Breast Cancer Res Treat (2011) 126:287–294
DOI 10.1007/s10549-011-1343-3

REVIEW

Dietary glycemic index, glycemic load, and risk of breast cancer: meta-analysis of prospective cohort studies

Jia-Yi Dong · Li-Qiang Qin

Received: 14 December 2010 / Accepted: 2 January 2011 / Published online: 11 January 2011

Abstract Consumption diets of high glycemic index (GI) and glycemic load (GL) may increase the risk of breast cancer. We aimed to conduct a meta-analysis of prospective cohort studies to evaluate the associations between dietary GI and GL and risk of breast cancer. We searched the PubMed database for relevant studies through November 2010, with no restrictions. We included prospective cohort studies that reported relative risk (RR) with 95% confidence intervals (CIs) for the associations of dietary GI and GL with breast cancer risk. Summary RRs were calculated using both fixed- and random-effects models. We identified 10 prospective cohort studies eligible for analysis, involving 15,839 cases and 577,538 participants. The summary RR of breast cancer for the highest GI intake compared with the lowest was 1.08 (95% CI: 1.02–1.14), with no evidence of heterogeneity ($P = 0.72$, $I^2 = 0\%$). For GL, the summary RR was 1.04 (95% CI: 0.95–1.15), and substantial heterogeneity was observed ($P = 0.02$, $I^2 = 55.6\%$). The GI and GL and breast cancer associations did not significantly modified by geographic region, length of follow-up, number of cases, or menopausal status at baseline. Dose–response analysis was not performed due to limited number of eligible studies. There was no evidence of publication bias. In summary, the present meta-analysis of prospective cohort studies suggests that high dietary GI is associated with a significantly increased risk of breast cancer. However, there is no significant association between dietary GL and breast cancer risk.

J.-Y. Dong (✉) · L.-Q. Qin
Department of Nutrition and Food Hygiene, School of Radiation Medicine and Public Health, Soochow University, Suzhou, People's Republic of China
e-mail: dongjy@mail2.sysu.edu.cn

Keywords Glycemic index · Glycemic load · Breast cancer · Cohort studies · Meta-analysis

Introduction

There is growing interest in the role of dietary glycemic index and glycemic load in relation to risk of breast cancer. The glycemic index (GI), introduced by Jenkins et al. [1] in 1981, ranks the carbohydrate content of individual foods according to their postprandial glycemic effects. Consumption of high-GI diets is associated with high blood glucose and insulin levels [2], which are proposed to be important risk factors for breast cancer [3–5]. The glycemic load (GL), which is the product of the GI of a food item and the available carbohydrate content, quantifies both the overall glycemic effects and insulin demand [6]. High dietary GI and GL, therefore, may potentially increase risk for breast cancer.

During the past decade, a number of epidemiologic studies that examined the associations between dietary GI and GL and risk of breast cancer have been published. However, the results were inconsistent, with most studies showing null or weak associations. A previous meta-analysis [7] summarized these individual studies but failed to detect significant associations of GI or GL with risk of breast cancer. The absence of association was likely due to the insufficient statistical power, as only seven cohort studies were included in their analysis. Recently, several cohort studies [8–10] subsequent to that meta-analysis have emerged, and most showed positive, although not significant, associations of dietary GI and GL with breast cancer risk.

With the most up-to-date evidence, we aimed to conduct a meta-analysis of prospective cohort studies to evaluate the associations between dietary GI and GL and risk of breast cancer.

Methods

Search strategy

We attempted to follow the proposed MOOSE guidelines [11] to plan, conduct, and report this meta-analysis. A PubMed database search through November 2010 was conducted to identify relevant studies describing the associations between dietary GI and GL and risk of breast cancer. We used two search themes and combined them by the Boolean operator "AND". The first theme is "glycemic index OR glycemic load"; and the second, "breast cancer OR breast neoplasms". No restrictions were imposed. In addition, we reviewed the reference lists of retrieved articles. We did not contact authors of primary studies for additional information. No attempt was made to identify unpublished studies.

Study selection

We first performed an initial screen of identified abstracts or titles. The second screen was based on full-text review. Studies were considered eligible if they met the following criteria: (1) prospective cohort design; (2) the exposure of interest was dietary GI or GL intake; (3) the outcome of interest was breast cancer; and (4) relative risks (RRs) with corresponding 95% confidence intervals (CIs) for the highest versus lowest categories of GI or GL were reported.

Data collection

We extracted all data using a standardized data-collection form. Information was recorded as follows: last name of the first author, publication year, and location; study period and duration of follow-up; number of cases and participants; range of dietary GI and GL intake; RRs from the most fully adjusted model for the highest versus the lowest category of GI and GL intake and the corresponding 95% CIs; and statistical adjustments for the main confounding factors of interest. Two authors independently conducted the studies selection and data extraction. Any disagreements were resolved by discussion.

Statistical analysis

The RR was used as the common measure of association across studies, and the hazard ratio was directly considered as RR. RRs from individual studies for each category of GI and GL and the corresponding standard errors, which were derived from CIs, were transformed to their natural logarithms to stabilize the variances and to normalize the distributions.

Homogeneity of RRs across studies was tested by Cochran Q statistic (significance level at $P < 0.10$) and the I^2 statistic, which is a quantitative measure of inconsistency across studies [12]. Both the fixed- and random-effects models [13] were used to calculate the summary risk estimates.

We conducted a subgroup analysis stratified by geographic region, duration of follow-up, number of cases, and menopause status at baseline to assess the impacts 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 planned to quantify dose–response relationships of GI and GL with risk of breast cancer. This analysis is based on data for categories of average GI and GL intake, number of cases, person-year of follow-up, and adjusted logarithm of the RR with its standard error [14, 15]. However, nearly half of the included studies did not provide required data (e.g., number of cases or average GI and GL intake in each category). Due to limited number of eligible studies, the dose–response analysis was not performed.

Potential publication bias was assessed by visual inspection of Begg's funnel plot and Egger's regression test at the $P < 0.10$ level of significance [16]. All analyses were performed using STATA version 10.0 (StataCorp, College Station, Texas). P value < 0.05 was considered statistically significant, except where otherwise specified.

Results

Literature search

We initially retrieved 44 unique citations. Of these, 31 citations were excluded after the first screening based on abstracts or titles, mainly because they were reviews, case–control studies, or not relevant to our analysis. Manual search of the reference lists of retrieved articles did not identify additional studies. Therefore, 13 articles were left for full-text review. One study [17] was excluded, because it used a retrospective cohort design. We further excluded two studies [18, 19] in which GI and GL were treated as continuous variables but not category of intake. We therefore included 10 prospective cohort studies [8–10, 20–26] for this meta-analysis. A flow chart showing the study selection is presented in Fig. 1.

Study characteristics

The characteristics of the 10 prospective cohort studies are presented in Table 1. The association between GI and GL

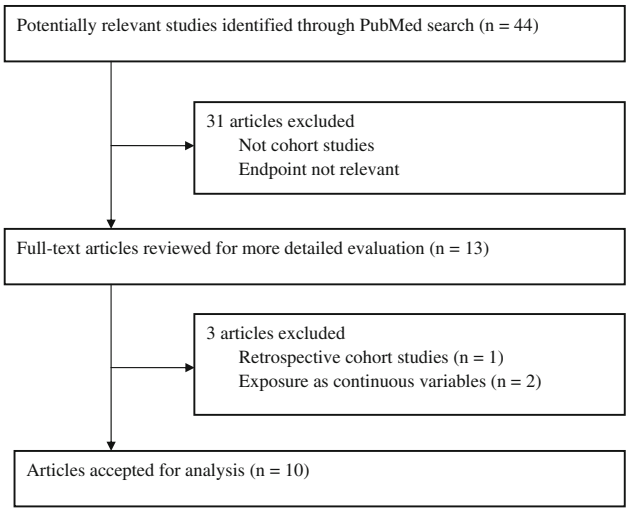

Fig. 1 Flow chart of study selection

and breast cancer was the primary outcome of interest in nine studies, whereas it was a secondary question in one study [10]. The included studies were published between 2003 and 2010. Five studies were conducted in United States, three in Europe, one in Canada, and one in China. The number of cases diagnosed in these studies ranged from 289 to 4,092, with a sum of 15,839. The number of participants ranged from 8,959 to 90,655, with a sum of 577,538. Two studies involved premenopausal women only, two studies involved postmenopausal women only, and the other six studies included overall women, of which five presented results separately by menopausal status. The length of follow-up ranged from 5 to 18 years, with a median of 8.5 years. Ranges of GI and GL intake varied across studies, e.g., average intake of GI in the highest categories across studies ranged from 55 to 96 g/day. Most risk estimates were adjusted for age, body mass index (BMI), family history of breast cancer, age at menarche, age at first birth, parity, oral contraceptives use, hormone replacement therapy use, alcohol use, and intake of total energy. However, smoking and physical activity, two potential confounding factors [27, 28], were controlled in only a few studies.

GI and GL and risk of breast cancer

The adjusted RRs for each study and the summary RRs for the highest versus the lowest categories of GI and GL intake are presented in Fig. 2. Among the 10 included studies, all but one [24] found a positive association between GI and risk of breast cancer, whereas only one [25] reached statistical significance. GL intake was associated with an increased risk of breast cancer in six studies, among which one [25] showed a significant relation. The summary RR of breast cancer for the highest GI intake compared with the lowest was 1.08 (95% CI: 1.02–1.14, fixed-effect model), with no evidence of heterogeneity ($P = 0.72$, $I^2 = 0\%$). For GL, the summary RR was 1.04 (95% CI: 0.95–1.15, random-effects model), and substantial heterogeneity was observed ($P = 0.02$, $I^2 = 55.6\%$).

Subgroup and sensitivity analyses

The results of subgroup analyses according to geographic region, length of follow-up, number of cases, and menopausal status are presented in Table 2. No evidence of heterogeneity was observed within any subgroup for dietary GI and risk of breast cancer, and a significantly increased risk was observed among studies in Europe, with duration of follow-up $\geq$9 years, with number of cases $\geq$1000, and among studies in postmenopausal women. However, no significant association of GL was observed in any subgroup. In addition, the magnitudes of the associations between dietary GI and breast cancer risk across subgroups were similar and close to the combined risk estimate. Overall, the associations between dietary GI and GL and breast cancer did not significantly modified by these variables.

The sensitivity analyses omitting one study at a time and calculating the combined RR for the remaining studies showed the combined risk estimate for GI was not substantially affected by any single study. Of note, the summary RRs for GI were all statistically significant and similar among each other, with a narrow range from 1.07 (95% CI: 1.01–1.14) to 1.09 (95% CI: 1.03–1.15). The substantial heterogeneity in the GL and breast cancer association was most likely attributed to one study [25], as omitting this study resulted in a homogenous, although not significant, result (RR = 1.02, 95% CI: 0.97–1.08, $P_{\text{heterogeneity}} = 0.47$, $I^2 = 0\%$).

Publication bias

The Begg's funnel plot did not show substantial asymmetry (plot not shown). Egger's regression test also indicated no evidence of publication bias ($P = 0.80$ for GI, $P = 0.37$ for GL).

Discussion

The present meta-analysis of 10 prospective cohort studies involving 15,839 cases and 577,538 participants provided evidence that high dietary GI intake was associated with a significantly increased risk for breast cancer. The highest GI intake compared with the lowest was associated with a significant increase of 8% in breast cancer risk. There was no evidence of heterogeneity among studies on GI and breast cancer. In addition, the GI and breast cancer

Table 1 Characteristics of the included studies

Author	Location, period	Age (years), menopausal status	Follow-up (years)	No. of cases/no. of participants	Comparison for GI, GL (g/day)	RR (95% CI) for GI, GL	Adjustments
Cho et al. [20]	United States, 1991–1999	26–46, Premenopause	8	714/90,655	82.0 vs. 70.0, 211 vs. 138	1.05 (0.83–1.33), 1.06 (0.78–1.45)	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, and intake of alcohol, energy, and animal fat
Jonas et al. [21]	United States, 1992–1997	40–87, Postmenopause	5	1,442/63,307	78.7 vs. 70.4, 127 vs. 101	1.03 (0.87–1.22), 0.90 (0.76–1.07)	Age, age at menarche, age at menopause, number of live births, age at first birth, oral contraceptive and HRT use, family history of breast cancer, personal history of breast cysts, education, BMI, adult weight gain, location of body weight gain, height, physical activity, energy, diethylstilbestrol use, alcohol use, race, and smoking status
Higginbotham et al. [22]	United States, 1993–2000	≥45, Overall	6.8	946/38,446	55.0 vs. 50.0, 143 vs. 92	1.03 (0.83–1.27), 1.01 (0.76–1.35)	Age, BMI, alcohol, smoking, age at menarche, age at first pregnancy, number of pregnancies, oral contraceptive and HRT use, family history of breast cancer, physical activity, and intake of total energy, energy-adjusted total fat, fiber, and folate
Holmes et al. [23]	United States, 1980–1998	34–59, Overall	18	4,092/88,678	81.0 vs. 69.0, 186 vs. 166	1.08 (0.97–1.19), 0.99 (0.89–1.10)	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 years, HRT use, and menopausal status
Silvera et al. [24]	Canada, 1980–2000	40–59, Overall	16.6	2,518/49,111	>96 vs. <60, >175 vs. <115	0.88 (0.63–1.22), 0.95 (0.79–1.14)	Age, BMI, menopausal status, alcohol, use of HRT and oral contraceptives, parity, age at menarche, age at first birth, family breast cancer, history of benign breast disease, and intake of energy and total fiber
Sieri et al. [25]	Italy, 1987–2001	34–70, Overall	11.5	289/8,959	59.2 vs. 51.9, 151.5 vs. 96.6	1.57 (1.04–2.36), 2.53 (1.54–4.16)	Age, height, weight, age at menarche, smoking status, education, oral contraceptive use, parity, and intake of energy, alcohol, fiber, and saturated fat.
Lajous et al. [26]	France, 1993–2002	42–72, Postmenopause	9	1,812/62,739	65.6 vs. 44.3, 165 vs. 84	1.14 (0.99–1.32), 1.11 (0.96–1.29)	Age, region of residence, education, family breast cancer, history of benign breast disease, age at menarche, parity, breastfeeding, oral contraceptives and HRT use, age at menopause, regular mammographic evaluation, height, BMI, vitamin supplement use, total energy intake, folate intake, fiber intake, alcohol intake, and physical activity
Larsson et al. [8]	Sweden, 1987–2007	40–74, Overall	17.4	2,952/61,433	>83.4 vs. <75.8, >200 vs. <164	1.08 (0.96–1.21), 1.13 (1.00–1.29)	Age, education, BMI, height, parity, age at first birth, age at menarche, age at menopause, oral contraceptives and HRT use, family history of breast cancer, history of benign breast disease, and intakes of alcohol, coffee, energy-adjusted cereal fiber, and total energy
Wen et al. [9]	China, 1997–2005	40–70, Overall	7.35	616/74,942	76.8 vs. 63.9, 239.4 vs. 163.8	1.03 (0.79–1.34), 1.07 (0.82–1.39)	Age, total energy intake, education, BMI, age at first birth, family history of breast cancer, personal history of benign breast diseases, and physical activity

Table 1 continued

Author	Location, period	Age (years), menopausal status	Follow-up (years)	No. of cases/no. of participants	Comparison for GI, GL (g/day)	RR (95% CI) for GI, GL	Adjustments
Linos et al. [10]	United States, 1998–2005	34–53, Premenopause	7.8	455/39,268	58.4 vs. 51.6, 203 vs. 142	1.18 (0.88–1.58), 0.89 (0.66–1.20)	Age, total energy intake, family history of breast cancer, history of benign breast disease, menopausal status, age at menarche, parity, age at first birth, weight gain since age 18 y, BMI, current oral contraceptive, and adult alcohol use

BMI body mass index, *CI* confidence interval, *GI* glycemic index, *GL* glycemic load, *HRT* hormone replacement therapy, *RR* relative risk

association did not significantly affected by study characteristics. However, there was no significant association between dietary GL and breast cancer risk.

In contrast to the previous meta-analysis [7], we did not observe heterogeneity among studies on GI and breast cancer. This is possibly because our analysis included prospective cohort studies only and had an enlarged number of studies. Unlike the previous one [7], we did not perform main analysis separately by menopausal status. Although menopausal status may have potential impacts on the relations between GI and GL and breast cancer, our subgroup analysis showed there were no significant differences in the associations according to menopausal status. For GL, the substantial heterogeneity was most likely due to one exception [25], which found GL was strongly and significantly associated with an increased risk of breast cancer (RR = 2.53, 95% CI: 1.54–4.16). However, chance may explain their finding as the numbers of cases ($n = 289$) and participants ($n = 8{,}959$) were much smaller than other studies.

In our subgroup analysis, the GI and GL and breast cancer associations did not significantly modified by geographic region, length of follow-up, number of cases, or menopausal status at baseline. In addition to these variables we examined, other factors are worth considering, including BMI, waist circumference, and estrogen receptor status. BMI, a predictor of insulin resistance, may affect the relations between GI and GL and breast cancer risk. The previous meta-analysis [7] has combined studies that reported results by BMI categories and found the associations did not significantly differ by BMI. One subsequent Swedish study [8] also did not find significant differences according to BMI. On the other hand, waist circumference is suggested to be a better predictor of insulin resistance than BMI [29]. The French cohort study has found strong and significant associations between GI and GL and breast cancer among women with the highest category of waist circumference (RR = 1.35, 95% CI: 1.04–1.75 for GI; RR = 1.37, 95% CI: 1.05–1.77 for GL) [26]. However, none of other cohort studies examined the effects of waist circumference on the GI and GL and breast cancer relations. Similarly, there were few studies [8, 18, 19, 26] that assessed the associations stratified by estrogen receptor status. Moreover, the results were rather conflicting. Two studies [18, 26] found a positive relation of GI or GL with estrogen receptor-negative breast cancer, whereas another study [8] observed significant dose–response relationship between GI and GL and risk of estrogen receptor-positive/progesterone receptor-negative breast cancer. Given the limited available data, no clear conclusion can be drawn, and further studies regarding these factors are warranted.

The positive relation between GI and breast cancer risk potentially involves insulin. High-GI meals initially

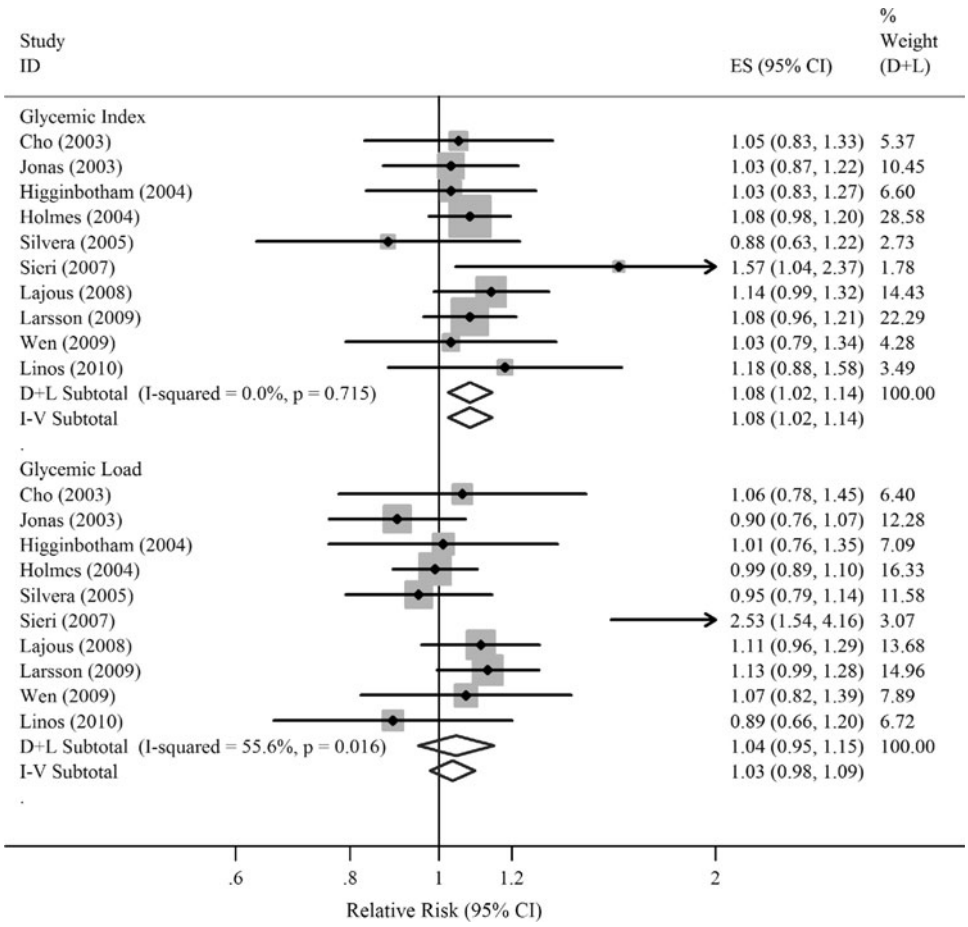

Fig. 2 Meta-analysis of associations between glycemic index, glycemic load, and breast cancer risk (D + L: random-effects model, I–V: fixed-effects model)

Table 2 Subgroup analyses of glycemic index, glycemic load, and breast cancer risk

Group	Glycemic index					Glycemic load				
	No. of studies	Relative risk (95% CI)	$P_{heterogeneity}$	I^2, %	$P_{interaction}$	No. of studies	Relative risk (95% CI)	$P_{heterogeneity}$	I^2, %	$P_{interaction}$
Total	10	1.08 (1.02–1.14)	0.72	0		10	1.04 (0.95–1.15)	0.02	55.6	
Geographic region					0.22					0.12
United States	5	1.07 (0.99–1.15)	0.94	0		5	0.97 (0.89–1.05)	0.81	0	
Europe	3	1.12 (1.03–1.23)	0.22	34.4		3	1.29 (0.99–1.66)	0.007	79.9	
Length of follow-up (years)					0.52					0.36
<9	5	1.05 (0.95–1.16)	0.95	0		5	0.96 (0.86–1.07)	0.74	0	
≥9	5	1.09 (1.03–1.17)	0.28	21.2		5	1.11 (0.96–1.28)	0.03	75.1	
No. of cases					0.80					0.59
<1000	5	1.10 (0.97–1.23)	0.42	0		5	1.15 (0.89–1.48)	0.01	69.5	
≥1000	5	1.08 (1.01–1.15)	0.68	0		5	1.02 (0.96–1.09)	0.16	40	
Menopausal status					0.89					0.88
Premenopause	7	1.09 (0.97–1.23)	0.29	18.9		7	1.13 (0.90–1.42)	0.005	67.3	
Postmenopause	7	1.11 (1.03–1.19)	0.16	35.8		7	1.02 (0.95–1.10)	0.4	3.4	

produce a period of high blood glucose levels, consequently resulting in elevated levels of insulin [2]. It is known that insulin promotes growth and progression of breast cancer cells. Two recent prospective cohort studies have documented that insulin is an important, probably independent, risk factor for breast cancer [4, 5].

Furthermore, chronic elevated insulin levels could lead to insulin resistance and hence type 2 diabetes, which is significantly associated with an increased risk of breast cancer [3].

Our study has several strengths. First, our meta-analysis involved a large number of cases and participants and, therefore, enhanced the statistical power to detect a significant association. Second, all the included studies used a prospective cohort design. Thus, the likelihood of recall and selective biases that are always of concern in case–control studies were greatly reduced. Third, the absence of heterogeneity among studies on GI and breast cancer and consistent results from sensitivity analyses indicated our findings were reliable and robust. Finally, publication bias was unlikely to account for our findings, as suggested by Begg's funnel plot and egger's regression test.

Limitations in the present meta-analysis should be acknowledged. Although there was no evidence of heterogeneity among studies on GI and breast cancer, study features were inconsistent. For instance, the ranges of GI intake between the highest and lowest categories differed across studies, which probably resulted from the differences in dietary assessment tools, i.e., the scales and contents of the food frequency questionnaires. In fact, these food frequency questionnaires were not primarily designed to assess GI and GL. Moreover, residual confounders were of concern. Many potential risk factors for breast cancer were adjusted for in most studies, whereas smoking and physical activity, two important risk factors [27, 28], were controlled in only half of the included studies. Although two cohort studies [22, 24] showed that physical activity did not significantly modify the relations between GI and GL and breast cancer, we still can not rule out the possibility that these uncontrolled confounders might bias the associations. Nevertheless, more complete adjustments for potential confounders help achieve accurate results. In addition, dietary assessment is inevitably subject to measurement errors. Few studies [8, 9, 20] measured dietary intakes more than once, and random misclassifications, therefore, may attenuate or mask the true relations. Finally, given the limited number of eligible studies, we were not able to perform dose–response analysis, which prevented us providing further evidence in support of the observed GI and breast cancer association.

Dietary GI and GL are of clinical and public health importance. High-GI food consumption has been hypothesized to increase risks for obesity, type 2 diabetes, and heart disease [2]. Recent systematic reviews and meta-analyses [30, 31] have provided evidence that diets with a high GI or GL, or both, are associated with greater risks for many chronic diseases. Our meta-analysis with most up-to-date evidence suggests that high dietary GI significantly increases the risk of breast cancer. Reducing intake of high-GI foods, such as refined carbohydrates, in the general populations may offer benefits in preventing breast cancer, which is the most common cancer in women.

In summary, the present meta-analysis of prospective cohort studies suggests that high dietary GI is associated with a significantly increased risk of breast cancer. However, there is no significant association between dietary GL and breast cancer risk.

Acknowledgments Jia-Yi Dong and Li-Qiang Qin were responsible for study design, data acquisition, statistical analysis, and results interpretation. Jia-Yi Dong wrote the article. Li-Qiang Qin provided material support and supervised the research. All authors critically revised the manuscript for important intellectual content and approved the final manuscript. There was no funding for this study. None of the authors had a conflict of interest.

References

1. Jenkins DJ, Wolever TM, Taylor RH et al (1981) Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr 34(3):362–366
2. Ludwig DS (2002) The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA 287(18):2414–2423
3. Larsson SC, Mantzoros CS, Wolk A (2007) Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer 121(4):856–862
4. Gunter MJ, Hoover DR, Yu H et al (2009) Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. J Natl Cancer Inst 101(1):48–60
5. Kabat GC, Kim M, Caan BJ et al (2009) Repeated measures of serum glucose and insulin in relation to postmenopausal breast cancer. Int J Cancer 125(11):2704–2710
6. Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC (1997) Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. JAMA 277(6):472–477
7. Mulholland HG, Murray LJ, Cardwell CR, Cantwell MM (2008) Dietary glycaemic index, glycaemic load and breast cancer risk: a systematic review and meta-analysis. Br J Cancer 99(7):1170–1175
8. Larsson SC, Bergkvist L, Wolk A (2009) Glycemic load, glycemic index and breast cancer risk in a prospective cohort of Swedish women. Int J Cancer 125(1):153–157
9. Wen W, Shu XO, Li H, Yang G, Ji BT, Cai H, Gao YT, Zheng W (2009) Dietary carbohydrates, fiber, and breast cancer risk in Chinese women. Am J Clin Nutr 89(1):283–289
10. Linos E, Willett WC, Cho E, Frazier L (2010) Adolescent diet in relation to breast cancer risk among premenopausal women. Cancer Epidemiol Biomarkers Prev 19(3):689–696
11. Stroup DF, Berlin JA, Morton SC et al (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283(15):2008–2012
12. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560
13. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7(3):177–188
14. Greenland S, Longnecker MP (1992) Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 135(11):1301–1309

15. Berlin JA, Longnecker MP, Greenland S (1993) Meta-analysis of epidemiologic dose–response data. Epidemiology 4(3):218–228
16. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109):629–634
17. Frazier AL, Li L, Cho E, Willett WC, Colditz GA (2004) Adolescent diet and risk of breast cancer. Cancer Causes Control 15(1):73–82
18. Nielsen TG, Olsen A, Christensen J, Overvad K, Tjonneland A (2005) Dietary carbohydrate intake is not associated with the breast cancer incidence rate ratio in postmenopausal Danish women. J Nutr 135(1):124–128
19. Giles GG, Simpson JA, English DR, Hodge AM, Gertig DM, Macinnis RJ, Hopper JL (2006) Dietary carbohydrate, fibre, glycaemic index, glycaemic load and the risk of postmenopausal breast cancer. Int J Cancer 118(7):1843–1847
20. Cho E, Spiegelman D, Hunter DJ, Chen WY, Colditz GA, Willett WC (2003) Premenopausal dietary carbohydrate, glycemic index, glycemic load, and fiber in relation to risk of breast cancer. Cancer Epidemiol Biomarkers Prev 12(11 Pt 1):1153–1158
21. Jonas CR, McCullough ML, Teras LR, Walker-Thurmond KA, Thun MJ, Calle EE (2003) Dietary glycemic index, glycemic load, and risk of incident breast cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev 12(6):573–577
22. Higginbotham S, Zhang ZF, Lee IM, Cook NR, Buring JE, Liu S (2004) Dietary glycemic load and breast cancer risk in the Women's Health Study. Cancer Epidemiol Biomarkers Prev 13(1):65–70
23. Holmes MD, Liu S, Hankinson SE, Colditz GA, Hunter DJ, Willett WC (2004) Dietary carbohydrates, fiber, and breast cancer risk. Am J Epidemiol 159(8):732–739
24. Silvera SA, Jain M, Howe GR, Miller AB, Rohan TE (2005) Dietary carbohydrates and breast cancer risk: a prospective study of the roles of overall glycemic index and glycemic load. Int J Cancer 114(4):653–658
25. Sieri S, Pala V, Brighenti F et al (2007) Dietary glycemic index, glycemic load, and the risk of breast cancer in an Italian prospective cohort study. Am J Clin Nutr 86(4):1160–1166
26. Lajous M, Boutron-Ruault MC, Fabre A, Clavel-Chapelon F, Romieu I (2008) Carbohydrate intake, glycemic index, glycemic load, and risk of postmenopausal breast cancer in a prospective study of French women. Am J Clin Nutr 87(5):1384–1391
27. Monninkhof EM, Elias SG, Vlems FA, van der Tweel I, Schuit AJ, Voskuil DW, van Leeuwen FE (2007) Physical activity and breast cancer: a systematic review. Epidemiology 18(1):137–157
28. Ambrosone CB, Kropp S, Yang J, Yao S, Shields PG, Chang-Claude J (2008) Cigarette smoking, *N*-acetyltransferase 2 genotypes, and breast cancer risk: pooled analysis and meta-analysis. Cancer Epidemiol Biomarkers Prev 17(1):15–26
29. Racette SB, Evans EM, Weiss EP, Hagberg JM, Holloszy JO (2006) Abdominal adiposity is a stronger predictor of insulin resistance than fitness among 50–95 year olds. Diabetes Care 29(3):673–678
30. Barclay AW, Petocz P, McMillan-Price J, Flood VM, Prvan T, Mitchell P, Brand-Miller JC (2008) Glycemic index, glycemic load, and chronic disease risk—a meta-analysis of observational studies. Am J Clin Nutr 87(3):627–637
31. Gnagnarella P, Gandini S, La Vecchia C, Maisonneuve P (2008) Glycemic index, glycemic load, and cancer risk: a meta-analysis. Am J Clin Nutr 87(6):1793–1801