RESEARCH ARTICLE

Dose-Dependent Associations 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 - riskfactor - 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 chemo-protective 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 risk attracted much attention. Several epidemiological studies have demonstrated that alcohol consumption was associated with an increased risk of breast cancer (Smith-Warner et al., 1998; Corrao et al., 1999; Ellison et al., 2001; Singletary and Gapstur, 2001; Hamajima et al., 2002; Chen et al., 2011). However, results 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

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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, sparking 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), number and type of control subjects (case-control 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,

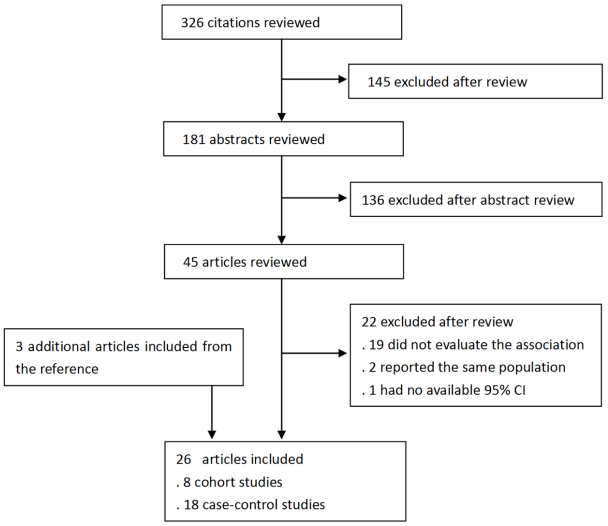

Figure 1. Reference Searched and Selection of Studies in the Meta-analysis

eight in America, three in Canada and one across both continentals. 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 [a]

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 caloric 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
					Q2	0.95 (0.86-1.06)	
					Q3	1.03 (0.92-1.14)	
					Q4	0.98 (0.88-1.09)	
					Q5	1.12 (1.01-1.25)	
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	0	1.0 (Referent)	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
					<3 serving/week	0.95 (0.73-1.22)	
					≥3 serving/week	0.75 (0.48-1.17)	
				ER +	0	1.0 (Referent)	
					<3 serving/week	1.00 (0.91-1.09)	
					≥3 serving/week	1.16 (1.02-1.32)	
Mattission I, 2004, Sweden	Int J Cancer	342 women	11726 postmenopausal women, Malm¨o Diet and Cancer Cohort, 10y (1991-2001)	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)	

Table 1. Characteristics of Prospective Cohort Studies of Wine Drinking and Breast Cancer Risk[a] (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)	
				Postmenopausal (<70 years)	<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)	
				Postmenopausal (≥70 years)	<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)	invasive breast cancer	Non-drinkers	1.0 (Referent)	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 g/day	1.0 (0.9-1.2)	
					5-19 g/day	1.3 (1.0-1.6)	
					≥20 g/day	1.7 (1.2-2.4)	
Zhang Y, 2000, USA	Am J Epidemiol	221 (Original Cohort) and 66 (Offspring Cohort) women	Framingham Heart Study, 2764 women (Original Cohort), 40y (1948-1993), 2284 women (Offspring Cohort), 24y (1971-1993)	breast cancer	None	1.0 (Referent)	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
					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)	
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	Abstainers	1.0 (Referent)	age, race, Quetelet index, and smoking.
					Infrequent	0.91 (0.51-1.60)	
					Regular	1.36 (0.86-2.17)	

Table 1. Characteristics of Prospective Cohort Studies of wine Drinking and Breast Cancer Risk[a] (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
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
					<5.0	1.1 (0.9-1.3)	
					>5.0	1.4 (1.1-1.7)	

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

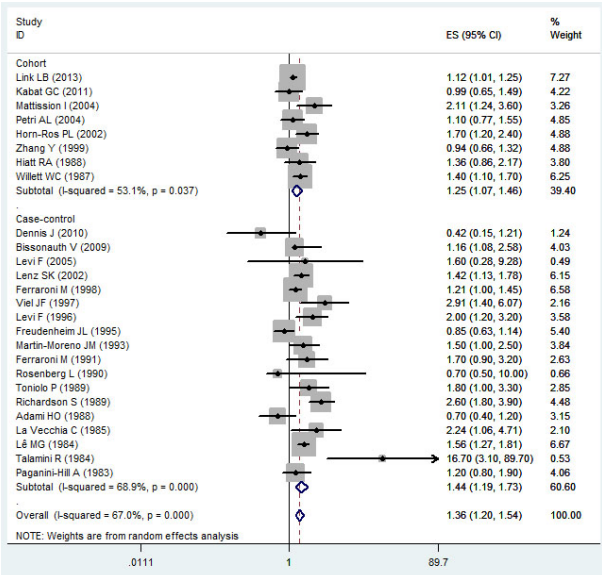

Figure 2. Estimates (95% CIs) of Wine Drinking (Highest Versus Lowest Category) and Breast Cancer Risk

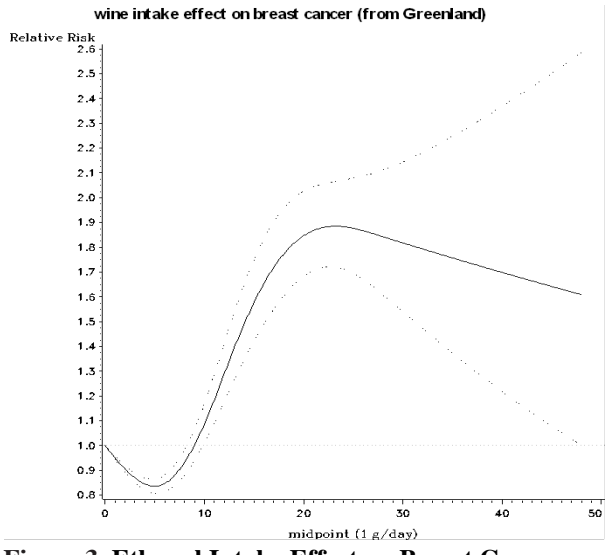

Figure 3. Ethanol Intake Effect on Breast Cancer

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*=0.344), while

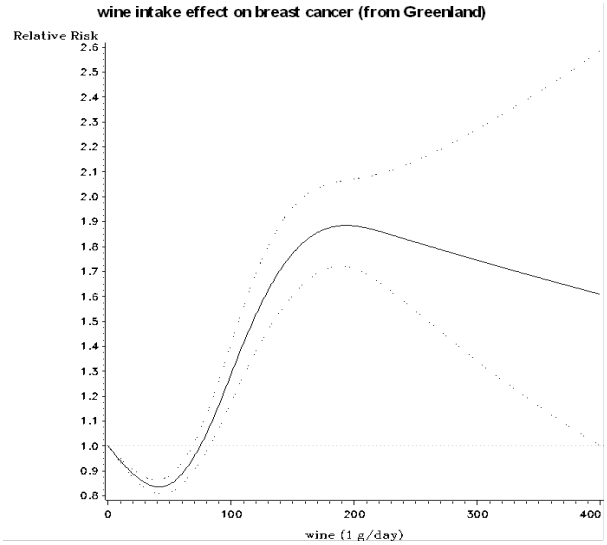

Figure 4. Wine Intake Effect on Breast Cancer

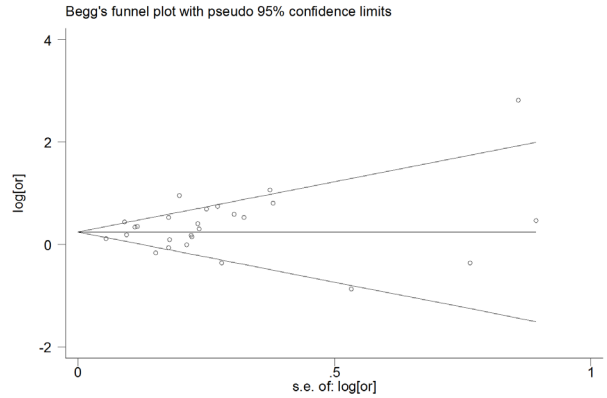

Figure 5. Beeg's Test of Studies for Wine Drinking and Breast Cancer Risk

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[a]

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)	ethnicity, menopause, oral contraceptive use, HRT use, smoking, oophorectomy, BMI, and parity
					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)	
				BRCA2 mutation	None	1.0 (Referent)	
					0-3 per week	1.09 (0.60-1.95)	
					4-9 per week	1.12 (0.49-2.60)	
					≥10 per week	0.50 (0.08-3.02)	
Bissonauth V, 2009, Canada	Breast J	78 women	103 women, population based	Noncarriers of BRCA1 or BRCA2 nutation	≤5 oz/week	1.0 (Referent)	age, education, physical activity, smoking, coffee consumption and total energy
					>5 to ≤10 oz/week	1.06 (0.32-1.97)	
					>10 oz/week	1.16 (1.08-2.58)	
Levi F, 2005, Switzer-land,	Eur J Cancer Prev	369 women	602 women, hospital based	breast cancer	T1 b	1.0 (Referent)	age, education, BMI, hormone replacement therapy, menopausal status, parity, energy intake, and total alcohol consumption
					T2	1.05 (0.18-6.25)	
					T3	1.60 (0.28-9.28)	
Lenz SK, 2002, Canada	Cancer Causes Control	556 postmenopausal women	577 women, hospital based	breast cancer	Never	1.0 (Referent)	age, family history, age at oophorectomy, education, marital status, ethnicity, age at menarche, oral contraception use, duration of hormone replacement therapy use, total duration of breastfeeding, smoking status, body mass index, age at first full-term pregnancy, and proxy respondent status
					Ever	1.4 (1.0–1.9)	
					Regular 20-29 y	1.2 (0.7–2.0)	
					Regular 30-39 y	1.4 (0.9–2.2)	
					Regular 40-49 y	1.4 (0.9–2.2)	
					Regular 50-59 y	1.6 (1.1–2.5)	
Ferraroni M, 1998, Italy	Eur J cancer	2569 women	2588 women, hospital based	Overall breast cancer	Abstainers	1.0 (Referent)	age, centre, education, age at first birth, parity, age at menarche, BMI and family history of breast cancer
					1.00-12.76 g/day	1.24 (1.04-1.49)	
					12.77-13.45 g/day	1.15 (0.96-1.39)	
					13.46-26.33 g/day	1.24 (1.03-1.49)	
					≥26.34 g/day	1.21 (1.00-1.45)	
				Premenopausal	Abstainers	1.0 (Referent)	
					1.00-12.76 g/day	1.33 (0.99-1.80)	
					12.77-13.45 g/day	0.98 (0.71-1.37)	
					13.46-26.33 g/day	1.35 (0.99-1.85)	
					≥26.34 g/day	1.69 (1.20-2.40)	
				Postmenopausal	Abstainers	1.0 (Referent)	
					1.00-12.76 g/day	1.13 (0.89-1.42)	
					12.77-13.45 g/day	1.14 (0.91-1.43)	
					13.46-26.33 g/day	1.11 (0.87-1.40)	
					≥26.34 g/day	0.98 (0.78-1.23)	

Table 2. Characteristics of Case-control Studies of Wine Drinking and Breast Cancer Risk[a] (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 Epedemiol	154 women	154 women, population based	Premenopausal breast cancer	Red wine		total calory intake and parity
					0 l/month	1.0 (Referent)	
					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)	
Levi F, 1996, Switzer-land	Eur J Cancer	230 women	507 women, hospital based	breast cancer	0 drinks/day	1.0 (Referent)	age, plus marital status, education, parity, age at first birth, menopausal status, age at menopause, family history of breast cancer, smoking habits, oral contraceptives and hormonal replacement therapy use
					>0 - <1 drinks/day	1.2(0.8-1 .9)	
					1- <2 drinks/day	1.7(1.0-2.7)	
					≥ 2 drinks/day	2.0(1.2-3.2)	
Freuden-heim JL, 1995, USA	Nutr Cancer	740 women	810 women, population based	breast cancer	2 yrs ago		age, pregnancy, family history of breast cancer, previous benign breast disease, Quetelet index, and intake of kilocalories, fat, carotenoids beer, and hard liquor.
					0 drinks/mo	1.0 (Referent)	
					1-2 drinks/mo	0.97 (0.75-1.26)	
					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	0.93 (0.69-1.26)	
					≥28 drinks/mo	1.03 (0.62-1.69)	
					20 yrs ago		
					0 drinks/mo	1.0 (Referent)	
					1-2 drinks/mo	1.13 (0.89-1.44)	
					3-27 drinks/mo	0.99 (0.73-1.34)	
					≥28 drinks/mo	0.74 (0.38-1.42)	
					At 16 yrs of age		
					0 drinks/mo	1.0 (Referent)	
					1-2 drinks/mo	1.08 (0.66-1.77)	
					3-27 drinks/mo	1.07 (0.42-2.69)	
					≥28 drinks/mo	0.31 (0.03-3.48)	
Martin-Moreno JM, 1993, Spain	Cancer Causes Control	762 women	988 women, population based	breast cancer	0 g/day	1.0 (Referent)	age group, geographical region, socioeconomic status, Quetelet's index, family history of breast cancer, age at menarche, menopausal status, age at menopause, age at first full-term pregnancy and total energy intake
					<0.7 g/day	1.2 (0.9-1.7)	
					0.70-5.12 g/day	1.0 (0.8-1.4)	
					5.13-18.00 g/day	1.8 (1.3-2.3)	
					>18.00 g/day	1.5 (1.0-2.5)	
Ferraroni M, 1991, Italy	Int J Epidemiol	215 women	214 women, hospital based	breast cancer	None	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 simoutaneously
					0.11-5.82 g/day	1.3 (0.6-2.5)	
					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)	
Rosenberg L, 1990, Canada	Am J Epidemiol	358 women	671 women, population based	breast cancer	<1 per month	1.0 (Referent)	Age
					1-6 per week	1.0 (0.7-1.3)	
					≥ 1 per day	0.7 (0.5-10)	

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[a] (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 0-10 g/day 10-20 g/day 20-30 g/day 30-40 g/day >40 g/day	1.0 (Referent) 0.9 (0.5-1.5) 1.2 (0.8-1.9) 1.0 (0.6-1.5) 1.3 (0.6-2.5) 1.8 (1.0-3.3)	Age, Quetelet index, menopausal status, and energy intake (total calories minus calories from alcohol).
Richardson S, 1989, France	Int J Cancer	349 women	459 women, hospital based	breast cancer	<1 drinks/week 1-7 drinks/week >7 drinks/week	1.0 (Referent) 2.2 (1.6-3.0) 2.6 (1.8-3.9)	
Adami HO, 1988, Sweden and Norway	Br J Cancer	422 women	597 women, population based	breast cancer	0 dl/week 1-4 dl/week 5+ dl/week	1.0 (Referent) 0.7 (0.5-1.0) 0.7 (0.4-1.2)	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.
La Vecchia C, 1985, Italy	J Nat Cancer Inst	437 women	437 women, hospital based	breast cancer	0 drinks/day ≤3 drinks/day >3 drinks/day	1.0 (Referent) 1.16 (0.85-1.59) 2.24 (1.06-4.71)	all identified potential confounding factors (including available dietary items)
Le MG, 1984, France	Am J Epidemiol	1010 women	1950 women, hospital bsed	breast cancer	Never <80 g 80-159 g ≥ 160 g	1.0 (Referent) 1.33 (1.03-1.73) 1.78 (1.31-2.42) 1.56 (1.27-1.81)	(OR and 95%CI were calculated from the original cases and controls due to no available 95%CI were extracted from the article presented)
Talamini R, 1984, Italy	Br J Cancer	368 women	373 women, hospital based	breast cancer	Not used ≤ 0.5 l/day >0.5 l/day	1.0 (Referent) 2.4 (1.6-3.5) 16.7 (3.1-89.7)	all identified potential distorting factors
Paganini-Hill A, 1983, USA	Lancet	2062 women	2185 women, population based	breast cancer	Never Ever <50 g/wk 50-149 g/wk ≥ 50 g/wk	1.0 (Referent) 0.8 (0.7-1.1) 0.8 (0.6-1.0) 0.9 (0.6-1.2) 1.2 (0.8-1.9)	history of benign breast disease, family history of breast cancer, age at first full-term pregnancy, menopausal status, education, age at diagnosis or interview, religion, number of pack-years of cigarettes smoked, and Quetelet's index, consumption of other alcoholic beverages

[a]OR = odds ratio; CI = confidence interval; BMI = body mass index; BRAC = ; T = tertile; BRCA = breast cancer susceptibility gene; b intake from wine was 0.0 of resveratrol for the 1st tertile, ranged between 0.1 and 176.8 for the 2nd tertile, > 176.8 for the 3rd tertile;

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-oxdation, 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 b	Outcome assessment	Follow-up long enough for outcomes to occur c	Adequacy of follow-up of cohorts d	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	—	☆	☆	☆	☆☆	☆	—	☆	☆	8
Zhang Y, 2000, USA	☆	☆	☆	☆	☆☆	☆	☆	—	—	8
Hiatt RA, 1988, USA	☆	☆	☆	☆	☆☆	☆	—	—	—	7
Willett WC, 1987, USA	—	☆	☆	☆	☆	☆	—	☆	☆	8

[a] A study could be awarded a maximum of one star for each item except for the item Control for important factor or additional factor; [b] 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; [c] A cohort study with a follow-up time >8 y was assigned one star; [d] A cohort study with a follow-up rate >75% was assigned one star

substances obtained after moderate wine ingestion might have a protective effect against breast cancer(Damianaki 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.

Table 4. Methodological Quality of Case-Control Studies Included in the Meta-Analysis[a]

First author, year	Adequate definition of cases	Representativeness of cases	Selection of control subjects	Definition of control subjects	Control for important factor or additional factors [b]	Exposure assessment	Same method of ascertainment for all subjects	Nonresponse rate [c]	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,	—	☆	—	s☆	—	☆	☆	—	—	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
Toniolo 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
Lê MG, 1984, France	—	☆	—	☆	☆☆	—	☆	☆	—	6
Paganini-Hill A, 1983, USA	—	☆	☆	—	☆☆	—	☆	☆	—	6

[a] A study could be awarded a maximum of one star for each item except for the item Control for important factor or additional factor.
[b] 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.
[c] 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 ($P>0.05$)

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Table 5. Summary Relative Risks (RRs) of the Association between wine Drinking and Breast Cancer Risk[a]

	No. of studies	No. of cases	RR (95%CI)	Test of heterogeneity		
				Q	P	I^2%
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
Study design						
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						
Premenopausal	3	2062	1.79 (1.34-2.40)	2.13	0.344	6.3
Postmenopausal	5	7396	1.20 (0.94-1.53)	10.96	0.027	63.5
Geographic region						
Europe	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)	1.39	0.498	0.0
Adjustments						
Family history	13	15991	1.29 (1.10-1.52)	35.66	<0.001	66.3
BMI	16	17237	1.26 (1.09-1.45)	35.67	0.002	58.0
Total energy	10	8009	1.50 (1.15-1.94)	31.15	<0.001	71.1
Other alcoholic beverage	9	5396	1.24 (0.93-1.67)	25.94	0.001	69.2
Smoking	12	8553	1.30 (1.02-1.65)	32.36	0.001	66.0
Menopause	16	15126	1.35 (1.14-1.59)	42.15	<0.001	64.4
Hormone therapy	10	10328	1.26 (1.01-1.56)	26.63	0.002	66.2
Pregnancy	15	16620	1.29 (1.11-1.51)	41.87	<0.001	66.6
Education	12	8652	1.36 (1.10-1.67)	29.02	0.002	62.1
Physical activity	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	0.00060	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
Freudenheim JL 1995 USA1	-0.01523	0.01380	0.98489	0.95861	1.01188
Freudenheim JL 1995 USA2	-0.01152	0.01510	0.98854	0.95971	1.01824
Freudenheim JL 1995 USA3	-0.01613	0.01776	0.98400	0.95033	1.01887
Freudenheim JL 1995 USA4	-0.02766	0.05681	0.97272	0.87023	1.08728
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
Lê MG 1984 France	0.01624	0.00321	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	0.01251	1.07472	1.04869	1.10139
Rosenberg L 1990 Canada	-0.00231	0.02481	0.99770	0.95034	1.04741
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	1.05717	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	0.82873	1.04118

Table 7. Does-response Analysis[a] in Linear Model

Model	Pooled E (SE)	RR/OR(CI)	Z-score	Linear Treand	Test for hererogeneity		
				p-value	p-value	Q	df
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			

[a] Greenland method for test of non-linearity: χ^2=1763.9 P<0.0001

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