INTRODUCTION

Breast cancer is the most common cancer and the second leading cause of death from cancer in women in the United States (1). The high prevalence and incidence of breast cancer have resulted in a large public health burden. Lifestyle factors are believed to play an important role in the prevention of breast cancer, among which diet has received considerable interest (2–4).

It has been long hypothesized that dietary fiber intake may reduce the risk of breast cancer by lowering circulating estrogen concentrations (5). Two decades ago, a meta-analysis (6) of 12 case-control studies supported this hypothesis by showing that fiber intake of 20 g/d was associated with a 15% reduction in risk of breast cancer. Of note, case-control studies are prone to recall and selection biases, which limit the strength and quality of the evidence. In fact, many subsequent prospective cohort studies (7–19) that examined the association between dietary fiber intake and risk of breast cancer have yielded mixed results, with most showing a weak or null association. Results from the Second World Cancer Research Fund/American Institute for Cancer Research Report on Food, Nutrition, Physical Activity and the Prevention of Cancer in 2007 (www.wcrf.org) were inconclusive because of the limited evidence at that time. Until recently, several newly emerging studies (12, 15, 18) have observed a significantly inverse association of dietary fiber intake with breast cancer risk.

Given the inconsistency of the existing literature and the insufficient statistical power of primary studies, we conducted a meta-analysis of prospective cohort studies with the following objectives: 1) to review and summarize the epidemiologic evidence on the association of dietary fiber intake with risk of breast cancer; 2) to examine the dietary fiber intake in relation to the risk of breast cancer according to study designs and characteristics of study populations; and 3) to assess the possible dose-response pattern between dietary fiber intake and risk of breast cancer.

SUBJECTS AND METHODS

Literature search

We attempted to report this meta-analysis in accordance with the Meta-Analysis of Observational Studies in Epidemiology guidelines (20). We conducted a systematic literature search of the PubMed database (www.ncbi.nlm.nih.gov/pubmed) through January 2011 by using the following search terms: “dietary fiber,” “fiber,” and “fibre” in combination with “breast cancer” and “risk of breast cancer;” and “breast neoplasms,” with no restrictions. Reference lists of the retrieved articles were also reviewed. We did not contact authors of the primary studies for additional information.

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DIETARY FIBER AND BREAST CANCER

Study selection

Studies were included in this meta-analysis if they met the following criteria: 1) had a prospective cohort study design; 2) the exposure of interest was intake of total dietary fiber, including fiber from cereal, fruit, vegetable, and other foods; 3) the endpoint of interest was breast cancer incidence; and 4) the RR and the corresponding 95% CI for the highest compared with the lowest category of dietary fiber intake were reported. If the same population was studied in more than one study, we included the study with the longest follow-up time.

Data extraction and quality assessment

We extracted all data using a standardized data-collection form. Information was recorded as follows: last name of the first author, publication year, and study location; study period and length of follow-up; number of cases and participants; dietary assessment; range of dietary fiber intake; RR from the most fully adjusted model for the highest compared with the lowest dietary fiber intake and the corresponding 95% CI; and adjustment for potential confounders in a multivariate analysis. Total dietary fiber intake was expressed uniformly as g/d.

Instead of providing aggregate scores, we assessed the quality of individual studies by reporting the key components of study designs (20), including characteristics of study populations, assessments of exposure and outcome, duration of follow-up, and statistical control for potential confounding factors. Two authors (J-YD and L-QQ) independently conducted the literature search, study selection, and data extraction. Any disagreements were resolved by discussion.

Statistical analyses

RR was used as the common measure of association across studies, and hazard ratios and incidence rate ratios were directly considered as RR. Homogeneity of effect size across studies was tested by $Q$ statistics at the $P < 0.10$ level of significance. We also calculated the $I^2$ statistic—a quantitative measure of inconsistency across studies (21). Both fixed-effects and random-effects models (22) were used to calculate the combined RR. Results from the random-effects model, which considered both within- and between-study variation (22), were presented. In fact, both models yielded essentially identical results.

Prespecified subgroup analyses according to geographic region, length of follow-up, and menopausal status were performed to assess the potential effect modification of these variables on outcomes. We also conducted a sensitivity analysis to investigate the influence of a single study on the overall risk estimate by omitting one study in each turn.

We also conducted a dose-response analysis based on data for categories of average dietary fiber dose, number of cases, person-year of follow-up, and adjusted logarithm of the RR with its SE (23, 24). Studies were not eligible if the required data were not reported or could not be estimated.

Potential publication bias was assessed by Begg’s funnel plots and Egger’s regression test (25). All analyses were performed by using STATA version 11.0 (StataCorp). A $P$ value $<0.05$ was considered significant, except where otherwise specified.

RESULTS

Literature search

We initially identified 753 potentially eligible studies; most were excluded because they were not prospective studies or because the exposure or endpoint was not relevant to our analysis. After assessing the full-text of the 21 potentially relevant articles, we identified 10 eligible studies (7–16), including 11 data sets for analysis; one study (12) reported the results separately by menopausal status. The main reasons for exclusion were as follows: 2 studies (17, 18) were duplicate reports of 2 other studies (11, 13) on the same populations, one study (26) used a nested case-control design, and one study (27) used a retrospective cohort study design. Another study (28) was excluded because it focused on the recent diet and the length of follow-up was too short (<2 y). We further excluded one study (19) in which dietary fiber intake was treated as a continuous variable but not category of intake. A flow chart showing the study selection process is presented in Figure 1.

Study characteristics

The characteristics of the included studies are presented in Table 1. Of these, 5 studies were conducted in North America, 4 in Europe, and 1 in China. All individual studies were population-based, except the Nurses’ Health Study (11) and the Nurses’ Health Study II (10). Results were presented by menopausal status in 2 of these studies, 4 in overall women, 2 in premenopausal women, and 5 in entire postmenopausal women. The length of the follow-up period ranged from 4.3 to 18 y, with a median of 8 y. All the RRs in each cohort study were estimated based on the highest compared with the lowest quintile of dietary fiber intake. All original studies measured dietary intakes using a food-frequency questionnaire. Ranges of dietary fiber...
<table>
<thead>
<tr>
<th>Study</th>
<th>Location, period</th>
<th>Age, menopause status</th>
<th>Length of follow-up</th>
<th>No. of cases/size of cohort</th>
<th>Exposure range</th>
<th>Adjusted RR (95% CI)</th>
<th>Adjustment for covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graham et al, 1992(7)</td>
<td>USA, 1980–1987</td>
<td>40–107 y, Postmenopause</td>
<td>y 7</td>
<td>344/18,586</td>
<td>Q5: &gt;32.7; Q1: &lt;16</td>
<td>1.07 (0.76, 1.51)</td>
<td>Age and education</td>
</tr>
<tr>
<td>Verhoeven et al, 1997(8)</td>
<td>Netherlands, 1986–1990</td>
<td>55–69 y, Postmenopause</td>
<td>4.3</td>
<td>650/62,573</td>
<td>Q5: 34.5; Q1: 16.9</td>
<td>0.83 (0.56, 1.24)</td>
<td>Age, energy intake, alcohol intake, history of benign breast disease, family history of breast cancer, parity, and age at menarche, menopause, and first birth</td>
</tr>
<tr>
<td>Terry et al, 2002(9)</td>
<td>Canada, 1980–2000</td>
<td>40–59 y, Not specified</td>
<td>16.2</td>
<td>2536/89,835</td>
<td>Q5: &gt;25.8; Q1: &lt;15.2</td>
<td>0.92 (0.78, 1.09)</td>
<td>Age, BMI, smoking, education, physical activity, oral contraceptive use, HRT use, parity, history of benign breast disease, history of breast self-examination, family history of breast cancer, menopausal status, and intakes of energy, alcohol, and saturated fat</td>
</tr>
<tr>
<td>Cho et al, 2003(10)</td>
<td>USA, 1991–1999</td>
<td>26–46 y, Premenopause</td>
<td>8</td>
<td>714/90,655</td>
<td>Q5: 24.8; Q1: 12.5</td>
<td>0.88 (0.67, 1.14)</td>
<td>Age, smoking, height, parity and age at first birth, BMI, age at menarche, family history of breast cancer, history of benign breast disease, oral contraceptive use, menopausal status, alcohol intake, energy intake, and animal fat intake</td>
</tr>
<tr>
<td>Holmes et al, 2004(11)</td>
<td>USA, 1980–1998</td>
<td>34–59 y, Not specified</td>
<td>18</td>
<td>4092/88,678</td>
<td>Q5: &gt;30; Q1: &lt;10</td>
<td>0.68 (0.43, 1.06)</td>
<td>Age, BMI, total energy intake, alcohol intake, parity and age at first birth, height, family history of breast cancer, history of benign breast disease, age at menarche (in y), HRT use, and menopausal status</td>
</tr>
<tr>
<td>Cade et al, 2007(12)</td>
<td>United Kingdom, 1995–2004</td>
<td>35–50 y, Premenopause</td>
<td>7.5</td>
<td>257/15,951</td>
<td>Q5: &gt;30; Q1: &lt;20</td>
<td>0.48 (0.24, 0.96)</td>
<td>Age, BMI, physical activity, smoking, oral contraceptive use, number of children, alcohol intake, and total energy intake</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51–60 y, Postmenopause</td>
<td>7.5</td>
<td>350/17,781</td>
<td>Q5: &gt;30; Q1: &lt;21</td>
<td>1.18 (0.70, 1.99)</td>
<td>Age, BMI, physical activity, smoking, oral contraceptive use, HRT use, number of children, alcohol intake, and total energy intake</td>
</tr>
<tr>
<td>Sonestedt et al, 2008(13)</td>
<td>Sweden, 1991–2004</td>
<td>46–75 y, Not specified</td>
<td>10.3</td>
<td>544/15,773</td>
<td>Q5: 26.0; Q1: 12.0</td>
<td>0.82 (0.61, 1.09)</td>
<td>Age, season of data collection, diet interviewer, method version, total energy, weight, height, education, smoking, physical activity, household activities, alcohol intake, age at menopause, parity, and HRT use</td>
</tr>
<tr>
<td>Suzuki et al, 2008(14)</td>
<td>Sweden, 1987–1997</td>
<td>39–73 y, Postmenopause</td>
<td>8.3</td>
<td>1284/51,823</td>
<td>Q5: 29.0; Q1: 16.6</td>
<td>0.85 (0.69, 1.05)</td>
<td>Age, height, BMI, education, parity, menopausal status, oral contraceptive use, HRT use, family history of breast cancer, history of benign breast disease, total energy intake, total fat intake, fruit and vegetable intake, alcohol intake, and age at first birth, menarche, and menopause</td>
</tr>
<tr>
<td>Park et al, 2009(15)</td>
<td>USA, 1995–2003</td>
<td>50–71 y, Postmenopause</td>
<td>7</td>
<td>5461/185,598</td>
<td>Q5: 26.0; Q1: 11.0</td>
<td>0.87 (0.77, 0.98)</td>
<td>Age, race, education, BMI, age at first birth, parity, family history of breast cancer, age at menopause, physical activity, smoking, HRT use, breast biopsy, gynecologic surgery, and intakes of alcohol, total fruit and vegetables, total fat, and total energy intake</td>
</tr>
<tr>
<td>Wen et al, 2009(16)</td>
<td>China, 1997–2005</td>
<td>40–70 y, Not specified</td>
<td>7.35</td>
<td>616/74,942</td>
<td>Q5: 16.3; Q1: 7.7</td>
<td>1.09 (0.84, 1.40)</td>
<td>Age, total energy intake, education, BMI, age at first birth, family history of breast cancer, personal history of benign breast disease, and physical activity</td>
</tr>
</tbody>
</table>

1 HRT, hormone replacement therapy; Q, quintile.
intake were comparable in most studies, except in the Shanghai Women’s Health Study (16). Case ascertainment were not consistent across studies, with most using medical record or cancer registry data and some using self-report of physician diagnoses. The New York State Cohort (7) only adjusted for age and education levels, whereas the other 9 studies adjusted for a wide range of potential confounders for breast cancer, including age, BMI, family history of breast cancer, smoking, use of hormone replacement therapy, and intake of total energy, alcohol, and animal fat.

Main analysis

The multivariable-adjusted RRs for each study and the combined RR for the highest compared with the lowest categories of dietary fiber intake are presented in Figure 2. Of the 10 selected prospective cohort studies, 8 showed an inverse association between dietary fiber intake and risk of breast cancer, 2 of which (12, 15) were statistically significant. No evidence of heterogeneity was found across studies ($P = 0.44, I^2 = 0\%$). Overall, the combined RR of breast cancer for the highest compared with the lowest dietary fiber intake was 0.89 (95% CI: 0.83, 0.96).

Subgroup and sensitivity analyses

The results of subgroup analyses according to geographic region, length of follow-up, and menopausal status are presented in Table 2. No evidence of heterogeneity was observed within any subgroup. A significant inverse association between dietary fiber intake and risk of breast cancer was observed in all subgroups, except in premenopausal women. The association between dietary fiber intake and breast cancer risk was not significantly modified by geographic region, length of follow-up, or menopausal status.

The sensitivity analyses that omitted one study at a time and calculated the combined RR for the remaining studies yielded consistent results. The combined RRs were all statistically significant and similar with one another, with a narrow range from 0.87 (95% CI: 0.81, 0.95) to 0.90 (95% CI: 0.82, 0.98).

Dose-response analysis

Four studies (9–11, 16) were not eligible for the dose-response analysis because they did not provide the required data (eg, the number of cases in each category). The dose-response analysis of the remaining studies showed that the risk of breast cancer decreased significantly, on average, by 7% for every 10-g/d increment in dietary fiber intake (RR: 0.93; 95% CI: 0.88, 0.98; $P$ for trend = 0.004), and little evidence of heterogeneity was found ($P = 0.16$).

Publication bias

The Begg’s funnel plot did not show any substantial asymmetry. Egger’s regression test also indicated little evidence of publication bias ($P = 0.67$).

DISCUSSION

This meta-analysis of 10 prospective cohort studies involving 16,848 cases and 712,195 participants supports a significant inverse association of dietary fiber intake with risk of breast cancer. The risk of breast cancer was reduced by 11% in a comparison of the highest with the lowest quintile of dietary fiber intake. There was no evidence of heterogeneity throughout our study. Furthermore, the dose-response analysis showed that the risk of breast cancer decreased significantly, by 7% for every 10-g/d increment of dietary fiber intake.

Heterogeneity is often a concern in a meta-analysis. However, little evidence of heterogeneity was observed throughout our study. This was partially explained by the following facts: all the studies used a prospective cohort study design; all the studies, except one (16), were conducted in Western countries, where populations share much in terms of genetic background, lifestyle, dietary pattern, and breast cancer incidence; and the ranges of dietary fiber intake in most studies were comparable.

The results from our subgroup and sensitivity analyses were quite similar and robust, and the associations were neither significantly modified by geographic region, length of follow-up, or menopausal status nor substantially driven by any single study. A significant inverse association was observed in all subgroups, except in premenopausal women. Although estrogen metabolism pathways may differ between premenopausal and postmenopausal women (29), the nonsignificant association in premenopausal women was likely due to the small number of studies (n = 4) and, hence, insufficient statistical power. As for individual studies, several studies differed from others in various aspects. For example, the New York State Cohort (7), the earliest one started in 1980, only adjusted for age and education; the Shanghai Women’s Health Study (16), the only one conducted in Asia, covered a rather narrow range of dietary fiber intake between the highest and lowest quintiles (16.3 compared with 7.7 g/d); and the National Institutes of Health–AARP Diet and Health Study (15) was the largest cohort study, accounting for nearly 35% of the total weight in the current meta-analysis. Nevertheless, the combined risk estimate was not significantly driven by any single study.

In addition to the variables we examined, other factors, including hormone receptor status and type and source of dietary fiber, merit consideration. Few studies (13–15) examined the dietary fiber and breast cancer association stratified by hormone receptor status. One study (15) observed an inverse relation of dietary fiber intake to hormone receptor–negative tumors (RR: 0.56; 95% CI: 0.35, 0.90), whereas others suggested no association regardless of hormone receptor status. Similarly, only 3 studies (9, 10, 15) examined the association of different types of dietary fiber (ie, soluble or insoluble) with breast cancer risk. Although one study found that soluble fiber, but not insoluble fiber, was inversely related to breast cancer risk, the result should be interpreted with caution because soluble and insoluble fiber intakes were highly correlated (15). As for source of dietary fiber, most studies (9–15) found that dietary fiber from specific food sources, such as cereal, fruit, and vegetable, were not related to breast cancer risk. Because of the limited available evidence, future studies concerning these factors are needed.

Several mechanisms may be involved in the inverse association of dietary fiber intake with breast cancer risk. Dietary fiber may decrease circulating estrogen concentrations by suppressing bacterial β-glucuronidase activity in the gut, which inhibits the reabsorption of estrogens in the colon and increases the excretion of estrogens in feces (5, 30–32), thereby reducing the risk of breast cancer. In addition to the estrogen-related pathway, dietary fiber may play a role in the control of insulin resistance and insulin-like growth factors, which are proposed to be risk factors for breast cancer (34–36), and hence protect against type 2 diabetes mellitus (33). Our study had some important strengths. Because individual studies had insufficient statistical power, our meta-analysis of 10 studies involving a large number of cases and participants enhanced the power to detect a significant association and provided more reliable estimates. All the original studies used a prospective cohort study design, which greatly reduced the likelihood of recall and selection biases. In addition, we found a significant dose-response relation between dietary fiber intake and risk of breast cancer, which thereby further strengthened this association.

Potential limitations of this study should be considered. First, residual confounders are always of concern in observational studies. Women with high intakes of dietary fiber are likely to adopt other healthy lifestyles. Although most included studies adjusted for a wide range of potential confounders for breast cancer, we still could not exclude the possibility that other unmeasured or inadequately measured factors have confounded the true association. Second, random misclassification of dietary fiber intake may influence the results. However, all adjusted RRs were estimated on the basis of the highest compared with the lowest quintile of dietary fiber intake, and the wide ranges of dietary fiber intake in most cohort studies probably reduced this bias. Third, because all participants enrolled in cohort studies were women, we could not examine the effects of dietary fiber intake during earlier life on the risk of breast cancer. Fourth, potential publication bias might influence the findings, yet little evidence of publication bias was observed. Our relatively strict inclusion criteria might have introduced selection bias. However, our findings were robust; for example, the additional inclusion of the nested case-control study (26) in the meta-analysis yielded virtually unchanged results (RR: 0.88; 95% CI: 0.82, 0.95). Finally, because the results of the current analysis were mainly

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**TABLE 2**

Combined RR of breast cancer related to dietary fiber intake by study design and population characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of studies</th>
<th>RR (95% CI)</th>
<th>P-heterogeneity</th>
<th>I² (%</th>
<th>P-interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10</td>
<td>0.89 (0.83, 0.96)</td>
<td>0.44</td>
<td>0.54</td>
<td>0</td>
</tr>
<tr>
<td>Geographic area</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>5</td>
<td>0.89 (0.81, 0.97)</td>
<td>0.60</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Europe</td>
<td>4</td>
<td>0.84 (0.73, 0.97)</td>
<td>0.38</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Length of follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8 y</td>
<td>5</td>
<td>0.91 (0.83, 0.99)</td>
<td>0.17</td>
<td>35.4</td>
<td></td>
</tr>
<tr>
<td>≥8 y</td>
<td>5</td>
<td>0.87 (0.78, 0.96)</td>
<td>0.78</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Menopause status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopause</td>
<td>4</td>
<td>0.91 (0.77, 1.07)</td>
<td>0.27</td>
<td>23.2</td>
<td>0.87</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>7</td>
<td>0.92 (0.85, 0.99)</td>
<td>0.52</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
based on data from Western populations, additional research in other populations is warranted to generalize the findings.

Our findings have important public health implications. In Western countries, breast cancer remains the most common cancer in women. On the other hand, dietary fiber intake in the United States and many European countries is ~15 g/d, which is only half the recommended amount (37, 38). Controversies continue regarding the effects of dietary fiber on breast cancer risk. Findings from our study aimed at addressing this issue and resolving the inconsistency are both important and timely. Although the magnitude of risk reduction reported here is small at the individual level, given the high incidence and large burden of breast cancer, increasing dietary fiber intake in the general population is of great public health significance with respect to breast cancer prevention. In conclusion, this meta-analysis of prospective cohort studies provides evidence of a significant inverse dose-response association between dietary fiber intake and risk of breast cancer.

The authors’ responsibilities were as follows—J-YD and L-QQ: conception and design of the study and analysis and interpretation of the data; J-YD: drafting of the manuscript; and J-YD, L-QQ, KH and PW: critical revision of the article for important intellectual content. No conflicts of interest were reported.

REFERENCES