

Dietary fiber and breast cancer risk: a systematic review and meta-analysis of prospective studies

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Background: Evidence from case–control studies suggest that dietary fiber may be inversely related to breast cancer risk, but it is unclear if this is supported by prospective data. We conducted a systematic review and meta-analysis of the evidence from prospective studies.

Methods: PubMed was searched for prospective studies of fiber intake and breast cancer risk until 31st August 2011. Random effects models were used to estimate summary relative risks (RRs).

Results: Sixteen prospective studies were included. The summary RR for the highest versus the lowest intake was 0.93 [95% confidence interval (CI) 0.89–0.98, $I^2 = 0\%$] for dietary fiber, 0.95 (95% CI 0.86–1.06, $I^2 = 4\%$) for fruit fiber, 0.99 (95% CI 0.92–1.07, $I^2 = 1\%$) for vegetable fiber, 0.96 (95% CI 0.90–1.02, $I^2 = 5\%$) for cereal fiber, 0.91 (95% CI 0.84–0.99, $I^2 = 7\%$) for soluble fiber and 0.95 (95% CI 0.89–1.02, $I^2 = 0\%$) for insoluble fiber. The summary RR per 10 g/day of dietary fiber was 0.95 (95% CI 0.91–0.98, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.82$). In stratified analyses, the inverse association was only observed among studies with a large range (≥ 13 g/day) or high level of intake (≥ 25 g/day).

Conclusion: In this meta-analysis of prospective studies, there was an inverse association between dietary fiber intake and breast cancer risk.

Key words: breast cancer, cancer prevention, diet, dietary fiber, meta-analysis

introduction

Breast cancer is the most common cause of cancer in women, with 1.4 million new cases diagnosed worldwide in 2008, accounting for ~23% of all cancer cases and 14% of all cancer deaths among women [1]. Breast cancer rates increase with industrialization and urbanization and are higher in high-income countries than in low- and middle-income countries, however, rates are rapidly increasing in low- and middle-income countries [2, 3]. The large international variation in breast cancer rates [1], coupled with the rapidly increasing rates observed in secular trend studies [2, 3] and migration studies [4, 5], suggest the importance of modifiable risk factors in breast cancer etiology.

Dietary factors have long been suspected to be implicated in the development of breast cancer, however, in spite of the large literature existing, few convincing dietary risk factors have been identified (e.g. alcohol intake) [6]. Dietary fiber has been hypothesized to reduce breast cancer risk based on observations that vegetarian women have increased fecal estrogens and lower blood concentrations of estrogen compared with omnivorous women [7, 8]. It has been shown that dietary fiber may inhibit intestinal reabsorption of estrogens and may increase fecal

excretion of estrogens [9]. However, epidemiological studies of dietary fiber intake and breast cancer risk have reported inconsistent findings. An early meta-analysis of 12 case–control studies reported an inverse association [summary odds ratio (OR) = 0.85] between dietary fiber intake and breast cancer risk [10]. In contrast, most [11–27] but not all [28] prospective studies have reported no statistically significant association between fiber intake and breast cancer risk. It is unclear whether the seemingly discrepant results by study design are explained by differences in the range or level of fiber intake, low statistical power in individual studies, population characteristics or measurement error in prospective studies or by selection and recall biases in case–control studies. It is also not clear if specific types of fiber are associated with breast cancer risk. The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report from 2007 “Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective” stated that the evidence for an association between fiber intake and breast cancer risk was either too limited or inconsistent for a conclusion [6]. Since that report was released, eight prospective studies (nine publications) have been published on dietary fiber intake and breast cancer risk [20–28]. Here, we systematically review the evidence with an aim of clarifying the dose–response relationship between dietary fiber intake and breast cancer risk, to explore potential sources of heterogeneity across study

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results and whether the results differ by the range or level of fiber intake or by type of fiber.

methods

search strategy

The literature search and data extraction up to December 2005 was conducted by several reviewers at Istituto Nazionale Tumori, Milan. Initially, several databases were searched including PubMed, Embase, CAB Abstracts, ISI Web of Science, BIOSIS, Latin American and Caribbean Center on Health Sciences Information, Cochrane library, Cumulative Index to Nursing and Allied Health Literature, The Allied and Complementary Medicine Database, National Research Register and In Process Medline. All the relevant prospective studies were identified by the PubMed searches and therefore a change in the protocol was made and only PubMed was used for the updated searches from January 2006 up to 31st August 2011. We followed a prespecified protocol, which includes details of the search terms used, for the review (http://www.dietandcancerreport.org/downloads/SLR_Manual.pdf). We also searched the reference lists of all the studies that were included in the analysis. We followed standard criteria for conducting and reporting meta-analyses [29].

study selection

We included prospective cohort, case-cohort and nested case-control studies investigating the association between dietary fiber intake and breast cancer incidence. Relative risk (RR) estimates (such as hazard ratio or risk ratio) and 95% confidence intervals (CIs) had to be available in the publication. For the dose-response analysis, a quantitative measure of intake and the total number of cases and person-years or participants had to be available in the publication. Twenty-six potentially eligible full text publications were identified [11–28, 30–37]. Five duplicate publications were excluded [30–33, 36], three publications on adolescent dietary fiber intake were excluded [34, 35, 37], and one publication was excluded because the continuous result provided per standard deviation increase in intake was not quantified [19]. Data from one of the publications were only included in the subgroup analysis of high versus low fiber intake among postmenopausal women [21], because a larger overlapping publication was used for the main analysis, but did not report results separately for postmenopausal women [23]. One additional publication was excluded

from the dose-response analysis because the comparison was provided only for the highest versus the lowest intake [25]. In total, 17 publications were included in the high versus low analyses [11–18, 20–28] and 15 of these were included in the dose-response analyses (Figure 1, Table S1, available at *Annals of Oncology* online) [11–18, 20, 22–24, 26–28].

data extraction

The following data were extracted from each study: first author's last name, publication year, country where the study was conducted, study name, follow-up period, sample size, menopausal status, age, number of cases, dietary assessment method (type, number of items and whether it was validated), exposure, quantity of intake, RRs and 95% CIs and variables adjusted for in the analysis. We did not assess study quality using a quality score but investigated whether study characteristics such as duration of follow-up, number of cases, menopausal status and adjustment for confounders, which are indicators of study quality, influenced the results in subgroup analyses.

statistical methods

Random effects models were used to calculate summary RRs and 95% CIs for the highest versus the lowest level of fiber intake and for the dose-response analysis [38]. The average of the natural logarithm of the RRs was estimated and the RR from each study was weighted by the inverse of its variance. A two-tailed $P < 0.05$ was considered statistically significant.

For the dose-response analysis, we used the method by Greenland and Longnecker [39] to compute study-specific slopes (linear trends) and 95% CIs from the natural logs of the RRs and CIs across categories of fiber intake. The method requires that the distribution of cases and person-years or noncases and the RRs with the variance estimates for at least three quantitative exposure categories are known. We estimated the distribution of cases or person-years in studies that did not report these but reported the total number of cases or person-years. The median or mean level of fiber intake in each category of intake was assigned to the corresponding RR for each study when provided in the paper. For studies that reported fiber intake by ranges of intake, we estimated the mean intake in each category by calculating the average of the lower and upper bound. When the highest or lowest category was open-ended, we assumed the open-ended interval length to be the same as the adjacent interval. In two studies [12, 24] where the upper bound of the highest category was extreme and may have led to exaggerated ranges of intake, we also used the width of the adjacent interval to calculate the upper bound and midpoint. The dose-response results are

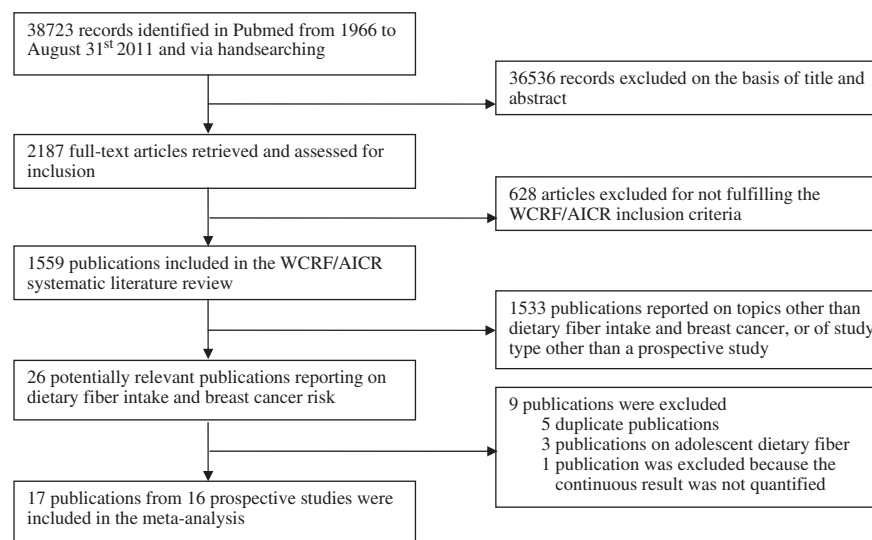


Figure 1. Flow-chart of study selection.

presented for a 10 g/day increment. A potential nonlinear dose–response relationship between fiber intakes and breast cancer was examined using fractional polynomial models [40]. We determined the best fitting second order fractional polynomial regression model, defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity [41]. Heterogeneity between studies was assessed using Q and I^2 statistics [42].

Potential sources of heterogeneity were investigated in subgroup and meta-regression analyses. We assessed small-study effects, such as publication bias, using a funnel plot and Egger’s test [43] and Begg’s test [44] with results considered to indicate potential small-study bias when $P < 0.10$. We also conducted sensitivity analyses excluding one study at a time to check whether the result was driven by a very large study or a study with an extreme result. Stata version 10.1 software (StataCorp, College Station, TX) was used for the statistical analyses.

results

Sixteen prospective studies (17 publications) [11–18, 20–28] were included in the analysis of dietary fiber intake and breast cancer risk (Figure 1, Table S1, available at *Annals of Oncology* online). Six of the studies were from Europe, nine from America and one from Asia (Table S1, available at *Annals of Oncology* online). The range of intake varied from 8.6 to 21.5 g/day in the various studies and the mean range was 14.7, 14.0 and 8.6 among American, European and Asian studies (results not shown). The highest level of intake varied from 16.3 to 35.2 g/day (Table S1, available at *Annals of Oncology* online) and the mean intake in the highest category was 25.7, 29.9 and 16.3 g/day in the American, European and Asian studies (results not shown).

dietary fiber

high versus low analysis. Sixteen cohort studies [11–18, 20, 22–28] investigated the association between high versus low dietary fiber intake and breast cancer risk and included 26 523 cases among 999 271 participants. The summary RR for high versus low intake was 0.93 (95% CI 0.89–0.98), with no evidence of heterogeneity, $I^2 = 0\%$ and $P_{\text{heterogeneity}} = 0.89$ (supplemental Figure S1, available at *Annals of Oncology* online). The summary RR ranged from 0.92 (95% CI 0.87–0.97) when the Nurses’ Health Study was excluded to 0.95 (95% CI 0.89–1.00) when the NIH-AARP Diet and Health Study was excluded. There was no evidence of publication bias with Egger’s test, $P = 0.89$, or with Begg’s test, $P = 0.56$.

dose–response analysis. Fifteen cohort studies [11–18, 20, 22–24, 26–28] were included in the dose–response analysis. The summary RR per 10 g/day was 0.95 (95% CI 0.91–0.98), with no evidence of heterogeneity, $I^2 = 0\%$ and $P_{\text{heterogeneity}} = 0.82$ (Figure 2A). The test for nonlinearity was not statistically significant, $P_{\text{nonlinearity}} = 0.11$ (Figure 2B).

fruit fiber

high versus low analysis. Six cohort studies [14, 17, 18, 20, 22, 28] were included in the high versus low analysis fruit fiber intake and breast cancer risk, including 14 694 cases among 502 082 participants. The summary RR for high versus low intake was 0.95 (95% CI 0.86–1.06), with moderate heterogeneity, $I^2 = 46\%$ and $P_{\text{heterogeneity}} = 0.10$ (supplemental

Figure S2A, available at *Annals of Oncology* online). The summary RR ranged from 0.92 (95% CI 0.83–1.03) when the Canadian National Breast Screening Study was excluded to 0.97 (95% CI 0.90–1.05) when the Swedish Mammography Cohort Study was excluded. There was no evidence of publication bias with Egger’s test, $P = 0.91$, or Begg’s test, $P = 1.00$.

dose–response analysis. Six cohort studies were included in the dose–response analysis [14, 17, 18, 20, 22, 28]. The summary RR per 10 g/day was 0.88 (95% CI 0.75–1.03), with moderate heterogeneity, $I^2 = 48\%$ and $P_{\text{heterogeneity}} = 0.09$ (Figure 3A). There was no evidence of a nonlinear association between fruit fiber intake and breast cancer risk, $P_{\text{nonlinearity}} = 0.21$ (results not shown).

vegetable fiber

high versus low analysis. Six cohort studies [14, 17, 18, 20, 22, 28] were included in the analysis of high versus low vegetable fiber intake and breast cancer, including 14 694 cases among 502 082 participants. The summary RR was 0.99 (95% CI 0.92–1.07). There was little evidence of heterogeneity, $I^2 = 15\%$, $P_{\text{heterogeneity}} = 0.32$ (supplemental Figure S2B, available at *Annals of Oncology* online). There was no evidence of small-study bias with Egger’s test, $P = 0.96$, or with Begg’s test, $P = 0.71$. The summary RR ranged from 0.95 (95% CI 0.87–1.03) when excluding the NIH-AARP Diet and Health Study to 1.01 (95% CI: 0.92–1.12) when excluding the Nurses’ Health Study.

dose–response analysis. Six cohort studies [14, 17, 18, 20, 22, 28] were included in the dose–response analysis. The summary RR per 10 g/day was 0.97 (95% CI 0.55–1.12) with moderate evidence of heterogeneity, $I^2 = 39\%$ and $P_{\text{heterogeneity}} = 0.14$ (Figure 3B). There was no evidence of a nonlinear association between vegetable fiber intake and breast cancer risk, $P_{\text{nonlinearity}} = 0.32$ (results not shown).

cereal fiber

high versus low analysis. Six cohort studies [14, 17, 18, 20, 22, 28] were included in the analysis of high versus low cereal fiber intake and breast cancer risk, including 14 694 cases among 502 082 participants. The summary RR was 0.96 (95% CI 0.90–1.02) and there was little evidence of heterogeneity, $I^2 = 5\%$, $P_{\text{heterogeneity}} = 0.39$ (supplemental Figure S2C, available at *Annals of Oncology* online). There was no evidence of small-study bias with Egger’s test, $P = 0.46$, or with Begg’s test, $P = 0.71$. The summary RR ranged from 0.92 (95% CI 0.86–0.98) when excluding the Nurses’ Health Study to 0.97 (95% CI 0.90–1.04) when excluding the Canadian National Breast Screening Study.

dose–response analysis. Six cohort studies [14, 17, 18, 20, 22, 28] were included in the dose–response analysis. The summary RR per 10 g/day was 0.91 (95% CI 0.79–1.04) with moderate evidence of heterogeneity, $I^2 = 56\%$, $P_{\text{heterogeneity}} = 0.05$ (Figure 3C). There was no evidence of a nonlinear association between cereal fiber intake and breast cancer risk, $P_{\text{nonlinearity}} = 1.00$ (results not shown).

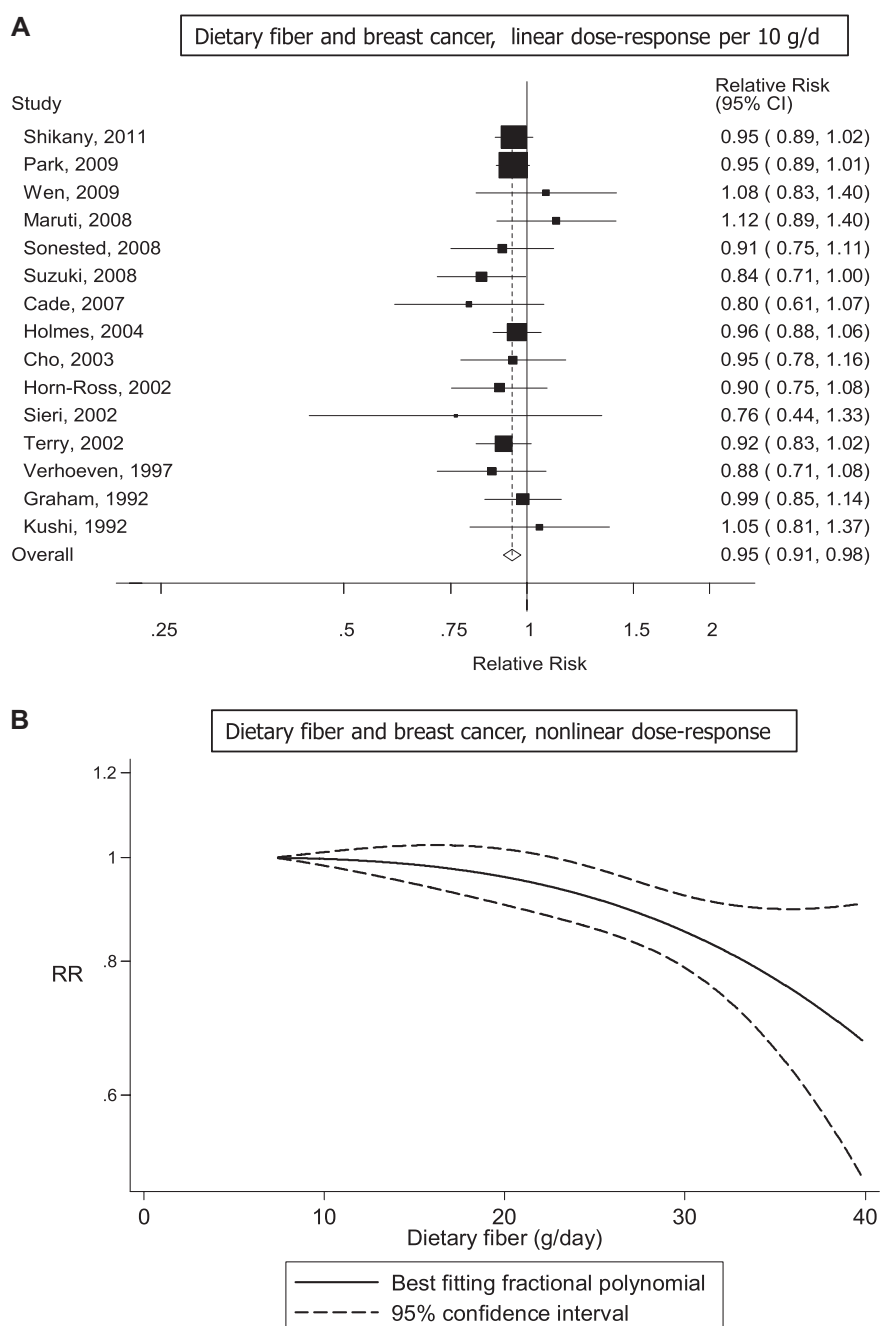


Figure 2. Dietary fiber and breast cancer, linear and nonlinear dose response. CI, confidence interval.

soluble and insoluble fiber

high versus low analysis. Five studies [14, 17, 25, 27, 28] investigated soluble fiber and six studies [14, 17, 24, 25, 27, 28] investigated insoluble fiber in relation to breast cancer risk. The summary RRs for high versus low intake were 0.91 (95% CI 0.84–0.99, $I^2 = 7%$, $P_{\text{heterogeneity}} = 0.36$) for soluble fiber (supplemental Figure S3A, available at *Annals of Oncology* online) and 0.96 (95% CI 0.88–1.04, $I^2 = 0%$, $P_{\text{heterogeneity}} = 0.55$) for insoluble fiber (supplemental Figure S3B, available at *Annals of Oncology* online), respectively.

dose–response analysis. In the dose–response analysis, four studies of soluble fiber [14, 17, 27, 28] and five studies of insoluble fiber

[14, 17, 24, 27, 28] were included. The summary RR was 0.74 (95% CI 0.63–0.88, $I^2 = 0%$, $P_{\text{heterogeneity}} = 0.77$) (Figure 4A) and 0.96 (95% CI 0.86–1.07, $I^2 = 36%$, $P_{\text{heterogeneity}} = 0.18$) (Figure 4B) per 10 g/day, respectively. There was no evidence of a nonlinear association between soluble fiber and breast cancer risk, $P_{\text{nonlinearity}} = 0.69$ (Figure 4C), but some suggestion of a nonlinear association with insoluble fiber, although the test for nonlinearity was not significant, $P = 0.07$ (Figure 4D).

subgroup and sensitivity analyses. In stratified analyses (Table 1), the association between high versus low fiber intake and breast cancer risk was inverse in most strata, although not always statistically significant. In meta-regression analyses,

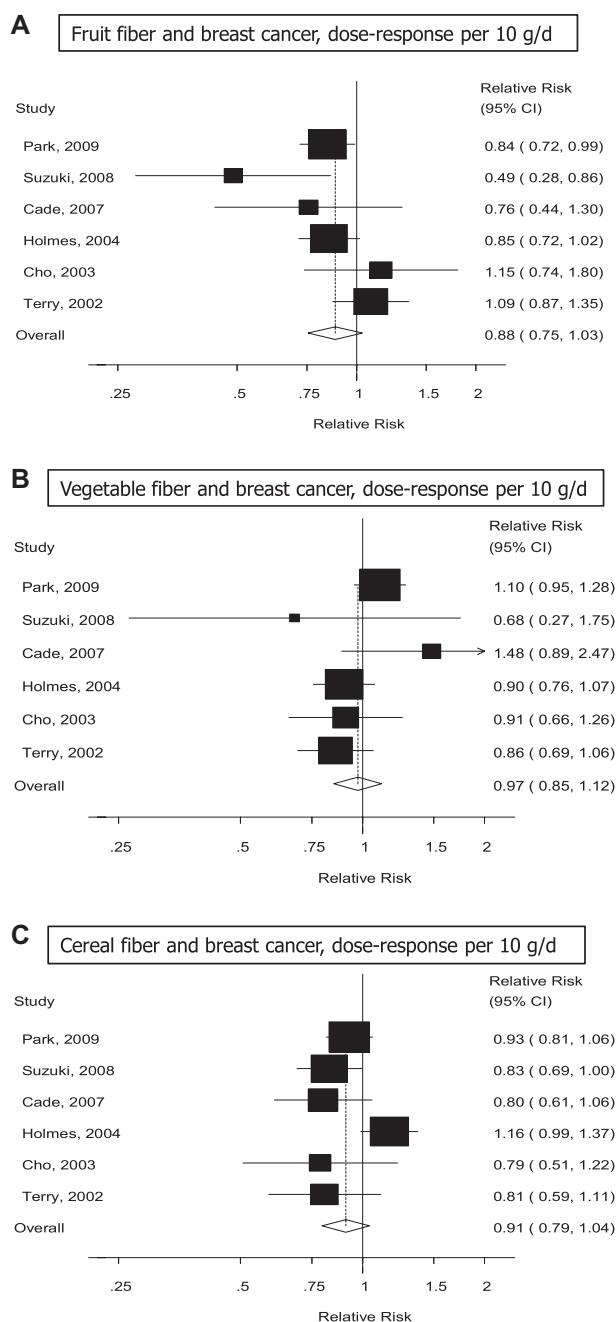


Figure 3. Fiber types and breast cancer, dose-response analysis per 10 g/day. CI, confidence interval.

there was no evidence of a difference in the results between strata defined by menopausal status (Table 1) and estrogen and progesterone receptor status. Only three studies could be included in the analysis stratified by hormone receptor status, the summary RR for high versus low fiber intake was 0.91 (95% CI 0.79–1.06, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.83$) for ER+/PR+ tumors, 0.89 (95% CI 0.67–1.19, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.37$) for ER+/PR- tumors and 0.76 (95% CI 0.52–1.11, $I^2 = 24\%$, $P_{\text{heterogeneity}} = 0.27$) for ER-/PR- tumors with no heterogeneity between subgroups ($P_{\text{heterogeneity}} = 0.33$; results not shown) [22, 28, 33]. The summary estimates in premenopausal and postmenopausal breast cancers were

similar. No significant difference emerged when stratified by study characteristics such as number of cases, duration of follow-up and geographic location or for adjustment for confounding variables ($P \geq 0.08$ for all comparisons) (Table 1). When analyzed by food source, intakes of fruit, vegetable or cereal fiber were not significantly associated with breast cancer risk in subgroup analyses and there was no evidence of heterogeneity in the subgroup analyses (supplemental Table S2, available at *Annals of Oncology* online).

One study reported results using more extreme categorizations of intake (>30 g/day versus ≤ 10 g/day) in addition to quintile-based analyses [18]. In a sensitivity analysis, using the results from the more extreme categorization instead of the quintile-based analysis for that study, the summary RR for high versus low intake was 0.92 (95% CI 0.87–0.97, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.84$).

We conducted additional subgroup analyses for total dietary fiber stratified by the level of intake in the highest category and by the range of intake. In the high versus low analysis, the summary RR was 0.98 (95% CI 0.90–1.08) for studies where the highest intake was <25 g/day (mean: 21.8 g/day) and 0.91 (95% CI 0.86–0.97) for studies where the highest intake was ≥ 25 g/day (mean: 29.4 g/day). When stratified by the range of intake, the summary RR was 0.96 (95% CI 0.88–1.05) for studies with a range <13 g/day (mean: 11.5 g/day) and 0.92 (95% CI 0.86–0.98) for studies with a range ≥ 13 g/day (mean: 15.8 g/day) (results not shown).

Furthermore, to assess whether exclusion of one study [25] from the dose-response analysis of total dietary fiber might have influenced the results, we repeated the high versus low intake analysis restricted to the studies included in the dose-response analysis. The summary RRs for dietary fiber intake and breast cancer risk were 0.92 (95% CI 0.88–0.98), almost identical to the result from the high versus low analysis including all studies.

discussion

We found an inverse association between dietary fiber intake and breast cancer risk in this meta-analysis based on prospective studies; however, the association appeared to be most pronounced in studies with high levels (≥ 25 versus <25 g/day) or large ranges (≥ 13 versus <13 g/day) of fiber intake. We found that intake of soluble fiber but not insoluble fiber, fruit fiber, vegetable fiber or cereal fiber was inversely associated with breast cancer risk. Fewer studies were included in these analyses and may have limited our power to detect associations.

Our results of a lower breast cancer risk with high fiber intake are consistent with a meta-analysis of 12 case-control studies, which found an inverse association (summary OR = 0.85) between dietary fiber intake and breast cancer risk [10]. However, our results that are based on prospective studies are less prone to recall and selection biases. Such biases can make it difficult to draw firm conclusions; thus, these results confirm this hypothesis with more reliable evidence than available previously.

Our meta-analysis may have several limitations that must be taken into consideration. The inverse association between fiber intake and breast cancer risk could be due to unmeasured or residual confounding. Higher intake of dietary fiber is often associated with other lifestyle factors including higher levels of physical activity, lower prevalence of overweight/obesity and

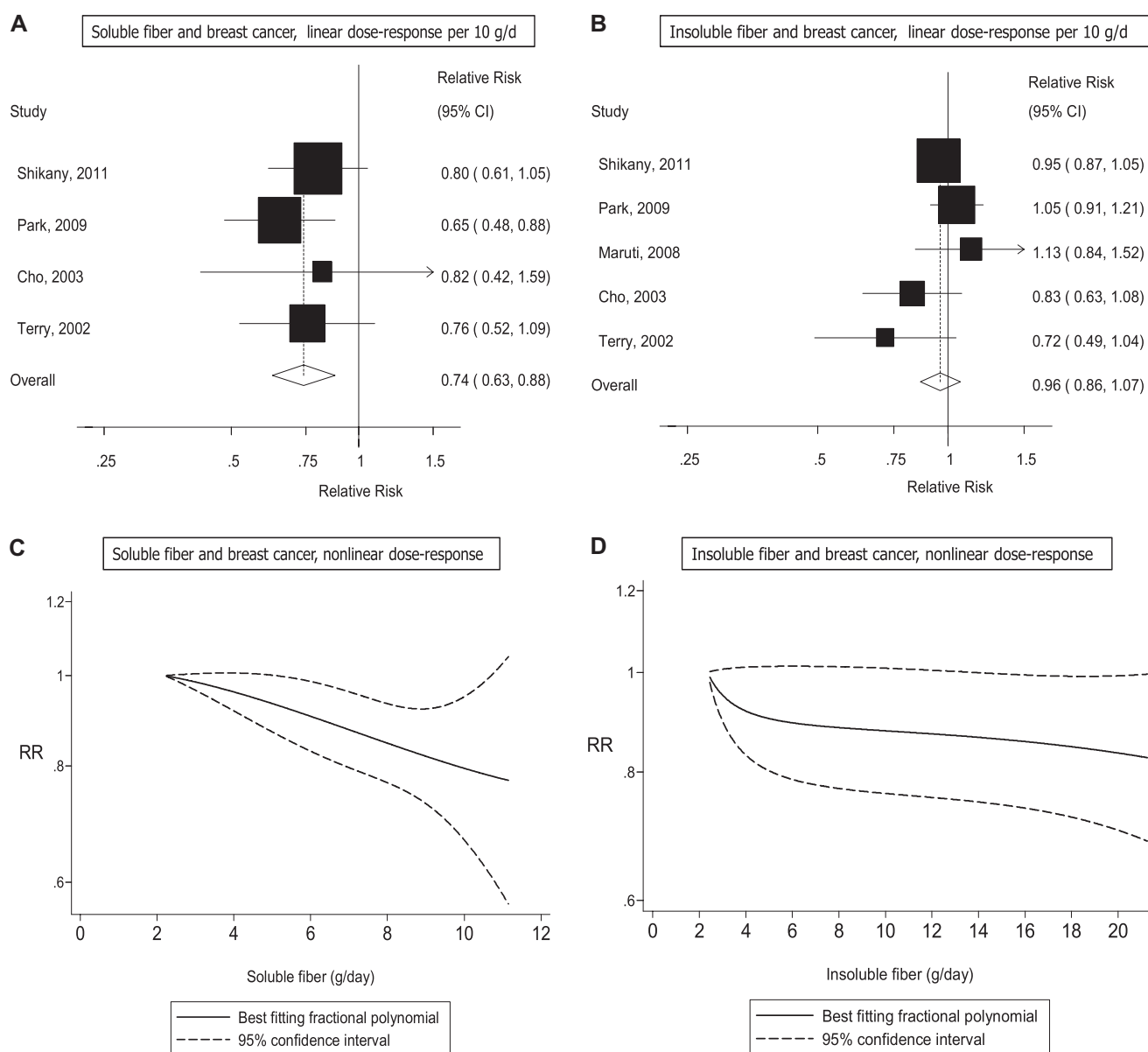


Figure 4. Soluble and insoluble fiber and breast cancer. CI, confidence interval.

lower intakes of alcohol and dietary fat [28]. However, many of the studies included in this meta-analysis adjusted for these and other potential confounders. Furthermore, in subgroup and meta-regression analyses, we found no difference in the results when stratified by whether they adjusted for confounding factors or not. Only few studies reported results stratified by hormone receptor status and this may have limited our statistical power to detect significant associations in these subgroup analyses.

Measurement errors in the assessment of dietary intake are known to bias effect estimates. However, because of the prospective design of the included studies, such measurement errors are most likely to have resulted in bias toward the null and attenuated associations. Only one of the studies compared the results with and without correction for measurement error [28]. The age-adjusted RR for a 10 g/day increase in fiber intake was 0.94 (95% CI 0.90–0.98) and after correction for measurement error the RR became 0.89 (95% CI 0.82–0.97),

suggesting important attenuation of the risk estimates by measurement errors. The level or range of intake may have been too low or narrow to detect associations in some of the studies included in this meta-analysis and this may have led to an underestimation of the association in the high versus low and linear dose-response analyses; thus, examining the shape of the dose-response relationship may be important to clarify inconsistencies in the results between studies. Consistent with this are the results from the subgroup analyses stratified by the level and range of intake, which showed that the inverse association was only observed in the subgroup of studies with a level of intake of ≥ 25 g/day in the highest category or a range of ≥ 13 g/day. In addition, one study reported no association between fiber intake in quintile-based analyses (RR = 0.98, 95% CI 0.87–1.11) and in decile-based analyses, but when absolute cut points were used for the analysis, a suggestive inverse association was observed for intakes above 30 g/day compared

Table 1. Subgroup analyses of dietary fiber intake and breast cancer, high versus low intake

	Dietary fiber				
	<i>n</i>	RR (95% CI)	<i>I</i> ² (%)	<i>P</i> _h ^a	<i>P</i> _h ^b
All studies	16	0.93 (0.89–0.98)	0	0.89	
Duration of follow-up					
<10 years follow-up	14	0.93 (0.87–0.98)	0	0.89	0.65
≥10 years follow-up	2	0.94 (0.82–1.09)	18.8	0.27	
Menopausal status					
Premenopausal	4	0.90 (0.73–1.10)	23.2	0.27	0.81
Pre- and postmenopausal	5	0.95 (0.88–1.04)	0	0.62	
Postmenopausal	13	0.93 (0.88–0.99)	0	0.68	
Geographic location					
Europe	6	0.90 (0.81–1.00)	0	0.76	0.31
America	9	0.93 (0.88–0.99)	0	0.83	
Asia	1	1.09 (0.84–1.41)			
Number of cases					
Cases <500	3	1.00 (0.79–1.27)	0	0.68	0.92
Cases 500 to <1500	8	0.91 (0.83–1.01)	0	0.67	
Cases ≥1500	5	0.93 (0.88–0.99)	0	0.64	
Adjustment for confounders					
Hormone therapy	Yes	9 0.93 (0.88–0.98)	0	0.70	0.67
	No	7 0.95 (0.85–1.08)	0	0.81	
OC use	Yes	6 0.92 (0.86–1.00)	0	0.90	0.78
	No	10 0.94 (0.88–1.01)	0	0.64	
Age at menarche	Yes	9 0.95 (0.89–1.01)	0	0.88	0.43
	No	7 0.91 (0.84–0.98)	0	0.65	
Age at menopause	Yes	9 0.93 (0.88–0.98)	0	0.67	0.83
	No	7 0.94 (0.85–1.04)	0	0.83	
Age at first birth	Yes	11 0.94 (0.89–0.99)	0	0.75	0.65
	No	5 0.91 (0.80–1.03)	0	0.78	
Parity	Yes	12 0.92 (0.87–0.97)	0	0.94	0.08
	No	4 1.08 (0.92–1.26)	0	0.95	
Education	Yes	8 0.92 (0.86–0.98)	0	0.59	0.55
	No	8 0.95 (0.88–1.02)	0	0.91	
Alcohol	Yes	12 0.92 (0.88–0.98)	0	0.87	0.39
	No	4 1.00 (0.85–1.17)	0	0.62	
Smoking	Yes	5 0.89 (0.83–0.96)	0	0.91	0.15
	No	11 0.97 (0.90–1.04)	0	0.86	
Body mass index, weight or WHR	Yes	13 0.93 (0.88–0.98)	0	0.83	0.98
	No	3 0.93 (0.73–1.20)	0	0.52	
Physical activity	Yes	9 0.93 (0.87–0.99)	0	0.69	0.83
	No	7 0.94 (0.86–1.03)	0	0.81	
Fruit, vegetables	Yes	2 0.86 (0.78–0.96)	0	0.85	0.13
	No	14 0.95 (0.90–1.01)	0	0.94	
Fat	Yes	5 0.89 (0.82–0.97)	0	0.63	0.22
	No	11 0.96 (0.90–1.02)	0	0.92	
Energy intake	Yes	15 0.93 (0.88–0.98)	0	0.89	0.44
	No	1 1.07 (0.76–1.51)			

n denotes the number of studies.

^a*P* for heterogeneity within each subgroup.

^b*P* for heterogeneity between subgroups with meta-regression analysis. CI, confidence interval; OC, oral contraceptive; RR, relative risk; WHR, waist-to-hip ratio.

with intakes of ≤10 g/day (RR = 0.68, 95% CI 0.43–1.06); however, only 0.7% of the cohort had an intake above 30 g/day [18]. We found no statistical evidence of small-study bias, such

as publication bias, in this meta-analysis and there was also no asymmetry in the funnel plots when inspected visually.

Several potential mechanisms may explain an inverse association between fiber intake and breast cancer risk. Experimental studies found that a modified citrus pectin (a soluble fiber) reduced mammary tumor growth, angiogenesis and metastasis in mice [45] and that a high dietary fiber diet reduced mammary tumor incidence in rat models [46, 47]. One study reported a lower mammary tumor incidence in rats fed equal amounts of soluble and insoluble fiber compared with rats fed only insoluble fiber [48]. Epidemiological studies [49–52] and intervention studies [9, 53] have shown reductions in circulating estrogen and androstenedione levels with a high fiber intake, although not all studies found an association [54, 55] and the results by type of fiber type are inconsistent [49, 52, 53]. Conjugated estrogens in the liver are excreted into the bile and reabsorbed in the intestine. Fiber may bind estrogens in the colon during the enterohepatic circulation and increase the fecal excretion of estrogens. In addition, dietary fiber may reduce intestinal β-glucuronidase activity, which is necessary for hydrolysis of conjugated estrogens before absorption, thus, resulting in less reabsorption of estrogens [48]. Soluble fiber may delay gastric emptying and increase small intestine transit time, thereby slowing glucose absorption, reducing insulin secretion and hyperinsulinemia [56, 57]. High intake of dietary fiber may also reduce the risk of overweight/obesity [58], which is an established risk factor for postmenopausal breast cancer [6]; however, the association was also present in studies that adjusted for body mass index or weight, suggesting an association independent of overweight/obesity.

Our meta-analysis also has several strengths. Because we based our analyses on prospective studies, we have minimized the possibility that our findings may be due to recall and selection bias. The studies included a large number of cases and participants and with a total of ~500 000 to 1 000 000 participants and 15 000–26 000 cases, we had sufficient statistical power to detect moderate associations. There was little evidence of heterogeneity in the analyses and we did not find evidence that the results differed when stratified by numerous study characteristics.

To our knowledge, this is the first meta-analysis to explore a potential nonlinear association of fiber intake with breast cancer risk. Although we did not find evidence of nonlinearity with the statistical tests used, significant inverse associations were observed only among studies with a large range or high level of intake. Studies in populations with a low intake and small range of intake were less able to detect associations than the studies with higher variability and intake. Achieving such a level of fiber intake may be a challenge in many populations, nevertheless, considering the few dietary risk factors that have been established for breast cancer and the relatively low or moderate fiber intake in many populations [17, 18, 24, 26], diets with high intake of plant-based foods rich in fiber could have an impact in the prevention of breast cancer. In addition, such diets may reduce the risk of cardiovascular disease [59], obesity [58], type 2 diabetes [60], colorectal cancer [61] and other chronic diseases [62].

In conclusion, our results suggest that diets rich in fiber are associated with reduced breast cancer risk. Further studies of

specific types of fiber and breast cancer risk stratified by hormone receptor status could clarify the biological mechanism(s) behind this finding.

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Contributors: The systematic literature review team at the Istituto Nazionale Tumori, Milan, conducted the search, data selection and data extraction up to the end of 2005. RV was responsible for developing and managing the database for the Continuous Update Project. TN wrote the protocol for the review and she is the principal investigator of the Continuous Update Project at Imperial College and coordinated it. DSMC and ARV did the updated literature search and data extraction and DSMC, ARV and DA did the study selection. DA did the statistical analyses and wrote the first draft of the original manuscript. DCG was expert statistical advisor and contributed toward the statistical analyses. All authors contributed to the revision of the manuscript.

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disclosure

The authors declare no conflicts of interest.

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