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Original Paper

Alcohol Consumption and Risk of Breast Cancer: a Multicentre Italian Case–Control Study

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The relationship between alcohol consumption and breast cancer risk was investigated using data from a co-operative case–control study conducted in Italy between 1991 and 1994 on 2569 incident, histologically confirmed breast cancer cases and 2588 controls in hospital for acute, non-neoplastic, non-hormone related conditions. Overall, 915 (38%) cases and 1048 (43%) controls were abstainers. Compared with them, the odds ratio (OR), adjusted only for age, was 1.31 (95% confidence interval (CI) 1.13–1.53) for drinkers and became 1.39 (95% CI 1.(1)21–1.60) after correction for measurement error. The multivariate OR was 1.21 for drinkers of ≤ 5.87 g/day and 1.23, 1.19, 1.21, 1.41 for drinkers of 5.88–13.40, 13.41–24.55, 24.56–27.60, >27.60 g/day, respectively. The trend in risk was significant ($\chi^2 = 12.28$, $P < 0.0005$). The association was apparently stronger in premenopausal women (OR = 1.80 for >27.60 g/day). Considering the different types of alcoholic beverages (wine, beer, digestives, grappa and other spirits), a significant direct trend in breast cancer risk was seen for wine with an OR of 1.27 (95% CI 1.06–1.53) for the category >26.34 g/day. The ORs were also above unity for beer, grappa, digestives and spirits drinkers. No appreciable interaction was observed between alcohol drinking and body mass index, smoking, or any other covariate considered. Thus, the present data, based on a validated alcohol consumption questionnaire and on a population characterised by a relatively high alcohol consumption in women, confirmed that alcohol drinking is moderately related to breast cancer risk. If causal, this association could explain 12% (95% CI, 5–19%) of breast cancers in Italy, thus representing one of the major avoidable risk factor for breast cancer. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

SINCE THE early 1980s, several epidemiological studies have considered the relationship between alcohol consumption and breast cancer risk, showing, in general, moderate positive associations. However, the data are not totally consistent and the issue of casual inference remains open to discussion. In a recent meta-analysis [1] of 38 different studies, a positive dose–response relationship was observed with relative risks associated with consumption of one, two, or three drinks a day of 1.11, 1.24 and 1.38, respectively.

Most of the information, however, came from North America, where alcohol consumption in women is relatively infrequent and generally modest. For instance, in the Nurses' Health Study [2], the highest consumption category was ≥ 15 g of ethanol (i.e. approximately one drink) per day and in the largest case–control study of 6888 cases and 9424 controls from New England and Wisconsin, over 55% of the drinking controls drank less than 5 g of ethanol per day and only approximately 2% more than 33 g (i.e. approximately three drinks) per day [3]. Also data from New Zealand [4] and South Australia [5] are restricted to moderate alcohol consumption, but still indicate a moderate non-significant association with breast cancer. In a Netherlands cohort study on postmenopausal women [6], even though only 33% of

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cases and 31% of controls drank more than 5 g of alcohol per day, the relative risks were of 1.29, 1.28 and 1.72 for women who consumed 5–14, 15–29 and ≥ 30 g of alcohol per day, respectively.

Data from Southern Europe are able to provide information on higher consumption levels. Thus, studies conducted in northern Italy [7–10], France [11, 12], Spain [13], Greece [14] and Switzerland [15] gave relative risks between 1.5 and 2.7 for levels of intake of or above 20–30 g of ethanol, i.e. two to three drinks per day. Further information over a broad range of alcohol intake is, however, still required to understand better the pattern of dose–risk relationship and hence, formulate any causal inference. The potential role of various types of alcoholic beverage, and their impact on breast cancer rates on a population scale, also requires additional elucidation.

Other open issues include the duration–risk relationship, or the role of any other time factors, including age at starting drinking, age at cancer diagnosis and menopausal status [16]. Whereas most studies, in fact, have not found a consistent duration–risk relationship, in some [5, 17–19], but not all [3, 9, 12, 13, 20], published studies, the association was apparently stronger at younger age, or in premenopausal women.

Because of the public health importance of breast cancer, and of the modifiable nature of alcohol drinking, the issue retains a high priority. In order to contribute to the current debate, we analysed the largest case–control study of diet and breast cancer so far [21–23]. This dataset is of particular interest, since the strongest associations between alcohol and breast cancer were found in Italy and other Mediterranean countries, where alcohol consumption is socially acceptable in both genders and usually begins in early adult life.

A large number of dietary and non-dietary covariates were considered in this study and could, therefore, be taken into account in the present analyses. Furthermore, the dietary questionnaire used was assessed for reproducibility and validity, specifically concerning alcohol consumption [24], thus allowing measurement error to be incorporated in the present evaluation.

PATIENTS AND METHODS

A multicentre case–control study on breast cancer was conducted between June 1991 and April 1994 in six Italian areas: the provinces of Pordenone and Gorizia, the greater Milan area, the urban area of Genoa, the province of Forlì in northern Italy, the province of Latina in central Italy and the urban area of Naples in southern Italy. The general design of this investigation has already been described [22].

Cases were 2569 women (aged 23–74 years, median age 55 years) admitted to the major teaching and general hospitals of the study areas, with histologically confirmed breast cancer first diagnosed no longer than 1 year before the interview and no history of cancer at the time of diagnosis. Controls were patients (aged 20–74 years, median age 56 years), with no history of cancer, admitted to hospitals within the same catchment areas as those where cases were identified. Of the 2588 control women, 22% had trauma (other than alcohol related), 33% other orthopaedic disorders (such as low back pain and disc disorders), 15% acute surgical disorders, 18% eye diseases and 12% other miscellaneous diseases (ear, nose, and throat, skin and dental conditions). Controls were not individually matched to cases, but were similar in terms of age in quinquennia and area of residence. Less than 4% of cases and controls refused to be interviewed.

Dietary habits were investigated by means of a validated food-frequency questionnaire (FFQ) [24–27], administered by centrally trained and routinely supervised interviewers. The FFQ was developed to assess the habitual diet of the participants, including total energy intake as well as intake of selected micro- and macronutrients. Information was obtained on average weekly frequency of consumption of 78 specific foods or groups of foods, as well as complex recipes (including the most common ones in the Italian diet) during the previous 2 years.

The FFQ looked more like the menu of a restaurant than a shopping list, having one section specifically on alcoholic beverages. The daily of drinks of wine (125 ml), beer (330 ml), grappa (30 ml), a typical Italian liquor, amari and digestives (30 ml), and spirits (30 ml) was investigated. The alcohol content per 100 g of beverage was estimated as 10.45 g for wine, 2.8 g for beer, 33.6 g for grappa, 27.3 g for amari and digestives and 32.6 g for spirits on the basis of a food composition database specifically designed for the present study [28].

Daily intakes of alcohol from different beverages were computed using the number of days per week on which each type of beverage was consumed and the average number of drinks per day. Information about age at first and last use, for ex-drinkers, was also collected. A satisfactory level of reproducibility and validity of the pattern of alcoholic consumption across different levels and types of alcoholic beverage intake was observed [24]. The reproducibility of wine and total alcohol intake showed correlation coefficients $r > 0.75$ in both sexes. The validity was higher for wine (r approximately 0.70) than for other alcoholic beverages and total alcohol intake (r approximately 0.60) [24].

Data analysis

The association between various measures of alcohol consumption and breast cancer was evaluated by means of odds ratios (OR) and the corresponding 95% confidence intervals (CI), derived from multiple logistic regression equations, including terms for age (< 45; 45–54; 55–64; ≥ 65 years), centre (six centres), education (≤ 6; 7–11; ≥ 12 years), age at first birth (≤ 23; 24–26; ≥ 27 years), parity (0–1; 2; 3; ≥ 4), age at menarche (≤ 11; 12; 13; ≥ 14 years), body mass index (< 22; 23–25; > 26 kg/m^2) and family history (no; yes). Allowance for 5-year age groups, as well as for selected dietary factors (starch, fibre, beta-carotene and vitamin E) did not substantially modify the estimates. The ORs for total alcohol, or specified alcoholic beverage consumption, were obtained without considering ex-drinkers. For all the subjects considered in this study, information about alcoholic consumption was available. Ex-drinkers were defined as women who stopped drinking at least 1 year before the interview.

Total alcohol consumption was computed, adding the intakes of various alcoholic beverages and then allowed for total energy intake not due to alcohol by using the residual regression method [29] and classified into six categories. The abstainers were defined as < 1 g/day drinkers.

Analyses were also conducted separately for all types of alcoholic beverages, i.e. wine, beer, amari, grappa and spirits. A distinction between subjects who did not consume each specific beverage, but drank some other alcoholic beverage and those who consumed that beverage was carried out.

Breast cancer risk in relation to age at first alcohol consumption and total duration in years of alcohol consumption

Table 1. *Distribution of* 2569 *cases (Ca) of breast cancer and* 2588 *controls (Co) according to alcohol intake and corresponding odds ratio (OR). Multicentre Italian case–control study,* 1991–1994

	Overall ($n = 5157$)		Premenopausal‡ ($n = 1832$)		Postmenopausal‡ ($n = 3322$)	
Total alcohol (g/day)*	Numbers Ca:Co	OR† (95% CI)	Numbers Ca:Co	OR† (95% CI)	Numbers Ca:Co	OR† (95% CI)
Abstainers§	915:1048	1	337:370	1	578:678	1
1.00–5.87	303:278	1.21 (1.00–1.47)	141:104	1.45 (1.06–1.97)	162.174	1.01 (0.79–1.30)
5.88–13.40	303:278	1.23 (1.02–1.50)	110:96	1.12 (0.80–1.55)	193:182	1.23 (0.97–1.56)
13.41–24.55	291:278	1.19 (0.98–1.45)	121:75	1.55 (1.10–2.18)	170:203	0.98 (0.77–1.25)
24.56–27.60	276:277	1.21 (0.99–1.47)	102:79	1.47 (1.04–2.08)	173:198	1.03 (0.81–1.30)
> 27.60	337:278	1.41 (1.17–1.71)	144.87	1.80 (1.30–2.50)	191:191	1.13 (0.89–1.44)
Ex-drinkers	144:151	1.12 (0.87–1.44)	34:32	1.07 (0.62–1.84)	110:119	1.05 (0.78–1.41)
χ^2_{trend}‖		12.28 ($P = 0.0005$)		14.13 ($P = 0.0002$)		0.62 (NS)

*Adjusted for intake of energy not due to alcohol consumption by means of regression model. †Derived from multiple logistic repression including terms for age, centre, education, age at first birth, parity, age at menarche, body mass index and family history of breast cancer. ‡Menopausal status was not available for 3 subjects. §Defined as < 1 g/day drinkers, reference category. ‖Ex-drinkers were not included. CI, confidence interval; NS, non-significant.

Table 2. *Distribution of* 2569 *cases (Ca) of breast cancer and* 2588 *controls (Co) according to alcohol intake from specific beverages and corresponding odds ratios (OR). Multicentre Italian case–control study,* 1991–1994

	Overall ($n = 5157$)		Premenopausal ($n = 1832$)		Postmenopausal ($n = 3322$)	
Type of alcoholic beverages (g/day)	Numbers Ca:Co	OR* (95% CI)	Numbers Ca:Co	OR* (05% CI)	Numbers Ca:Co	OR* (95% CI)
Abstainers†	915:1048	1	337:370	1	578:678	1
Alcohol from wine‡						
No wine drinkers	110:107	1.11 (0.83–1.48)	62:49	1.48 (0.96–2.27)	48:58	0.85 (0.56–1.29)
1.00–12.76	366:320	1.29 (1.08–1.55)	161:111	1.47 (1.09–1.99)	205:209	1.12 (0.89–1.42)
12.77–13.45	337:320	1.19 (0.99–1.43)	116:94	1.10 (0.79–1.52)	221:226	1.13 (0.90–1.42)
13.46–26.33	347:318	1.29 (1.08–1.56)	145:108	1.52 (1.12–2.07)	201:210	1.11 (0.88–1.41)
≥ 26.34	348:322	1.27 (1.06–1.53)	133:77	1.87 (1.33–2.62)	213:245	0.99 (0.79–1.24)
Ex-wine drinkers	146:153	1.12 (0.87–1.44)	35:34	1.05 (0.62–1.78)	111:119	1.06 (0.79–1.42)
χ^2_{trend}§		11.20 ($P = 0.0008$)		13.27 ($P = 0.0003$)		0.45 (NS)
Alcohol from beer						
No beer drinkers	1238:1184	1.16 (1.02–1.32)	461:347	1.36 (1.09–1.70)	775:837	1.00 (0.85–1.17)
Beer drinkers	266:187	1.44 (1.16–1.79)	157:89	1.78 (1.29–2.46)	108:98	1.12 (0.82–1.52)
Ex-beer drinkers	150:169	1.02 (0.80–1.31)	34:37	0.94 (0.56–1.59)	116:132	0.96 (0.72–1.28)
Alcohol from amari						
No amari drinkers	1419:1305	1.19 (1.05–1.35)	571:413	1.40 (1.13–1.74)	845:892	1.02 (0.87–1.19)
Amari drinkers	82:64	1.28 (0.90–1.82)	45:22	2.27 (1.29–4.01)	37:42	0.83 (0.51–1.34)
Ex-amari drinkers	153:171	1.03 (0.80–1.31)	36:38	0.97 (0.58–1.62)	117:133	0.96 (0.72–1.28)
Alcohol from grappa						
No grappa drinkers	1400:1299	1.18 (1.04–1.34)	574:404	1.44 (1.16–1.78)	823:895	0.99 (0.84–1.16)
Grappa drinkers	100:71	1.57 (1.12–2.19)	41:32	1.49 (0.89–2.51)	59:39	1.54 (0.99–2.41)
Ex-grappa drinkers	154:170	1.04 (0.81–1.33)	37:37	1.02 (0.61–1.71)	117:133	0.97 (0.73–1.29)
Alcohol from spirits						
No spirits drinkers	1426:1322	1.18 (1.04–1.34)	583:414	1.44 (1.16–1.78)	840:908	0.99 (0.85–1.16)
Spirits drinkers	74:48	1.51 (1.02–2.22)	32:22	1.50 (0.82–2.73)	42:26	1.59 (0.94–2.67)
Ex-spirits drinkers	154:170	1.04 (0.81–1.33)	37:37	1.01 (0.61–1.69)	117:133	0.96 (0.72–1.28)
All beverages combined						
Wine						
1.00–12.76		1.24 (1.04–1.49)		1.33 (0.99–1.80)		1.13 (0.89–1.42)
12.77–13.45		1.15 (0.96–1.39)		0.98 (0.71–1.37)		1.14 (0.91–1.43)
13.46–26.33		1.24 (1.03–1.49)		1.35 (0.99–1.85)		1.11 (0.87–1.40)
≥ 26.34		1.21 (1.00–1.45)		1.69 (1.20–2.40)		0.98 (0.78–1.23)
Beer drinkers		1.24 (1.01–1.54)		1.39 (1.02–1.88)		1.08 (0.80–1.46)
Grappa drinkers		1.28 (0.92–1.79)		0.90 (0.53–1.51)		1.55 (1.00–2.41)
Amari drinkers		0.99 (0.70–1.41)		1.65 (0.93–2.93)		0.75 (0.47–1.21)
Spirits drinkers		1.21 (0.82–1.79)		0.90 (0.48–1.68)		1.57 (0.93–2.65)

*Derived from multiple logistic regression including terms for age, centre, education, age at first birth, parity, age at menarche, body mass index and family history of breast cancer. †Defined as < 1 g/day drinkers, reference category. ‡Adjusted for intake of energy not due to alcohol consumption by means of regression model. §Ex-drinkers were not included. CI, confidence interval; NS, non-significant.

was also examined. This analysis was restricted only to current drinkers. In the interval between the age when alcohol drinking started and the age at interview, drinking was assumed to be steady.

Finally, using available data on the validation study, the measurement error related to alcohol intake obtained by means of a FFQ was estimated according to the model proposed by Rosner [30]. This model belongs to the class of adjacent category models for ordinal regression and permits evaluation, for each subject, of the probability of being in the 'true' category of alcohol consumption assuming that it has been 'observed' in a specific category with FFQ. This approach allows, at every observed category of consumption, the 'expected true category' to be determined, if no measurement error is made. These 'expected true categories' estimated from the validation study have also been evaluated for every subject included in the case–control study.

RESULTS

The percentage of cases (58.8% $n = 1510$) that were currently drinkers of some type of alcoholic beverage was slightly greater than the percentage of controls (53.7% $n = 1389$). The mean total alcohol intake was 20.3 g (standard deviation (S.D.) = 16.5) for cases and 20.0 g (S.D. = 17.3) for controls.

Because of a significant interaction with menopausal status ($P = 0.032$), the results are given for the whole series and for pre- and postmenopausal status separately (Table 1). A trend ($\chi^2_{trend} = 12.28$, $P = 0.0005$) of increasing risk with greater alcohol intake was seen overall, with an OR of 1.41 (95% CI 1.17–1.71) for drinkers of 27.6 g alcohol per day or more as compared with abstainers. In premenopausal women, the trend was significant ($P = 0.0002$), with an OR of 1.80 (95% CI 1.30–2.50) in the highest intake category, whereas in postmenopausal women, no significant association was observed. When the heavy drinkers were defined as those with alcohol intake of 39 g/day or more, analogous figures were obtained. The multivariate OR of breast cancer for drinkers versus abstainers was 1.25 (95% CI 1.12–1.41) overall, 1.46 (95% CI 1.19–1.79) in premenopausal and 1.07 (95% CI 0.92–1.25) in postmenopausal women.

Table 2 shows breast cancer ORs according to the intake of various alcoholic beverages. All types of alcoholic beverages showed a moderate positive association. ORs for the highest consumption level of wine were 1.87 (95% CI 1.33–2.62) in pre- and 0.99 (95% CI 0.79–1.42) in postmenopause. Also drinkers of alcoholic beverages other than wine showed a non-significant association, indicating that other alcoholic beverages were also associated with breast cancer risk. Ex-drinkers had ORs moderately, but not significantly, above unity. When all types of alcoholic beverages were included simultaneously in the same model (Table 2) most ORs remained above unity. Significant ORs persisted for wine and beer consumption. In premenopause, the only significant ORs were seen in the highest category of wine consumption (OR = 1.69, 95% CI 1.20–2.40) and in beer drinkers (OR = 1.39, 95% CI 1.02–1.88).

Breast cancer risk increased with later age at starting, with a significant positive trend overall ($P = 0.0009$) and in premenopause ($P = 0.0026$) (Table 3). Overall, the OR was 1.32 (95% CI 1.10–1.57) for women with age at first consumption ≥ 25 years compared with abstainers. Consequently, there was no tendency for the risk to increase with increasing duration of alcohol drinking, with an OR of 0.95 for duration ≥ 40 years, as compared with abstainers. These findings were reproduced in premenopausal women and comparable results were found when similar analyses were made within categories of total alcohol consumption (data not shown).

The modifying effect of various potential correlates of breast cancer risk is considered in Table 4. The significance levels are difficult to interpret because of the large number of comparisons. Except for age, there was no statistically significant interaction between alcohol consumption and all the other variables when evaluated by means of logistic regression. The association with alcohol consumption was apparently stronger among women with a low level of education, in those with an age at first birth before 27 years, one or two births only and late age at menarche. No consistent risk pattern was observed across strata of body mass index, family history of breast cancer, smoking habits, marital status, oral contraceptive use and menopausal replacement therapy.

Table 3. Odds ratio (OR) of breast cancer for age at first alcohol consumption and duration of alcohol consumption. Multicentre Italian case–control study, 1991–1994

	Numbers Ca:Co	Overall OR* (95% CI)	Premenopause OR* (95% CI)	Postmenopause OR* (95% CI)
Age at first consumption (years)				
Abstainers†	915:1048	1	1	1
≤ 15	200:206	1.07 (0.86–1.34)	1.50 (1.02–2.20)	0.87 (0.65–1.15)
15–19	396:408	1.08 (0.91–1.29)	1.45 (1.09–1.93)	0.85 (0.68–1.07)
20–24	464:425	1.22 (1.03–1.44)	1.40 (1.06–1.84)	1.05 (0.85–1.31)
≥ 25	431:333	1.32 (1.10–1.57)	1.57 (1.13–2.17)	1.13 (0.91–1.40)
χ^2_{trend}‡		11.03 ($P = 0.0009$)	9.04 ($P = 0.0026$)	1.32 (NS)
Duration of consumption (years)				
Abstainers†	915:1048	1	1	1
< 20	199:173	1.26 (0.99–1.61)	1.42 (1.05–1.92)	1.20 (0.74–1.93)
20–29	385:270	1.48 (1.22–1.80)	1.58 (1.22–2.05)	0.96 (0.69–1.35)
30–39	410:350	1.24 (1.03–1.49)	1.37 (0.99–1.90)	1.15 (0.92–1.44)
≥ 40	497:579	0.95 (0.80–1.13)	1.00 (0.42–2.39)	0.91 (0.75–1.09)
χ^2_{trend}‡		1.28 (NS)	7.62 ($P = 0.0058$)	0.33 (NS)

*Derived from multiple logistic regression including terms of age, centre, education, age at first birth, parity, age at menarche, body mass index, family history of breast cancer and total caloric intake. †Defined as < 1 g/day drinkers, reference category. ‡Ex-drinkers were not included. NS, non-significant; Ca, cases; Co, controls; CI, confidence interval.

Table 4. Odds ratios (OR) for breast cancer according to total alcohol consumption in separate strata of selected confounders. Multicentre Italian case–control study, 1991–1994

		OR* for total alcohol consumption†							
	Numbers Ca:Co	Abstainers‡	1§	2	3	4	5	Ex	χ^2_{trend}‖	*P*
Age (years)										
≤ 44	470:472	1	1.68††	1.27	1.63††	1.16	1.93††	0.85	5.84	0.0157
45–54	722:694	1	1.30	1.31	1.24	1.62††	1.75††	1.20	11.57	0.0007
55–64	799:802	1	0.92	1.28	0.81	1.07	1.09	0.93	0.17	NS
≥ 65	528:620	1	1.08	1.02	1.25	0.94	1.08	1.20	0.12	NS
Education (years)										
≤ 6	1273:1592	1	1.05	1.12	1.16	1.17	1.35††	1.19	5.71	0.0169
7–11	714:642	1	1.61††	1.55††	1.36	1.42	1.55††	1.08	6.51	0.0107
≥ 12	582:354	1	1.17	1.24	1.01	1.08	1.52	0.91	1.84	NS
Age at first birth (years)										
≤ 23	1095:1341	1	1.01	1.04	1.23	1.17	1.36††	0.93	5.59	0.0181
24–27	814:740	1	1.76††	1.01	1.12	1.38	1.51††	1.24	4.38	0.0364
≥ 28	660:507	1	1.25	1.90††	1.11	1.08	1.40	1.35	1.66	NS
Parity (no. of births)										
0	401:380	1	0.98	1.47	1.11	0.97	1.27	0.42	0.73	NS
1	584:494	1	1.96††	1.90††	1.39	1.19	2.31††	2.21††	8.76	0.0031
2	968:909	1	1.14	1.02	1.16	1.34	1.37	1.12	4.82	0.0281
3	406:489	1	1.05	1.14	1.00	1.19	1.00	1.12	0.12	NS
≥ 4	210:316	1	1.12	1.12	1.50	1.16	1.41	0.87	1.53	NS
Age at menarche (years)										
≤ 11	501:492	1	1.29	1.34	1.55	1.17	1.25	1.19	1.88	NS
12	626:579	1	1.28	1.19	0.95	1.25	1.21	1.40	0.89	NS
13	594:568	1	1.21	1.05	1.19	1.22	1.80††	0.79	6.09	0.0136
≥ 14	848:949	1	1.20	1.43††	1.22	1.25	1.52††	1.27	6.47	0.0110
Body mass index (kg/m^2)										
< 22	594:567	1	1.35	1.30	1.40	1.26	1.75††	1.19	10.60	0.0011
22–25	823:799	1	1.07	1.27	0.91	0.93	1.16	1.15	3.44	NS
> 25	1152:1222	1	1.27	1.20	1.41††	1.40††	1.44††	1.10	27.05	0.0000
Family history of breast cancer										
No	2270:2453	1	1.24	1.21	1.17	1.20	1.40††	1.12	10.46	0.0012
Yes	299:135	1	1.02	1.81	1.50	1.59	1.89	1.18	3.77	NS
Smoking habits										
Never	1684:1759	1	1.15	1.13	1.15	1.21	1.42††	1.33	7.77	0.0053
Current	541:577	1	1.28	1.29	1.21	1.57	1.60††	0.78	6.91	0.0086
Ex	344:252	1	1.50	2.36††	1.72	0.73	1.22	0.59	0.07	NS
Marital status										
Never	288:233	1	1.25	1.93	1.24	1.44	1.71	0.46	2.88	NS
Ever	2341:2355	1	1.23††	1.18	1.19	1.20	1.39††	1.22	10.27	0.0014
Oral contraceptive use¶										
Never	1684:1685	1	1.16	1.32††	1.18	1.24	1.44††	1.01	9.83	0.0017
Ever	357:283	1	1.52	1.19	1.02	1.65	1.71††	2.00	3.30	NS
Menopause replacement therapy**										
No	1392:1569	1	1.02	1.22	1.01	1.06	1.12	1.00	0.74	NS
Yes	185:176	1	1.12	1.52	0.95	0.75	1.50	1.60	0.27	NS

*Derived from multiple logistic regression including terms for age, centre, education, age at first birth, parity, age at menarche, body mass index and family history of breast cancer. †Adjusted for intake of energy not due to alcohol consumption by means of regression model. ‡Defined as < 1 g/day drinkers, reference category. §Levels of total alcohol consumption as reported in Table 1. ‖Ex-drinkers were not included. ¶Only subjects below the age of 65 years. **Restricted to women in postmenopausal status. ††$P < 0.05$. Ca, cases; Co, controls; NS, non-significant.

In Table 5, the effect of the measurement error is estimated by comparing the $\hat{\beta}$ values and the related standard errors (SE($\hat{\beta}$)) of the regression models with alcohol intake given by FFQ (uncorrected) and alcohol intake modified according to the validation study evidence (corrected) [30]. The uncorrected OR for women with FFQ alcohol consumption in the highest category of consumption versus abstainers was 1.31 (95% CI 1.13–1.53), whereas the corresponding corrected OR was 1.39 (95% CI 1.21–1.60), indicating that the measurement error produces a moderate risk underestimation.

DISCUSSION

The present findings, based on the largest study to date of diet and breast cancer, confirm that alcohol drinking is a correlate of breast cancer risk in this Mediterranean population. The OR was elevated by approximately 40% in the highest consumption quintile (corresponding to approximately two drinks or more per day), and the association was consistent for wine—which represents by far the largest source of alcohol in this population—and for other alcoholic beverages. It was, however, also seen for beer and spirits, thus suggesting that ethanol *per se* is the most likely correlate of

Table 5. *Odds ratio (OR) of breast cancer for alcohol consumption adjusted for age. Comparison between uncorrected and corrected values. Multicentre Italian case–control study,* 1991–1994

	Overall			Premenopausal			Postmenopausal		
Alcohol consumption	$\hat{\beta}$	SE ($\hat{\beta}$)	OR (95% CI)	$\hat{\beta}$	SE ($\hat{\beta}$)	OR (95% CI)	$\hat{\beta}$	SE ($\hat{\beta}$)	OR (95% CI)
Uncorrected	0.054	0.016	1.31* (1.13–1.53)	0.097	0.027	1.63* (1.25–2.11)	0.019	0.020	1.10* (0.91–1.34)
Corrected†	0.066	0.014	1.39* (1.21–1.60)	0.121	0.023	1.83* (1.47–2.28)	0.022	0.019	1.12* (0.92–1.35)

*Comparing the last category of alcohol consumption versus abstainers. The OR and relative CI are computed following the indication in Rosner [30]. †Expected true categories are estimated on the basis of measurement error model. CI, confidence interval.

risk. Such risk elevation is similar to the one shown by a meta-analysis on 38 different studies [1].

It has been suggested that the association between alcohol and breast cancer may be greater for consumption started at younger age [31]. However, in this study, no clear duration or dose–risk relationships was observed and the association seemed restricted to younger and/or premenopausal women, and more marked in women who had started drinking later. In other studies [7, 15, 32], a greater effect of early drinking was not observed. The absence of a duration–risk relationship was observed in several previous studies [7, 14, 32], but does not necessarily preclude causal inference. Alcohol modifies hepatic metabolism of steriod hormones, and their serum levels and availability, thus possibly showing a differential effect in pre- versus postmenopausal women. It is known, moreover, that most hormone-related factors have a short-term impact on breast carcinogenesis, acting as late stage (promoting) factors, thus being independent from duration [33].

At least 19 studies have explored the heterogeneities by age or menopausal status. In eight investigations, no substantial heterogeneity was found [2, 4, 7, 14, 34–37]. These included the prospective Nurses' Health Study [2], where all women were below the age of 60 years and, therefore, had, at most, undergone menopause only relatively recently. In five studies, the association of breast cancer risk with alcohol consumption was stronger or restricted to premenopausal women [5, 15, 17–19]. In another investigation, the only group where a trend in risk was observed, was represented by perimenopausal women [38]. Conversely, in four case–control studies [3, 9, 12, 13] and in one prospective investigation [20], risk elevations in alcohol drinkers emerged especially or exclusively in women who were above the age of 50 years or postmenopausal. In the light of this lack of consistent evidence from previous work, the interaction of alcohol effect and age or menopausal status observed in our study should probably be attributed to chance or to some unknown characteristic of the Italian women in the study.

In several studies, the association between alcohol intake and breast cancer risk was assessed separately, in strata of various breast cancer correlates [4, 6, 7, 14, 38]. In general, however, no consistent interaction or modifying effect was observed [4, 7, 14, 38]. Likewise, apart from age and menopausal status, this study did not provide convincing evidence of any other significant or meaningful association between alcohol drinking and major risk factors for breast cancer. This study did not support the hypothesis that alcohol drinking at a younger age is of specific importance for subsequent breast cancer risk [31]. This absence of interactions is of special interest too, given the large size of the dataset.

This study has several strengths, as well as potential weaknesses, of hospital-based case–controls investigations. Of relevance for this study, however, are the satisfactory participation of cases and controls approached for interview and the similar interview setting, which should have increased reliability and comparability of information on alcohol consumption. Approximately one third of controls had traumatic conditions, which may be related to alcohol drinking and, hence, may lead to some underestimate of the real association. The ORs, however, were similar when separate comparisons were made across major diagnostic categories of controls. The major strength of this study, moreover, was the large size of the study population and the comparatively broad range of alcohol consumption in Italian women.

Furthermore, the questionnaire was shown to be a satisfactorily reliable and valid instrument for collecting information on alcohol drinking, as shown also by the modest effect of correction for measurement error. In fact, the correction for measurement error as proposed by Rosner [30] increased the OR by 26% overall and for 32% and 20% in premenopause and postmenopause, respectively.

In the absence of clear biological mechanisms, and in view of the moderate extent of the association, any cause–effect inference remains open to discussion. None the less, assuming that the association reflects causality, alcohol intake would be one of the major avoidable causes of breast cancer in Italy. In terms of population attributable risk, alcohol drinking would account for 12% (95% CI 5–19%) [39] of breast cancer cases in this population. According to the present data in premenopausal women, two drinks per day may be a relevant threshold both in the light of the flat dose–risk relationship below such a level and of the overall association between alcohol intake and total mortality [40, 41]. Critical consideration of all alcohol related health outcomes, which may include a protective effect of moderate drinking against heart disease [42], should be the base of broader public health recommendations.

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