Dose-Dependent Association Between Wine Drinking and Breast Cancer Risk - Meta-Analysis Findings

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Abstract

Purpose: To investigate any potential association between wine and breast cancer risk. Materials and Methods: We quantitatively assessed associations by conducting a meta-analysis based on evidence from observational studies. In May 2014, we performed electronic searches in PubMed, Embase and the Cochrane Library to identify studies examining the effect of wine drinking on breast cancer incidence. The relative risk (RR) or odds ratio (OR) were used to measure any such association. Results: The analysis was further stratified by confounding factors that could influence the results. A total of twenty-six studies (eight case–control and eighteen cohort studies) involving 21,149 cases were included in our meta-analysis. Our study demonstrated that wine drinking was associated with breast cancer risk. A 36% increase in breast cancer risk was observed across overall studies based on the highest versus lowest model, with a combined RR of 1.0059 (95%CI 0.97-1.05) in dose-response analysis. However, 5 g/d ethanol from wine seemed to have protective value from our non-linear model. Conclusions: Our findings indicate that wine drinking is associated with breast cancer risk in a dose-dependent manner. High consumption of wine contributes to breast cancer risk with protection exerted by low doses. Further investigations are needed for clarification.

Keywords: Breast cancer - risk factor - wine - alcohol - dose-dependent influence - meta-analysis

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Introduction

Breast cancer is an important public health issue, as it is the leading malignancy with high incidence and mortality among women globally (Arveux and Bertaut, 2013). Several risk factors, such as first-degree family history, breast cancer susceptibility gene 1 (BRCA1) and BRCA2 mutations, were identified and related to breast cancer (Espie et al., 2013). Wine, as a special type of alcohol beverage, contains more than one chemoprotective chemical, including iso-flavone phytoestrogens, flavones, and procyanidin B dimmers (Eng et al., 2003; Key et al., 2006). In 2007, the International Agency for Research on Cancer (IARC) classified alcohol as carcinogenic to several human malignancies (Seitz and Stickel, 2007). Since then, the association between alcohol and breast cancer still remain complex and not well understood, such as the different effect of beverage choice (wine, liquor or beer). There was little evidence on whether different types of alcoholic beverage, including wine, liquor, and beer, play similar roles.

Meanwhile the dose-risk relation of wine intake with breast cancer hasn’t yet been completely studied in detail. In particular, it is still not clearly established whether low dose wine consumption was associated with protective effect on breast cancer. It seems that more precise quantification and identification of a possible threshold for effect of wine are needed to be decided.

We herein performed a dose-response meta-analysis to investigate the potential association between wine and breast cancer risk.

Materials and Methods

Search strategy and selection criteria

Medline, Embase, and the Cochrane Library were from studies seem controversial (Willett et al., 1997; Higgins et al., 2003; Bessaoud and Daures, 2008). Some issues about alcohol and breast cancer still remain complex and not well understood, such as the different effect of beverage choice (wine, liquor or beer). There was little evidence on whether different types of alcoholic beverage, including wine, liquor, and beer, play similar roles.

Meanwhile the dose-risk relation of wine intake with breast cancer hasn’t yet been completely studied in detail. In particular, it is still not clearly established whether low dose wine consumption was associated with protective effect on breast cancer. It seems that more precise quantification and identification of a possible threshold for effect of wine are needed to be decided.

We herein performed a dose-response meta-analysis to investigate the potential association between wine and breast cancer risk.

Materials and Methods

Search strategy and selection criteria

Medline, Embase, and the Cochrane Library were
searched from inception to May 8th 2015 with the following subject heading terms and/or text words: “breast cancer”, “breast neoplasm” in combination with “wine”, “alcohol”, “drinking”, “beverage”. In addition, a broader search on diet and breast cancer was also conducted. Further, the reference lists of retrieved articles and relevant review articles were scanned. No language restrictions were imposed.

According to “Food, nutrition, physical activity, and the prevention of cancer: a global perspective”, wine was defined as alcoholic drinks produced from grapes and contain between around 9 to 15 per cent alcohol; The composition of wine depends on the grape varieties used, including red wine, white wine, sparkling wine, et al (Wiseman, 2008). Studies were included if they (i) had a case-control or cohort design; (ii) evaluated the association between wine drinking and breast cancer risk; (iii) presented odds ratio (OR), relative risk (RR) estimates with 95% confidence interval (CI). If publications were duplicated or articles from the same study population, the publication with a larger scale was included. Non-peer-reviewed articles, ecologic assessments, correlation studies, experimental animal studies and mechanistic studies were excluded. All the process was conducted by two independent investigators (Jiayan Chen and Hongcheng Zhu).

Data extraction and quality assessment
Two independent investigators (Jiayan Chen and Hongcheng Zhu) extracted the following data from each study that met the criteria for inclusion: first author, year of publication, geographic regions, journal, number of cases, cohort size, cohort name and duration of follow-up (cohort studies), type of cancer, consumption categories, adjusted ORs, or RRs with 95%CI, and adjusted variables. When several risk estimates were presented for pre- and post-menopause, year group, and et al. the detailed information was also extracted.

A 9-star system on the basis of the Newcastle-Ottawa Scale was used to assess the study quality from 3 broad perspectives. Considering that there is possibly a direct or indirect caloric intake with breast cancer risk, an energy-adjusted residual or nutria-density model was added as an item for the scoring system (Willett et al., 1997). Hence, the full score was 10 stars, and a study with ≥7 awarded stars was defined the high-quality study (Willett et al., 1997).

Data synthesis and statistical analyses
RRs with 95% CIs were calculated using random-effects model. ORs were considered to be equivalent to RRs since breast cancer is a rare outcome. If association estimations were provided separately from subtypes or age group of cancer, combined RRs with 95% CIs were used in the overall analysis.

Statistical analyses based on comparison of the highest intake category with the lowest intake category (which included people do not drink) were conducted. Subgroup analyses were conducted by study quality, study design (cohort studies and case-control studies), control source (population-based and hospital-based), menopause, geographic region (Europe and North America), country (Italy, France, USA, and Canada) and study adjustments (family history, body mass index, total energy, other alcohol/beverage, smoking, menopause, hormone therapy, pregnancy, and education).

In addition, categorical dose-response regression analysis was utilized. The fixed-effects linear model was first used and non-linearity test was checked. Otherwise, Flexible nonlinear meta-regression models were used. The amount of wine consumption was converted into grams of ethanol per day using the following equivalencies: 1 drink=12.5g, if not otherwise specified in the original report; 1 ounce=28.35g. Midpoint of the range of categories reported in the original reports was assigned as levels of wine consumption, and for open-ended upper categories, as 1.2 times its lower bound. Wines are estimated as 12v/v of ethanol approximately according to the majority products in the market.

Heterogeneity among studies were examined using the chi-square test, defining a significant heterogeneity as a P value < 0.10 and quantified the inconsistency using the I-squared statistic (Higgins et al., 2003). Publication bias was evaluated by generating funnel plots and the Egger’s test (Egger et al., 1997).

Results
Study characteristics
26 eligible articles were identified from the database (Figure 1), including 8 cohort studies and 18 case-control studies (Table 1 and 2) (Webster et al., 1983; Le et al., 1984; Talamini et al., 1984; La Vecchia et al., 1985; Willett et al., 1987; Adami et al., 1988; Hiatt et al., 1988; Richardson et al., 1989; Toniolo et al., 1989; Rosenberg et al., 1990; Ferraroni et al., 1991; Martin-Moreno et al., 1993; Freudenheim et al., 1995; Levi et al., 1996; Viel et al., 1997; Ferraroni et al., 1998; Zhang et al., 1999; Horn-Ross et al., 2002; Lenz et al., 2002; Mattisson et al., 2004; Petri et al., 2004; Levi et al., 2005; Bissonauth et al., 2009; Dennis et al., 2010; Kabat et al., 2011; Link et al., 2013). Fourteen studies were conducted in Europe, Figure 1. Reference Searched and Selection of Studies in the Meta-analysis
eight in America, three in Canada and one across both continents. A total of 1,8106 breast cancer cases were included. Study-specific quality scores are summarized in Tables 3 and 4, which ranged from 4 to 10 stars with a median score of 8 stars. High-quality studies (≥7 stars) included 10 case-control studies and all 8 cohort studies.

### Association between wine and breast cancer

The summary RR was 1.36 (95% CI: 1.20-1.54, P<0.001) across all the studies based on the highest versus lowest model (Figure 2), consistent with the results of cohort studies (RR=1.25, 95% CI: 1.07-1.46, P=0.037), case-control studies (RR=1.44, 95% CI: 1.19-1.73, P<0.001), and high-quality (score ≥7) studies (RR=1.26, 95% CI: 1.12-1.43, P=0.002).

### Subgroup analysis

The subgroup analysis on geographic area showed an RR of 1.66 (95% CI: 1.35-2.05, P<0.001) in European studies, an RR of 1.18 (95% CI: 1.09-1.27, P=0.58)

#### Table 1. Characteristics of Prospective Cohort Studies of Wine Drinking and Breast Cancer Risk *

| Author, year, region | Journal | No. of cases | Cohort size, cohort name and duration of follow-up | Cancer type | Consumption categories | Adjusted RR (95% CI) | Adjusted variables |
|----------------------|---------|--------------|------------------------------------------------|-------------|-----------------------|---------------------|-------------------|
| Link LB, 2013, USA   | Am J Clin Nutr | 4140 women   | 91779 women, California Teachers Study cohort, 14y (1995-2009) | breast cancer | Q1 | 1.0 (Referent) | Race-ethnicity/birthplace, family history of breast cancer, age at menarche, parity/age at first full-term pregnancy, average daily calorie intake, physical activity, socioeconomic status, history of a benign breast biopsy and its interaction with time-dependent age, BMI, height, menopausal status/hormone therapy use, and the other 4 dietary patterns |
| Kabat GC, 2011, USA  | Cancer Causes Control | 300 TNBC and 2479 ER+ postmenopausal women | 148030 women, Women’s Health Initiative cohort, 5y (1993-1998) | TNBC | <3 serving/week | 0.95 (0.73-1.22) | age, education, ethnicity, BMI, waist circumference, oral contraceptive use, hormone therapy, age at menarche, age at first birth, age at menopause, pack-years of smoking, family history of breast cancer, history of breast biopsy, mammogram with in past 2 years, physical activity, and treatment/control arm assignment in the estrogen alone, estrogen plus progestin, calcium plus vitamin D, and dietary modification trials |
|                      |         |              |                                               | ER+ | ≥3 serving/week | 0.75 (0.48-1.17) | |
| Mattisson I, 2004, Sweden | Int J Cancer | 342 women postmenopausal women, Malmö Diet and Cancer Cohort, 10y (1991-2001) | 11726 breast cancer | Abstainers | 1.21 (0.86-1.72) | diet interviewer, method version, season of diet interview, age at baseline, TE, change of dietary habits, height, waist, current hormone use, age at birth of first child, age at menarche, leisure time physical activity, smoking habits, educational level |
|                      |         |              |                                               | ≤2.9 cl/day | 1.0 (Referent) | |
|                      |         |              |                                               | >2.9 to ≤20.8 cl/day | 0.88 (0.69-1.13) | |
|                      |         |              |                                               | >20.8 cl/day | 2.11 (1.24-3.60) | |

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### Table 1. Characteristics of Prospective Cohort Studies of Wine Drinking and Breast Cancer Risk* (continued)

| Author, year, region | Journal | No. of cases | Cohort size, cohort name and duration of follow-up | Cancer type | Consumption categories | Adjusted RR (95%CI) | Adjusted variables |
|----------------------|---------|--------------|-----------------------------------------------|-------------|------------------------|---------------------|--------------------|
| Petri AL., 2004, Denmark | Alcohol Clin Exp Res | 76 premenopausal and 397 postmenopausal women | 13074 women, the Copenhagen City Heart Study and the Research Center for Prevention and Health | Premenopausal | <1 per week | 1.0 (Referent) | age, cohort, parity, and use of HRT |
|                       |         |              |                                               | 1-3 per week | 0.83 (0.46-1.50) |
|                       |         |              |                                               | 4-6 per week | 0.87 (0.41-1.82) |
|                       |         |              |                                               | >6 per week | 1.43 (0.67-3.01) |
|                       |         |              |                                               | <1 per week | 1.0 (Referent) |
|                       |         |              |                                               | 1-3 per week | 0.97 (0.70-1.35) |
|                       |         |              |                                               | 4-6 per week | 1.38 (0.92-2.07) |
|                       |         |              |                                               | >6 per week | 1.12 (0.70-1.82) |
|                       |         |              |                                               | <1 per week | 1.0 (Referent) |
|                       |         |              |                                               | 1-3 per week | 1.22 (0.80-1.90) |
|                       |         |              |                                               | 4-6 per week | 0.96 (0.48-1.91) |
|                       |         |              |                                               | >6 per week | 0.81 (0.40-1.65) |
| Horn-Ros PL, 2002, USA | Cancer Causes Control | 711 women | 111526 women, the California Teachers Study, 3y (1995-1998) | Postmenopausal (<70 years) | <5 g/day | 1.0 (0.9-1.2) | age, race, daily caloric intake, family history of breast cancer, age at menarche, nulliparity/age at first full-term pregnancy, physical activity, and an interaction term for body mass index and menopausal status |
|                       |         |              |                                               | 5-19 g/day | 1.3 (1.0-1.6) |
|                       |         |              |                                               | ≥20 g/day | 1.7 (1.2-2.4) |
|                       |         |              |                                               | None | 1.0 (Referent) |
|                       |         |              |                                               | 0.1-<1.0 drinks/week | 0.9 (0.6-1.4) |
|                       |         |              |                                               | 1.0-<3.0 drinks/week | 0.7 (0.3-1.7) |
|                       |         |              |                                               | ≥3 drinks/week | 1.0 (0.7-1.5) |
|                       |         |              |                                               | None | 1.0 (Referent) |
|                       |         |              |                                               | 0.1-<1.0 drinks/week | 1.0 (0.5-2.1) |
|                       |         |              |                                               | 1.0-<3.0 drinks/week | 0.7 (0.4-1.4) |
|                       |         |              |                                               | ≥3 drinks/week | 0.7 (0.3-1.5) |
|                       |         |              |                                               | Abstainers | 1.0 (Referent) |
|                       |         |              |                                               | Infrequent | 0.91 (0.51-1.60) |
|                       |         |              |                                               | Regular | 1.36 (0.86-2.17) |
| Zhang Y., 2000, USA | Am J Epidemiol | 221 (Original Cohort) and 66 (Offspring Cohort) women | 2284 women (Offspring Cohort), 24y (1971-1993) | breast cancer | 0.1-<1.0 drinks/week | 0.9 (0.6-1.4) | education, height, body mass index, physical activity index, age at first pregnancy (Original Cohort only), parity, age at menarche (Offspring Cohort only), age at menopause, average number of cigarettes smoked, postmenopausal estrogen use, and intake of other alcoholic beverages |
|                       |         |              |                                               | 1.0-<3.0 drinks/week | 0.7 (0.4-1.4) |
|                       |         |              |                                               | ≥3 drinks/week | 0.7 (0.3-1.5) |
|                       |         |              |                                               | None | 1.0 (Referent) |
|                       |         |              |                                               | 0.1-<1.0 drinks/week | 1.0 (0.5-2.1) |
|                       |         |              |                                               | 1.0-<3.0 drinks/week | 0.7 (0.4-1.4) |
|                       |         |              |                                               | ≥3 drinks/week | 0.7 (0.3-1.5) |
|                       |         |              |                                               | Abstainers | 1.0 (Referent) |
|                       |         |              |                                               | Infrequent | 0.91 (0.51-1.60) |
|                       |         |              |                                               | Regular | 1.36 (0.86-2.17) |
| Hiatt RA., 1988, USA | Cancer Res | 303 women | 69000 women, members of a large prepaid health plan in Northern California, 24y (1960-1984) | breast cancer | Infrequent | 0.91 (0.51-1.60) | age, race, Quetelet index, and smoking. |
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in North American (American and Canadian) studies. Notably, the RR was 2.12 in French studies (95% CI = 1.37–3.27, \( P = 0.024 \)) and 1.89 in Italy studies (95% CI = 1.17–3.07, \( P = 0.011 \)), respectively. Three studies reported data for premenopausal breast cancer patients, with a pooled RR of 1.79 (95% CI = 1.34–2.40, \( P = 0.0344 \)), while

| Author, year, region | Journal | No. of cases | Cohort size, cohort name and duration of follow-up | Cancer type | Consumption categories | Adjusted RR (95% CI) | Adjusted variables |
|----------------------|---------|--------------|--------------------------------------------------|-------------|-----------------------|---------------------|------------------|
| Willett WC, 1987, USA | New Eng J Med | 496 women | 89538 women, The Nurses’ Health Study Cohort, 8y (1976-1984) | breast cancer | None | 1.0 (Referent) | Five-year age categories, dummy variables for beer, wine, and liquor with “no alcohol” as the common reference group |

\( ^* \) RR = relative risk (rate ratio or hazard ratio); CI = confidence interval; BMI = body mass index; TNBC = triple-negative breast cancer; ER = estrogen receptor;

5 studies had results for postmenopausal cases, with a RR of 1.20 (95% CI = 0.94–1.53, \( P = 0.027 \)). When data were adjusted by some confounding factors (family history, body mass index, total energy, other alcohol beverage smoking, menopause, hormone therapy, pregnancy, education, physical activity), the association was still statistically significant (Table 5).

Dose-response analysis

Furthermore, dose-response meta-analyses were conducted. Most of the slope of each study was greater than 0, indicating that more wine consumption might
lead to higher risk of breast cancer (Table 6). The fixed-effects model was first used. The heterogeneity between studies was detected. Therefore, a random-effect model was implemented next. Table 7 showed the combined RR was 1.0059 (95% CI=0.9670-1.0464, p=0.6156) for overall meta-analysis, indicating a 0.59% increase in the risk of breast cancer for each increment of 1g per day ethanol from wine under random effect model. The test of non-linearity was significant ($\chi^2=1763.9$ P<0.0001), thus a non-linear dose-response model was performed. Figure 3 and 4 illustrated RR variation of breast cancer according to curvilinear thresholds of regular ethanol/wine consumption. Wine was associated with breast cancer in a dose-dependent manner. The risk decreased when women who consumed below 10g (ethanol) / 80g (wine) [<1 standard drink] per day. The risk declined to the bottom at the threshold of 5g/d of ethanol and 40g/d of wine, respectively.

**Publication bias**

Figure 5 shows the contour-enhanced funnel plot of studies on the association between wine and breast cancer.

### Table 2. Characteristics of Case-control Studies of Wine Drinking and Breast Cancer Risk*

| Author, year, region | Journal | No. of cases | No. and type of control subjects | Cancer type | Consumption categories | Adjusted OR (95% CI) | Adjusted variables |
|----------------------|---------|--------------|----------------------------------|-------------|------------------------|----------------------|-------------------|
| Dennis J, 2010, eight countries of Europe and North America | The Breast | 541 (BRCA1 mutation) and 148 (BRCA2 mutation) women | 501 (BRCA1 mutation) and 141 (BRCA2 mutation) women, population based | BRCA1 mutation | None | 1.0 (Referent) | 0.3 per week: 0.62 (0.45-0.87), 4-9 per week: 0.82 (0.41-1.67), ≥10 per week: 0.39 (0.11-1.45) |
| Bissomauth V, 2009, Canada | Breast J | 78 women | 103 women, population based | Noncarriers of BRCA1 or BRCA2 mutation | ≤5 oz./week: 1.06 (0.32-1.97), >5 to ≤10 oz./week: 1.16 (0.18-2.58) | Age, education, physical activity, smoking, coffee consumption and total energy |
| Levi F, 2005, Switzerland | Eur J Cancer Prev | 369 women | 602 women, hospital based | breast cancer | T1 b | 1.0 (Referent) | T2: 1.05 (0.18-6.25), T3: 1.60 (0.28-9.28) |
| Lenz SK, 2002, Canada | Cancer Causes Control postmenopausal women | 577 women, hospital based | breast cancer | 556 | Never | 1.0 (Referent) | 46.8 | 30.0 | 12.77-13.45 g/day | 1.24 (0.71-1.37), 1.24 (0.71-1.37), 1.24 (0.71-1.37) | Age, centre, education, age at first birth, parity, age at menarche, BMI and family history of breast cancer |

*The table includes data from multiple studies, showing the number of cases, type of control subjects, cancer type, consumption categories, adjusted OR with 95% CI, and adjusted variables for the association between wine drinking and breast cancer risk.
risk. The graph appears to be symmetrical, suggesting the absence of a publication bias. Likewise, we found no asymmetry according to the Egger’s test ($P=0.151$) and Begg’s test ($P=0.243$).

Table 2. Characteristics of Case-control Studies of Wine Drinking and Breast Cancer Risk (continued)

| Author, year, region | Journal | No. of cases | No. and type of control subjects | Cancer type | Consumption categories | Adjusted OR (95%CI) | Adjusted variables |
|----------------------|---------|--------------|----------------------------------|-------------|-----------------------|---------------------|-------------------|
| Viel JF, 1997, France | Eur J Epidemiol | 154 women | 154 women, population based | Premenopausal breast cancer | Red wine | 0 l/month | 1.0 (Referent) | total calory intake and parity |
|                      |         |              |                                  |             | 4 l/month | 1.52 (0.88-2.63) |                      |                   |
|                      |         |              |                                  |             | >4 l/month | 3.96 (1.59-9.84) |                      |                   |
|                      |         |              |                                  |             | White wine | 0 l/month | 1.0 (Referent) |                      |
|                      |         |              |                                  |             | 1 l/month | 0.41 (0.12-1.37) |                      |                   |
|                      |         |              |                                  |             | >1 l/month | 1.62 (0.46-5.62) |                      |                   |
|                      |         |              |                                  |             | 0 drinks/day | 1.0 (Referent) |                      |                   |
|                      |         |              |                                  |             | >0 - <1 drinks/day | 1.2 (0.84-1.9) |                      |                   |
|                      |         |              |                                  |             | 1-<2 drinks/day | 1.7 (1.0-2.7) |                      |                   |
|                      |         |              |                                  |             | ≥2 drinks/day | 2.0 (1.2-3.2) |                      |                   |
| Levi F, 1996, Switzerland | Eur J Cancer | 230 women | 507 women, hospital based | breast cancer | 0 l/month | 1.0 (Referent) |                      |
|                      |         |              |                                  |             | 1 l/month | 0.41 (0.12-1.37) |                      |               |
|                      |         |              |                                  |             | >1 l/month | 1.62 (0.46-5.62) |                      |                   |
|                      |         |              |                                  |             | 0 drinks/day | 1.0 (Referent) |                      |
|                      |         |              |                                  |             | >0 - <1 drinks/day | 1.2 (0.84-1.9) |                      |                   |
|                      |         |              |                                  |             | 1-<2 drinks/day | 1.7 (1.0-2.7) |                      |                   |
|                      |         |              |                                  |             | ≥2 drinks/day | 2.0 (1.2-3.2) |                      |                   |
| Freudenheim JL, 1995, USA | Nutr Cancer | 740 women | 810 women, population based | breast cancer | None | 0 drinks/mo | 1.0 (Referent) | age, pregnancy, family history of breast cancer, previous benign breast disease, Quetelet's index, and intake of kilocalories, fat, carotenoids beer, and hard liquor. |
|                      |         |              |                                  |             | 1-2 drinks/mo | 1.21 (0.94-1.55) |                      |                   |
|                      |         |              |                                  |             | 3-27 drinks/mo | 0.90 (0.67-1.21) |                      |                   |
|                      |         |              |                                  |             | ≥28 drinks/mo | 0.80 (0.51-1.25) |                      |                   |
|                      |         |              |                                  |             | 10 yrs ago | 0 drinks/mo | 1.0 (Referent) |                      |
|                      |         |              |                                  |             | 1-2 drinks/mo | 1.21 (0.94-1.55) |                      |                   |
|                      |         |              |                                  |             | 3-27 drinks/mo | 0.90 (0.67-1.21) |                      |                   |
|                      |         |              |                                  |             | ≥28 drinks/mo | 0.80 (0.51-1.25) |                      |                   |
|                      |         |              |                                  |             | 20 yrs ago | 0 drinks/mo | 1.0 (Referent) |                      |
|                      |         |              |                                  |             | 1-2 drinks/mo | 1.21 (0.94-1.55) |                      |                   |
|                      |         |              |                                  |             | 3-27 drinks/mo | 0.90 (0.67-1.21) |                      |                   |
|                      |         |              |                                  |             | ≥28 drinks/mo | 0.80 (0.51-1.25) |                      |                   |
| Martin-Moreno JM, 1993, Spain | Cancer Causes Control | 762 women | 988 women, population based | breast cancer | <1 per month | 1.0 (Referent) | age group, geographical region, socioeconomic status, Quetelet’s index, and intake of kilocalories, fat, carotenoids beer, and hard liquor. |
|                      |         |              |                                  |             | 1-6 per week | 1.0 (0.7-1.3) |                      |                   |
|                      |         |              |                                  |             | ≥1 per month | 0.7 (0.5-1.0) |                      |                   |
| Ferraroni M, 1991, Italy | Int J Epidemiol | 215 women | 214 women, hospital based | breast cancer | None | 0 gt/day | 1.0 (Referent) | Parity, family history of breast cancer, education, age at first birth, age at menarche, age at menopause, Quetelet index, all specific beverages simultaneously |
|                      |         |              |                                  |             | <0.7 gt/day | 1.2 (0.9-1.7) |                      |                   |
|                      |         |              |                                  |             | 0.70-5.12 gt/day | 1.0 (0.8-1.4) |                      |                   |
|                      |         |              |                                  |             | 5.13-18.00 gt/day | 1.8 (1.3-2.3) |                      |                   |
|                      |         |              |                                  |             | ≥18.00 gt/day | 1.5 (1.0-2.5) |                      |                   |
| Rosenberg L, 1990, Canada | Am J Epidemiol | 358 women | 671 women, population based | breast cancer | None | 0.11-5.82 g/day | 1.3 (0.6-2.5) | Parity, family history of breast cancer, education, age at first birth, age at menarche, age at menopause, Quetelet index, all specific beverages simultaneously |
|                      |         |              |                                  |             | 5.83-11.94 g/day | 1.0 (0.5-2.1) |                      |                   |
|                      |         |              |                                  |             | 11.95-23.45 g/day | 1.8 (0.8-3.8) |                      |                   |
|                      |         |              |                                  |             | 23.50+ g/day | 1.7 (0.9-3.2) |                      |                   |
|                      |         |              |                                  |             | <1 per month | 1.0 (Referent) |                      |                   |
|                      |         |              |                                  |             | 1-6 per week | 1.0 (0.7-1.3) |                      |                   |
|                      |         |              |                                  |             | ≥1 per month | 0.7 (0.5-1.0) |                      |                   |
### Table 2. Characteristics of Case-control Studies of Wine Drinking and Breast Cancer Risk (continued)

| Author, year, region | Journal | No. of cases | No. and type of control subjects | Cancer type | Consumption categories | Adjusted OR (95% CI) | Adjusted variables |
|----------------------|---------|--------------|----------------------------------|-------------|-----------------------|---------------------|--------------------|
| Toniolo P, 1989, Italy | Cancer Res | 250 women | 499 women, population based | breast cancer | 0 g/day | 1.0 (Referent) | Age, Quetelet index, menopausal status, and energy intake (total calories minus calories from alcohol). |
| | | | | | | 0-10 g/day | 0.9 (0.5-1.5) |
| | | | | | 10-20 g/day | 1.2 (0.8-1.9) |
| | | | | | 20-30 g/day | 1.0 (0.6-1.5) |
| | | | | | 30-40 g/day | 1.3 (0.6-2.5) |
| | | | | | >40 g/day | 1.8 (1.0-3.3) |
| | | | | | <1 drinks/week | 1.0 (Referent) |
| | | | | | 1-7 drinks/week | 2.2 (1.6-3.0) |
| | | | | | >7 drinks/week | 2.6 (1.8-3.9) |
| Richardson S, 1989, France | Int J Cancer | 349 women | 459 women, hospital based | breast cancer | 0 dl/week | 1.0 (Referent) | education, age at menarche, age at first full-term pregnancy, parity, menopause, history of operation for benign breast disease, family history of breast cancer, total duration of OC use, smoking (cigarettes day-1), and the consumption of other alcoholic beverages than those analysed. |
| | | | | | 1-4 dl/week | 0.7 (0.5-1.0) |
| | | | | | 5+ dl/week | 0.7 (0.4-1.2) |
| Adami HO, 1988, Sweden and Norway | Br J Cancer | 422 women | 597 women, population based | breast cancer | 0 drinks/day | 1.0 (Referent) | all identified potential confounding factors (including available dietary items) |
| | | | | | ≤3 drinks/day | 1.16 (0.85-1.59) |
| | | | | | >3 drinks/day | 2.24 (1.06-4.71) |
| | | | | | Never | 1.0 (Referent) |
| | | | | | <80 g | 1.33 (1.03-1.73) |
| | | | | | 80-159 g | 1.78 (1.31-2.42) |
| | | | | | ≥ 160 g | 1.56 (1.27-1.81) |
| | | | | | Not used | 1.0 (Referent) |
| | | | | | ≤ 0.5 l/day | 2.4 (1.6-3.5) |
| | | | | | >0.5 l/day | 16.7 (3.1-89.7) |
| | | | | | Never | 1.0 (Referent) |
| | | | | | Ever | 0.8 (0.7-1.1) |
| | | | | | <50 g/wk | 0.8 (0.6-1.0) |
| | | | | | 50-149 g/wk | 0.9 (0.6-1.2) |
| | | | | | ≥ 50 g/wk | 1.2 (0.8-1.9) |

Discussion

To our knowledge, our meta-analysis, for the first time, evaluated the dose-response relationship between exposure to wine and risk of breast cancer. Our comprehensive meta-analysis indicated that wine consumption may increase the risk of breast cancer. However, when evaluating women drinking wine in different dosages, we found that a low dose may have some protective effect rather than an increased risk in heavy drinkers.

Consistent with many other studies, wine drinking is associated with increased risk of breast cancer risk in the highest versus lowest model. Wine, as a specific alcoholic drink, contains ethanol, which contribute to cancer risk in many published articles. The effects of ethanol may be mediated through the production of prostaglandins, lipid per-oxidation, and the generation of free radical oxygen species. Ethanol also acts as a solvent, enhancing penetration of carcinogens into cells (Wiseman, 2008). Interestingly, a recent study suggested that low dose of wine intake can decreased the risk of breast cancer (Bessaoud and Daures, 2008). In this study, the risk associated with women who consumed wine at low dose also showed decreased tendency at a non-linear dose-response model. The protective effect of low dose wine consumption on breast cancer is plausible for several reasons. First, wine contains high levels of anticancer compounds, such as polyphenols and resveratrol. A preclinical study tested the anti-proliferative activity of these compounds on the proliferation of different breast cancer cell lines, showing that low concentrations (nanomolar or even the picomolar range) of these active
Table 3. Methodological Quality of Cohort Studies Included in the Meta-analysis

| Author, year, region | Representativeness of the exposed cohort | Selection of the unexposed cohort | Ascertainment of exposure | Outcome of interest not present at start of study | Control for important factor or additional factors | Follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | Data analysis that used an energy-adjusted residual or nutrient-density model | Total quality scores |
|----------------------|----------------------------------------|-----------------------------------|---------------------------|-----------------------------------------------|-----------------------------------------------|-------------------------------------------|-------------------------------|----------------------------------|---------------------|
| Link LB, 2013, USA    | —                                      | ★                                 | ★                         | ★                                             | ★                                             | ★                                         | ★                            | ★                                 | 9                   |
| Kabat GC, 2011, USA   | —                                      | ★                                 | ★                         | ★                                             | ★                                             | ★                                         | ★                            | —                                 | 8                   |
| Mattission I, 2004, Sweden | —                        | ★                                 | ★                         | ★                                             | ★                                             | ★                                         | ★                            | —                                 | 9                   |
| Petri AL, 2004, Denmark | ★                                   | ★                                 | ★                         | ★                                             | ★                                             | ★                                         | ★                            | ★                                 | 9                   |
| Horn-Ros PL, 2002, USA | —                                      | ★                                 | ★                         | ★                                             | ★                                             | —                                         | ★                            | ★                                 | 9                   |
| Zhang Y, 2000, USA    | ★                                      | ★                                 | ★                         | ★                                             | ★                                             | ★                                         | —                            | —                                 | 8                   |
| Hiart RA, 1988, USA   | ★                                      | ★                                 | ★                         | ★                                             | —                                             | —                                         | —                            | —                                 | 7                   |
| Willett WC, 1987, USA | —                                      | ★                                 | ★                         | ★                                             | ★                                             | —                                         | ★                            | ★                                 | 8                   |

* A study could be awarded a maximum of one star for each item except for the item Control for important factor or additional factor; A maximum of 2 stars could be awarded for this item. Studies that controlled for smoking and alcohol received one star, whereas studies that controlled for other important confounders such as family history or somking received an additional star; A cohort study with a follow-up rate >75% was assigned one star; A cohort study with a follow-up time >8 y was assigned one star.

substances obtained after moderate wine ingestion might have a protective effect against breast cancer (Damianakī et al., 2000). In vitro experiments, polyphenols found in grapes showed the activity to induce cancer cells apoptosis and delay tumor growth (Castillo-Pichardo et al., 2009). In the animal model, transgenic mice also demonstrated decreased incidence rates of cancers with red wine solid food ingestion (Clifford et al., 1996). Secondly, some studies explored other mechanism pathways in which wine may serve as a kind of nutritional aromatase inhibitors (AI) (Byrne et al., 2002). The results showed that sex hormone binding globulin (SHBG) and luteinizing hormone (LH) were higher in serum with red wine consumption, which was explained by the hypothalamic up-regulation in response to lower estrogen levels. Thus, wine may not increase breast cancer risk via the hormonal shift patterns. Thirdly, a previous cohort study suggested that wine consumption induce breast density inversion in postmenopausal women after adjusting for other sources of alcohol (Boyd et al., 2006). Some epidemiologic studies have confirmed that breast density was risk factor for breast cancer (Flom et al., 2009). Other possible mechanisms of action need to be investigated in future.

In subgroup analysis by study design, case-control studies, especially hospital-based case-control studies, seemed to report much higher relative risks than cohort studies. The inconsistent findings may have been attributed to greater recall and selection biases in case-control studies because of their retrospective nature. And most non-high-quality studies are case-control ones, which further explain these results. When compared the RRs in different regions, we observed great difference in RR across geographic area. The RRs in European countries, especially France and Italy, were higher than that of USA and Canada. This may be due to the distinctions of diet patterns among different geographic regions. In many European countries, wine is usually an integral part of the resident’s dietary habits daily diet.

Strengths of our studies include a large size (18106 breast cancer cases from 8 cohort studies and 18 case-control studies) and a quantitative dose-response analysis. Also, results from high-quality, cohort studies and studies adjusted for a variety of confounders are relatively consistent. Nevertheless, several limitations in our meta-analysis need to be mentioned. First of all, we noted that the majority of the cases were extracted from case-control studies, which are generally based on the memory and past record leading to more recall bias than cohort studies. Secondly, all the studies included only covered the Whites, lacking the diversity of races. Thirdly, as food-frequency questionnaires were used in each component studies, our findings were likely to be influenced by the underestimation of wine consumption. Besides, the potential misclassification of wine ingestion dose also may affect our results due to the broad range of definition of conversion in wine consumption.

Considering drinking is associated with increased risk of other health problems in women, such as birth defects, stroke, and other many types of cancers (Wiseman, 2008). Because wine consumption has increased in the general population, especially among young women, further research to clarify the relative safety in women is needed.

In conclusion, our analysis indicates that high dose of wine drinking is associated with increased risk of breast cancer, while low dose reduce the risk. However, future well-designed cohort or interventional studies are needed to confirm the findings and elucidate the underlying mechanisms.
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### Table 4. Methodological Quality of Case-Control Studies Included in the Meta-Analysis

| First author, year, country | Adequate definition of cases | Representativeness of cases | Selection of control subjects | Definition of control subjects | Control for important factor or additional factors | Exposure assessment | Same method of ascertainment for all subjects | Nonresponse rate | Data analysis that used an energy-adjusted residual or nutrient-density model | Total quality scores |
|-----------------------------|-----------------------------|-----------------------------|------------------------------|--------------------------------|-----------------------------------------------|---------------------|---------------------------------------------|-----------------|-----------------------------------------------|---------------------|
| Dennis J, 2010, Eight countries of Europe and North America | — | ♦ | — | ♦ | ♦ ♦ | — | ♦ | — | — | 5 |
| Bissonauth V, 2009, Canada | ♦ | ♦ | ♦ | ♦ | — | ♦ | ♦ | — | — | 7 |
| Levi F, 2005, Switzerland, Canada | — | ♦ | — | ♦ ♦ | — | ♦ | ♦ | — | — | 4 |
| Lenz SK, 2002, Canada | ♦ | ♦ | — | ♦ ♦ | ♦ | ♦ | ♦ | — | — | 8 |
| Ferraroni M, 1998, Italy | — | ♦ | — | ♦ ♦ ♦ | ♦ | ♦ | ♦ | ♦ | ♦ | 8 |
| Viel JF, 1997, France | — | ♦ | ♦ | ♦ ♦ | — | ♦ | ♦ | ♦ | ♦ | 8 |
| Levi F, 1996, Switzerland | ♦ | ♦ | — | ♦ ♦ ♦ | ♦ | ♦ | ♦ | ♦ | — | 8 |
| Freudenheim JL, 1995, USA | ♦ | ♦ | ♦ | ♦ ♦ ♦ | ♦ | ♦ | ♦ | ♦ | ♦ | 9 |
| Martin-Moreno JM, 1993, Spain | ♦ | ♦ | ♦ | ♦ ♦ ♦ | ♦ | ♦ | ♦ | ♦ | ♦ | 10 |
| Ferraroni M, 1991, Italy | — | ♦ | — | ♦ ♦ ♦ | ♦ | ♦ | ♦ | — | — | 6 |
| Rosenberg L, 1990, Canada | — | ♦ | ♣ | ♦ ♦ | ♦ ♦ | ♦ | ♦ | ♦ | — | 7 |
| Tonisolo P, 1989, Italy | ♦ | ♦ | ♦ | ♦ ♦ ♦ | — | ♦ | ♦ | ♦ | — | 8 |
| Richardson S, 1989, France | — | ♦ | — | ♦ ♦ ♦ | — | ♦ | ♦ | ♦ | — | 5 |
| Adami HO, 1988, Sweden and Norway | ♦ | ♦ | ♦ | ♦ ♦ ♦ | ♦ | ♦ | ♦ | ♦ | ♦ | 9 |
| La Vecchia C, 1985, Italy | — | ♦ | — | ♦ ♦ ♦ | — | ♦ | ♦ | ♦ | ♦ | 6 |
| Talamini R, 1984, Italy | — | ♦ | — | ♦ ♦ ♦ | — | ♦ | ♦ | — | — | 6 |
| Le MG, 1984, France | — | ♦ | — | ♦ ♦ ♦ | — | ♦ | ♦ | — | — | 6 |
| Paganini-Hill A, 1983, USA | — | ♦ | ♦ | ♦ ♦ ♦ | — | ♦ | ♦ | ♦ | — | 6 |

* A study could be awarded a maximum of one star for each item except for the item Control for important factor or additional factor.
* A maximum of 2 stars could be awarded for this item. Studies that controlled for smoking and alcohol received one star, whereas studies that controlled for other important confounders such as family history or fresh vegetables and fruit intake received an additional star.
* One star was assigned if there was no significant difference in the response rate between control subjects and cases by using the chi-square test (P>0.05)
Table 5. Summary Relative Risks (RRs) of the Association between wine Drinking and Breast Cancer Riska

| Geographic region | Study design | No. of studies | No. of cases | RR (95%CI) | Test of heterogeneity |
|-------------------|-------------|---------------|-------------|------------|-----------------------|
|                   | Overall studies | 26 | 21149 | 1.36 (1.20-1.54) | 75.69 <0.001 67.0 |
|                   | High-quality studies (score 7) | 18 | 15650 | 1.26 (1.12-1.43) | 38.89 0.002 56.3 |
|                   | Cohort studies | 8 | 9531 | 1.25 (1.07-1.46) | 14.94 0.037 53.1 |
|                   | Case-control studies | 18 | 11618 | 1.44 (1.19-1.73) | 54.61 <0.001 68.9 |
|                   | Population-based controls | 9 | 5515 | 1.14 (0.85-1.53) | 20.47 0.009 60.9 |
|                   | Hospital-based controls | 9 | 6103 | 1.72 (1.38-2.15) | 23.77 0.003 66.3 |
|                   | Menopause | 3 | 2062 | 1.79 (1.34-2.40) | 2.13 0.344 6.3 |
|                   | Premenopausal | 5 | 7396 | 1.20 (0.94-1.53) | 10.96 0.027 63.5 |
|                   | Postmenopausal | 3 | 992 | 1.34 (1.10-1.64) | 1.59 0.498 0.0 |
|                   | European | 14 | 7950 | 1.66 (1.35-2.05) | 39.05 <0.001 66.7 |
|                   | Italy | 5 | 3839 | 1.89 (1.17-3.07) | 13.09 0.011 69.4 |
|                   | France | 3 | 1513 | 2.12 (1.37-3.27) | 7.49 0.024 73.3 |
|                   | North America | 11 | 12510 | 1.18 (1.09-1.27) | 17.98 0.055 44.4 |
|                   | USA | 8 | 11518 | 1.16 (1.01-1.35) | 14.59 0.042 52.0 |
|                   | Canada | 3 | 992 | 1.34 (1.10-1.64) | 1.59 0.498 0.0 |
|                   | Adjustments | 13 | 15991 | 1.29 (1.10-1.52) | 35.66 <0.001 66.3 |
|                   | Family history | 16 | 17237 | 1.26 (1.09-1.45) | 35.67 0.002 58.0 |
|                   | BMI | 10 | 8009 | 1.50 (1.15-1.94) | 31.15 <0.001 71.1 |
|                   | Total energy | 9 | 5396 | 1.24 (0.93-1.67) | 25.94 0.001 69.2 |
|                   | Other alcoholic beverage | 12 | 8553 | 1.30 (1.02-1.65) | 32.36 0.001 66.0 |
|                   | Smoking | 16 | 15126 | 1.35 (1.14-1.59) | 42.15 <0.001 64.4 |
|                   | Menopause | 10 | 10328 | 1.26 (1.01-1.56) | 26.63 0.002 66.2 |
|                   | Hormone therapy | 15 | 16620 | 1.29 (1.11-1.51) | 41.87 <0.001 66.6 |
|                   | Pregnancy | 12 | 8652 | 1.36 (1.10-1.67) | 29.02 0.002 62.1 |
|                   | Education | 8 | 9142 | 1.38 (1.06-1.79) | 24.46 0.001 71.4 |

a RR = relative risk (odds ratio); CI = confidence interval; BMI = body mass index

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Table 6. Slope of Each Study and Relative Risks

| study | B  | Se (B) | RR | LB | UB |
|-------|----|--------|----|----|----|
| Adami HO 1988 Sweden and | -0.06803 | 0.03849 | 0.93423 | 0.86634 | 1.00745 |
| Dennis J 2010 1 | -0.11580 | 0.00600 | 0.89065 | 0.88960 | 0.89170 |
| Dennis J 2010 2 | 0.00858 | 0.01081 | 1.00862 | 0.98747 | 1.03022 |
| Ferraroni M 1991 Italy | 0.01830 | 0.01034 | 1.01847 | 0.99804 | 1.03933 |
| Freudenjelm JL 1995 USA1 | -0.01523 | 0.01380 | 0.98489 | 0.95861 | 1.01188 |
| Freudenjelm JL 1995 USA2 | -0.01152 | 0.01510 | 0.98854 | 0.95971 | 1.01824 |
| Freudenjelm JL 1995 USA3 | -0.01613 | 0.01776 | 0.98400 | 0.95033 | 1.01887 |
| Horn-Ros PL 2002 USA | 0.02306 | 0.00635 | 1.02333 | 1.01068 | 1.03614 |
| Levi F 1996 Switzerland | -0.02391 | 0.00772 | 1.02419 | 1.00881 | 1.03982 |
| Lé MG 1984 France | 0.01624 | 0.00352 | 1.01637 | 1.01001 | 1.02278 |
| Martin-Moreno JM 1993 Sp | 0.03065 | 0.00858 | 1.03113 | 1.01393 | 1.04862 |
| Paganini-Hill A 1983 USA | 0.00657 | 0.00740 | 1.00659 | 0.99209 | 1.02129 |
| Petri AL 2004 Denmark1 | 0.01934 | 0.02693 | 1.01953 | 0.96711 | 1.07479 |
| Petri AL 2004 Denmark2 | 0.01968 | 0.01614 | 1.01988 | 0.98812 | 1.05266 |
| Petri AL 2004 Denmark3 | -0.00840 | 0.02359 | 0.99164 | 0.94683 | 1.03856 |
| Richardson S 1989 France | 0.07206 | 0.01125 | 1.07472 | 1.04869 | 1.10139 |
| Rosenberg L 1990 Canada | -0.00231 | 0.02481 | 0.99770 | 0.95034 | 1.01824 |
| Talamini R 1984 Italy | 0.04674 | 0.00923 | 1.04785 | 1.02906 | 1.06697 |
| Viel JF 1997 France1 | 0.09981 | 0.03298 | 1.10496 | 1.03579 | 1.17874 |
| Viel JF 1997 France2 | 0.03227 | 0.18599 | 1.03280 | 0.71730 | 1.48707 |
| Willett WC 1987 USA | 0.05560 | 0.01849 | 1.05171 | 1.01955 | 1.09618 |
| Zhang Y 2000 USA1 | -0.00053 | 0.03012 | 0.99947 | 0.94216 | 1.06026 |
| Zhang Y 2000 USA2 | -0.07375 | 0.05822 | 0.92890 | 0.8873 | 1.04111 |

Table 7. Does-response Analysis* in Linear Model

| Model | Pooled E (SE) | RR/OR(CI) | Z-score | Linear Trend | Test for heterogeneity |
|-------|--------------|-----------|---------|-------------|-----------------------|
| Fixed | -0.1053 (0.0006) | 0.9001(0.8991,0.9011) | -182.19 | 0 | <0.0001 | 89.13 | 23 |
| Random | 0.0059 (0.0201) | 1.0059(0.9670,1.0464) | 0.2939 | 0.7688 | |

* Greenland method for test of non-linearity; χ²=1763.9 P<0.0001

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