Null Results in Brief

No Association between Dietary Phytoestrogens and Risk of Premenopausal Breast Cancer in a French Cohort Study

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Introduction

Phytoestrogens, plant food components with estrogen-like biological properties, are hypothesized to contribute to the 5-fold lower breast cancer incidence in Asian compared with Western countries (1). Isoflavones comprise the phytoestrogens most abundant in soy, the traditional staple food in Asia, and a recent meta-analysis concluded that there was a slight reduction in premenopausal breast cancer risk with higher soy consumption (1). Because consumption of soy and isoflavones is typically low in Western countries, lignans and their derived metabolites, the enterolignans, might be more relevant for breast cancer prevention in these populations (2). Further large prospective studies of phytoestrogens in breast cancer are needed in Western populations to test this hypothesis. We thus examined the association between the usual dietary intake of phytoestrogens and the risk of premenopausal invasive breast cancer in a large French cohort.

Materials and Methods

E3N (Étude Épidémiologique auprès de femmes de la Mutuelle Générale de l'Éducation Nationale) is a large ongoing prospective cohort consisting of 98,995 French women born between 1925 and 1950, subscribing to the health insurance plan for public education system employees, and who voluntarily enrolled in 1990-1991 (3). After a baseline questionnaire, follow-up questionnaires have been sent biennially to ascertain occurrence of diseases and to update menopausal status and exposure factors. Usual diet over the previous year was assessed using a validated 208-item diet history questionnaire administered between 1993 and 1995 and available for 74,524 participants (4). We estimated daily phytoestrogen intake using a food composition table updated for four isoflavones (genistein, daidzein, formononetin, and biochanin A), one coumestan (coumestrol), four plant lignans (pinoresinol, lariciresinol, secoisolariciresinol, and matairesinol), and two enterolignans (enterodiol and enterolactone). Dietary intake of total phytoestrogens was computed as the sum of isoflavones, coumestrol, and plant lignans.

All premenopausal women with dietary data, without a history of cancer (except for skin basal cell carcinoma or breast lobular carcinoma in situ), and who were not consuming soy dietary supplements were included in the present analysis (n = 26,868). Participants contributed person-years of follow-up starting from the date they had completed the dietary questionnaire to the date of diagnosis of premenopausal invasive breast cancer as first primary cancer (for the cases), date of diagnosis of another cancer, date of menopause, date of death, or July 2002, whichever came first. We calculated multivariate relative risks and their two-sided 95% confidence intervals in Cox proportional hazards regression models for quartiles of phytoestrogen intake, adjusting for potential confounding variables as listed in the footnotes to Table 1. We also conducted analyses stratified on the joint estrogen receptor (ER) and progesterone receptor (PR) status of the tumors.

Results

During 117,652 person-years of follow-up (median duration, 4.2 years), 402 cases of invasive breast cancer were diagnosed among 26,868 premenopausal women (mean age, 47 years at baseline). Median dietary intake of total phytoestrogens was 1,101 μg/d, mostly consisting of plant lignans (97%). Premenopausal breast cancer risk was not related to isoflavone, coumestrol, plant lignan, or enterolignan intakes (Table 1). Nor was any association observed with individual intakes of genistein, daidzein, formononetin, biochanin A, coumestrol, pinoresinol, lariciresinol, secoisolariciresinol, matairesinol, enterodiol, or enterolactone (data not shown).

Most (80%) of the 322 breast cancer cases with known receptor status were positive for both ER and PR [191 (59%) ER+/PR+, compared with 51 (16%) ER−/PR−, 44 (14%) ER+/PR−, and 36 (11%) ER−/PR−]. When we stratified the analysis on the joint ER/PR status, no association was found (data not shown).

Conclusions

In this prospective study, we found no evidence of an association between dietary intake of phytoestrogens and risk...
of premenopausal invasive breast cancer, either overall or by ER/PR status. The absence of an association in the present study probably indicates that there are no effects of low isoflavone and high lignan levels in premenopausal breast cancer. However, a balanced diet rich in plant foods remains recommended for Western premenopausal women, as a healthy diet is likely to be beneficial over the long term (23).

Acknowledgments

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Table 1. Multivariate relative risks and their 95% confidence intervals for invasive breast cancer according to quartiles of daily intake of dietary phytoestrogens among 26,868 premenopausal women in the E3N cohort

<table>
<thead>
<tr>
<th>Dietary intake*</th>
<th>Range 1, µg/d</th>
<th>Cases (N = 402)</th>
<th>Person-years (117,652)</th>
<th>Adjusted RR (95% CI) ±</th>
<th>P-trend †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total isoflavones</td>
<td>1-22</td>
<td>107</td>
<td>29,799</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22-28</td>
<td>78</td>
<td>29,549</td>
<td>0.73 (0.54-0.98)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>29-35</td>
<td>110</td>
<td>29,097</td>
<td>1.03 (0.79-1.34)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>36-112</td>
<td>107</td>
<td>29,207</td>
<td>1.00 (0.76-1.31)</td>
<td>0.48</td>
</tr>
<tr>
<td>Coumestrol</td>
<td>0</td>
<td>63</td>
<td>20,659</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.00-0.02</td>
<td>126</td>
<td>32,317</td>
<td>1.32 (0.97-1.80)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.03-0.05</td>
<td>97</td>
<td>31,944</td>
<td>1.02 (0.74-1.40)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.06-0.60</td>
<td>116</td>
<td>32,732</td>
<td>1.22 (0.89-1.66)</td>
<td>0.68</td>
</tr>
<tr>
<td>Total plant lignans</td>
<td>41-843</td>
<td>101</td>
<td>30,918</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>844-1,070</td>
<td>106</td>
<td>29,509</td>
<td>1.06 (0.81-1.40)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,071-1,356</td>
<td>91</td>
<td>28,843</td>
<td>0.93 (0.70-1.23)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,357-4,611</td>
<td>104</td>
<td>28,381</td>
<td>1.07 (0.81-1.41)</td>
<td>0.80</td>
</tr>
<tr>
<td>Total enterolignans</td>
<td>168-902</td>
<td>107</td>
<td>30,520</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>903-1,075</td>
<td>105</td>
<td>29,644</td>
<td>0.99 (0.75-1.30)</td>
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</tr>
<tr>
<td></td>
<td>1,076-1,288</td>
<td>90</td>
<td>28,785</td>
<td>0.86 (0.65-1.14)</td>
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<tr>
<td></td>
<td>1,289-3,361</td>
<td>100</td>
<td>28,903</td>
<td>0.94 (0.71-1.24)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Abbreviations: RR, relative risk; 95% CI, 95% confidence interval.

1 The range for each energy-adjusted phytoestrogen quartile was calculated by adding the residual range to the predicted phytoestrogen intake for the mean caloric intake from food (2,149 kcal) for the whole population according to the regression model. Specifically for coumestrol, we computed the lowest category with null values (18%) and higher categories from tertiles of non-null values.

2 Multivariate RRs and 95% confidence intervals calculated by Cox proportional hazards regression models using age as the time scale and adjusted for years of education (<12, 13-16, ≥17.5), height (as continuous variable), body mass index category (as a time-dependent variable according to the height at baseline and the weight at the start of each follow-up interval), age at menarche (<13, 13-14, ≥15 years), personal history of benign breast disease (including fibrocystic breast disease, mastosis, and adenoma) or lobular carcinoma in situ (yes or no), family history of breast cancer in first- or second-degree relatives (yes or no), lifetime use of oral contraceptive (yes or no), age at first full-term pregnancy (FFTP) and parity (nulliparous, age at FFTP <30 years and 1-2 children, age at FFTP <30 years and ≥3 children, or age at FFTP ≥30 years whatever the number of children), geographic area, alcohol consumption (as continuous variable), and dietary energy intake from food.

3 Test for linear trend using median values in each quartile as an ordinal variable.

4 To account for the lack of data for some enterolignan values in the food composition table, we computed enterolignan values from lignan content using conversion factors obtained in vitro (25).

5 For the test of null association, enterolignans were grouped in four categories (0.00-0.02, 0.03-0.05, 0.06-0.60, >0.60 µg/d).

6 Dietary isoflavone intake was computed as the sum of individual isoflavones (genistin, daidzein, formononetin, and biochanin-A), total plant lignans as the sum of individual plant lignans (pinoresinol, laricresinol, secoisolaricresinol, and matairesinol), and total enterolignans as the sum of individual enterolignans (enterodiol and enterolactone). All were adjusted for energy intake from food (excluding energy from alcohol from total energy intake) by the residual method (24).

7 A maximum of 1% of data were missing.

8 When computing the adjusted RR, we used mean energy intakes of the 1993 French nutrition survey, as a proxy of mean energy intakes in the E3N cohort.

9 The corresponding RRs were adjusted for age at menarche, age at menopause, age at first childbearing, whether or not the woman used postmenopausal hormones, personal history of benign breast disease (fibrocystic breast disease, mastosis, and adenoma), lobular carcinoma in situ, family history of breast cancer in first- or second-degree relatives, age at first full-term pregnancy, parity, number of children, age at menopause, body mass index, and regional area.
References


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