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EPIDEMIOLOGY

Carotenoids and breast cancer risk: a meta-analysis and meta-regression

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Abstract The purpose of this article is to comprehensively summarize the associations between carotenoids and breast cancer and quantitatively estimate their dose–response relationships. We searched PubMed, Embase, and Cochrane databases (from January 1982 to 1 May 2011) and the references of the relevant articles in English with sufficient information to estimate relative risk or odds ratio and the 95% confidence intervals, and comparable categories of carotenoids. Two reviewers independently extracted data using a standardized form; with any discrepancy adjudicated by the third reviewer. 33 studies met the inclusion criteria. Comparing the highest with the lowest intake: dietary α-carotene intake significantly reduced the breast cancer risk by 9.0% (pooled RR = 0.91; 95% CI: 0.85–0.98; $P = 0.01$), dietary β-carotene intake reduced the risk by 6.0% (pooled RR = 0.94; 95% CI: 0.88–1.00; $P = 0.05$); total β-carotene intake reduced the risk by 5.0% (pooled RR = 0.95; 95% CI: 0.90–1.01; $P = 0.08$) when data from cohort studies were pooled. Significant dose–response relationships were observed in both the higher intake of dietary and total β-carotene with reduced breast cancer risk when data from cohort studies ($P_{trend} < 0.01$, $P_{trend} = 0.03$) and case–control studies ($P_{trend} < 0.01$, $P_{trend} < 0.01$) were pooled, respectively. Dietary α-carotene intake could reduce the breast cancer risk. The relationships between dietary and total β-carotene intake and breast cancer need to be confirmed. No significant association between dietary intake of β-cryptoxanthin, lutein/+zeaxanthin, and lycopene and breast cancer was observed.

Keywords Carotenoids · Breast cancer · Meta-analysis · Meta-regression

Introduction

Breast cancer is by far the most frequent cancer among women with an estimated 1384,000 new cases and 458,000 deaths worldly in 2008 [1]. Its etiology is multifactorial, and is not completely known. Since the changes in the incidence of breast cancer among migrant populations were reported [2, 3], environmental factors, particularly dietary factors, have been postulated to play important roles in the etiology of breast cancer [3–5]. Carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein/+zeaxanthin, and lycopene) are hypothesized to reduce the risk of breast cancer due to their capacity for scavenge DNA damaging free radicals, inhibit cell proliferation, induce apoptosis, and suppress angiogenesis [6–8]. A number of case–control and prospective cohort studies have investigated the relationships between the carotenoids and breast cancer. However, the results remain inconsistent. Two meta-analyses have been reported; the first on the association between dietary β-carotene and breast cancer in 2000 [9], pooling the results of 7

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case–control and 4 cohort studies; the second [10] on the association between β-carotene supplements and breast cancer in 2010, which pooled the results of 4 RCTs. No meta-analysis about the associations between α-carotene, β-cryptoxanthin, lutein/+zeaxanthin, and lycopene and breast cancer has been reported. Since the first two meta-analyses were published, 20 inconsistent observational studies with large samples have been published [11–30]. Meanwhile, among the carotenoids, which one play a greater role in reducing breast cancer risk remains unclear. Therefore, we performed a meta-analysis and meta-regression to comprehensively and comparatively assess the associations between carotenoids and breast cancer.

Materials and methods

Primary search strategy

We conducted a literature search using PubMed, Embase, and the Cochrane library from January 1982 to 1 May 2011 with the following subject terms: 'carotenoids', 'α-carotene', 'β-carotene', 'β-cryptoxanthin', 'lutein/+zeaxanthin', 'lycopene', and 'breast, mammary cancer, and/or carcinoma and/or neoplasm'. Papers were restricted to human studies published in English. Additional articles were obtained from the reference lists of the selected articles, reviews and from the PubMed option "Related articles".

Criteria for inclusion and exclusion

Observational studies about the association between carotenoids and breast cancer, regardless of sample size, were only included if they met the following criteria: (1) Sufficient information was provided to estimate the relative risk (RR) or odds ratio (OR) and 95% confidence intervals. (2) The reported categories for consumption of these carotenoids had to be comparable. (3) The studies were unrelated. (4) For articles with same population resources or overlapping datasets, the largest or most recent one was included.

Data extraction

Two reviewers (F.L and B.N) independently extracted data using a standardized data extraction form. Any discrepancy was discussed and adjudicated by a third reviewer (W.C) until a consensus was achieved. Information extracted from each article included the following: first author, year of publication, country, types of study design, number of cases and controls, odds ratio (OR) or relative risk (RR), and corresponding 95% confidence intervals for "non-reference vs. reference" intake including "the highest vs. the lowest", and adjustment factors.

We considered β-carotene intake as combined intake in the following two situations: (1) the author described that the β-carotene intake was from food and supplements together without detailed information of β-carotene intake from food and supplements separately; (2) the authors presented the results of β-carotene intake from food and supplements both combined and separately. In conducting meta-analysis, the combined intake and dietary intake of β-carotene were pooled together as total intake. Because less supplements of α-carotene, β-cryptoxanthin, lutein/+zeaxanthin, and lycopene were used in the studies reviewed, we considered them as dietary intake.

The distributions of intake levels of these carotenoids were partitioned into 2–5 categories in the articles reviewed. All the categories with different units (e.g., mg/day, IU/day, g/day) were conversed into μg/day. The midpoint of every category was used as the intake level; for the highest category, the intake level was defined as its 1.2 times [31].

For α-carotene, the highest intake level was approximately "2000 μg/day", the lowest intake level was about "300 μg/day"; for β-carotene, they were about "7000 μg/day" and "1500 μg/day"; for β-cryptoxanthin, they were about "200 μg/day" and "20 μg/day"; for lutein/+zeaxanthin, they were about "5000 μg/day" and "1000 μg/day"; for lycopene, they were about "10,000 μg/day" and "2000 μg/day".

In order to eliminate the variance of categories, the following dosages were used to conduct meta-regression: 500 μg/day, 1000 μg/day, and 1500 μg/day for α-carotene; 2000 μg/day, 3000 μg/day, and 5000 μg/day for β-carotene; 50 μg/day, 100 μg/day and 150 μg/day for β-cryptoxanthin; 2000 μg/day, 3000 μg/day and 4000 μg/day for lutein/+zeaxanthin and lycopene.

Most of estimated associations between breast cancer and these carotenoids were adjusted for some confounders or their combinations. If both the crude OR/RR (95% CI) and multivariate adjusted OR/RR (95% CI) were provided, the one reflecting the greatest adjustment was extracted, as suggested by Chene et al. [32]. If only crude OR/RR (95% CI) or number of cases and controls was provided, the crude OR/RR (95% CI) or number of cases and controls was extracted to pool the risk estimates. For studies that displayed both crude OR/RR (95% CI) and multivariate adjusted OR/RR (95% CI), the data was extracted separately and compared, as suggested by Trock et al. [33]. The ratio of the pooled odds ratios of adjusted ORs and crude ORs were considered as a confounding odds ratio (ORc). If $ORc > 1$, it indicated that ORs adjusted for confounding factors exhibited larger odds ratios than that not adjusted. Conversely, if $ORc < 1$, it indicated that ORs adjusted for confounding factors exhibited smaller odds ratios than that not adjusted [33].

Statistical analysis

We pooled study-specific ORs or RRs and 95% CI for comparing the highest with the lowest intake to evaluate the associations between carotenoids and breast cancer. I^2 was adopted to assess heterogeneity among studies [34]. When heterogeneity was not an issue ($I^2 < 50\%$), fixed effect model with Mantel-Haenszel method was used to calculate the pooled OR/RR. Otherwise, a random effect model with inverse variance method was used [35]. We conducted sensitivity analyses to evaluate whether the removal of one study at a time would influence the results and whether the category levels would influence the results. The significant α level of 0.05 was used.

We conducted meta-regression to estimate dose–response relationships across studies, and conducted spearman correlation to analyze the significance of dose–response relationships. The individual LnOR/RR in a single study related to an exposure was modeled in the following way [31]:

$$\mathrm{LnRR}_j = bxj$$

where xj, $j = 1, \ldots, j-1$, was the value of exposure in the jth non-reference exposure category, and b was estimated by the inverse variance-weighted least squares as follows:

$$\hat{b} = \frac{\sum w_j x_j y_j}{\sum w_j x_j^2}$$

where $w_j = \mathrm{v}^{-1}, y_j = \mathrm{lnRR_j}$, and x was the value of exposure. When the $j-1$ values of yj was independent, the standard error of b was:

$$\mathrm{SE}(\hat{b}) = \left(\sum w_j x_j^2\right)^{-1/2}$$

The variance of the LnRR was calculated by the following way:

$$v = (\ln u\mathrm{RR}_j - \ln l\mathrm{RR}_j)/(2 \times 1.96)^2$$

The value of b in a single study and its standard error was transformed into OR/RR and 95% CI, and then pooled RR/ORs and 95% CI were calculated.

Publication bias was investigated with funnel plots. Furthermore, linear regression approach [36] and rank correlation method [37] were adopted. Meta-analysis was conducted with comprehensive meta-analysis (Version 2 Biostat, Inc., USA). Meta-regression was performed by SAS 9.1 (SAS Institute, Cary, NC, USA).

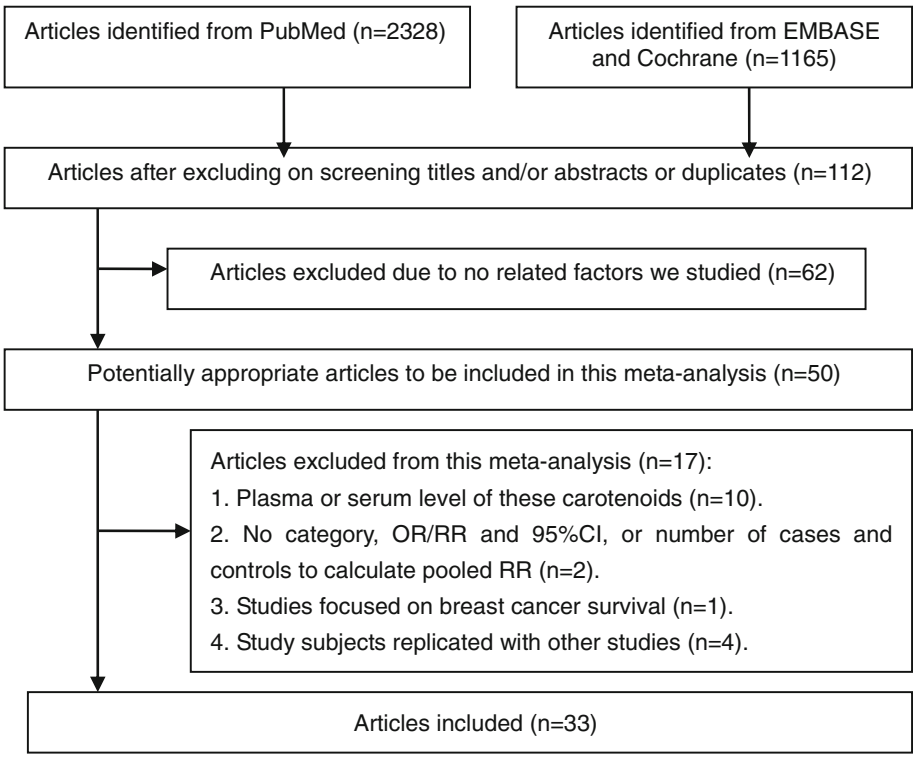

Fig. 1 Flow chart of study identifying and including trials

Results

Characteristics of included studies

Figure 1 summarizes the process of identifying eligible articles. After screening by two reviewers independently according to the inclusion criteria, 33 studies entered this meta-analysis. As shown in Table I in Supplementary material, there were 24 case–control studies including 13 hospital-based case–control studies [12, 13, 15–17, 23, 28, 38–43] and 11 population-based case–control studies [18, 19, 22, 24, 26, 27, 44–48], 1 nested case–control study [29], 2 case–cohort studies [21, 49], and 6 cohort studies [11, 14, 20, 25, 30, 50].

Associations between carotenoids and breast cancer

α-Carotene

There were 5 cohort studies and 9 case–control studies on the relationship between α-carotene and breast cancer. However, in 2 of these studies the OR/RR was analyzed in pre- and post-menopausal status, respectively [14, 22], so we regarded them as four independent comparisons. As shown in Table II in Supplementary material and Figs. 2a and 3a, 6 cohort comparisons and 10 case–control comparisons entered the meta-analysis. Comparing the highest with the lowest intake, the dietary intake of α-carotene significantly ($P = 0.01$) reduced the breast cancer risk by 9.0% (pooled RR = 0.91; 95% CI: 0.85–0.98; $I^2 = 0.00\%$) when data from cohort studies were pooled. In further subgroup analyses, the significant results only remained in studies after 2000 (pooled RR = 0.90; 95% CI: 0.82–0.98) and studies with follow-up time ≤8.0 years (pooled RR = 0.88; 95% CI: 0.78–0.99).

When data from case–control studies were pooled, the dietary intake of α-carotene significantly ($P = 0.02$) reduced the breast cancer risk by 18.0% (pooled OR = 0.82; 95% CI: 0.70–0.97; $I^2 = 66.32\%$). The significant results only remained in hospital-based case–control studies (pooled OR = 0.54; 95% CI: 0.42–0.70; $I^2 = 43.15\%$), and in pre- and post-menopausal women (pooled OR = 0.78; 95% CI: 0.62–0.99; $I^2 = 76.37\%$) in further subgroup analyses based on the types of control, menopausal status, year of publication, and countries.

As to types of control, the heterogeneity was reduced in both subgroups. The pooled OR of 3 hospital-based case–control studies was significantly different from that of 7 population-based controls (Pooled OR = 0.92, 95% CI: 0.85–1.00, with I^2 of 31.55).

β-Carotene

There were 8 cohort studies and 23 case–control studies on the relationship between β-carotene and breast cancer. In 3 of these studies, the RR/OR was analyzed in pre- and post-menopausal status, respectively [14, 22, 25], in another study the OR was analyzed from vegetable and from non-vegetable sources, respectively [47]. As shown in Table II in Supplementary material and Figs. 2b, c, d and 3b, c, 10 cohort comparisons and 25 case–control comparisons entered the meta-analysis. Comparing the highest with the lowest intake, the dietary intake of β-carotene reduced the breast cancer risk by 6.0% (pooled RR = 0.94; 95% CI: 0.88–1.00; $I^2 = 12.15\%$; $P = 0.05$), and the total intake of β-carotene reduced the breast cancer risk by 5.0% (pooled RR = 0.95; 95% CI: 0.90–1.01; $I^2 = 0.00\%$; $P = 0.08$) when data from cohort studies were pooled. In further subgroup analyses based on menopausal status, year of publication, country, and time of follow-up, significant results only remained in post-menopausal women and studies with follow-up time ≤8.0 years for dietary β-carotene (pooled RR = 0.89 (95% CI: 0.81–0.97) and 0.87 (95% CI: 0.78–0.98), respectively), no significant result was observed for total β-carotene.

When data from case–control studies were pooled, the dietary intake of β-carotene significantly ($P < 0.01$) reduced the breast cancer risk by 25.0% (pooled OR = 0.75; 95% CI: 0.67–0.85; $I^2 = 69.00\%$), and the total intake of β-carotene significantly ($P < 0.01$) reduced the breast cancer risk by 24.0% (pooled OR = 0.76; 95% CI: 0.67–0.85; $I^2 = 67.67\%$). The associations between dietary and total intake of β-carotene and breast cancer risk were all significant in further subgroup analyses.

As to the types of control, the heterogeneity for the association between dietary β-carotene and breast cancer was not reduced in 12 hospital-based case–control studies ($I^2 = 69.43\%$), but it decreased in 12 population-based case–control studies ($I^2 = 43.31\%$). The pooled ORs of the hospital-based case–control studies was 0.63 (95% CI: 0.53–0.74), significantly lower than that of population-based controls (pooled RR = 0.90; 95% CI: 0.84–0.96) ($P < 0.01$).

For the association between total β-carotene and breast cancer, the heterogeneity was not reduced in 13 hospital-based case–control studies ($I^2 = 67.07$), but it decreased in 12 population-based case–control studies ($I^2 = 43.17$). The pooled OR of hospital-based case–control studies was 0.64 (95% CI: 0.54-0.75), significantly lower than that of population- based controls (pooled OR = 0.90; 95% CI: 0.84-0.96) ($P < 0.01$).

The combined intake of β-carotene had no statistically significant association with breast cancer (pooled RR = 0.94; 95% CI: 0.87–1.03) when data from 4 cohort

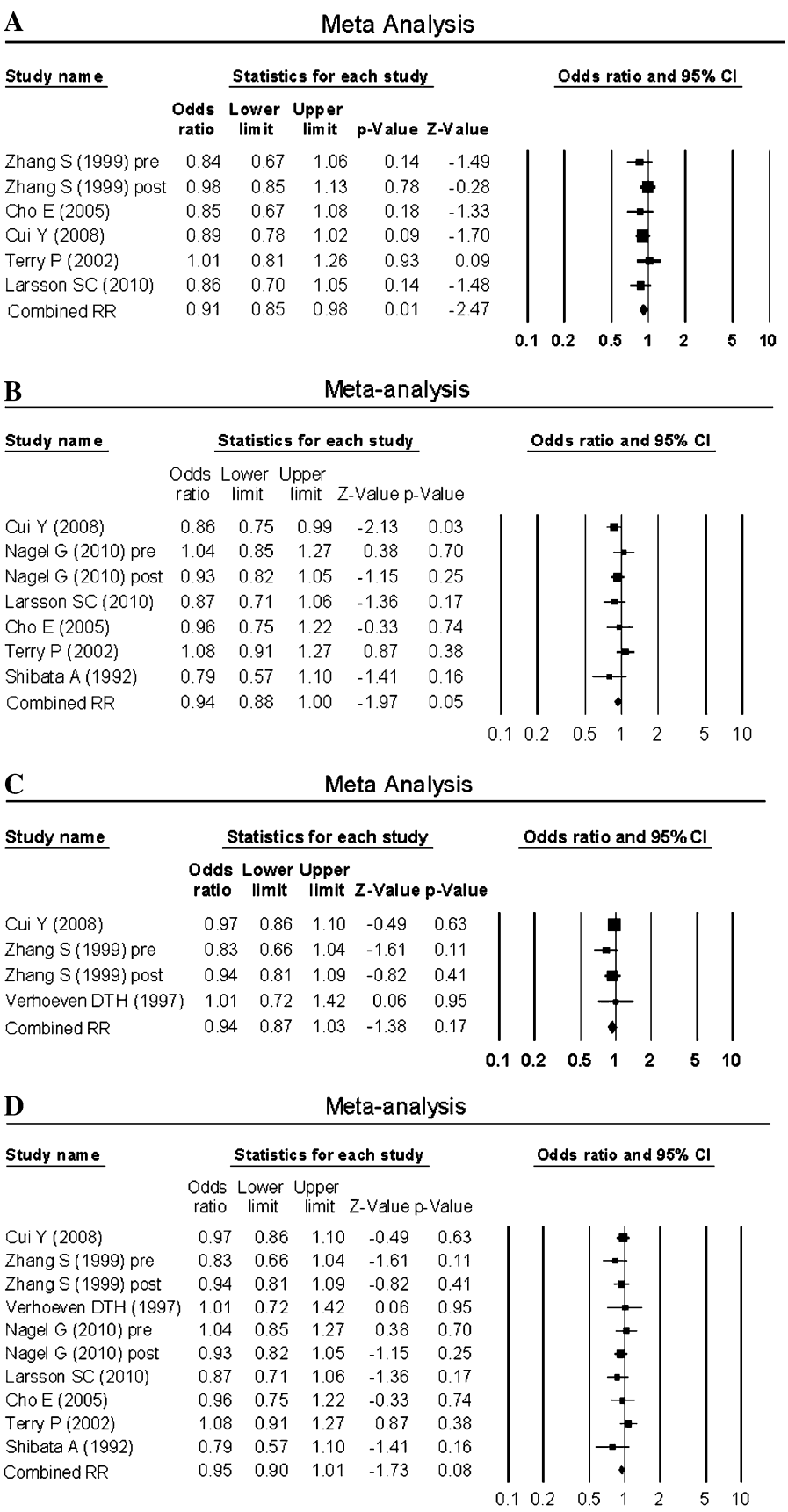

Fig. 2 The forest plots for the associations between dietary α-carotene (**a**), dietary β-carotene (**b**), combined intake of β-carotene (**c**), total β-carotene (**d**) and the breast cancer pooling on cohort studies

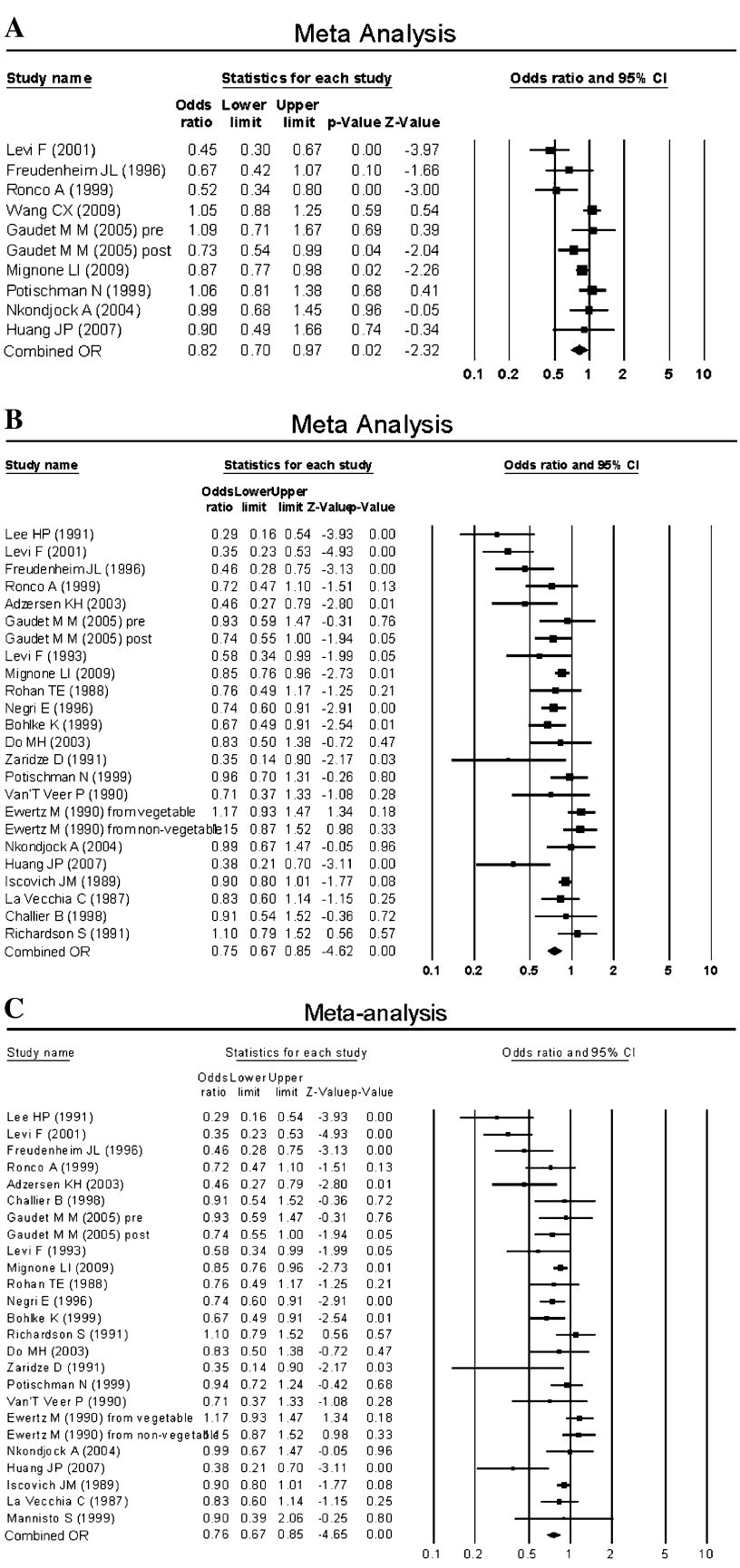

Fig. 3 The forest plots for the associations between dietary α-carotene (**a**), dietary β-carotene (**b**), total β-carotene (**c**) and the breast cancer pooling on case–control studies

comparisons were pooled. Only 2 population-based case–control studies focused on the combined intake of β-carotene and breast cancer risk (OR = 1.04; 95% CI: 0.85–1.35).

β-Cryptoxanthin, lutein/+zeaxanthin, and lycopene

There were 4 cohort studies and 10 case–control studies on the relationship between lutein/+zeaxanthin and breast cancer. However, in 2 of them the RR/OR was analyzed in pre- and post-menopausal status, respectively [14, 22], and in another study the OR between lutein and zeaxanthin and breast cancer was analyzed, respectively [27]. At last, 6 cohort comparisons and 11 case–control comparisons entered this meta-analysis (Table II in Supplementary material; Appendix Figs. 6b, 7b). Comparing the highest with the lowest intake, dietary intake of lutein/+zeaxanthin reduced the breast cancer risk by 6.0% (pooled RR = 0.94; 95% CI: 0.87–1.02; $I^2 = 0.00\%$; $P = 0.13$) when data from cohort studies were pooled. Additionally, no significant association was observed in further subgroup analyses.

When data from case–control studies were pooled, dietary intake of lutein/+zeaxanthin significantly ($P = 0.01$) reduced the breast cancer risk by 21.0% (pooled OR = 0.79; 95% CI: 0.66-0.94; $I^2 = 70.37\%$). The significant results only remained in hospital-based case–control studies (pooled OR = 0.54; 95% CI: 0.35–0.84; $I^2 = 61.66\%$), and in studies published before 2000 (pooled OR = 0.69; 95% CI: 0.55-0.88; $I^2 = 47.44\%$) in further subgroup analyses based on the types of control, menopausal status, year of publication, and countries.

As to the types of control, the heterogeneity decreased in both subgroups of controls. The pooled OR of hospital-based case–control studies was significantly lower than that of population-based controls (pooled OR = 0.92, 95% CI, 0.85–1.00; $I^2 = 41.47\%$) ($P < 0.01$).

There were 6 cohort studies and 9 case–control studies on the relationship between lycopene and breast cancer. In 2 of these studies the RR/OR was analyzed in pre- and post-menopausal status, respectively [14, 22]. Therefore 7 cohort comparisons and 10 case–control comparisons entered the meta-analysis (Tables II in Supplementary material; Appendix Figs. 6c, 7c). Comparing the highest with the lowest intake, dietary intake of lycopene did not significantly reduce the breast cancer risk (pooled RR = 0.99; 95% CI: 0.93–1.06; $I^2 = 0.00\%$) when data from cohort studies were pooled. Furthermore, no significant association was observed in further subgroup analyses.

When data from case–control studies were pooled, dietary intake of lycopene significantly ($P = 0.01$) reduced the breast cancer risk by 29.0% (pooled OR = 0.71; 95% CI: 0.56–0.92; $I^2 = 84.71\%$). The significant results remained in pre- and post-menopausal women, studies published after 2000, and hospital-based case–control studies in further subgroup analyses.

Subgroup analysis based on the types of control suggested that the heterogeneity decreased in both subgroups; the pooled OR of 3 hospital-based case–control studies was 0.34 (95% CI: 0.26–0.45, with I^2 of 10.12%), significantly lower than that of population-based controls (pooled OR = 0.92; 95% CI: 0.85–1.01, with I^2 of 41.94%) ($P < 0.01$).

There was insufficient evidence to support the hypothesis that dietary intake of β-cryptoxanthin had a significant association with reduced breast cancer risk (Table II in Supplementary material; Appendix Figs. 6a, 7a).

Sensitivity analysis

The removal of one study at a time had no influence on the pooled RR/ORs of the associations between these carotenoids and breast cancer.

For β-carotene, 3 of the 31 studies [22, 41, 49] provided lower lowest intake level (197, 538, and 599.35 μg/day) than other studies (887 to 2400 μg/day). Other 5 studies [16, 24, 40, 43, 48] provided higher lowest intake level (>3000 μg/day). Omitting 1 of the 8 studies or all the 8 studies had no significant influence on the pooled ORs.

Dose–response relationship

We evaluated and identified significant dose–response relationships in both increasing dietary intake and total intake of β-carotene and reduced breast cancer risk using data from cohort studies. For the dietary intake of β-carotene, RRs were 0.97 (95% CI: 0.96–0.99), 0.96 (95% CI: 0.93–0.98), and 0.93 (95% CI: 0.89–0.97) for 2000, 3000, and 5000 μg/day intake, respectively ($P_{trend} < 0.01$). For the total intake of β-carotene, RRs were 0.99 (95% CI: 0.97–1.00), 0.98 (95% CI: 0.96–1.00), and 0.96 (95% CI: 0.93–1.00) for the same corresponding intake dosages ($P_{trend} = 0.03$) (Table 1).

Significant dose–response relationships were also identified in both increasing dietary intake and total intake of β-carotene and reducing breast cancer risk using data from case–control studies.

Confounding OR

Confounding OR was adopted to analyze the effect of confounding factors on the pooled OR in case–control studies. All the ORcs were lower than 1 without statistical significance except the ORc of the associations between dietary lutein/+zeaxanthin and breast cancer (ORc = 1.02) (data not shown).

Table 1 Dose–response analysis on the associations between carotenoids and the risk of breast cancer in cohort and case–control studies

Carotenoids	Cohort studies				Case–control studies			
	No. of comparisons	Pooled RR and 95% CI	*P* value for *Z* test	I^2	No. of comparisons	Pooled RR and 95% CI	*P* value for *Z* test	I^2
Dietary α-carotene								
500 μg/day	4	0.97 (0.95–0.99)	0.01	1.38	7	0.91 (0.85–0.97)	0.01	86.26
1000 μg/day	4	0.94 (0.91–0.98)	0.01	1.41	7	0.82 (0.73–0.93)	0.01	86.26
1500 μg/day	4	0.91 (0.87–0.96)	0.01	1.40	7	0.75 (0.62–0.90)	0.01	86.26
P_{trend}		0.12				0.43		
Dietary β-carotene								
2000 μg/day	5	0.97 (0.96–0.99)	0.01	0.00	11	0.89 (0.86–0.92)	0.01	53.19
3000 μg/day	5	0.96 (0.93–0.98)	0.01	0.00	11	0.84 (0.80–0.88)	0.01	53.18
5000 μg/day	5	0.93 (0.89–0.97)	0.01	0.00	11	0.75 (0.69–0.81)	0.01	53.18
P_{trend}		<0.01				<0.01		
Total β-carotene								
2000 μg/day	5	0.99 (0.97–1.00)	0.02	0.00	12	0.89 (0.87–0.92)	0.01	53.35
3000 μg/day	5	0.98 (0.96–1.00)	0.02	0.00	12	0.85 (0.81–0.88)	0.01	53.35
5000 μg/day	5	0.96 (0.93–1.00)	0.02	0.00	12	0.76 (0.70–0.82)	0.01	53.72
P_{trend}		0.03				<0.01		
Dietary lutein/+zeaxanthin								
2000 μg/day	3	1.00 (0.94–1.08)	0.91	76.59	6	0.88 (0.84–0.92)	0.01	25.61
3000 μg/day	3	1.00 (0.91–1.12)	0.91	76.59	6	0.83 (0.77–0.89)	<0.01	25.61
4000 μg/day	3	1.01 (0.82–1.24)	0.96	76.59	6	0.88 (0.75–1.05)	0.15	79.52
P_{trend}		0.79				0.48		
Dietary lycopene								
2000 μg/day	3	1.00 (0.99–1.01)	0.88	0.00	6	0.87 (0.82–0.93)	0.01	91.17
3000 μg/day	3	1.00 (0.99–1.02)	0.88	0.00	6	0.82 (0.74–0.90)	0.01	91.17
4000 μg/day	3	1.00 (0.98–1.02)	0.88	0.00	6	0.76 (0.68–0.86)	<0.01	91.17
P_{trend}		0.59				0.40		

Publication bias

Publication bias was observed in the associations between dietary β-carotene, total β-carotene, dietary β-cryptoxanthin, and breast cancer when pooling data from case–control studies. As shown in Fig. 5, the funnel plots of them were asymmetric, and the *P* value for Egger's linear regression was less than 0.05.

After adjustment with trim and fill method, the significant associations between dietary and total intake of β-carotene and the breast cancer become marginally significant (pooled OR = 0.88 (95% CI: 0.77–1.00) and 0.88 (95% CI: 0.77–1.00), respectively). The association between dietary β-cryptoxanthin and breast cancer remain non-significant (Table 2). The funnel plots for associations between dietary α-carotene, dietary β-carotene, combined intake of β-carotene, total β-carotene, dietary β-cryptoxanthin, lutein/+zeaxanthin, and lycopene and breast cancer pooling on data from cohort and case–control studies are shown in Figs. 4 and 5.

Discussion

Our meta-analysis showed that the dietary intake of α-carotene significantly reduced the risk of breast cancer in both cohort studies and case–control studies; the dietary intake and total intake of β-carotene reduced the risk of breast cancer with marginal significance when data from cohort studies were pooled. There were significant dose–response relationships in both higher intake of dietary and total β-carotene and reduced breast cancer risk when data from cohort studies and case–control studies were pooled, respectively.

In comparing the highest intake with the lowest intake of these carotenoids, only α-carotene significantly reduced the breast cancer risk in both cohort studies and case–control studies. Nishino et al. [51] also found that α-carotene have higher activity than β-carotene to suppress the tumorigenesis in skin, lung, liver, and colon, although β-carotene is up to date the most extensively studied carotenoid to suppress the process of carcinogenesis.

Table 2 Publication bias for associations between carotenoids and breast cancer comparing the highest with the lowest category in case–control studies

Carotenoids	Cohort studies				Case–control studies				
	Publication bias	*P* value for Beggs	*P* value for Egger	No. of trim and fill	Publication bias	*P* value for Beggs	*P* value for Egger	No. of trim and fill	Adjusted RR
Dietary α-carotene	No	0.45	0.54	0	No	0.37	0.30	2	–
β-Carotene									
Dietary β-carotene	No	1.00	0.89	0	Yes	0.01	0.01	7	0.88 (0.77–1.00)
Combination (diet + sup)	No	0.65	0.53	0	–	–	–	–	–
Total β-carotene	No	0.72	0.48	1	Yes	0.01	0.01	7	0.88 (0.77–1.00)
Dietary β-cryptoxanthin	No	1.00	0.91	0	Yes	0.18	0.02	4	1.12 (0.93–1.34)
Dietary lutein/ +zeaxanthin	No	0.26	0.68	0	No	0.06	0.11	4	–
Dietary lycopene	No	0.23	0.26	0	No	0.21	0.13	2	–

The association between dietary intake of β-carotene and breast cancer was only marginally significant in pooling the 8 cohort studies from developed countries. It has been reported that β-carotene could suppress the process of mammary carcinogenesis through inhibiting cell proliferation and inducing apoptosis [7]. However, in rats models dietary β-carotene inhibits mammary carcinogenesis depending on dietary α-linolenic acid content [52]. The interactions between α-linolenic acid and β-carotene may influence the associations between dietary β-carotene and the risk of breast cancer.

One cohort study based on ten European countries with a cohort size of 288776 found no evidence for the association between dietary intake of β-carotene and breast cancer risk [25]. Additionally, the meta-analysis by Druesne-Pecollo et al. [10] pooling the results of 4 RCTs also found no significant results between β-carotene supplements and breast cancer risk (RR, 0.96; 95% CI: 0.85–1.10). However, the meta-analysis conducted by Gandini et al. [9] pooling on 7 case–control and 4 cohort studies derived that intake of dietary β-carotene could reduce the breast cancer risk, which may be influenced by the significant results of case–control studies.

Dietary lutein inhibits mouse mammary tumor growth by regulating angiogenesis and apoptosis [6]. However, the lutein uptake can be significantly impaired by a mixture of carotenoids (lycopene plus β-carotene) [53]. In vitro model, lycopene has limited effect on cell proliferation [54, 55]. The effects of lycopene on mammary tumorigenesis in mice's models were also ambiguous [56–58]. This may explain the non-significant association between dietary intake of lutein/ +zeaxanthin and lycopene and breast cancer in the meta-analysis. Dietary β-cryptoxanthin were reported to have an anticancer effect through stimulating the expression of RB gene, an anti-oncogene and p73 gene [51]. However, the association between dietary intake of β-cryptoxanthin and breast cancer risk was neither significant in cohort studies nor in case–control studies, the interaction and absorption of these carotenoids may be considered to explain the results.

The median time of follow-up in the nine cohort studies varied from 7.6 to 9.9 years except the Netherlands cohort study with a 4.3-year follow-up [49] and the Nurses' Health Study with a 14-year follow-up [14]. In subgroup analyses, the time of follow-up had no significant influence on the results. The results pooling on cohort studies were reliable and stable. In this meta-analysis, the pooled ORs of case–control studies tended to be more statistically significant than those in cohort studies. Recall and selection bias inherent in the case–control studies might explain the differences in results between case–control and cohort studies [59]. The collection of dietary information, definition of food groups, and time period before interview varied across studies might also explain the differences. In most case–control studies, the adjusted OR was smaller than the crude OR. However, from the results of confounding ORs, we can see that the confounding factors did not significantly influence the results of meta-analysis in case–control studies.

The heterogeneity persisted in case–control studies. The followings may explain the high heterogeneity: Firstly, different ages of the study population, the heterogeneity decreased in post-menopausal groups but slightly increased in pre- and post-menopausal groups in subgroup analyses based on menopausal status. Secondly, different controls of the study population, the heterogeneity decreased in both subgroups of controls (except β-carotene, the heterogeneity only decreased in population-based case–control studies) in

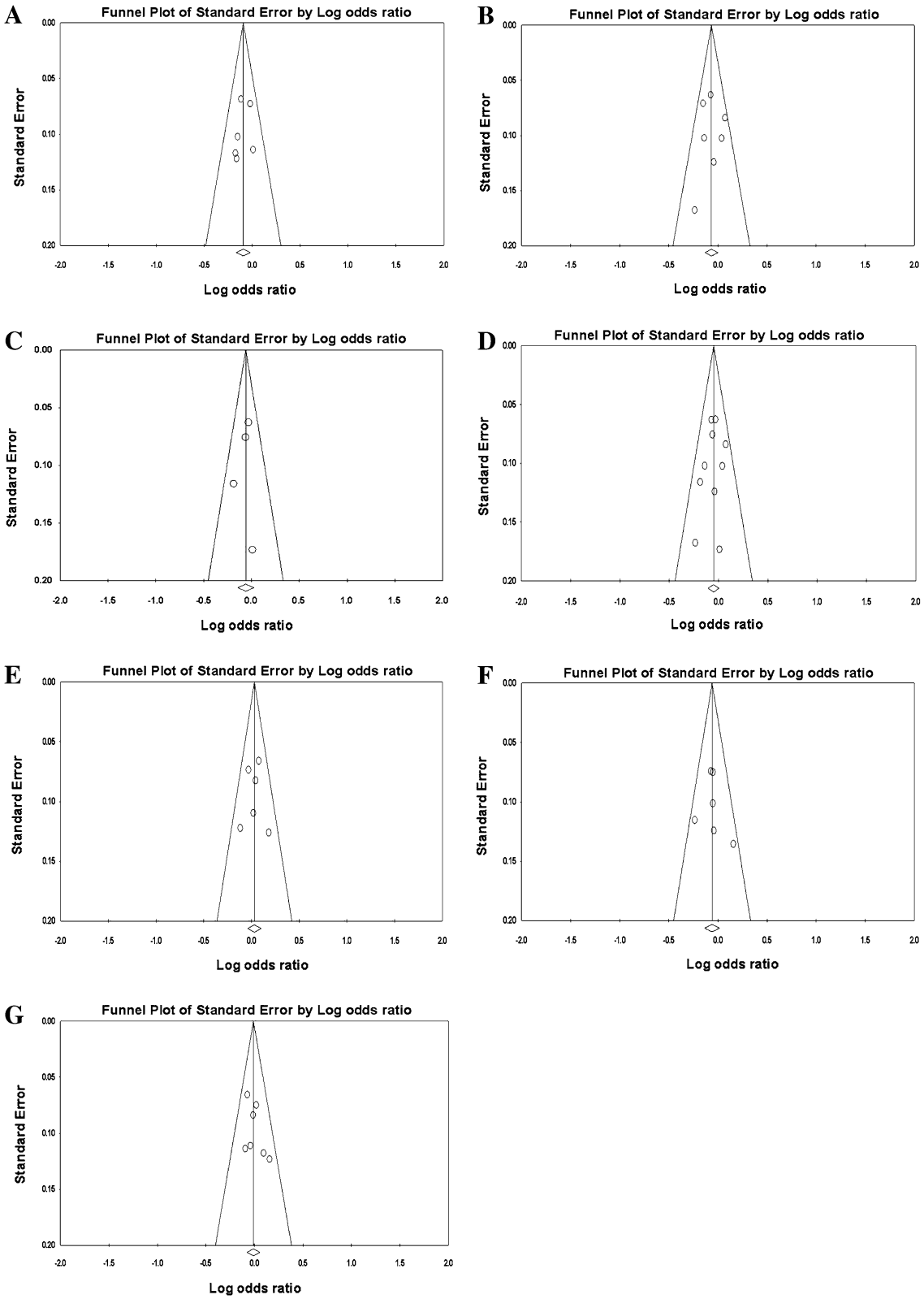

Fig. 4 The funnel plots for the associations between dietary α-carotene (**a**), dietary β-carotene (**b**), combined intake of β-carotene (**c**), total β-carotene (**d**), dietary β-cryptoxanthin (**e**), dietary lutein/+zeaxanthin (**f**), and dietary lycopene (**g**) and the breast cancer pooling on cohort studies

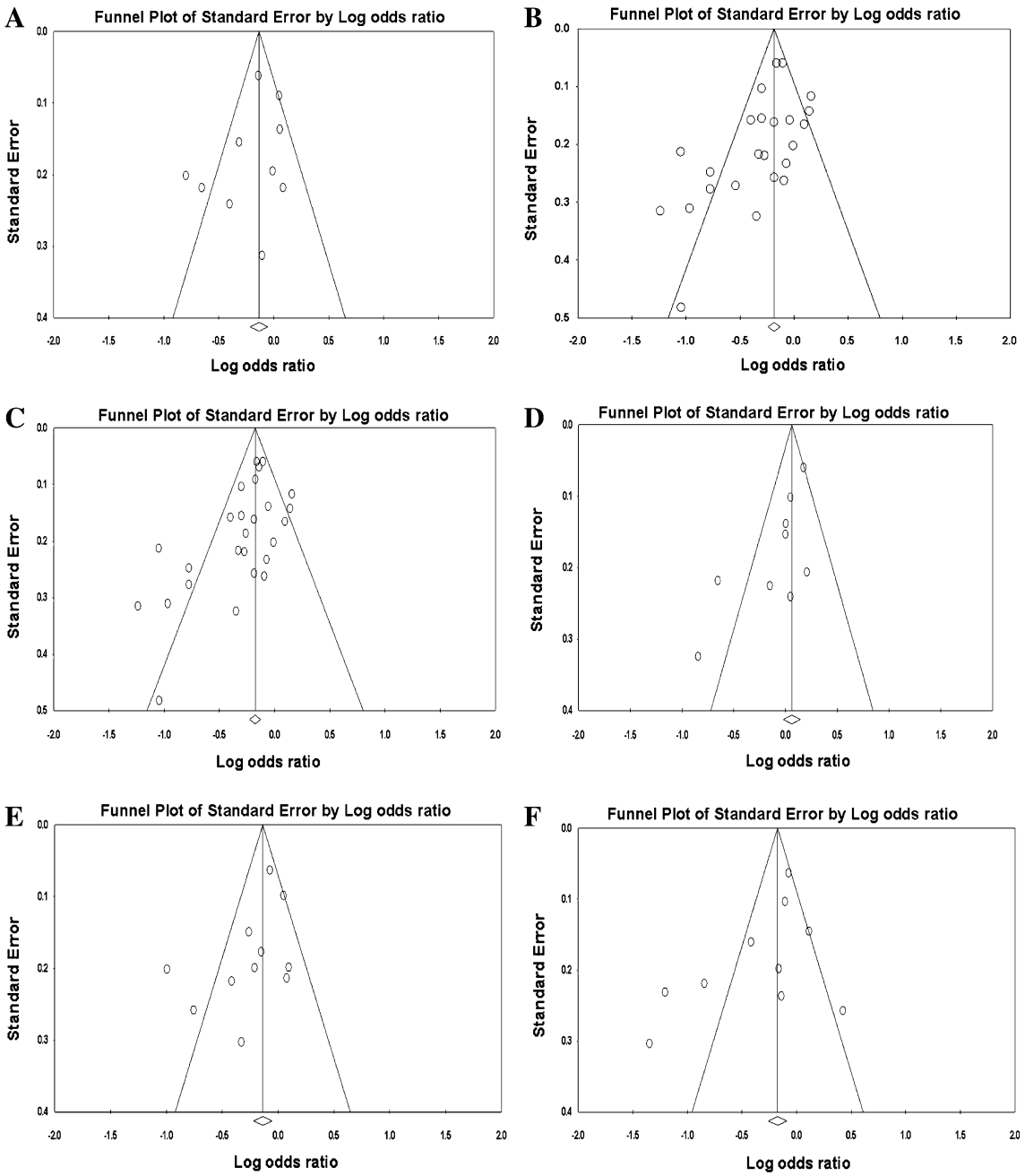

Fig. 5 The funnel plots for the associations between dietary α-carotene (**a**), dietary β-carotene (**b**), total β-carotene (**c**), dietary β-cryptoxanthin (**d**), dietary lutein/+zeaxanthin (**e**), and dietary lycopene (**f**) and the breast cancer pooling on case–control studies

subgroup analyses based on types of control. Finally, different stages of breast cancer patients, 2 of the 24 case–control studies selected invasive breast cancer patients [17, 24], one of the 24 case–control studies selected early-stage breast cancer patients [26]. Whereas other studies selected all the in situ, early-stage, and invasive breast cancer patients.

Publication bias was judged by the funnel plots, Beggs rank correlation and Egger's linear regression. If the results of Beggs rank correlation and Egger's linear regression were contradictory, we judged publication bias by the more sensitive Egger's linear regression. Furthermore, we used trim and fill method to analyze whether the adjusted OR was significant [60]. Publication bias persisted in the associations between β-carotene and dietary β-cryptoxanthin and breast cancer when pooling data from case–control studies. The adjusted ORs of dietary and total intake of β-carotene after trim and fill method were marginally significant, similar to the pooled RRs in cohort studies.

The pooled risk estimates generated on the 33 studies can significantly increase the statistical power. However, like

all meta-analyses, limitations should be considered in this meta-analysis. Firstly, the interactions among these factors may reinforce the association with breast cancer; the socioeconomic position may influence the intake level of these carotenoids. The lack of original data of the studies reviewed limited our further evaluation of potential interactions of these carotenoids and the influence of the socioeconomic position on the results. Secondly, no cohort study in Asia focused on the associations between carotenoids and breast cancer. Thirdly, we did not assess the quality score of every study included in this meta-analysis because of no unified quality score assessment. Finally, not all studies on the carotenoids were used to calculate meta-regression because of non-comparable reference category intake and discrepant distance between two quartiles.

In conclusion, total α-carotene intake could reduce the breast cancer risk. The relationship between dietary and total β-carotene intake and breast cancer needs to be confirmed. No significant association between dietary β-cryptoxanthin, lutein/+zeaxanthin, and lycopene and the breast cancer was observed.

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Conflict of interest All authors read and approved the final manuscript. None of the authors had any conflicts of interest.

Appendix

See Figs. 6 and 7.

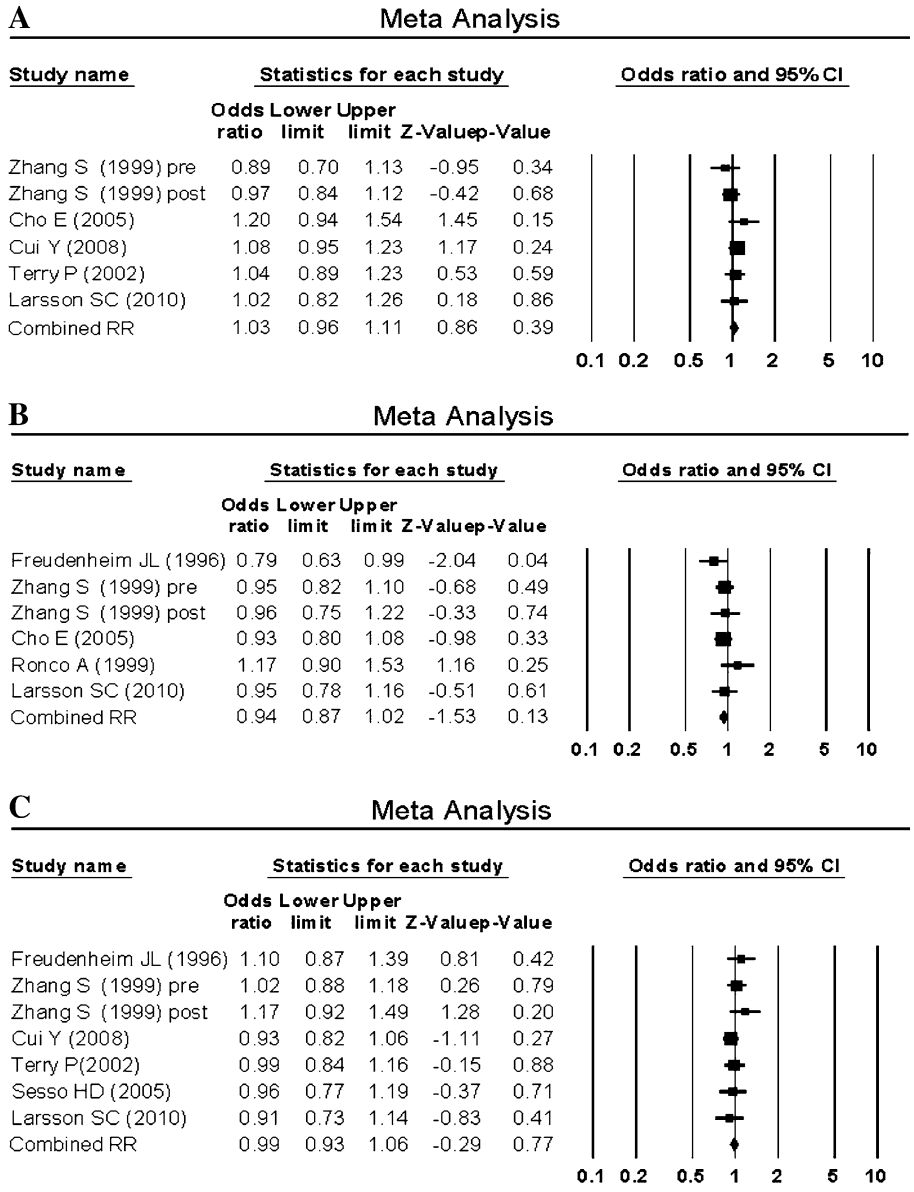

Fig. 6 The forest plots for the associations between dietary β-cryptoxanthin (**a**), dietary lutein/+zeaxanthin (**b**), and dietary lycopene (**c**) and the breast cancer pooling on cohort studies

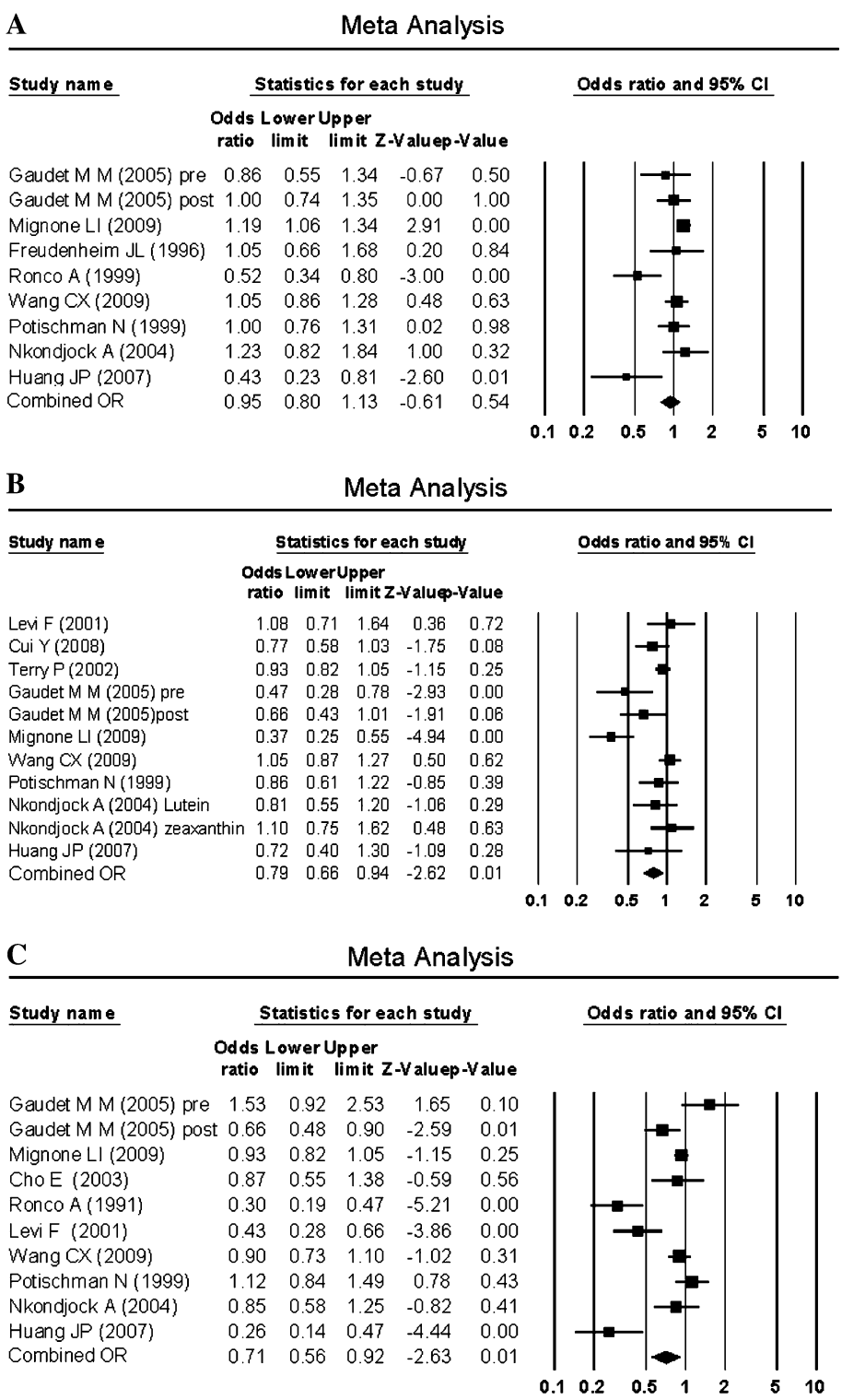

Fig. 7 The forest plots for the associations between dietary β-cryptoxanthin (**a**), dietary lutein/+zeaxanthin (**b**), and dietary lycopene (**c**) and the breast cancer pooling on case–control studies

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