Alcohol Consumption and Breast Cancer Survival: A Meta-analysis of Cohort Studies

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Abstract

**Background and Objectives:** Evidence for associations between alcohol consumption with breast cancer survival are conflicting, so we conducted the present meta-analysis. **Methods:** Comprehensive searches were conducted to find cohort studies that evaluated the relationship between alcohol consumption with breast cancer survival. Data were analyzed with meta-analysis software. **Results:** We included 25 cohort studies. The meta-analysis results showed that alcohol consumption was not associated with increased breast cancer mortality and recurrence after pooling all data from highest versus lowest comparisons. Subgroup analyses showed that pre-diagnostic or post-diagnostic consumption, and ER status did not affect the relationship with breast cancer mortality and recurrence. Although the relationships of different alcohol consumption with breast cancer mortality and recurrence were not significant, there seemed to be a dose-response relationship of alcohol consumption with breast cancer mortality and recurrence. Only alcohol consumption of >20 g/d was associated with increased breast cancer mortality, but not with increased breast cancer recurrence. **Conclusion:** Although our meta-analysis showed alcohol drinking was not associated with increased breast cancer mortality and recurrence, there seemed to be a dose-response relationship of alcohol consumption with breast cancer mortality and recurrence and alcohol consumption of >20 g/d was associated with increased breast cancer mortality.

**Keywords:** Alcohol - breast neoplasms - survival - meta-analysis

RESEARCH ARTICLE

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Introduction

Breast cancer patients are often concerned that their lifestyle might affect their survival, so they often wonder whether modifying these behavior factors would improve their prognosis (Newcomb et al., 2013). Of these lifestyle factors, alcohol consumption is a modified factor. However, the available evidence is controversial. Both meta-analysis and pooled study showed that (Poli et al., 2012; Bagnardi et al., 2013) alcohol consumption increases risk of breast cancer. However, the information on whether alcohol consumption is related to breast cancer survival is mixed (Hebert et al., 1989; Fuchs et al., 1995; Jain et al., 2000; McDonald et al., 2002; Borugian et al., 2004; Barnett et al., 2008; Reding et al., 2008; Franceschi et al., 2009; Hellmann et al., 2010; Breslow et al., 2011; Harris et al., 2012; Holm et al., 2013; Newcomb et al., 2013). Some studies reported that alcohol consumption was associated with reduced breast cancer mortality (Barnett et al., 2008; Reding et al., 2008; Flatt et al., 2010), while other studies revealed that alcohol consumption was associated with increased breast cancer mortality (Hebert et al., 1989; Fuchs et al., 1995; Jain et al., 2000; McDonald et al., 2002; Allemann et al., 2011; Vrieling et al., 2012). Even though, most studies found no relationship between alcohol consumption and breast cancer mortality (Ewertz et al., 1991; Rohan et al., 1993; Zhang et al., 1995; Thun et al., 1997; Holmes et al., 1999; Saxe et al., 1999; Jain et al., 2000; McDonald et al., 2002; Borugian et al., 2004; Barnett et al., 2008; Reding et al., 2008; Franceschi et al., 2009; Flatt et al., 2010; Hellmann et al., 2010; Kwan et al., 2010; Allemann et al., 2011; Beasley et al., 2011; Breslow et al., 2011; Harris et al., 2012; Holm et al., 2013; Kwan et al., 2013; Newcomb et al., 2013). For the association of alcohol consumption with breast cancer recurrence, available evidence was also conflicted (Hebert et al., 1989; Saxe et al., 1999; Kwan et al., 2010; Holm et al., 2013; Kwan et al., 2013). So a meta-analysis is necessary to investigate the relationship of alcohol intake and breast cancer survival (mortality and recurrence).
Results of meta-analysis

25 studies (Hebert et al., 1989; Ewertz et al., 1991; Rohan et al., 1993; Fuchs et al., 1995; Zhang et al., 1995; Thun et al., 1997; Holmes et al., 1999; Saxe et al., 1999; Jain et al., 2000; McDonald et al., 2002; Borugian et al., 2004; Barnett et al., 2008; Dal Maso et al., 2008; Reding et al., 2008; Franceschi et al., 2009; Flatt et al., 2010; Hellmann et al., 2010; Kwan et al., 2010; Allemanni et al., 2011; Beasley et al., 2011; Breslow et al., 2011; Harris et al., 2012; Vrieling et al., 2012; Holm et al., 2013; Kwan et al., 2013; Newcomb et al., 2013) (patients) were included (Figure 1).

Characteristic of included studies

All studies focused on breast cancer mortality and only five studies (Hebert et al., 1989; Saxe et al., 1999; Kwan et al., 2010; Holm et al., 2013; Kwan et al., 2013) focused on breast cancer recurrence. Of 25 studies, 14 were from USA, three were from Denmark, two were from Germany, and the rest were from Italy, Australia, Canada, France, Sweden and UK, separately. 14 studies were about pre-diagnostic alcohol drinking, and ten were about post-diagnostic alcohol drinking, and one is about both pre- and post-diagnostic alcohol drinking. The total sample size for all included cohort studies were 719,555, the number of the breast cancer death was 10,912, and the number of the breast cancer recurrence was 2,027. The median follow-up ranged from 2.9 years to 18 years. And the other characteristics were presented in Table 1.

Results

Search results

After systematic search, we found 1547 citations. After duplicating 239 citations, we excluded studies that were not about survival (n=317), not about breast cancer (n=438), and not cohort studies (n=422). After reading full-texts, we excluded studies that were not cohort studies (n=61) and not about survival (n=61). Finally, 25 cohort studies (Hebert et al., 1989; Ewertz et al., 1991; Rohan et al., 1993; Fuchs et al., 1995; Zhang et al., 1995; Thun et al., 1997; Holmes et al., 1999; Saxe et al., 1999; Jain et al., 2000; McDonald et al., 2002; Borugian et al., 2004; Barnett et al., 2008; Dal Maso et al., 2008; Reding et al., 2008; Franceschi et al., 2009; Flatt et al., 2010; Hellmann et al., 2010; Kwan et al., 2010; Allemanni et al., 2011; Beasley et al., 2011; Breslow et al., 2011; Harris et al., 2012; Vrieling et al., 2012; Holm et al., 2013; Kwan et al., 2013; Newcomb et al., 2013) (patients) were included (Figure 1).

Materials and Methods

We did this systematic review of the available literature in accordance with Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies [MOOSE] (Stroup et al., 2000) for the conduct of meta-analyses of observational studies.

Search Strategy

PubMed, EMBASE, and ISI Web of Knowledge were searched using (alcohol* or ethanol) and (breast cancer* OR breast neoplasm* OR breast tumor* OR breast adenocarcinoma). Subject heading terms were added in all searches for PubMed and EMBASE searches. Reference lists from the review articles and identified studies were reviewed to identify further relevant citations. All the searches were conducted independently by two reviewers (Yunjiu Gou and Dingxiong Xie) in February 2013 without language restrictions; differences were resolved by discussion.

Inclusion criteria and study selection

We identified all published cohort studies that evaluated whether alcohol consumption affect the survival (including mortality or recurrence) in breast cancer patients. When multiple articles for a study were published, we used the most comprehensive data. Letters, comments, editorials, practice guidelines and trials published without the outcome measures of interest were excluded. Two reviewers (Yunjiu Gou and Yali Liu) independently assessed potentially relevant citations for inclusion, disagreements were resolved involved with a third reviewer (Kehu Yang).

Data abstraction

Using a standardized data extraction form by two authors (Li Bin and Zhang Jianhua), we collected the following baseline characteristics for cases and control groups: lead author, publication year, variation in age, sample size and outcomes. Any disagreements in abstracted data were resolved by a third reviewer (Xiaodong He).

Data analysis

Meta-analysis was conducted by comprehensive meta-analysis software. And we expressed the data using hazard ratio (HR) and its 95% confidence interval (95% CI). Data was pooled using the random-effects model. The percentage of variability across trials attributable to heterogeneity was estimated with the I² test, which was deemed significant when p was less than 0.05. Subgroup analyses of different ER statuses (ER positive vs. ER negative), different menopausal statuses (premenopausal vs. postmenopausal) and different doses based available data were conducted. Publication bias was assessed by visually inspecting a funnel plot. The small-study effect in terms of publication bias was also estimated using Egger’s linear regression test.
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1.19, increased breast cancer mortality (HR 1.05, 95% CI 0.93 – 1.17, I^2 = 30%) (Figure 3).

Subgroup analysis of different ER statuses showed the relationship of alcohol consumption with mortality and recurrence did not differ in ER positive and negative breast cancer patients. Subgroup analysis of different menopausal statuses showed the relationship of alcohol consumption with breast cancer mortality and recurrence did not differ in postmenopausal and premenopausal breast cancer patients. However, increased breast cancer recurrence was associated with premenopausal status, but not with postmenopausal status (Table 2).

**Table 1. The Characteristics of Included Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Age</th>
<th>Sample size</th>
<th>Event (death/recurrence)</th>
<th>Alcohol drinking</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allemani 2011</td>
<td>Italy</td>
<td>34-70</td>
<td>264</td>
<td>43/0</td>
<td>Pre-diagnosis</td>
<td>7.6 years</td>
</tr>
<tr>
<td>Barnett 2008</td>
<td>UK</td>
<td>&lt;70 years</td>
<td>4,560</td>
<td>564/0</td>
<td>Pre-diagnosis</td>
<td>6.82 years</td>
</tr>
<tr>
<td>Beasley 2011</td>
<td>USA</td>
<td>20-79</td>
<td>4441</td>
<td>137/0</td>
<td>Post-diagnosis</td>
<td>7 years</td>
</tr>
<tr>
<td>Borugian 2004</td>
<td>Canada</td>
<td>19-75</td>
<td>603</td>
<td>112/0</td>
<td>Post-diagnosis</td>
<td>10 years</td>
</tr>
<tr>
<td>Breslow 2011</td>
<td>USA</td>
<td>&gt;18</td>
<td>82605</td>
<td>677/0</td>
<td>Post-diagnosis</td>
<td>11 years</td>
</tr>
<tr>
<td>Ewertz 1991</td>
<td>Denmark</td>
<td>&lt;70</td>
<td>1612</td>
<td>485/0</td>
<td>Post-diagnosis</td>
<td>6 years</td>
</tr>
<tr>
<td>Fuchs 1995</td>
<td>USA</td>
<td>30-55</td>
<td>121,700</td>
<td>350/0</td>
<td>Post-diagnosis</td>
<td>12 years</td>
</tr>
<tr>
<td>Flatt 2010</td>
<td>USA</td>
<td>18-70</td>
<td>3088</td>
<td>315/0</td>
<td>Pre-diagnosis</td>
<td>7.3 years</td>
</tr>
<tr>
<td>Franceschi 2009</td>
<td>France</td>
<td>23-74</td>
<td>1,453</td>
<td>503/0</td>
<td>Pre- and post- diagnosis</td>
<td>12.6 years</td>
</tr>
<tr>
<td>Harris 2012</td>
<td>Sweden</td>
<td>-</td>
<td>3146</td>
<td>73/109</td>
<td>Pre-diagnosis</td>
<td>8-10 years</td>
</tr>
<tr>
<td>Hebert 1998</td>
<td>USA</td>
<td>20-80</td>
<td>472</td>
<td>323/0</td>
<td>Post-diagnosis</td>
<td>7.8 years</td>
</tr>
<tr>
<td>Hellmann 2010</td>
<td>Denmark</td>
<td>33.1–95.4</td>
<td>528</td>
<td>323/0</td>
<td>Pre-diagnosis</td>
<td>7.8 years</td>
</tr>
<tr>
<td>Holm 2013</td>
<td>Denmark</td>
<td>59–77</td>
<td>1,052</td>
<td>106/110</td>
<td>Pre-diagnosis</td>
<td>6 years</td>
</tr>
<tr>
<td>Holmes 1999</td>
<td>USA</td>
<td>54</td>
<td>1982</td>
<td>378/0</td>
<td>Post-diagnosis</td>
<td>18 years</td>
</tr>
<tr>
<td>Jain 2000</td>
<td>Germany</td>
<td>40-59</td>
<td>49,165</td>
<td>241/0</td>
<td>Pre-diagnosis</td>
<td>10.3 years</td>
</tr>
<tr>
<td>Kwan 2010</td>
<td>USA</td>
<td>18-70</td>
<td>2,269</td>
<td>273/293</td>
<td>Post-diagnosis</td>
<td>7.4 years</td>
</tr>
<tr>
<td>Kwan 2013</td>
<td>USA</td>
<td>58.8 years</td>
<td>9,329</td>
<td>911/1487</td>
<td>Post-diagnosis</td>
<td>10.3 years</td>
</tr>
<tr>
<td>McDonald 2002</td>
<td>USA</td>
<td>64.2 ± 12.2</td>
<td>125</td>
<td>33/0</td>
<td>Post-diagnosis</td>
<td>64.8 months</td>
</tr>
<tr>
<td>Newcomb 2013</td>
<td>USA</td>
<td>20-79</td>
<td>23,344</td>
<td>3,484/0</td>
<td>Pre-diagnosis</td>
<td>11.3 years</td>
</tr>
<tr>
<td>Reding 2008</td>
<td>USA</td>
<td>&lt; 45 years</td>
<td>1286</td>
<td>335/0</td>
<td>Pre-diagnosis</td>
<td>12 years</td>
</tr>
<tr>
<td>Rohan 1993</td>
<td>Australia</td>
<td>20-74</td>
<td>451</td>
<td>112/0</td>
<td>Post-diagnosis</td>
<td>5.5 years</td>
</tr>
<tr>
<td>Saxe 1999</td>
<td>USA</td>
<td>26-95</td>
<td>149</td>
<td>26/28</td>
<td>Post-diagnosis</td>
<td>&gt;5 years</td>
</tr>
<tr>
<td>Thun 1997</td>
<td>USA</td>
<td>35-69</td>
<td>451876</td>
<td>691/0</td>
<td>Post-diagnosis</td>
<td>9 years</td>
</tr>
<tr>
<td>Vrieling 2012</td>
<td>Germany</td>
<td>50–74</td>
<td>3,252</td>
<td>299</td>
<td>Pre-diagnosis</td>
<td>5.5 years</td>
</tr>
<tr>
<td>Zhang 1995</td>
<td>USA</td>
<td>55-69</td>
<td>698</td>
<td>56</td>
<td>Pre-diagnosis</td>
<td>2.9 years</td>
</tr>
</tbody>
</table>

**Figure 2. Meta-analysis Results of Subgroup Analysis of the Relationship of Pre- and Post- Alcohol Consumption Statuses with Breast Cancer Mortality**

Consumption was not associated with increased breast cancer mortality (HR 1.06, 95% CI 0.97 – 1.17, I^2 = 31%) (Figure 2) and recurrence (HR 1.21, 95% CI 0.95 – 1.53, I^2 = 31%) (Figure 3).

12 studies (Ewertz et al., 1991; Rohan et al., 1993; Fuchs et al., 1995; Holmes et al., 1999; McDonald et al., 2002; Borugian et al., 2004; Franceschi et al., 2009; Flatt et al., 2010; Kwan et al., 2010; Beasley et al., 2011; Breslow et al., 2011; Kwan et al., 2013) evaluated the relationship of post-diagnostic alcohol consumption with breast cancer mortality and two studies (Kwan et al., 2010; Kwan et al., 2013) evaluated the relationship of post-diagnostic alcohol consumption with breast cancer recurrence. And the meta-analysis results showed post-diagnostic alcohol consumption was not associated with increased breast cancer mortality (HR 1.08, 95% CI 0.94 – 1.25, I^2 = 30%) (Figure 2) and recurrence (HR 1.17, 95% CI 0.80 – 1.73, I^2 = 0%) (Figure 3).

**Figure 3. Meta-analysis Results of Subgroup Analysis of the Relationship of Pre- and Post- Alcohol Consumption Statuses with Breast Cancer Recurrence**

12 studies (Ewertz et al., 1991; Rohan et al., 1993; Fuchs et al., 1995; Holmes et al., 1999; McDonald et al., 2002; Borugian et al., 2004; Franceschi et al., 2009; Flatt et al., 2010; Kwan et al., 2010; Beasley et al., 2011; Breslow et al., 2011; Kwan et al., 2013) evaluated the relationship of post-diagnostic alcohol consumption with breast cancer mortality and two studies (Kwan et al., 2010; Kwan et al., 2013) evaluated the relationship of post-diagnostic alcohol consumption with breast cancer recurrence. And the meta-analysis results showed post-diagnostic alcohol consumption was not associated with increased breast cancer mortality (HR 1.08, 95% CI 0.94 – 1.25, I^2 = 30%) (Figure 2) and recurrence (HR 1.17, 95% CI 0.80 – 1.73, I^2 = 0%) (Figure 3).
We included 25 cohort studies. The meta-analysis results showed that alcohol consumption was not associated with increased breast cancer mortality and recurrence after pooling all data from highest versus lowest comparisons. Subgroup analyses showed that pre-diagnostic or post-diagnostic, and ER negative or ER positive did not affect the relationship of alcohol consumption with breast cancer mortality and recurrence. Subgroup analysis of menopausal statuses showed that menopausal statuses did not affect the relationship of alcohol consumption with breast cancer mortality. But menopausal statuses might affect the relationship of alcohol consumption with breast cancer recurrence. Although the relationships of different alcohol consumption (<10 g/d, >10 g/d, <15 g/d, >15 g/d, and >20 g/d) with breast cancer mortality and recurrence were not significant, there seemed to be a dose-response relationship of alcohol consumption with breast cancer mortality and recurrence. Only alcohol consumption of >20 g/d was associated with increased breast cancer mortality, but not with increased breast cancer recurrence.

The association between alcohol consumption and an increased risk of breast cancer has been established (Longnecker 1994; Suzuki et al., 2008). Studies have shown that mechanisms underlying the association of alcohol intake and breast cancer risk included increased estrogen and androgen levels, enhanced mammary gland susceptibility to carcinogenesis, increased mammary carcinogen DNA damage, and greater metastatic potential of breast cancer cells (Singletary et al., 2001; Reding et al., 2008). That is why reductions in alcohol intake were expected to improve breast cancer survival through similar mechanisms (Newcomb et al., 2013). However, our meta-analysis showed alcohol consumption was not associated with increased breast cancer mortality and recurrence. This is consistent with the result form a recent systematic review (Hauner et al., 2011). So based on available evidence, alcohol consumption did not affect breast cancer survival.

Cancer survivors face significant morbidity and mortality associated with their disease and treatment regimens, some of which can be improved through modifying behavioral and psychosocial risk factors (Carmack et al., 2011). However, a recent study showed that women with breast cancer did not modify their alcohol use compared with cancer-free women (Bidstrup et al., 2011). But overall, our meta-analysis showed alcohol consumption was not associated with increased breast cancer mortality and recurrence. Although the relationships of different alcohol consumption (<10 g/d, >10 g/d, <15 g/d, >15 g/d, and >20 g/d) with breast cancer mortality and recurrence were not significant, there seemed to be a dose-response relationship of alcohol consumption with breast cancer mortality and recurrence. Only alcohol consumption of >20 g/d was associated with increased breast cancer mortality, but not with increased breast cancer recurrence. The association between alcohol consumption and an increased risk of breast cancer has been established (Longnecker 1994; Suzuki et al., 2008). Studies have shown that mechanisms underlying the association of alcohol intake and breast cancer risk included increased estrogen and androgen levels, enhanced mammary gland susceptibility to carcinogenesis, increased mammary carcinogen DNA damage, and greater metastatic potential of breast cancer cells (Singletary et al., 2001; Reding et al., 2008). That is why reductions in alcohol intake were expected to improve breast cancer survival through similar mechanisms (Newcomb et al., 2013). However, our meta-analysis showed alcohol consumption was not associated with increased breast cancer mortality and recurrence. This is consistent with the result form a recent systematic review (Hauner et al., 2011). So based on available evidence, alcohol consumption did not affect breast cancer survival.

Cancer survivors face significant morbidity and mortality associated with their disease and treatment regimens, some of which can be improved through modifying behavioral and psychosocial risk factors (Carmack et al., 2011). However, a recent study showed that women with breast cancer did not modify their alcohol use compared with cancer-free women (Bidstrup et al., 2011).
Based on the results of our meta-analysis, pre-diagnostic and post-diagnostic alcohol consumption were not associated with increased breast cancer mortality and recurrence. This is to say, both pre-diagnostic and post-diagnostic alcohol consumption did not affect breast cancer survival.

It is reported that the magnitude of damage by alcohol intake likely depends on the amount of alcohol consumed (Stroup et al., 2000; Bagnardi et al., 2013). A meta-analysis (Longnecker 1994) showed there was a modest dose-response relationship between alcohol drinking and breast cancer. Our meta-analysis showed that the relationships of different alcohol consumption (<10 g/d, >10 g/d, <15 g/d, >15 g/d, and <20 g/d) with breast cancer mortality and recurrence were not significant, but there seemed to be a dose-response relationship of alcohol consumption with breast cancer mortality and recurrence. And alcohol consumption of >20 g/d was associated with increased breast cancer mortality, but not with increased breast cancer recurrence. Combining with the results of the associations of pre-diagnostic and post-diagnostic alcohol consumption with breast cancer mortality and recurrence, we could suggest that too much alcohol intake (>20 g/d) should be avoided.

It is said ER statuses could affect the relationship of alcohol consumption with breast cancer risk (Suzuki et al., 2008), as increased estrogen and androgen levels in women consuming alcohol appear to be important mechanisms underlying the association (Breslow et al., 2011). But based on the results of our meta-analysis, ER statuses did not affect the relationship of alcohol consumption with breast cancer mortality and recurrence. This might be due to few studies that stratified ER statuses when they evaluated the relationship of alcohol consumption with breast cancer mortality and recurrence. Available evidence showed that menopausal statuses could not affect the relationship of alcohol intake with breast cancer mortality, but might affect the relationship of alcohol intake with breast cancer recurrence. But there were also few studies that evaluated the relationship of alcohol intake with breast cancer mortality and recurrence by stratifying the menopausal statuses.

Strength and limitation: Our meta-analysis is the first meta-analysis that evaluated the relationship of alcohol intake with breast cancer mortality and recurrence. Our meta-analysis also conducted subgroup analyses of different ER statuses, menopausal statuses and different doses. Even though, our meta-analysis has its own limitations: first: few studies evaluated the relationship of alcohol intake with breast cancer mortality and recurrence by stratifying the menopausal and ER statuses. And few studies evaluated the relationship of alcohol intake with breast cancer recurrence. Second, as we did not find a suitable criterion to evaluate quality of these included studies, we skipped this part. It could make our analysis not as powerful as we expected.

Implications to research and practice: Based on our meta-analysis, alcohol drinking was not associated with increased breast cancer mortality and recurrence. Menopausal and ER statuses did not affect the relationship of alcohol drinking with breast cancer mortality, but whether menopausal and ER statuses affect the relationship of alcohol drinking with breast cancer recurrence deserves further researches. And as few studies evaluated the relationship of alcohol intake with breast cancer recurrence and evaluated the relationship of alcohol intake with breast cancer mortality by stratifying the menopausal and ER statuses, so these kinds of studies should be conducted.

And our meta-analysis also showed that the relationships of different alcohol consumption (<10 g/d, >10 g/d, <15 g/d, >15 g/d, and <20 g/d) with breast cancer mortality and recurrence were not significant, there seemed to be a dose-response relationship of alcohol consumption with breast cancer mortality and recurrence. And alcohol consumption of >20 g/d was associated with increased breast cancer mortality, but not with increased breast cancer recurrence. So in clinical practice, breast cancer patients should avoid too much alcohol drinking, such as alcohol consumption of >20 g/d.

Conclusion: Although our meta-analysis showed alcohol drinking was not associated with increased breast cancer mortality and recurrence, there seemed to be a dose-response relationship of alcohol consumption with breast cancer mortality and recurrence and alcohol consumption of >20 g/d was associated with increased breast cancer mortality. So in clinical practice, breast cancer patients should avoid too much alcohol drinking, such as alcohol consumption of >20 g/d. And studies that evaluated the relationship of alcohol intake with breast cancer recurrence and the relationship of alcohol intake with breast cancer mortality by stratifying the menopausal and ER statuses should be conducted.

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