 1573 378 417 407 125 949 378 1283 48 760 363	 1.00 1.15 (1.00 -1.320 1.00 1.10 (0.94–1.29) 1.26 (1.03–1.53) 1.00 1.13 (0.81–1.58) 1.16 (1.00–1.35) 1.00 1.10 (0.85–1.42) 1.13 (0.87–1.46) 1.12 (0.78–1.62) 1.00 0.90 (0.72–1.12) 1.00 0.70 (0.41–1.19) 1.00 1.12 (0.89–1.41)	Adjusted for a number of confounding factors including age at mammography, BMI, and screening program, plus number of live births, current smoker status, current alcohol status and HRT use	Non-drinker was the reference category	8 stars

Table 17. Combined analysis of studies involving other breast cancer risk factors including alcohol consumption							
Reference, study location, period	**Cohort description**	**Exposure assessment**	**Exposure categories**	**Cases/Control**	**Relative risk (95% CI)**	**Adjustment factors**	**Comments**
Conroy et al. (2012) Maskarinec et al. 2005 Ursin et al. 2003 Nagata et al. 2005	Combined analysis of three case control studies from different populations (Japan, Hawaii and California)	Self-administered questionnaires in the Hawaii and Japan studies and recorded as ever vs. never during face-to-face interviews in the Californian study	**Drinking Status** Never Drinker Ever Drinker By mammographic density Never Drinker <20% 20–35 >35 1 SD (18.4%)c Ever Drinker <20% 20–35 >35 1 SD (18.4%)c High intake (>1 drink/day) <20% 20–35 >35 1 SD (18.6%)	 622/828 585/835 175/288 197/242 250/298 622/828 145/245 173/256 267/334 585/835 17/34 26/37 42/44 85/115	 1.00 1.03 (0.87,1.22) 1.00 1.57 (1.16, 2.11) 1.61 (1.18, 2.19) 1.21 (1.05, 1.39) 1.00 1.48 (1.08, 2.03) 2.05 (1.47, 2.86) 1.29 (1.12, 1.49) 1.00 3.65 (1.30, 10.3) 6.58 (2.28, 19.0) 2.63 (1.62, 4.28)	Adjusted for age at mammogram, menopausal status, HRT use, family history of breast cancer, and location/ethnicity	Never drinkers were the reference category