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Alcohol cessation and breast cancer risk stratified by hormone receptor status

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Abstract

Because alcohol consumption is an established cause of female breast cancer, understanding whether cessation affects risk is of public health importance. In a recent meta-analysis, compared with continuing consumption, the relative risk (RR) for cessation was 0.95 (95% confidence interval [CI] 0.88–1.01). Because intake of alcohol is more consistently associated with estrogen receptor positive (ER+) than negative (ER-) subtypes, we conducted a meta-analysis of alcohol cessation for ER-specific breast cancer risk using data from three cohort studies and one population-based case-control study (ER+ $n=3,793$; ER- $n=627$) with information reported on cessation and ER status. Compared with continuing consumption, cessation was associated with lower risk of ER+ (RR = 0.88, 95%CI, 0.79–0.98) but not ER- (RR = 1.23, 95%CI, 0.98–1.55) breast cancer. These results suggest that, compared with continuing consumption, alcohol cessation may reduce ER + but not ER- breast cancer risk. However, research that considers duration of cessation is warranted.

Keywords Breast cancer, Alcoholic beverages, Alcohol cessation, Risk reduction, Hormone receptor, Estrogen receptor

Brief report

Alcoholic beverage consumption is an established cause of female breast cancer (BC) [1]. Compared with abstention, even consumption of less than 10 g of ethanol per day is associated with higher BC risk [2]. Globally, an estimated 4.4% of all new female BC cases in 2020 was attributable to alcohol consumption [3]. Understanding whether cessation affects risk is of public health importance. Recently, a comprehensive review and evaluation of the epidemiologic evidence on alcohol reduction or cessation and alcohol-related cancer risk "concluded that there was *limited* evidence that alcohol reduction or cessation reduces BC risk" compared with continuing consumption [4]. This conclusion was based, in part, on a meta-analysis of 10 case-control and 6 cohort studies of overall BC incidence in which the relative risk (RR) for alcohol cessation compared with continuing consumption was 0.95 (95% confidence interval [CI] 0.88–1.01). However, the associations for cessation in relation to estrogen receptor positive (ER+) and estrogen receptor negative (ER-) BC subtypes were not assessed. Because alcohol consumption, compared with abstention, is more consistently associated with a higher risk of ER+ than ER- BC [2], it is plausible that, compared with continuing consumption, cessation may be more strongly associated with a reduced risk of ER+ then ER- BC. We used meta-analytic techniques to assess the associations of cessation

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of alcoholic beverage consumption with risk of ER+and ER- BC.

Randomized controlled trials, individual case–control and cohort studies, meta-analyses, and pooled analyses with alcohol-related BC incidence outcomes were eligible for inclusion if they included data on alcohol cessation and ER-specific breast cancer. Studies with fewer than five BC cases – overall or in any subgroup – were not eligible for inclusion. We identified three cohort [5–7] studies and one population-based case-control [8] study that met the eligibility criteria; three studies reported results separately for ER status and progesterone receptor (PR) status, whereas one study reported results for combinations of ER and PR.

One author extracted numbers of cases, controls, totals, person-years, RRs and 95% CIs from each included paper. Data extractions were checked by two other authors. Because the four studies presented RRs for cessation and for continuing consumption relative to abstention, we first calculated the RR and its 95% CI for cessation versus continuing consumption for each study. Two studies [5, 8] presented RRs for several categories of amount of alcohol currently consumed versus abstention; for these studies, we first calculated a single RR combining all current consumption categories (excluding the occasional consumption category) relative to abstention before computing the RR and CI for cessation compared with continuing consumption. To account for correlated RRs within a study because of the use of a common reference group, we used the method of Greenland and Longnecker to estimate the covariances between RRs [9]. These calculations were done with a user-written routine in Stata [10, 11]. For one study [5] the data necessary to perform that calculation were not provided, therefore the correlation was ignored (ignoring the correlation leads to wider CI). We then performed separate random effects meta-analyses (using restricted maximum likelihood), for cessation versus continuing consumption and risk of ER+and ER- BC. One study [6] presented separate RRs for ER+/PR+and ER+/PR-; because the correlation between the two RRs is negligible [12], it was ignored in the meta-analysis.

The three cohorts included 3,374 ER+and 574 ER- prospectively ascertained BC cases in the cessation and continuing consumption categories; two cohort studies [5, 6] conducted in the U.S. included postmenopausal women only and one cohort study conducted in Japan included both pre- and postmenopausal women [7] (see Table 1 for details). The population-based case-control [8] study was conducted in the U.S. (n=419 ER+and 53 ER- BC cases in the cessation and continuing consumption categories), and included postmenopausal women only.

Among the four studies, compared with continuing consumption, cessation was consistently associated with lower ER+BC risk (i.e., RR range, 0.83–0.90) (Fig. 1), and higher ER- BC risk (RR range, 1.00-1.18 in three studies, and 2.32 in the fourth study). The meta-analytic results by ER status are also shown in Fig. 1. Compared with continuing consumption, alcohol cessation was associated with lower risk of ER+BC (RR=0.88, 95% CI, 0.79–0.98), but not ER- BC (RR=1.23, 95% CI, 0.98–1.55).

An important strength of our meta-analysis is the assessment of BC risk for alcohol cessation compared with that for continuing consumption rather than for abstention. This comparison better addresses the potential change in risk due to cessation and simulates a randomized controlled trial of alcohol cessation in which all study participants would be individuals who reported current consumption at the time of randomization.

The inverse association between alcohol cessation relative to continuation and risk of ER+BC supports the previously reported positive association between consumption and ER+BC risk. In three [5, 7, 8] of the four studies included in our meta-analysis, compared with abstention, former drinking was associated with higher risk of ER+BC, albeit the RRs were lower than those for continuing consumption. The higher risk for cessation compared with abstention may be due to longer term effects related to prior alcohol consumption. In the case-control study, recall bias could explain a potentially higher risk if cases were more likely to report cessation, rather than abstention, compared with controls. As a result, any beneficial effect of cessation compared with continuing consumption could be biased towards the null.

Reasons for the positive association between alcohol cessation and ER- BC risk compared with continuation in our meta-analysis are unclear. If the missing data on ER status differs by consumption category, and if cases with missing ER status in the current drinking category were more likely to have ER- BC, then an association for cessation compared with continuing consumption would be biased towards an increased risk. Indeed, in the study with the highest RR (i.e., 2.32) for cessation compared with continuing consumption,[7] 44.2% and 54.7% of cases in the former and current drinking categories, respectively, were missing ER status. After excluding that study, the association between cessation and risk of ER+BC was unchanged (RR=0.88; 95% CI, 0.79–0.99) but the association between cessation and risk of ER- BC was markedly attenuated (RR=1.15; 95% CI, 0.90–1.46). It is plausible that reverse causation could have more impact on ER- BC than ER+because ER- breast tumors are faster growing and women with undiagnosed ER- BC may be more likely to quit. We did not have information on why individuals quit, but the specific reasons for cessation are useful for interpretation.

Table 1 Description of Studies Included in the Meta-Analysis

Study	Study description	Exposure assessment	Outcome	Drinking Status	No. of cases	Adjustment factors
Li [8] (2003) Case-control Study USA 1997–1999	1007 population-based frequency matched controls drawn from Health Care Financing Administration records, 73.8% of eligible controls participated	Alcohol intake by type was collected by interviewers for the 20 years before diagnosis/reference date. Alcohol drinkers were defined as women who reported that they had consumed at least 12 beverages containing alcohol during the past 20 years and had consumed at least 1 alcohol-containing beverage a month for 6 months during the past 20 years. Former users of alcohol were defined as ever-users who reported no use of alcohol during the year before reference date.	Invasive breast cancer cases (n = 975) aged 65–79 years; ductal (n = 651), lobular (n = 196) based on ICDO 8520 and 8522; 80.6% of eligible cases participated	Never Former Current Never Former Current	***ER+*** 370 57 362 ***ER-*** 53 8 45	Age, first degree family history of breast cancer, BMI
Li et al. [6] USA Women's Health Initiative (WHI) Observational Cohort Study 1993–2005	87 724 postmenopausal women aged 50–79 years at enrolment (1993-1998) and followed for cancer incidence through 2005	Self-reported alcohol intake at baseline and FFQ, FFQ given priority if discrepancy; if 12 or more drinks of any kind were reported, women were classified as ever drinkers. Frequency of alcohol consumption only asked for current drinkers. Former drinkers reported no current drinking at baseline.	2944 invasive breast cancer cases. Cancers were self-reported using annual questionnaires and then verified by medical records; n = 1805 ductal ICDO code 8500; 720 lobular ICD-Oncology code 8520, 8522; data on ER and PR status available for 88% of cases	Never Former Current Never Former Current	***ER+*** 196 347 1633 ***ER-*** 46 74 239	Age, race, ethnicity, education, BMI, HRT, smoking, Gail model 5-year risk, first degree family history, parity, number of mammograms in past 5 years
Suzuki et al. [7]) Japan The Japan Public Health Center-based Prospective Cohort Study 1990–2006	50,757 pre- and postmenopausal women (ages 40–69 years) who participated in either one of two cohorts defined by region, which were pooled for this study (Cohort 1 and 2), response rate was 82.8%	Self-reported alcohol intake through a FFQ. Only Cohort 2 queried about ex-drinking; 5 types of alcohol were queried (sake, shochu, beer, whiskey, wine); 5 and 10 year follow-up surveys also collected alcohol intake from FFQ	572 BC cases	Never Former Current Never Former Current	***ER+*** 116 19 25 ***ER-*** 58 19 9	Height, BMI, smoking status, leisure-time physical activity, age at menarche, age at first birth, parity, menopausal status, use of exogenous hormones, energy adjusted isoflavone intake
Falk et al. [5] USA Prostate, Lung, Colorectal and Ovarian Screening Cohort Study (PLCO) 1992–2001	54,562 women aged 55–74 years, recruited from 10 screening centers, with no previous history of lung, ovarian or colorectal cancer; median follow-up of 8.9 years	Self-reported alcohol intake through a dietary history questionnaire introduced in 1998; 82% response rate from baseline enrolment; women who did not report alcohol intake within the 12 months prior to baseline were classified as former drinkers	1,905 invasive BC cases	Never Former Current Never Former Current	***ER+*** 175 235 1115 ***ER-*** 33 50 183	Race, education, region, BMI, height, family history of breast cancer, age at menarche, age at natural menopause, oral contraceptive use, menopausal hormone use, smoking

It is unclear whether potential differences in the amount of alcohol consumed (intensity and/or duration as well as age at cessation) between individuals who reported cessation and individuals who reported continuing consumption influenced the association . Not controlling for the amount of alcohol (previously/currently) consumed could bias an inverse association between cessation and BC risk towards the null if individuals who drink higher amounts are more likely to quit whereas the association could be biased away from the null (i.e. appear even more beneficial) if individuals who report lower amounts are more likely to quit. In our meta-analysis, the potential effects of amount consumed could not be determined because that information was

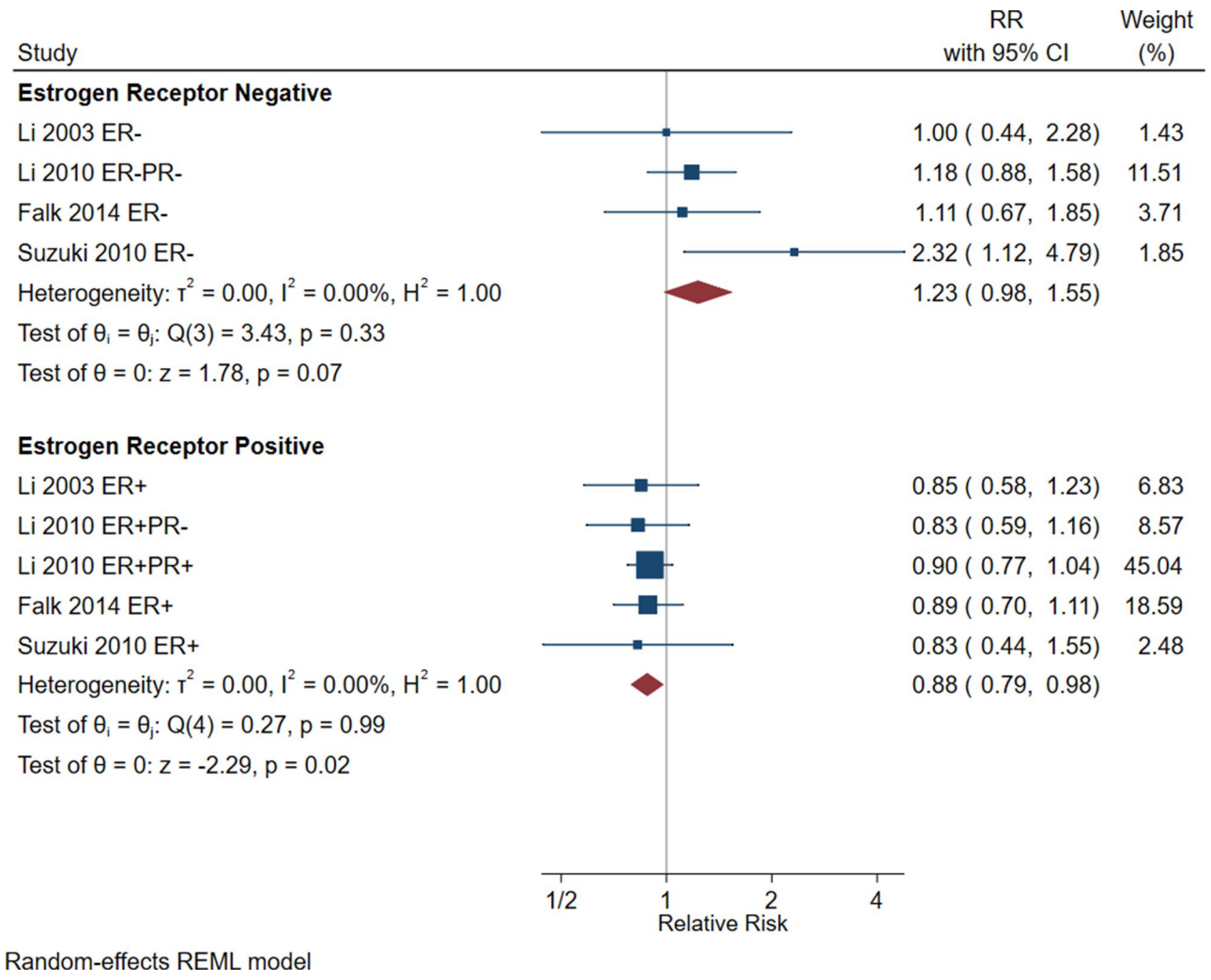

Fig. 1 Meta-Analytic Results by Estrogen Receptor Status

not available among those who reported cessation. Further, from a public health point perspective, it is critical to understand the potential differential impact from cessation for heavier versus lighter drinkers.

Though the results of our meta-analysis are intriguing, they are based on few studies. Further research is needed to establish the effect of alcohol cessation on BC risk. First, complete and unbiased ascertainment of molecular characteristics on breast cancer cases independent of alcohol consumption status is necessary to identify potential differences in associations of BC by hormone-receptor status, or by luminal, basal or other molecular characteristics. Identifying potential differences may be particularly important because, for example in the U.S., Luminal A is one of the most rapidly increasing molecular subtypes of BC in young women [13]. Second, studies of duration of alcohol cessation are needed to assess the potential role of reverse causation on the association between cessation and BC risk, and the amount of time needed to potentially eliminate a higher risk due to consumption. Third, existing cohorts with repeated measures of consumption over time, or reported past consumption, should assess whether amount of alcohol consumption confounds – or modifies – the association between cessation and BC risk. Finally, in the aforementioned comprehensive review of alcohol reduction or cessation and alcohol-related cancer risk [14], only four studies of the association between reduction and overall BC risk were identified. The results of these studies were inconsistent in part due to differences in how categories of reduction were defined. A pooled analysis of individual-level data from cohorts with repeated measures of consumption over time, or reported past consumption, is needed to more fully assess the association between alcohol reduction and BC, preferably using G-methods to simulate hypothetical interventions [15].

In conclusion, our results suggest that alcohol cessation compared with continuing consumption reduces ER+ but

not ER- BC risk. Further research is needed to corroborate these results. Confirmation of an inverse association between cessation and ER+BC risk could contribute to and further support (1) cancer prevention guidelines, which are largely based on studies of alcohol consumption not cessation; (2) public health campaigns aimed at increasing awareness of the link between alcohol and BC risk; and (3) health services actions aimed at screening for and providing effective interventions for alcohol cessation.

Abbreviations

BC	Breast Cancer
RR	relative risk
CI	confidence interval
IARC	International Agency for Research on Cancer
ER	estrogen receptor
PR	progesterone receptor
HR	hormone receptor

Author contributions

All authors participated in the study conceptualization, data interpretation and in paper writing. The data were curated by MBT, DE, SMG and DE did the formal analysis.

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Data availability

N/A (data provided in Table 1).

Declarations

Ethics approval and consent to participate

This report used only data from published studies which were available on Medline.

Disclaimer

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Consent for publication

N/A as only used publicly available data.

Competing interests

The authors declare no competing interests.

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References

1. Personal habits and indoor combustions. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 100E. Lyon, France: International Agency for Research on Cancer. 2012 (https://publications.iarc.fr/122).
2. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Alcoholic drinks and the risk of cancer. https://www.wcrf.org/wp-content/uploads/2021/02/Alcoholic-Drinks.pdf
3. Rumgay H, Shield K, Charvat H, et al. Global burden of cancer in 2020 attributable to alcohol consumption: a population-based study. Lancet Oncol Aug. 2021;22(8):1071–80. https://doi.org/10.1016/S1470-2045(21)00279-5.
4. Gapstur SM, Bouvard V, Nethan ST, et al. The IARC Perspective on Alcohol Reduction or Cessation and Cancer Risk. N Engl J Med Dec. 2023;28(26):2486–94. https://doi.org/10.1056/NEJMsr2306723.
5. Falk RT, Maas P, Schairer C, et al. Alcohol and risk of breast cancer in postmenopausal women: an analysis of etiological heterogeneity by multiple tumor characteristics. Am J Epidemiol Oct. 2014;1(7):705–17. https://doi.org/10.1093/aje/kwu189.
6. Li CI, Chlebowski RT, Freiberg M, et al. Alcohol consumption and risk of postmenopausal breast cancer by subtype: the women's health initiative observational study. J Natl Cancer Inst Sep. 2010;22(18):1422–31. https://doi.org/10.1093/jnci/djq316.
7. Suzuki R, Iwasaki M, Inoue M, et al. Alcohol consumption-associated breast cancer incidence and potential effect modifiers: the Japan Public Health Center-based prospective study. Int J Cancer Aug. 2010;1(3):685–95. https://doi.org/10.1002/ijc.25079.
8. Li CI, Malone KE, Porter PL, Weiss NS, Tang MTC, Daling JR, Malone KE. The relationship between alcohol use and risk of breast cancer by histology and hormone recepeptor status among women 65–79 years of age. CEBP 2003; 12(10):1061–6. PMID: 14578143.
9. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol Jun. 1992;1(11):1301–9. https://doi.org/10.1093/oxfordjournals.aje.a116237.
10. Orsini N. Weighted mixed-effects dose–response models for tables of correlated contrasts. Stata J. 2021;21(2):320–47. https://doi.org/10.1177/1536867X211025798.
11. StataCorp. Stata Statistical Software: Release 18. College Station. TX: StataCorp LLC; 2023.
12. Trikalinos TA, Olkin I. A method for the meta-analysis of mutually exclusive binary outcomes. Stat Med Sep. 2008;20(21):4279–300. https://doi.org/10.1002/sim.3299.
13. Acheampong T, Kehm RD, Terry MB, Argov EL, Tehranifar P. Incidence Trends of Breast Cancer Molecular Subtypes by Age and Race/Ethnicity in the US From 2010 to 2016. *JAMA Netw Open*. Aug 3. 2020;3(8):e2013226. https://doi.org/10.1001/jamanetworkopen.2020.13226
14. IARC. (2024) Reduction or cessation of alcoholic beverage consumption. IARC Handbooks of Cancer Prev. 2024;20A:1-334. https://publications.iarc.who.int/638
15. Robins J. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. Math Modelling. 1986;7. –12.):1393–512. https://doi.org/10.1016/0270-0255(86)90088-6

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