Synergistic Effect between Alcohol and Estrogen Replacement Therapy on Risk of Breast Cancer Differs by Estrogen/Progesterone Receptor Status in the Iowa Women’s Health Study

Susan M. Gapstur, John D. Potter, Carol Drinkard, and Aaron R. Folsom
Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, Minnesota 55454-1015

Abstract
Two cohort studies have reported that alcohol and estrogen replacement therapy (ERT) act synergistically to increase the incidence of breast cancer. Possible interactions between alcohol consumption and family history of breast cancer or body mass index were also reported in the Iowa Women’s Health Study data. In the Iowa Women’s Health Study cohort, alcohol appears to be associated only with estrogen receptor-negative (ER−) progesterone receptor-negative (PR−) breast cancers. Therefore, we investigated whether the interactions between alcohol and other risk factors differ according to ER/PR status. In January 1986, participants completed a questionnaire that included alcohol intake and other information. Through 1992, 939 breast cancer cases occurred among 37,105 postmenopausal women at risk. Cox proportional hazards regression was used to compute adjusted relative risks and to test for multiplicative interactions. Relative risks of ER+/PR+, ER+/PR−, and ER−/PR− breast cancer for women who consumed ≥4.0 g of ethanol/day and reported ever using ERT compared to abstainers who never used ERT were 1.8, 1.3, and 2.6, respectively. Relative risks of ER+/PR+, ER+/PR−, and ER−/PR− breast cancer associated with any alcohol intake and a positive family history of breast cancer compared to abstainers with no family history of breast cancer were 1.7, 0.8, and 3.1, respectively. Relative risks of ER+/PR+, ER+/PR−, and ER−/PR− breast cancer associated with the highest quintile of body mass index and drinking ≥4.0 g of ethanol/day compared to abstainers in the lower four-fifths of body mass index were 0.9, 1.8, and 2.0, respectively. These results suggest that interactions between alcohol and other risk factors differ according to estrogen-progesterone receptor status and provide a possible explanation for the weakness but consistency of the alcohol-breast cancer association reported by other studies.

Introduction
The association between usual alcohol consumption and breast cancer has been examined extensively in epidemiological studies. There appears to be a consistent, moderate increased risk of breast cancer for women who consume 1–2 alcoholic beverages/day compared to alcohol abstainers (RR = 1.5; Ref. 1). No unequivocal biological evidence to support a causal association between alcohol and breast cancer has been confirmed despite the relative consistency among observational studies.

The etiological role of alcohol intake on breast carcinogenesis may be better understood by considering the joint effects of alcohol and other potential risk factors. For example, two (2, 3) of three (2–4) cohort studies reported recently that the association between alcohol consumption and postmenopausal breast cancer was modified by use of ERT. Data from the Nurses’ Health Study were suggestive of an elevated risk of breast cancer among drinkers who said that they currently were using ERT (RR = 1.56; 95% CI = 1.2–2.0; Ref. 2). Similarly, data from the Iowa Women’s Health Study showed a dose-response relation between alcohol and breast cancer among women who reported ever using ERT; no association between alcohol and breast cancer was observed among never users of ERT (3). In addition, some (3, 5, 6) but not all studies (4, 7–18) exploring the interaction between alcohol and body mass index showed a greater risk of breast cancer among leaner women who drink compared to heavier women who drink. In one cohort study (3) there appeared to be a positive association between alcohol and breast cancer only among women with a history of breast cancer in a first-degree relative, whereas no association was observed among women without a family history; results from other cohort studies (4–6) do not support this finding. In stratified analyses by menopausal status, alcohol intake has been associated positively with premenopausal and/or postmenopausal breast cancer (3, 6, 8, 9, 11, 17–22).

In addition to considering possible interactions between alcohol and other characteristics affecting the risk of breast cancer, classifying breast cancer cases according to the presence of ERs and PRs provides another method of exploring the alcohol-breast cancer association. Generally, the existence of

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2 Present address: Department of Preventive Medicine, Northwestern University Medical School, Chicago, IL 60611.
3 To whom requests for reprints should be addressed, at Department of Preventive Medicine, Northwestern University Medical Center, 600 North Lakeshore Drive, Suite 1102, Chicago, IL 60611.
4 Present address: Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, WA 98104.

5 The abbreviations used are: RR, relative risk; ERT, estrogen replacement therapy; ER, estrogen receptor; PR, progesterone receptor; CI, confidence interval; df, degrees of freedom.

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three types of breast tumors are recognized: (a) ER+/PR+, hormone responsive; (b) ER-/PR-, hormone unresponsive; and (c) ER+/PR- (23, 24). The steroid hormone receptor status of breast tumors has important prognostic and therapeutic implications (23, 25, 26). It is not clear, however, whether there are differences in epidemiological risk factors according to the presence of estrogen and/or progesterone receptors (27–33). In the only cohort study reported to date exploring whether the association between alcohol and breast cancer differs according to steroid hormone receptor status, a 55% increase (P = 0.048) in age-adjusted risk of breast cancer associated with any alcohol intake compared to abstainers was observed only for ER-/PR- breast tumors (30). Furthermore, in a study examining dietary habits of women with breast cancer, Holm et al. (31) found a statistically significant inverse association between average daily alcohol consumption and the proportion of ER+ breast cancers.

The present study investigated whether the incidence of breast cancer associated with the joint effects of alcohol and ERT use differs among breast tumors classified by ER/PR status. In addition, interactions between usual alcohol consumption and history of breast cancer in a first-degree relative and alcohol consumption and body mass index were explored among the different tumor types.

Materials and Methods

Methods for the Iowa Women’s Health Study recruitment and data collection have been published previously (3). Briefly, this study was designed to examine associations between several host, dietary, and lifestyle factors and the incidence of cancer in 41,837 postmenopausal women, ages 55–69 years at baseline, who completed a 16-page self-administered questionnaire in January 1986. After excluding women who reported a personal history of cancer (except skin) who were premenopausal or who had a previous total or partial mastectomy, there were 37,105 women in the at-risk cohort.

Information ascertained from the mailed questionnaire included reproductive and menstrual history, use of oral contraceptives and ERT, personal history of cancer, and history of breast cancer in female relatives. Participants were asked to record their height and current weight; from this information, body mass index (kg/m²) was computed. A paper tape measure was enclosed along with detailed instructions for circumference measurements of the waist and hips in order to determine a waist:hip ratio. Kushi et al. (34) verified the high validity and reliability of this approach to obtaining anthropometric data.

Usual alcohol consumption was assessed with the use of the Harvard semiquantitative food frequency questionnaire developed by Willett et al. (35). A detailed description of the methods for computing total daily alcohol intake in this study was reported elsewhere (3). The reliability and accuracy of average daily alcohol intake assessed by the food frequency questionnaire used in the present study was good (36). Abstainers were women whose reported daily alcohol intake was 0 g/day. Alcohol consumers were classified a priori into 2 groups based on a median split (<4.0 and ≥4.0 g of alcohol/day) and for potential effect modification variables for all breast cancer cases combined and for each type of breast cancer categorized by the joint classification of ER/PR status (ER+/PR+, ER+/PR-, ER-/PR-, and ER or PR unknown; no estimates are presented for ER-/PR+ breast cancers because there were only 17 cases). Multivariate polychotomous logistic regression was used to account simultaneously for the five possible breast cancer outcomes (noncase, ER+/PR+, ER+/PR-, ER-/PR-, and ER or PR unknown); this allowed for comparison of respective β-coefficients across tumor types. The dependent variable was treated as a dichotomous nominal variable, and the logit estimator always compared receptor status-defined cases (e.g., ER+/PR+) to noncases. These results agreed very closely with the results computed with the use of Cox proportional hazards regression, but they are not reported here. Analyses were performed using PROC PHREG and PROC CATMOD of the SAS statistical package (37).

Results

Associations between breast cancer and known potential risk factors from the Iowa Women’s Health Study have been reported elsewhere (3, 38). Briefly, Mantel-Haenszel age-adjusted relative risks showed increasing body mass index, waist:hip ratio, older age at first live birth, and history of breast cancer in a first-degree relative (mother, sister, or daughter) were associated significantly and positively with breast cancer. Body mass index at age 18 years and age at menarche were inversely associated with breast cancer; education, age at menopause, parity, and use of oral contraceptives and ERT were not associated with breast cancer. Associations between potential risk factors and breast cancer defined by the combination of ER/PR status have also been reported for the Iowa Women’s Health Study (30). In general, an increased risk of ER+/PR+ breast cancer (hormone responsive) was associated with higher body mass index, higher waist:hip ratio, younger age at menopause, and alcohol use.
The distribution of breast cancers across strata of estrogen and progesterone receptors is shown in Table 1. There was a greater proportion of ER+/PR+ tumors (44%) compared to ER-/PR- (14%), ER-/PR+ (1.8%) or ER+/PR- (8.5%). Either ER or PR status was unknown for 35% of the breast cancers.

Multicollinearity interactions between alcohol consumption and ERT use, history of breast cancer in a first-degree relative or body mass index on risk of all breast cancer were recently reported for this cohort of postmenopausal women. For example, of 4 years of follow-up (3). Inclusion of cases after 7 years of follow-up did not change these results markedly. Briefly, after controlling for body mass index, age at menarche, age at first live birth and history of breast cancer in a first-degree relative, women who reported ever using ERT and who consumed ≥4.0 g of alcohol/day had a 53% higher risk of breast cancer than abstainers who never used ERT; there was no association between alcohol and breast cancer in women who did not use ERT (−2 log likelihood test for interaction \( \chi^2 = 10.6; df = 2; P = 0.005 \)). Among women without a family history of breast cancer, there was no association between any alcohol consumption and breast cancer; however, there was an 82% increased risk of breast cancer among women with a family history of breast cancer who drank alcohol compared to women with no family history who did not drink alcohol (−2 log likelihood test for interaction \( \chi^2 = 6.3; df = 1; P = 0.011 \)). There also appeared to be a synergistic effect of alcohol and body mass index on risk of breast cancer (−2 log likelihood test for interaction \( \chi^2 = 5.9; df = 2; P = 0.05 \)). Among women with only low body mass index (lower four-fifths) the relative risk of breast cancer for women who consumed ≥4 g of alcohol/day was 1.43 (95% CI = 1.1–1.9) compared to abstainers and there was no association between alcohol and breast cancer among women in the highest quintile of body mass index.

Results from Cox proportional hazards regression analyses exploring the interaction between alcohol and ERT use for categories of breast cancer classified according to the combination of ER/PR status are shown in Table 2. Overall, similar patterns emerged for each type of tumor. After controlling for potential confounders, there was no association between alcohol and any type of breast cancer among women who had never used ERT. There appeared to be a positive association between alcohol and each type of breast cancer among the ever users of ERT. However, the relative risk of ER-/PR- breast cancer associated with consumption of ≥4 g of ethanol/day and ever using ERT compared to abstainers who never used ERT was 2.6 and the corresponding relative risks for ER+/PR- and ER+/PR+ breast cancer were 1.8 and 1.3, respectively. The respective β-coefficients were not statistically significantly different between ER-/PR- and ER+/PR+ breast cancers (\( \chi^2 = 1.07; df = 1; P = 0.3 \)) as determined by multivariate polychotomous logistic regression.

Discussion

Williams and Horm (39) first reported a potential association between alcohol and breast cancer using cross-sectional data from the Third National Cancer Survey. Subsequently, several analytical, epidemiological studies have attempted to confirm this observation. Because the strength of the association is low (RR = 1.5 for moderate alcohol consumers compared to abstainers; Ref. 1), and because there is no unequivocal biological mechanism, the controversy continues over whether alcohol has a causal role in the etiology of breast cancer.

On the basis of prior hypotheses, we have attempted to take a step further by exploring possible interactions between alcohol and other risk factors in biologically distinct (23) subsets of breast cancer defined by the presence of detectable amounts of steroid-hormone receptors: (a) ER+/PR+; (b) ER-/PR-; and (c) ER-/PR-. It is important to recognize that the presence of estrogen and progesterone receptors was determined from laboratories affiliated with hospitals where breast cancer cases were diagnosed and not from a single reference laboratory. However, measurement of hormone receptors has been standardized (23), and the distribution of ER/PR-defined breast tumors in this study was comparable to those reported elsewhere (23, 40) for postmenopausal women.

Initial examination of data from the Iowa Women’s Health Study showed a 55% increase in age-adjusted risk of ER-/PR- breast cancers associated with any alcohol consumption compared to alcohol abstainers (30); there was no association between alcohol and any other type of receptor-specific breast cancer. To our knowledge, the only other report of the association between alcohol and receptor-specific breast cancers compared the amount of alcohol con-

Table 1: Distribution of 939 incident breast cancer cases by estrogen receptor and progesterone receptor status, Iowa Women’s Health Study, 1986–1992

<table>
<thead>
<tr>
<th>Estrogen receptor status</th>
<th>Progesterone receptor status</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>414</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>Positive</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>276</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>558</td>
</tr>
<tr>
<td></td>
<td></td>
<td>104</td>
</tr>
<tr>
<td></td>
<td></td>
<td>278</td>
</tr>
<tr>
<td></td>
<td></td>
<td>939</td>
</tr>
</tbody>
</table>
Alcohol and Breast Cancer by Receptor Status

**Table 2** Interaction between alcohol and ERT use on risk of breast cancer according to estrogen receptor and progesterone receptor status, Iowa Women’s Health Study, 1986–1992 (n = 939 cases*).

<table>
<thead>
<tr>
<th>Alcohol intake (g/day)</th>
<th>ERT use</th>
<th>ER+ /PR+</th>
<th>ER+ /PR−</th>
<th>ER− /PR−</th>
<th>ER or PR unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>RRb (95% CI)</td>
<td>n</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>0</td>
<td>Never</td>
<td>126</td>
<td>1.0</td>
<td>33</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Ever</td>
<td>81</td>
<td>1.1 (0.9-1.5)</td>
<td>14</td>
<td>0.7 (0.4-1.3)</td>
</tr>
<tr>
<td>&lt;4.0</td>
<td>Never</td>
<td>60</td>
<td>1.3 (1.0-1.8)</td>
<td>17</td>
<td>1.3 (0.7-2.3)</td>
</tr>
<tr>
<td></td>
<td>Ever</td>
<td>29</td>
<td>1.0 (0.6-1.5)</td>
<td>9</td>
<td>1.0 (0.5-2.1)</td>
</tr>
<tr>
<td>≥4.0</td>
<td>Never</td>
<td>39</td>
<td>1.0 (0.7-1.5)</td>
<td>8</td>
<td>0.7 (0.3-1.5)</td>
</tr>
<tr>
<td></td>
<td>Ever</td>
<td>47</td>
<td>1.8 (1.3-2.5)</td>
<td>11</td>
<td>1.3 (0.6-2.5)</td>
</tr>
</tbody>
</table>

*The total number of cases may sum to less than 939 because of missing data and the exclusion of ER−/PR+ breast cancer cases.

b RR coefficient for ER+ /PR+ was significantly different from that for ER− /PR− breast cancer (χ² = 10.9; df = 1; P < 0.001), and for ER− /PR− breast cancer (χ² = 4.9; df = 1; P = 0.028).

d Based on −2 log likelihood test for interaction.

**Table 3** Interaction between alcohol and history of breast cancer in a first-degree relative on risk of breast cancer according to estrogen receptor and progesterone receptor status, Iowa Women’s Health Study, 1986–1992 (n = 939 cases*).

<table>
<thead>
<tr>
<th>Alcohol intake (g/day)</th>
<th>Hx of breast cancer in first-degree relatives</th>
<th>ER+ /PR+</th>
<th>ER+/PR−</th>
<th>ER− /PR−</th>
<th>ER or PR unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>RRb (95% CI)</td>
<td>n</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Abstainer</td>
<td>No</td>
<td>186</td>
<td>1.0</td>
<td>43</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>21</td>
<td>0.8 (0.5-1.3)</td>
<td>4</td>
<td>0.7 (0.2-1.9)</td>
</tr>
<tr>
<td>Drinker</td>
<td>No</td>
<td>143</td>
<td>1.1 (0.9-1.3)</td>
<td>41</td>
<td>1.2 (0.7-1.8)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>32</td>
<td>1.7 (1.2-2.5)</td>
<td>4</td>
<td>0.8 (0.3-2.3)</td>
</tr>
</tbody>
</table>

*The total number of cases may sum to less than 939 because of missing data and the exclusion of ER−/PR+ breast cancer cases.

b RR coefficient for ER+ /PR+ did not differ from that for ER− /PR− breast cancer (χ² = 2.15; df = 1; P = 0.14).

d Based on −2 log likelihood test for interaction.

**Table 4** Interaction between alcohol and body mass index on risk of breast cancer according to estrogen receptor and progesterone receptor status, Iowa Women’s Health Study, 1986–1992 (n = 939 cases*).

<table>
<thead>
<tr>
<th>Alcohol intake (g/day)</th>
<th>Body mass index</th>
<th>ER+ /PR+</th>
<th>ER+/PR−</th>
<th>ER− /PR−</th>
<th>ER or PR unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>RRb (95% CI)</td>
<td>n</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>0</td>
<td>Low</td>
<td>127</td>
<td>1.0</td>
<td>42</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>80</td>
<td>1.5 (1.2-2.0)</td>
<td>5</td>
<td>0.3 (0.1-0.8)</td>
</tr>
<tr>
<td>&lt;4.0</td>
<td>Low</td>
<td>63</td>
<td>1.1 (0.8-1.5)</td>
<td>24</td>
<td>1.3 (0.8-2.1)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>26</td>
<td>1.7 (1.1-2.6)</td>
<td>2</td>
<td>0.4 (0.1-1.8)</td>
</tr>
<tr>
<td>≥4.0</td>
<td>Low</td>
<td>78</td>
<td>1.4 (1.1-1.9)</td>
<td>14</td>
<td>0.8 (0.4-1.4)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>8</td>
<td>0.9 (0.5-1.9)</td>
<td>5</td>
<td>1.8 (0.7-4.7)</td>
</tr>
</tbody>
</table>

*The total number of cases may sum to less than 939 because of missing data and the exclusion of ER−/PR+ breast cancer cases.

b RR coefficient for ER+ /PR+ was significantly different from that for ER− /PR− breast cancer (χ² = 10.9; df = 1; P < 0.001), and for ER− /PR− breast cancer (χ² = 4.9; df = 1; P = 0.028).

d Based on −2 log likelihood test for interaction.

Assumed between ER-rich and ER-poor breast cancer cases only (31). Average daily alcohol consumption was greater for cases whose breast tumors were ER poor (7.4 g/day) compared to cases whose tumors were ER rich (7.0 g/day; for difference P = 0.06). Similarly, analyses of data from the Iowa Women’s Health Study for the association between alcohol and breast cancer stratified only on estrogen receptor status showed the relative risk of ER− breast cancer associated with consumption of ≥4.0 g of alcohol/day compared to abstainers was 1.8 (95% CI = 1.2-2.9). There was no association between usual alcohol intake and ER+ breast cancer (RR = 1.2; 95% CI = 0.9-1.5).

The proportion of estrogen receptor-positive cancers increases with age (from 25% for women less than age 45 years to 57% for women age 55 years and older; Ref. 41) and therefore is greater among postmenopausal women compared to premenopausal women. It is not clear whether the association between alcohol and breast cancer differs between premeno-
pausal and postmenopausal women. Two (6, 18, 22) cohort studies that stratified on menopausal status reported positive associations only in postmenopausal women. Conversely, Friedenreich et al. (22) reported data suggestive of a positive association in premenopausal women (P for trend = 0.07) and no association in postmenopausal women. Data from the Framingham cohort (16) were suggestive of an inverse association between alcohol consumption and breast cancer for postmenopausal women (RR = 0.6 for any drinking women compared to nondrinking women); no association was observed for premenopausal women. Two case-control studies (9, 21) exploring the association between alcohol and breast cancer within the strata of menopausal status found an increased risk for premenopausal women and no association in postmenopausal women, whereas six other case-control studies (8, 11, 17, 19, 20, 42) reported no difference between pre- and postmenopausal women. The observed inconsistencies among studies for risk of breast cancer across strata of menopausal status could be explained by differences in the distribution of tumors by receptor status across study populations or as a consequence of differential survival that could ensure that fewer receptor-negative cases (poorer prognosis) would survive long enough to be included in a case-control study. If there are differences in the association between alcohol and breast cancer by receptor status, and the proportion of receptor-positive tumors varies by age, inclusion of all cases in one breast cancer group will reduce the magnitude of the relative risk estimates.

The study described here is the first to examine multiplicative interactions for alcohol and other characteristics on risk of receptor-specific breast cancer; potentially different patterns were observed. As mentioned earlier, data published previously (2, 3) were suggestive of a positive association between alcohol and breast cancer in women who ever used ERT and no association among women who never used ERT. Results of the present study showed the combination of alcohol consumption and the use of ERT may be associated more strongly with ER−/PR− breast cancer than with ER+/PR+ or ER+/PR− breast cancers. Therefore, it appears alcohol and ERT use may selectively enhance risk of ER−/PR− breast cancer. These results could be artifactual if a major effect of alcohol consumption and/or ERT use was to down-regulate receptor protein expression. Some studies have shown a greater proportion of ER− tumors among women using ERT at time of diagnosis compared to women with a prior history of ERT use (28, 32, 33). Exposure to estrogen lead to an up-regulation of estrogen receptors in T47D human breast cancer cells but not in MCF-7 breast cancer cells (43). The concentration of nuclear ER in liver tissue of rats ingesting alcohol and synthetic female hormones was greater compared to rats ingesting alcohol alone (44). Whether these findings offer evidence for a selective risk difference among different tumors defined by the presence or absence of steroid hormone receptors is unclear.

The pattern of risk across receptor-defined breast cancers for the multiplicative interaction between alcohol consumption and family history of breast cancer in a first-degree relative was similar to that for alcohol and ERT use (i.e., the suggestion of stronger associations for ER−/PR− breast cancer compared to ER+/PR+ or ER+/PR−). Conversely, the multiplicative interaction between alcohol and body mass index was most notable for ER+/PR− breast cancer. Fuqua et al. (24) reported recently that this subset of breast cancer includes a genetically variant ER that is capable of binding estrogen but is unable to induce PR expression. When the biology of this particular defect is fully elucidated, the mechanism whereby alcohol and body mass index selectively influences breast carcinogenesis in certain receptor-specific subtypes could be better understood.

In conclusion, the results of this study suggest that synergism between alcohol consumption and other risk factors could differ for different types of breast cancer classified according to receptor status. If supported by other studies, the variation in risk factor profiles across strata of receptor-defined tumors implies a complex etiological role of alcohol on breast carcinogenesis.

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References
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