Meta-analysis of studies of alcohol and breast cancer: methodological issues

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Abstract

Objective: To give an up-to-date assessment of the association of alcohol with female breast cancer, addressing methodological issues and shortfalls in previous overviews.

Methods: Meta-analysis of studies (any language) providing original data on incidence of first primary breast cancer and alcohol. Two reviewers independently extracted data. Study quality assessed by objective criteria; funnel plots examined for publication bias. Risks associated with drinking versus not drinking and dose-response not constrained through the origin estimated using random effects methods.

Results: 98 unique studies were included, involving 75,728 and 60,653 cases in drinker versus non-drinker and dose-response analyses respectively. For studies judged high quality, controlled for appropriate confounders, excess risk associated with alcohol drinking was 22% (95% CI 9 – 37%); each additional 10g ethanol/day was associated with risk higher by 10% (95% CI 5 – 15%). There was no evidence of publication bias. Risk did not differ significantly by beverage type or menopausal status. Estimated population attributable risks were 1.6% and 6.0% in USA and UK respectively.

Conclusions: Taking account of shortcomings in the study base and methodological concerns, we confirm the alcohol-breast cancer association. We compared our results to those of an individual patient data analysis, with similar findings. We conclude that the association between alcohol and breast cancer may be causal.

Key words alcohol, breast cancer, epidemiology, meta-analysis

Introduction

Meta-analysis provides a succinct and statistically powerful summary of data from different studies (REFS). However, there are particular challenges when meta-analysis is applied to observational data, as, unlike randomised controlled clinical trials (RCTs), they are prone to confounding and various biases which might distort the result (Egger *et al*). We explore here the application of meta-analysis to studies of the association of alcohol and breast cancer (REFS) with particular attention to issues of confounding and bias in observational data. We compare our results with those of a recent meta-analysis of individual patient data (IPD), which should be less affected by these problems, and assess the extent to which careful application of meta-analysis methods can aid interpretation and inform policy in an area where RCTs are not feasible.

Methods

Studies were identified by searching all relevant databases (Medline, EMBASE, Pascal (BIDS), Science Citation Index (BIDS), Social Sciences Citation Index (BIDS), Index to Scientific and Technical Proceedings (via BIDS), Biological Abstracts (BIOSIS), Biological Sciences, AIDS and Cancer Research Abstracts, Biology Digest, Conference Papers Index, Cochrane Library, NHS National Research Register (NRR), SIGLE (System for Information on Grey Literature), NTIS (National Technical Information Service), TOXLINE) using key words such as breast, neoplasm, and ethanol, and by scanning the references of identified papers. We used a variety of search methods to minimize publication bias, including citation searching, identification of grey literature and searches of conference proceedings. The initial search was kept broad in order to capture all relevant publications.

A study was eligible for inclusion if it i) gave original data, ii) assessed incidence (not mortality or prevalence), iii) considered first primary breast cancer, iv) was published in any language between January 1st 1966 and December 31st 2003. We identified 298 papers for abstraction of which 187 were excluded because of duplication, inappropriate or missing data, or not reporting original research (i.e. editorial, comment or review), leaving 111 for inclusion in our meta-analysis. These 111 papers related to 98 unique studies.

We then used a simple scoring system to assess study quality as follows: score 1 -- studies with inadequate design (information on alcohol consumption missing for at least 30% of participants, results not adjusted for age, for case-control studies response rate < 60%, for cohort studies loss to follow-up > 30%); score 2 -- studies with acceptable design but insufficient control for confounding; score 3 -- studies with acceptable design and adequate control for confounding, defined as control for three or more of the following variables: a reproductive characteristic (such as age at menarche, age at menopause, age at first birth, parity), family history of breast cancer, socio-economic status, oral contraceptive use/hormone replacement therapy. Data were abstracted and studies scored independently by two reviewers (JK, SH); any discrepancies were referred to a panel (RO, TJ, PE, ST) for resolution.

To avoid violating independence assumptions, studies were included once only; for the same reason, only one set of controls could be included. We therefore decided, a priori, on the following hierarchy: where a study had been published more than once, odds ratios adjusted for the most appropriate confounders were used in preference; otherwise, the analysis that included the greatest

number of participants was used. Where results for more than one control group were reported: community were preferred to hospital controls, and non-cancer to cancer controls.

Studies were categorized as either retrospective (i.e. case-control or retrospective cohort) or prospective (i.e. follow-up studies, including nested case-control studies). None of the cohort studies had more than one set of controls.

Statistical Analysis

Definition of non-drinker varied between studies and in some cases included infrequent drinkers (Table 1, study 8, 15, 16, 22, 30, 68, 71, 72), ex-drinkers (studies 1, 3, 14, 19, 20, 23, 25, 26, 28, 34, 36, 38, 41-43, 51, 52, 54, 57, 59, 60, 62, 64, 77-81, 83, 87-89, 91, 93, 95, 98) or both infrequent and ex-drinkers (studies 4, 10, 13, 37), while in some studies, the term non-drinker was not further defined (studies 2, 5-7, 9, 12, 21, 24, 27, 29, 32, 35, 40, 44, 46, 53, 58, 67, 69, 70, 73, 92, 97, 99). As it was not possible from the published data to reassign individuals to a common definition of non-drinker, the study specific definitions were used, recognising that this might lead to dilution of effect. Similarly, beer, wine and spirits were classified according to definitions used in each publication. Alcohol consumption was converted to g/day using conversion factors appropriate to each country *(7)*. As the data on alcohol consumption were presented categorically, we used the midpoint of each consumption band to estimate dose-response, and for the highest consumption band (which was usually open-ended) we assigned a value half the width of the previous interval above the uppermost cut point *(3)* (we carried out a sensitivity analysis to this choice).

Where estimates of risks were reported for subsets of the study population (e.g. pre/postmenopausal, oestrogen receptor status), we used a Woolfe adjusted method *(8)* to obtain study-wide risk estimates. We carried out an analysis of drinkers versus non-drinkers with use of random effects methods *(9)* to combine log odds ratios across studies, using a moment estimator of the between study variance. Where a study gave a dose-response analysis only, we calculated a crude odds ratio of drinkers versus non-drinkers using the numbers of cases and controls in each consumption band. This was not possible for eight studies where either data on numbers of cases and controls were not given (Table 1, studies 41, 42, 79, 90, 92) or data could not otherwise be pooled (studies 20, 34, 37), so these studies were excluded from the drinkers versus non-drinkers analysis.

Initial exploration of the dose-response data indicated a monotonic increasing function relating alcohol consumption with breast cancer risk; therefore we assumed that the logarithm of the odds ratio varied linearly with alcohol consumption. We calculated dose-response slopes (among drinkers) for each study with available data by use of log linear regression and a variable intercept; that is, we excluded non-drinkers and hence did not constrain the curve to go through the origin. We also compared results with a model that was constrained to go through the origin (zero intercept model). Finally we carried out a meta-analysis of dose-response slopes using random effects methods *(9)*.

We carried out a sensitivity analysis to assess how differing quality criteria (via the simple scoring system) and control for confounding affected the size of the risk estimate, giving seven separate analyses for each question of interest. Meta-regression with random effects *(10)* was used to explore heterogeneity. Characteristics of the studies examined for heterogeneity were as follows: whether the data were collected before or after disease onset; for case-control studies whether the controls were hospital or community based; pre or postmenopausal; and nationality of the study population (USA or Canada/Europe/other). Estimates of population attributable risks *(11)* for the USA and UK (calculated as a weighted average of that in England, Scotland, Wales and Northern Ireland) were obtained from surveys of drinking habits among women stratified by age *(12, 13)*, by use of age-specific cancer registration data for the USA *(14)* and UK *(15)*, and assuming 12g of ethanol in an "average" drink in the USA *(7)* and 8g in a unit of alcohol in the UK *(16)*. All analyses were carried out using Splus.

Results

Table 1 gives case and control numbers (most completely adjusted analyses) and brief details of all included studies, by country and dates of study, for both retrospective and prospective designs.

Drinkers Versus Non-Drinkers

Figure 1 shows crude odds ratios with 95% confidence intervals for the 89 studies included in the analysis of drinkers versus non-drinkers. Studies are ranked according to precision. Overall 29 studies had estimated odds ratio <1 and 60 studies ≥ 1, with combined estimate of 1.11 (95% confidence interval 1.06 – 1.17). Figure 2 gives results of the meta-analysis, shown for seven separate analyses according to degree of control for confounding and criteria for study quality (scores of 1, 2 or 3, see Methods). This sensitivity analysis shows effects of study quality and differing control for confounding on size of the estimate. The estimates ranged from 1.11 (95% CI 1.06-1.17) (least adjusted estimate including all studies, figure 2, a.) to 1.22 (95% CI 1.09-1.37) (multivariate adjustment for confounders in the 19 studies with score 3, figure 2, g.). We analysed data separately for drinkers versus non-drinkers of beer (30 studies), wine (32 studies) and spirits (31 studies) where relevant data were available; combined least adjusted odds ratios were estimated to be 1.16 (95% CI 1.04, 1.29) for beer, 1.14 (95% CI 1.05, 1.24) for wine and 1.14 (95% CI 1.06, 1.23) for spirits.

Dose Response

Figure 3 gives results of the meta-analysis of dose response and shows, amongst drinkers, the higher risk associated with drinking an extra 10g of ethanol a day. Again, results for the seven analyses are shown separately according to degree of control for confounding and study quality. The combined estimate of excess risk ranged from 10% (95% CI 5%, 15%) (multivariate adjustment for confounders in studies with score 3, figure 3, g.) to 13% (95% CI 9%, 17%) (least adjusted, studies with score 2 or 3, figure 3, b.). From the studies judged of high quality with control for appropriate confounders (figure 3, g.), and assuming in the USA an "average" drink contains 12g of ethanol *(7)*, a woman drinking an average of two drinks per day compared to a woman who drinks on average one drink per day has a risk estimated to be 12% (95% CI 7 – 19%) higher. For the UK, where an "average" drink contains 9.5 g ethanol *(7)*, the estimated risk is 10% (95% CI 5 – 15%) higher for two drinks per day compared with one.

Heterogeneity

All analyses showed significant heterogeneity ($P<0.05$) across studies in size of association between alcohol consumption and risk of breast cancer. Of the various factors entered into meta-regression analyses to explore the heterogeneity, retrospective (case control) studies with hospital controls were associated with significantly ($P<0.05$) higher odds ratio estimates than those with community controls (for example, odds ratios of 1.39 (95% CI 1.21 – 1.60) and 1.11 (95%CI 1.02 – 1.21) respectively based on multivariate odds ratios from studies scoring 2 or 3) in the analysis of drinkers versus non-drinkers; otherwise, none of the variables examined in meta-regression significantly reduced the heterogeneity across studies. Figure 4 shows the slopes fitted to each study, using the most completely adjusted analyses for studies that scored 3, for the variable and zero intercept models for dose-response.

Population Attributable Risk

We estimated the population attributable risk among drinkers of alcohol in the USA and UK to be 1.6% and 6.0% respectively; based on the lower and upper 95% confidence interval for the estimated slope, our population attributable risk estimate ranged from 0.9% to 2.4% in USA and 3.2% to 8.8% in the UK.

Sensitivity Analysis

We checked the sensitivity of our results to the dose-response calculation; sensitivity to fixing the first and last points of the dose response in each study (via comparison of zero and variable intercept models and by assigning different values to the highest consumption band where these were open-ended), and by using binomial logistic rather than log linear regression to estimate the dose-response curve at the study level. We also checked sensitivity to alternative choice of controls where these were reported. None of these appreciably altered the results. As can be seen in Figure 1 there was no indication that smaller studies (indicated by large confidence intervals) were more positive. Formal funnel plots *(17)* also did not indicate any evidence for publication bias**.**

Discussion

This is the largest and most comprehensive meta-analysis to date of the relationship of alcohol to breast cancer. We included 98 studies and some 20,000 more cases than the largest of the previous meta-analyses *(6)*. Compared with previous meta-analyses, all of which reported a positive association of alcohol to breast cancer *(1-6)*, we included non-English publications, an assessment of the association of drinking versus not drinking alcohol, extensive sensitivity analysis to quality of included studies and adjustments for confounders, assessment of the dose-response relationship among drinkers (i.e. excluding non-drinkers), and exploration of risk by type of alcoholic beverage. We also include an estimate of population attributable risk. Based on these extensive analyses, the positive association of alcohol to breast cancer is shown to be robust.

Methodological considerations

Bias and confounding can cause serious problems in observational research. A meta-analysis of such data will inherit these problems and therefore has to be conducted carefully to minimize bias, both in the pooling across studies and bias introduced by the analyst. Exploration of heterogeneity is also important, which may be due to bias or to true differences between populations, some of which may be measured but some may be unmeasurable. If heterogeneity cannot be fully explained it may be that a pooled risk estimate is inappropriate.

Bias can be introduced at the design stage of a meta-analysis by including studies favouring a positive result (publication bias) or by abstracting incorrect data. To ensure that publication bias was minimized we undertook an extensive literature search that was not restricted to publications in English and included searching grey literature; we found no evidence of publication bias in our analysis. Two researchers independently abstracted all data and resolved any discrepancies by consensus to reduce observer bias.

Another source of potential bias is at the study level, both design issues and inadequate control for confounding. We carried out a sensitivity analysis to explore these effects by excluding various studies according to pre-defined quality criteria. Our scoring system was simple and objective, as an over-complicated system might introduce subjectivity into the analysis. While our definition of "sufficient control for confounding" was broad enough to encompass a range of potential confounders, it did identify a subset of studies with at least a similar approach to the treatment of confounding. We

further explored the effects of confounding by comparing analyses of least adjustment, at least age adjustment, and multivariate adjustment. Although results varied, positive and significant associations were found in all analyses. Pooling multivariate adjusted results from studies of adequate design with sufficient control for confounding, is likely to be the optimal analysis in terms of accounting for bias, assuming the studies are sufficiently homogeneous.

Consideration of study design is important. Case-control studies are more prone to bias than cohort studies, in particular with respect to exposure assessment and recall bias. Among case-control studies, controls are either hospital or community-based. Ideally controls should be selected independently of exposure, but hospital patients may not be representative of the exposure distribution in the source population (though authors using hospital-based controls generally stated that they attempted to exclude subjects with diseases related to alcohol consumption). We used meta-regression to explore heterogeneity due to these factors. We did not find a significant difference between risks estimated using case-control and cohort studies. However, we did find that among case-control studies, risk estimated using hospital-based controls was significantly higher than that using community-based controls for the drinker versus non-drinker analysis – though a significant positive association was still found after exclusion of studies using hospital-based controls -- but not for the dose-response analysis. . We also explored for heterogeneity according to pre / postmenopausal status and country. Again using meta-regression, we did not find any significant differences.

Misclassification of exposure is another source of bias. There is potential for bias if light, infrequent or ex-drinkers are classified as non-drinkers, as was the case in many studies analyzed. However, this bias is not present in our analysis of dose-response since non-drinkers were excluded (affecting the vertical placement of the slope but not its estimate). In addition, people may under-report the amount of alcohol consumed, especially heavy drinkers (*18*). In an analysis of dose-response such a bias may exaggerate the slope, but should not generate a non-zero slope where there is no association. An important methodological feature was our use of a variable intercept model when assessing the dose-response relationship. There are several reasons for doing this: i) it does not assume that any linear dose-response relationship passes through the origin. For example, at small doses the relationship may be non-linear eg, with lower risks than for zero exposure. Thus a variable intercept model allows for departure from linearity around the origin, while still allowing a linear relationship with doses away from zero; ii) as noted, the reference group (non-drinkers) may be contaminated to some extent by the

inclusion of ex-drinkers or women who drink only occasionally, which makes it more difficult to estimate the effect around the origin; iii) to take account of systematic differences (other than alcohol intake) between women who drink and those who abstain from alcohol, as this may induce an "apparent" effect associated with drinking. iv) if there were a threshold effect at a low dose of alcohol, a zero intercept model would induce a dose-response relationship whereas a variable intercept model would not.

By anchoring all slopes at the same point, the zero intercept model forces the dose-response slopes of each study (i.e. the observed relationship) to differ, whereas the variable intercept model is more accepting of a common relationship, seen as parallel slopes. Therefore, with respect to the estimated dose-response slope, the zero intercept model forces more heterogeneity between the studies.

Comparison with an individual patient data analysis

An individual patient data analysis, where source data are obtained from the investigators rather than relying on published accounts, should give a more comprehensive assessment of risk than a standard meta-analysis, particularly with respect to exposure classification and dealing with confounders. However, IPDs are not widely carried out because they are expensive, time-consuming, and to avoid bias, data are required from all relevant studies, both published and unpublished. In practice, sample data are unlikely to be available from all investigators, and thus, unlike a standard meta-analysis, an IPD analysis may not include all the published studies. On the other hand, inclusion of unpublished data in an IPD analysis may give an advantage over standard meta-analysis.

Not all of the data and analytical problems associated with meta-analysis can be solved by carrying out an individual patient data analysis. For example, the definition of a non-drinker was not consistent across studies, and sometimes included infrequent or ex-drinkers, often reflecting data captured in the original study questionnaire. Study design issues such as low response rate or selection of controls are also problems that cannot be solved by an individual patient data analysis.

The Oxford collaborative study *(6)* is the largest of the previous meta-analyses and included reanalysis of individual data. They were able to include data from 19 unpublished studies which were therefore not included in our analysis. However, they did not include data from 67 studies, involving over 40,000 cases, which have been included in the meta-analysis reported here. The Oxford study did not account for quality of included studies and included non-drinkers in their estimate of dose-

response. Despite these differences, results are comparable with ours, with the Oxford study finding a 7.1% higher risk for each additional 10g ethanol per day compared with our estimate of 10% (95% CI 5-15%) based on studies judged of high quality with appropriate control for confounding.

Biological plausibility

Given the positive association of alcohol intake to breast cancer is robust and not readily explained by bias, confounding or heterogeneity, a causal interpretation needs to be considered. What then, might be the biological mechanism? Whilst alcohol may be directly carcinogenic to the breast, it is more likely to act indirectly through one or more mechanisms. For example, it may influence the metabolism of mammary carcinogens through induction or inhibition of P450 enzymes (19, 20). However, direct evidence for such involvement in breast cancer is lacking (21-23).

Several studies (24-26) have reported that alcohol consumption is associated with an increased amount of mammographically dense tissue in the breast. It has been found that mammographic density is positively associated with plasma insulin-like growth factor I (IGF-I) levels and inversely associated with plasma IGF binding protein 3 (IGFBP-3) in premenopausal women (30). Yu and Berkel (31) reported that moderate consumption of alcohol increases the production of IGFs by the liver and suggested that elevated circulating levels of IGFs may stimulate or promote the development and/or growth of breast cancer.

Breast cancer has a hormonal aetiology (32), and any effects of alcohol on the endogenous hormonal milieu in women could provide a potential mechanism for carcinogenesis. Alcohol increases endogenous oestrogen levels in pre- and postmenopausal women (33, 34), possibly via an increased rate of aromatization of testosterone or decreased rate of oxidation of oestradiol to oestrone (36), and elevated levels of oestrone sulphate, a long-term indicator of oestrogen levels, have been demonstrated in women who regularly consume alcohol (35). [NB: References 27-29 no longer cited]

There were insufficient data in our study to investigate possible interactions with hormone replacement therapy (HRT) and with oestrogen receptor/progesterone receptor (ER/PR) status of the tumour More studies are needed to assess such possibilities.

Summary

To summarize, we have shown that the epidemiological evidence of a positive association between alcohol consumption and risk of breast cancer is robust to the quality and type of study included, and cannot readily be explained by bias or confounding. We have compared our results with those of an analysis of individual patient data, with similar findings from the two approaches. Although the excess risk associated with drinking alcohol is relatively small compared with the major risk factors for breast cancer (*37*), it is one of the few modifiable risk factors associated with breast cancer. Given the high prevalence of drinking, even a small risk linking breast cancer with alcohol, if causal, has serious public health implications in terms of the number of breast cancer cases attributable to drinking alcohol.

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Table 1 Summary of included studies

	Country	Study ID and date	Control	Analysis	# cases in most adjusted analysis	# controls in most adjusted analysis	Confounders in most adjusted analysis
Retrospective studies							
1	Australia	Rohan (1988)	C	E, D	451	451	a, b, c, d, g, h, i, j, k, l, p, practice of breast self-examination
2	Australia	Price (1999)	C	E, D	276	1846	a
3	Brazil	Gomes (1995)	H	E	144	567	a
4	Canada	Rosenberg (1990)	C	E, D	534	1044	a, b, d, f, g, h, i, j, k, l, m, p, religion, dietary intake, neighbourhood
5	Canada	Band (2002)	C	E	1018	1025	a, d
6	Canada	Cotterchio (2003)	C	E, D	2509	3511	
7	Canada	Friedenreich (2001)	C	E	1233	1237	d
8	Canada	Lenz (2002)	H	E, D	556	577	a, b, e, g, h, i, j, l, m, o, p, age at oophorectomy, marital status, proxy respondent status
9	Chile	Atalah (2000)	H	E	170	340	a
10	Denmark	Ewertz (1991)	C	E, D	1361	1226	a
11	Finland	Mannisto (2000)	C	E, D	301	443	
12	France	Le (1984)	H	E, D	500	945	a, b, d, f, g, j, k, l
13	France	Richardson (1991), (1989)	H	E, D	234	325	a, b, c, d, f, g, j, k, l, m
14	France	Viel (1997)	C	E, D	154	154	a, f, total calorie intake
15	Germany	Kropp (2001)	C	E, D	706	1381	a, d, e, f, j, l
16	Germany	Nienhaus (2001)	H	E, D	681	651	a, d, j, survey location
17	Greece	Katsouyanni (1994)	C	E, D	798	1528	a, b, d, f, g, m, total energy intake, place of birth
18	Holland	Van't Veer (1989)	C	E, D	116	161	a, d, f, g, j, l, m, p, region, season, energy per cent fat intake
19	Italy	Talamini (1984)	H	E, D	368	373	a, b, c, f, g, h, i, l, m, p, marital status, food intake
20*	Italy	Ferraroni (1991), (1993)	H	E, D	210	214	a, b, c, d, f, g, j, l, m
21	Italy	La Vecchia (1989), Soler (1999), La Vecchia (1985)	H	E, D	2402	2220	a, b, c, d, f, g, h, i, j, l, p, geographic area, marital status, intake of meat, fats and green vegetables
22	Italy	Ferraroni (1998)	H	E, D	2425	2437	a, b, f, g, j, l, m, total energy intake
23	Italy	Toniolo (1989)	C	E, D	250	499	a, d, m, total energy intake
24	Sicily/ Italy	Cusimano (1989)	H	E	143	286	a, l

25	Italy	Franceschi (1991)	H	E, D	132	499	a, g, l, meat and vegetable intake
26	Japan	Kato (1989)	H	E	1740	8920	a
27	Japan	Hirose (1995), Hirose (2003)	H	E, D	1036	20797	a, d
28	Japan	Kikuchi (1990)	C	E	48	48	a
29	Japan	Kato (1992)	H	E	899	899	
30	Korea	Choi (2003)	H	E	346	377	a, j
31	New Zealand	Sneyd (1991)	C	E, D	840	1782	a, b, f, l, p
32	Nigeria	Adebamowo (1999)	H	E	251	251	
33	Poland	Pawlega (1992)	C	E	122	239	a, d, l, m, p, marital status, no. of persons in household
34	Russia	Zarridze (1991)	C		139	139	a, b, d, g
35	Spain	Viladiu (1996)	C	E, D	330	346	a, c, d, g, j
36	Spain	Martin-Moreno (1993)	C	E, D	762	988	a, b, c, d, g, j, l, m, geographic region, total energy intake
37	Sweden	Ranstam (1995)	C		393	449	
38	Sweden/ Norway	Adami (1988)	C	E, D	422	527	a, b, d, f, g, i, j, k, l, p
39	Switzerland	Levi (1996)	H	E, D	230	507	a, c, d, f, g, h, i, j, l, p, marrital status
40	Switzerland	Morabia (1996)	C	E, D	150	336	a, b, g, i, j, k, l, m, saturated fat intake
41	UK	Meara (1989)	H	D	998	998	a, b, d, g, i, j, l, m, p
42	UK	Meara (1989)	C	D	118	118	a, b, d, g, i, j, l, m, p
43	UK	Smith (1994)	C	E, D	753	753	a, b, d, e, f, g, i, j, k, p
44	USA	Boice (1995)	C	E, D	521	2611	a, b, c, d, f, g, j, k
45	USA	Vachon (2001)	C	E	558	8744	a, p, birth cohort, familial clustering, source of information
46	USA	Dupont (1989)	H	E	113	2483	a, length of follow-up
47	USA	Byers (1982)	H	E, D	1297	751	a
48	USA	Harris (1988)	H	E	1467	10178	a
49	USA	Harvey (1987)	C	E, D	1524	1896	
50	USA	O'Connell (1987)	C	E	275	1519	a
51	USA	Webster (1983), Chu (1989)	C	E, D	1206	1256	a, d, g, j, k, l, m, p, religion
52	USA	Young (1989)	C	E, D	255	358	
53	USA	Nasca (1994), (1990)	C	E, D	1608	1609	a, d, g, j, k, o
54	USA	Miller (1989)	H	E	404	421	I
55	USA,	Enger (1999), Longnecker	C	E, D	1844	1817	a, d, q

	Canada, Western Europe	(1995)					
56	USA	Bowlin (1997)	C	E, D	1211	1214	a, b, e, g, j, k, l, p, religion, marital status, ever pregnant
57	USA	Freudenheim (1995)	C	E, D	738	810	a, b, d, g, j, k, l, m, intake of calories, and various nutrients and vitamins
58	USA	Harris (1992)	H	E, D	604	520	a, b, c, d, e, f, g, i, j, p
59	USA	Rossing (1996)	C	E, D	537	489	a, d
60	USA	Longnecker (1995)	C	E, D	6662	9163	a, b, f, g, j, k, l, m
61	USA	Brinton (1997), Swanson (1997)	C	E, D	1579	1442	a, b, d, f, g, i, j, k, m, o
62	USA	Newcomb (1999)	C	E, D	3623	3783	a, d
63	USA	Baumgartner (1999)	C	E, D	688	804	a, b, d, e, f, g, i, j, k, l, m, o, p, physical activity, energy intake, energy adjusted fat intake
64	USA	Kabat (1997)	C	E, D	42	64	a, f, m, o, p, eostrogen metabolite ratio, chronic condition
65	USA	Kinney (2000)	C	E,D	856	784	a, b, f, j, k, l, m, o, p
66‡	USA	Zheng (2003)	H	E, D	317	334	a, d, e, g, j, m
67	USA	Claus (2001)	C	E	959	986	a, b, c, d, f, g, h, i, j, k, l, m, o, p, history of at least one screening mammogram one year before interview
68	USA	Wu (2003)	C	E	490	591	
69	USA	Zhu (2003)	C	E, D	288	291	a, b, d, f, g, h, j, k, l, m, p, employment, marital status, number of people in household, religion, use of electric blanket/matress pad, physical activity, on a diet to lose weight, number of miscarriages, having an infertility test, intake of vitamins, total energy intake
70	USA	Gammon (2002)	C	E	1508	1556	a
71	USA	Li (2003)	C	E, D	967	998	a, j, m
72	USA	Wrensch (2003)	C	E, D	285	286	a, b, d, e, f, h, i, j, k, l, m, p, religion, number of mammograms, previous radiation treatment
73	USA	Xiong (2001)	C	E	100	105	
74	USA/Canada /Israel	Rosenberg (1982)	H	E	1146	2694	a, c, d, f, g, j, k, l, n, o, religion, geographic area, year of interview, number of previous hospital admissions

75	Uruguay	Ronco (1999)	H	E	400	405	
76	†	Royo-Bordonada (1997)	C	E, D	315	364	a, b, c, d, f, g, h, j, k, m, p
77	Combined analysis	Howe (1991)	C	E, D	1573	1974	a, d

Prospective studies

78	Canada	Friedenreich (1993), Rohan (2000)		E, D	1336	5238	a, b, d, f, j, practice of breast self-examination, study centre, energy intake, study allocation
79	Denmark	Hoyer (1992)		D	51	5156	
80	Denmark	Tjonneland (2003)	C	E, D	416	23533	a, f, g, h, k, l, m
81	Holland	van den Brandt (1995)		E, D	422	1579	a, b, c, d, f, g, i, j, k, l, m, p, energy intake
82	Sweden	Holmberg (1995)		E, D	276	452	a, f, g, j, l, m
83	Sweden	Lahmann (2003)	C	E, D	246	11913	
84	USA	Zhang (1999)		E, D	221	2543	a, c, d, f, g, h, l, m, p, physical activity index
85	USA	Zhang (1999)		E, D	66	2218	a, b, c, d, f, h, l, m, p, physicical activity index
86	USA	Simon (1991)		E, D	87	1827	a, b, f, g, j, l, m, p, subscapular and triceps skin folds
87	USA	Hiatt (1984)		E, D	838	87570	a
88	USA	Schatzkin (1987)		E, D	121	7067	a, b, d, f, g, j, l, m, dietary fat
89	USA	Barrett-Connor (1993)		E	15	575	
90	USA	Hiatt (1988)		D	287	58044	a, m, o, p
91	USA	Zhang (1999), Willett (1987), Chen (2002)		E, D	3483	85335	a, b, c, d, f, g, h, j, k, m, length of follow-up, total energy intake
92	USA	Graham (1992)		D	367	3670	a, b, d, f, g, h, i, j, k, l, m, p, fat, fibre and energy intake
93	USA	Cerhan (1998)		E	46	1760	
94	USA	Lucas (1998)		E, D	121	7894	a, b, c, d, f, g, h, j, k, m, p, physical activity
95	USA	Potter (1995), Gapstur (1992)		E, D	939	36166	a, b, f, g, i, j, m, q, type of menopause, history of bilateral oophorectomy
96	USA	Garland (1999)		E, D	435	116236	a, b, d, f, g, j, k, m
97	USA	Feigelson (2003)	C	E, D	1303	65258	a, b, c, f, g, h, j, k, l, m, o, dietary folate, methionine, multivitamin use, mammographic history, physical activity, adult weight gein, energy intake
98	USA	Horn-Ross (2002)	C	E, D	681	104454	a, b, f, g, j, o, daily caloric intake, physical activity
99	Western	Clavel-Chapelon (2002)	C	E, D	2758	276473	a, b, f, g, l, m, p, energy intake, follow-up time

	Europe		
100	Combined analysis	Smith-Warner (1989)	a, b, d, f, g, h, i, j, k, l, m, p, fat, fibre and energy intake

Footnote
* There is a small overlap of cases between this study and study 21, it is therefore only used in a sensitivity anlaysis
† From 5 countries – Germany, Switzerland, Northern Ireland, Holland, Sapin
‡ Overlap of cases with 67, used in a sensitivity analysis for "ever never" and in the main analysis for dose-response

H = case-control study with hospital controls, C = case-control study with community controls, E = "ever" versus "never" drinkers analysis, D = dose-response analysis

Key to confounders: a=age, b=age at menarche, c=age at menopause, d=menopausal status, e=breast feeding, f=parity, g=age at first birth, h=HRT use, i=oral contraceptive use, j=family history of breast cancer, k=history of biopsy for benign breast disease, l=socio-economic status, m=BMI, n=obesity, o=ethnicity, p=smoking status, q=oestrogen receptor status

Figure 1 Individual study estimates of crude odds ratios (log scale) of the risk of breast cancer associated with drinkers versus non-drinkers and 95% confidence intervals

The estimates are ranked top to bottom by precision. Area of box showing study point estimate is proportional to precision. Study ID (Table 1) is given down the left-hand side. The diamond at the bottom of the plot denotes the random effects estimate of the combined result.

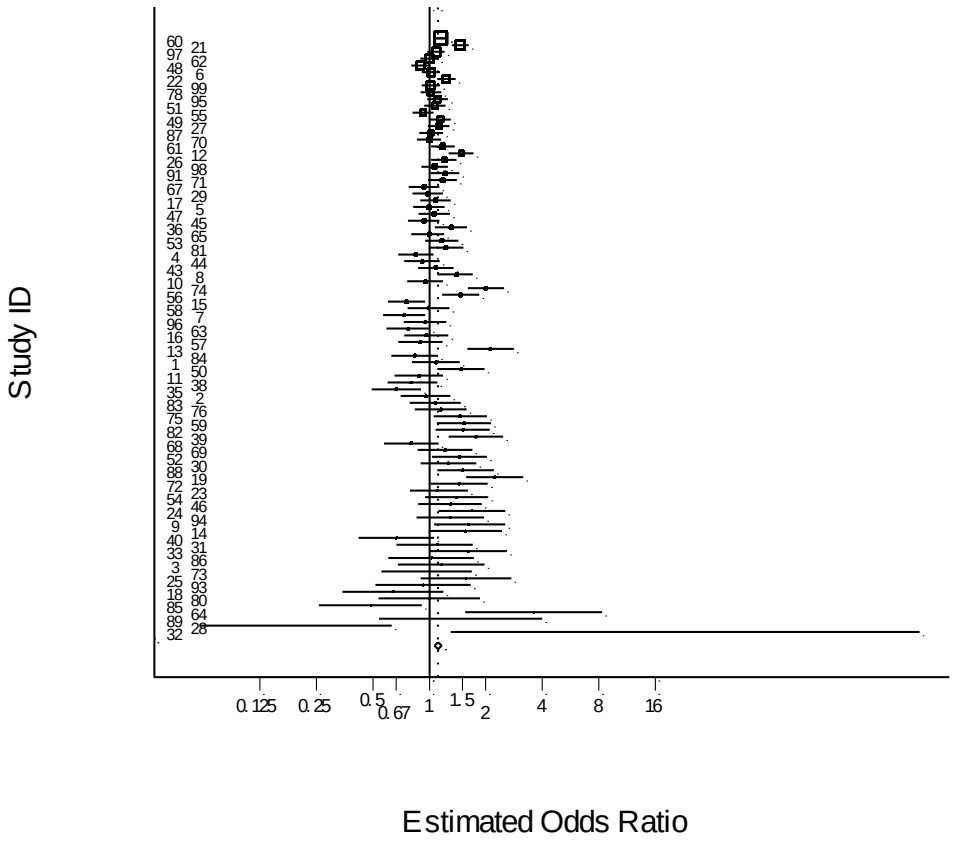

Figure 2 Estimates of the combined odds ratio and 95% confidence interval for drinkers versus non-drinkers

Each line corresponds to an analysis with different inclusion criteria according to study quality (see Methods) and degree of confounding. Odds ratios combined in each analysis are a) least adjusted odds ratios from all studies, b) least adjusted odds ratios, studies with score 2 or 3, c) at least age adjusted odds ratios from all studies, d) at least age adjusted odds ratios, studies with score 2 or 3, e) multivariate adjusted odds ratios from all studies, f) multivariate adjusted odds ratios, studies with score 2 or 3, g) multivariate adjusted odds ratios, studies with score 3.

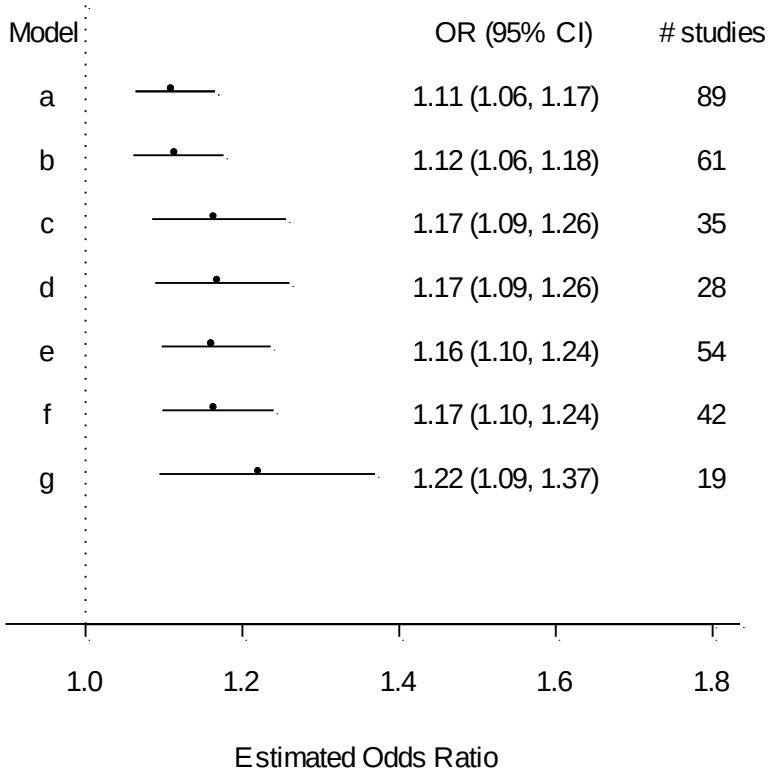

Figure 3 Estimates of the increase in risk of breast cancer amongst drinkers per 10g ethanol/day

Each line corresponds to an analysis with different inclusion criteria according to study quality (see Methods) and degree of confounding. a) – g) as in Figure 2.

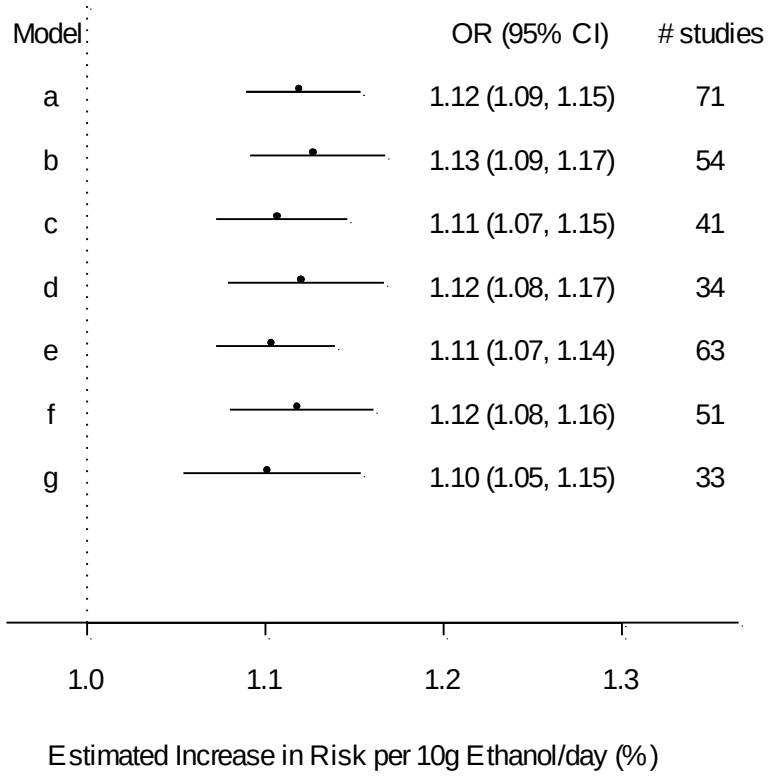

Figure 4 Comparison of variable and zero intercept models

Fitted slopes for most adjusted odds ratios from studies scoring 3. Left figure shows the slopes fitted using the variable intercept model, right figure shows the slopes fitted using the zero intercept model.