



Systematic or Meta-analysis Studies

To what extent is alcohol consumption associated with breast cancer recurrence and second primary breast cancer?: A systematic review

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ABSTRACT

Background: The association between alcohol intake and breast cancer recurrence or development of second primary breast cancer in the survivor population is unclear. The aim of this systematic review was to evaluate the existing evidence to assess the extent to which alcohol consumption is associated with breast cancer recurrence and second primary breast cancer.

Methods: Six databases (Cochrane Library, EMBASE, MEDLINE, PubMed, Scopus and Web of Science) were searched using the following search phrase: (breast cancer OR breast adenocarcinoma OR breast neoplasm OR breast tumour) AND (alcohol* OR alcohol intake OR alcohol consumption OR ethanol) AND (recurrence OR second primary). A narrative synthesis was conducted on studies meeting the inclusion criteria.

Results: After screening, 16 studies met the inclusion criteria, of which 11 assessed breast cancer recurrence and 5 assessed second primary breast cancer. Considerable clinical and methodological heterogeneity was observed between studies. Approximately half of the included studies observed a modest, but significant, association between alcohol consumption and increased risk of breast cancer recurrence or development of a second primary breast cancer, with some studies observing associations from as little as six grams of alcohol intake per day. Two studies suggest this association was stronger in postmenopausal women.

Conclusion: There is some evidence that alcohol consumption increases the risk of breast cancer recurrence, particularly in postmenopausal women. The association between alcohol and development of a second primary breast cancer is less clear. Inconsistencies in methodology and results across studies complicate attempts to develop a cohesive interpretation of findings.

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Introduction

Breast cancer is the most common type of cancer affecting women worldwide, with almost 1.7 million new cases diagnosed in 2012 alone [1]. With breast cancer survival rates continuing to improve, there has been increasing interest in the role of modifiable lifestyle factors relating to disease incidence and mortality. The link between alcohol consumption and risk of primary breast cancer has been extensively researched, with most recent literature supporting a linear dose–response relationship where each additional standard drink per day consumed is estimated to increase breast cancer risk by 2–12% [2–4]. Reducing alcohol intake is therefore considered important in primary breast cancer preven-

tion, and indeed significant public health education and awareness efforts have leveraged this link [5].

What then does this mean for people who have already been diagnosed with breast cancer? Of women who have undergone breast conserving surgery and radiotherapy, 12–15% will develop a local recurrence within 10 years [6,7]. Fear of recurrence is an issue that ranks consistently high on the list of patient reported worries in the post-treatment phase, as does a lack of medical advice that is specific to survivors [8]. Advice sought regarding appropriate levels of alcohol intake requires health care practitioners to interpret public health recommendations at the personal level [9].

In order to best guide recommendations regarding alcohol intake in the survivorship phase, this systematic review aimed to gather all literature investigating the association between alcohol consumption and breast cancer recurrence or second primary breast cancer to assess the extent to which alcohol consumption

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Table 1
Inclusion/exclusion criteria with corresponding exclusion code.

| Selection question | Inclusion | Exclusion | Exclusion code |
|--|--|---|----------------|
| Is this an article representing original data or secondary data manipulated in an original way? If no, code as EC1 | Article represents original data or secondary data analysed using an original analytical method | Article is a letter, case study or review of existing studies | EC1 |
| Is this a study of human participants? If no, code as EC2 | Human participants | Non-human participants | EC2 |
| Is this a study of adult participants (aged >18 years)? If no, code as EC3 | Study of participants >18 years of age | Study participants <18 years of age | EC3 |
| Does this study investigate participants who have been previously diagnosed with and treated for breast cancer? If no, code as EC4 | Study investigates participants previously diagnosed with and treated for breast cancer | Study investigates participants who have not been previously diagnosed with breast cancer | EC4 |
| Does this study investigate alcohol consumption in participants? If no, code as EC5 | Study investigates alcohol consumption in participants | Study does not investigate alcohol consumption in participants | EC5 |
| Does this study investigate alcohol consumption in relation to risk of breast cancer recurrence or second primary breast cancer? If no, code as EC6 | Study investigates alcohol consumption in relation to risk of breast cancer recurrence or second primary breast cancer | Study investigates alcohol consumption, but does not explore its relation to breast cancer recurrence or second primary breast cancer | EC6 |

is associated with these outcomes amongst breast cancer survivors.

Methods

The reporting of this systematic review is consistent with the PRISMA statement [10]. A protocol outlining the methods for literature search, study selection and data synthesis was registered on the PROSPERO database <http://www.crd.york.ac.uk/PROSPERO/> on 3 March 2016 with reference number CRD42016036041.

Literature search and sources

The following databases were searched for English language peer-reviewed publications in January 2016: Cochrane Library, EMBASE, MEDLINE, PubMed, Scopus and Web of Science. No date restrictions were applied. The following search phrase was used: (breast cancer OR breast adenocarcinoma OR breast neoplasm OR breast tumour) AND (alcohol* OR alcohol intake OR alcohol consumption OR ethanol) AND (recurrence OR second primary). ‘Second primary’ was a term specifically added to the search phrase after it became apparent that the term ‘recurrence’ was intended by some authors to include second primary breast cancer. Reference lists of publications identified to be relevant to this systematic review were also hand searched for potentially eligible articles.

Study selection

After compiling the search results from the aforementioned databases, duplicate papers were identified and removed. Titles and abstracts were screened, and inclusion and exclusion criteria applied independently by two reviewers (PS, AB). Peer-reviewed, English language articles were eligible for inclusion if they reported findings from studies using original data or secondary data with original analyses involving adult (age ≥ 18 years) human participants. For publications deemed potentially eligible, full text copies were retrieved and read in full to determine whether the inclusion criteria were met. Agreed reasons for exclusion were recorded. Included studies investigated alcohol consumption in relation to breast cancer recurrence or development of second primary breast cancer in women previously diagnosed with breast cancer. Because our review did not utilise a meta-analytic

approach, it was agreed that two pooled studies [11,12] would be included. These studies benefited from an increased sample size and longer follow up periods. Nechuta et al. [12] was the first study to investigate late breast cancer recurrence in ER+ participants specifically. Refer to Table 1 for detailed inclusion/exclusion criteria.

Data extraction

Data regarding authorship, study design, sample characteristics, method of recruitment, duration of study follow-up, measures of pre and post-diagnosis alcohol exposure and outcome were extracted. Outcome measures of interest were: (1) new onset of breast cancer recurrence or (2) new onset of second primary breast cancer. Where multiple analyses were performed adjusting for different confounding factors (e.g. age, BMI, stage of initial breast cancer), only effect estimates adjusting for the widest range of appropriate confounders were extracted. Extraction of data from included studies was performed by one reviewer (PS), with subsequent revision of the completed data set in reference to the original papers by two other reviewers (AB and AH) for accuracy and consistency.

Quality assessment

The quality of each included study was assessed using the Newcastle-Ottawa Scale for non-randomised studies [13]. This tool allows the scale to be modified to best address the parameters of review across three main study characteristics: selection of study groups, comparability of selected groups, and methods of assessing alcohol exposure and defining cancer status. A star was allocated for every study design characteristic deemed to be high quality, with a potential maximum allocation of 9 stars for each study. Quality assessment was performed by one reviewer (PS), with subsequent revision by two reviewers (AB, AH). Refer to [Supplementary Appendix A](#) for the modified version of the scale used.

Data synthesis

A narrative synthesis of results was used, rather than a meta-analytic approach, due to the high level of clinical and methodological heterogeneity between studies, particularly in the aspects of

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