

Association of retinol and carotenoids content in diet and serum with risk for Colorectal cancer: a meta-analysis

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Abstract

Background: Colorectal cancer (CRC) risk is linked to serum and dietary retinol and carotenoids, according to clinical and epidemiological research. However, the findings are not consistent. As a result, we did this meta-analysis to determine the link between them.

Methods: From 2000 through 2022, the PubMed, Web of Science, and Embase databases, as well as pertinent article references, were searched and filtered based on inclusion and exclusion criteria and literature quality ratings. High and low intake were used as controls, and OR (odds ratio) or RR (relative risk) and 95% confidence interval were extracted. The extracted data were plotted and analyzed using Stata12.0 software.

Results: A total of 22 relevant studies were included, including 18 studies related to diet and 4 studies related to serum. For high and low intake or concentration controls, the pooled OR was as follows: β -carotene (OR = 0.89, 95% CI: 0.78-1.03), α -carotene (OR = 0.87, 95% CI: 0.72 – 1.03), lycopene (OR = 0.93, 95% CI: 0.81 – 1.07), lutein/zeaxanthin (OR = 0.96, 95% CI: 0.87 – 1.07), β -cryptoxanthin (OR = 0.70, 95% CI: 0.54 – 0.90), total carotenoids (OR = 0.97, 95% CI: 0.81-1.15), retinol (OR = 0.99, 95% CI: 0.89 – 1.10) serum carotenoids (OR = 0.73, 95% CI: 0.58 – 0.93), serum retinol (OR = 0.62, 95% CI: 0.26 – 1.49). Subgroup analysis was performed according to tumor type, study type and sex.

Conclusions: Dietary intake of β -cryptoxanthin significantly reduced CRC risk and dietary β -carotene considerably decreased CRC risk in the male group. Alternatively, serum carotenoid concentrations were significantly inversely associated with CRC risk.

1 Introduction

In recent years, the incidence and mortality of malignant tumors have been increasing year by year, even exceeding other chronic diseases, becoming a veritable human health killer(1). Despite the fact that cancer efficacy has improved dramatically as a result of integrated therapies such as surgery, chemotherapy, radiation, targeted therapy, and immunotherapy, prognosis and early diagnosis remain poor, and the death rate remains high(2). Colorectal cancer (CRC) is the world's third most frequent disease and the second largest cause of cancer mortality, with a significant number of new cases and deaths every year (3).CRC has caused great burden and harm to the economy and society of the country(4). Economic development and changes in lifestyle and dietary choices have increased the prevalence and mortality of CRC in China in recent years, putting a strain on the health-care system (3, 5). The etiology of CRC is heavily influenced by environmental and genetic factors. Diet, history of benign adenomatous polyps and inflammatory bowel disease, age, diabetes, obesity, lack of physical activity, and a family history of CRC diet are all risk factors for CRC(6). Therefore, the prevention of CRC by changing dietary habits and lifestyle is an area that we should focus on.

Fruits and vegetables are among the daily foods required for good health since they include high levels of minerals, vitamins, carbs, proteins, dietary fiber, and different substances with nutritional medicinal value that can help prevent a variety of ailments(7). Many studies have indicated that eating fruits and vegetables helps prevent cancer, with vegetable-related protection being more substantial(8, 9).Vitamin A is an unsaturated hydrocarbon group that includes retinol and its derivatives such as retinaldehyde, retinoic acid, and retinyl ester(10). Cell development and differentiation, embryogenesis, reproduction, epithelial cell integrity, and immunological function are all regulated by vitamin A(11, 12). It also has antioxidant properties(13) and helps to reduce oxidative stress damage and inflammation (11, 14). Carotenoids are a good source of vitamin A and may be turned into it by the body(15). Carotenoids are natural pigments found in a wide range of fruits and vegetables, including lycopene, β -carotene, lutein, zeaxanthin, and β -cryptoxanthin(16). Carotenoids and retinoids share many biological actions, including antioxidant capabilities, suppression of malignant tumor development, and activation of apoptosis(17). Carotenoids can influence cell development, as well as gene expression and immunological responses(18, 19). Thus, retinol and carotenoids are indispensable in the human body. But retinol cannot

be synthesized in the human body, and it must be obtained from the diet(20). As a result, research into the relationship between their consumption and human illnesses, including cancer, is required.

Over the last two decades, researchers have conducted substantial research on the link between nutrition and cancer. Epidemiological studies have found a link between food and cancer incidence and aggressiveness (21). A high intake of dietary carotenoids or vitamin A (retinol) has been linked to a decreased risk of colorectal cancer in several studies (22–25). Other studies, however, have shown no substantial link between their use and the risk of cancer onset(25–27). Surprisingly, there has been interest in the research of serum retinol and carotenoids, and some studies have shown that their levels in the blood are related to the risk of colon cancer. As a result, we completed our meta-analysis in time to incorporate the most recent relevant data, providing more credible scientific support for CRC prevention.

2 Materials And Methods

Search strategy for literature

Two writers (Xiaoyong Han and Rangyin Zhao) separately conducted a literature search for the association between retinol, carotene, and related derivatives and the risk of CRC in humans using the PubMed, Web of Science and Embase databases. The following keywords were used in the search: “retinol” or “carotenoids” or “carotene” or “β-carotene” or “cryptoxanthin” or “lycopene” or “lutein” or “zeaxanthin” combined with “Colorectal cancer” or “colon cancer” or “rectal cancer”. All relevant literature was searched from 2000 to 2022. In addition, we performed a manual search of the reference lists of reviews, meta-analyses, and other relevant publications to prevent potentially missed articles. The language of included articles was limited to English.

Inclusion and exclusion criteria

Studies were included according to the following criteria: (1) patients were diagnosed with colon or rectal cancer; (2) observational studies, including cohort or case-control studies; (3) The associations of interest are about the association of serum or dietary retinol or carotenoids with CRC risk, and there are comparisons of high and low content.; (4) relative risk (RR) or odds ratio (OR) with 95% confidence interval for cancer-containing. The following exclusion criteria were used: (1) reviews or conferences or abstracts or letters to the editor; (2) duplicate study populations; (3) animal studies; (4) other cancer studies; (5) lack of RR or OR data; (6) other vitamin supplement studies.

Data extraction and quality evaluation

All included papers were examined and relevant data were retrieved independently by two researchers. Inclusion basic information included: name of first author, date of publication, country, type of study, vitamin type, cancer type, sample size of cases and controls, RR or OR and 95% CI for cancer, covariate correction. The disagreement between these two researchers was decided jointly by a third author. The quality of the included studies was assessed using the NOS scoring criteria (0 to 9 points), and those with a score > 6 were included in the meta-analysis.

Statistical Analysis

RRs or ORs with 95% confidence intervals were extracted from each study to assess the association of high retinol or carotenoid intake and low intake with cancer risk. The results generally combined in cohort studies are RR values, and the results generally combined in case-control studies are OR values. In order to better calculate and combine the results of studies, the difference between the two is negligible, and all the results are expressed as OR values. In addition,

heterogeneity among studies was assessed by Q-test and I^2 statistic. Q test (P_Q) p value < 0.1 and $I^2 > 50\%$ indicated that there was significant statistical heterogeneity between studies, and the results were analyzed using a random-effects model. Otherwise, a fixed effects model was used. We used forest plots to present the meta-analysis results and used Begg's test as well as Begg's funnel plots to assess publication bias. In addition, by eliminating each study one by one, a sensitivity analysis was performed to check the stability of the results. Analyses were performed using Stata12.0 for Windows (Stata, College Station, TX, USA) and $p < 0.05$ was considered statistically significant.

3 Results

3.1 Screening process for eligible literatures

The relevant literatures were searched in 3 main English databases according to the search strategy: PubMed (n = 235), Web of Science (n = 218), Embase (n = 173). After de-duplication (n = 376), the titles and abstracts of the remaining articles (n = 250) were examined and evaluated. 193 articles were rejected for purpose, article type (review, case study, or conference abstract), or irrelevant findings. 57 full-text articles were downloaded, of which 35 studies were rejected after initial analysis due to lack of important data or unsatisfactory quality of NOS scores. Finally, the meta-analysis comprised 22 papers that fully fulfilled the inclusion criteria and quality evaluation. **Figure 1** depicts the search flow chart.

3.2 Characteristics of included research projects

Table 1 shows the main characteristics of the 22 included studies. Regarding dietary aspects, a total of five cohort studies were included, and 399,558 individuals were followed up for 5 to 15 years, eventually resulting in 6919 CRC patients. A total of 13 case-control studies involving 11,029 cases and 19,024 controls were included. With respect to serum, two cohort studies were included, with 32,428 participants and, ultimately, 272 patients with CRC. Two case-control studies involving 1073 cases and 1116 controls were included. Studies were published between 2000 and 2019. Eight studies were from European countries, eight from North American countries and six from Asian countries. The major nutrient species studied were carotenoids, lycopene, α -carotene, β -carotene, carotenoids, lutein/zeaxanthin, β -cryptoxanthin, and retinol. The included studies were adjusted for covariates, mainly including: gender, age, smoking, alcohol consumption, family history of CRC and physical activity. The NOS was scored from 6 to 8.

3.3 Association between dietary retinol and various carotenoids and Colorectal cancer risk

3.3.1 β -carotene

We combined a total of 20 sets of data from 11 studies. Comparing high and low intakes, dietary intake of β -carotene reduced the risk of CRC by 11% (OR = 0.89, 95% CI: 0.78-1.03 **Figure2A**) but the association between the two was not significant ($p_t = 0.113$), and due to significant heterogeneity ($I^2 = 63.2\%$, $p < 0.001$), we used a random-effects model for pooled analysis. According to subgroup analysis by tumor type, it can be seen that there is no significant correlation between high intake and the risk of colon cancer (OR = 0.96, 95% CI: 0.84-1.09 **Figure3A**) and rectal cancer (OR = 1.06, 95% CI: 0.89-1.25 **Figure3A**). In the subgroup analysis by study type, both the cohort study (OR = 0.95, 95% CI: 0.85-1.07 **Figure4A**) and the case-control study (OR = 0.81, 95% CI: 0.63-1.05 **Figure4A**) showed a trend of β -carotene to reduce the risk of CRC, but none of them were significantly associated. Finally, according to gender subgroup analysis, β -carotene intake was not significantly associated with the risk of CRC in female (OR = 0.81, 95% CI: 0.97-1.19 **Figure5A**), but β -carotene intake was negatively associated with the risk of CRC in male (OR = 0.74, 95% CI: 0.55-0.99 **Figure5A**).

3.3.2 α -carotene

We combined a total of 10 sets of data from 5 studies. Comparing high and low intakes, dietary intake of α -carotene reduced the risk of CRC by 13% (OR = 0.87, 95% CI: 0.72 – 1.03 **Figure2B**), but the association between the two was not significant ($p_t=0.110$), and due to significant heterogeneity ($I^2 = 55.3\%$, $p=0.017$), we used a random-effects model for pooled analysis. Subgroup analysis by tumor type showed that high intake was not significantly associated with the risk of colon cancer (OR = 0.96, 95% CI: 0.84-1.09 **Figure3B**) and rectal cancer (OR = 1.01, 95% CI: 0.76-1.35 **Figure3B**). In the subgroup analysis by study type, the cohort study (OR = 1.00, 95% CI: 0.86-1.16 **Figure4B**) showed no significant association between their intake and CRC, and the case-control study (OR = 0.69, 95% CI: 0.47-1.02 **Figure4B**) showed a trend, but no significant association, of their intake to reduce CRC. Finally, intake of α -carotene tended to reduce CRC in male (OR = 0.71, 95% CI: 0.42-1.22 **Figure5B**) and female (OR = 0.89, 95% CI: 0.61-1.30 **Figure5B**) according to gender subgroup analysis, but there was no significant association.

3.3.3 Lycopene

Seven studies were included to combine a total of 13 sets of data. High lycopene (OR = 0.93, 95% CI: 0.81 – 1.07 **Figure2C**) intake slightly, but not significantly ($p_t=0.329$), reduced CRC risk. Due to significant heterogeneity ($I^2 = 65.6\%$, $p=0.000$), pooling was performed with a random-effects model. Subgroup analysis was performed according to tumor type, study type and gender. Colon cancer (OR = 0.97, 95% CI: 0.85 – 1.10 **Figure3C**), rectal cancer (OR = 1.11, 95% CI: 0.89 – 1.38 **Figure3C**), cohort study (OR = 1.04, 95% CI: 0.92 – 1.18 **Figure4C**), case-control study (OR = 0.82, 95% CI: 0.64 – 1.06 **Figure4C**), male (OR = 0.88, 95% CI: 0.65 – 1.18 **Figure5C**), female (OR = 0.96, 95% CI: 0.59 – 1.58 **Figure5C**). In subgroup analyses, case-control studies showed that lycopene intake was associated with a nonsignificant reduction in CRC risk. There was also a risk reduction effect in women, although it was not significant.

3.3.4 Lutein/Zeaxanthin

Six studies were included and a total of 12 sets of data were combined. There was no significant ($p_t=0.508$) association between high lutein/zeaxanthin (OR = 0.96, 95% CI: 0.87 – 1.07 **Figure2D**) intake and CRC risk. No significant heterogeneity was found ($I^2 = 10.6\%$, $p=0.341$), which was summarized using a fixed-effect model. Subgroup analysis was performed according to tumor type, study type and gender. Colon cancer (OR = 0.96, 95% CI: 0.84 – 1.09 **Figure3D**), rectal cancer (OR = 1.09, 95% CI: 0.86 – 1.39 **Figure3D**), cohort study (OR = 1.04, 95% CI: 0.90 – 1.21 **Figure4D**), case-control study (OR = 0.89, 95% CI: 0.76 – 1.04 **Figure4D**), male (OR = 0.89, 95% CI: 0.75 – 1.06 **Figure5D**), female (OR = 1.08, 95% CI: 0.88 – 1.32 **Figure5D**). In subgroup analysis, case-control studies showed that lutein/zeaxanthin intake was associated with a non-significant reduction in CRC risk. The risk reduction effect was also present in female, but was not significant.

3.3.5 β -cryptoxanthin

Eight studies were included and a total of 18 sets of data were combined. High β -cryptoxanthin (OR = 0.70, 95% CI: 0.54 – 0.90 **Figure2E**) intake was able to significantly ($p_t=0.005$) reduce CRC risk by 30%. High heterogeneity was found ($I^2 = 85.4\%$, $p=0.000$), which was combined using the random-effects model. Subgroup analysis was performed according to tumor type, study type, and gender. Colon cancer (OR = 0.95, 95% CI: 0.85 – 1.06 **Figure3E**), rectal cancer (OR = 0.87, 95% CI: 0.71 – 1.06 **Figure3E**), cohort study (OR = 0.92, 95% CI: 0.83– 1.03 **Figure4E**), case-control study (OR = 0.36, 95% CI: 0.19 – 0.72 **Figure4E**), male (OR = 0.52, 95% CI: 0.30 – 0.89 **Figure5E**), female (OR = 0.65, 95% CI: 0.43 – 0.98 **Figure5E**). In subgroup analysis, β -cryptoxanthin intake significantly reduced the risk of CRC, both in male and female.

3.3.6 Total carotenoids

Eight studies were included and a total of 19 sets of data were combined. There was no significant ($p_t=0.717$) association between high carotenoids (OR = 0.97, 95% CI: 0.81-1.15 **Figure2F**) intake and CRC risk. There was significant heterogeneity ($I^2 = 69.2\%$, $p=0.000$), which was combined using the random-effects model. Subgroup analysis was performed according to tumor type, study type and gender. Colon cancer (OR = 1.05, 95% CI: 0.92 – 1.20 **Figure3F**), rectal cancer (OR = 1.01, 95% CI: 0.81 – 1.26 **Figure3F**), cohort study (OR = 1.08, 95% CI: 0.94 – 1.25 **Figure4F**), case-control study (OR = 0.87, 95% CI: 0.70 – 1.08 **Figure4F**), male (OR = 1.08, 95% CI: 0.91 – 1.27 **Figure5F**), female (OR = 1.00, 95% CI: 0.80 – 1.25 **Figure5F**). No association was found between high carotenoids intake and the risk of CRC in any Subgroup group.

3.3.7 Retinol

Seven studies were included and a total of 15 sets of data were combined. There was no significant ($p_t = 0.850$) association between high retinol (OR = 0.99, 95% CI: 0.89 – 1.10 **Figure2G**) intake and CRC risk. There was no significant heterogeneity ($I^2 = 34.5\%$, $p=0.092$), and fixed effect model was used for combination. Subgroup analysis was performed according to tumor type, study type and gender. Colon cancer (OR = 1.05, 95% CI: 0.86 – 1.27 **Figure3G**), rectal cancer (OR = 0.99, 95% CI: 0.89 – 1.11 **Figure3G**), cohort study (OR = 0.92, 95% CI: 0.60 – 1.43 **Figure4G**), case-control study (OR = 0.99, 95% CI: 0.89 – 1.11 **Figure4G**), male (OR = 1.30, 95% CI: 1.02 – 1.66 **Figure5G**), female (OR = 0.79, 95% CI: 0.61 – 1.01 **Figure6G**). Retinol appeared to play a protective role in women, reducing CRC risk by 21%, although there was no significant association.

3.4 Association of serum retinol and carotenoid levels with Colorectal cancer risk

With regard to serum carotenoids, three studies were included and a total of 11 sets of data were combined. Serum total carotenoids (OR = 0.73, 95% CI: 0.58 – 0.93 **Figure6A**) were significantly ($p_t = 0.01$) negatively associated with CRC risk. The results showed significant heterogeneity ($I^2 = 67.5\%$, $p=0.001$), which was combined using the random-effects model. The subgroup analysis was performed according to the type of nutrients. Serum α -carotene (OR = 0.61, 95% CI: 0.37 – 0.99 **Figure6B**) was significantly inversely associated with CRC risk. However, the serum content of β -carotene (OR = 0.83, 95% CI: 0.64 – 1.08 **Figure6B**), Lycopene (OR = 0.58, 95% CI: 0.22 – 1.54 **Figure6B**), and β -Cryptoxanthin (OR = 0.69, 95% CI: 0.28 – 1.69 **Figure6B**), although negatively correlated with CRC risk, was not significant. There was no correlation between serum Lutein/Zeaxanthin (OR = 0.99, 95% CI: 0.63 – 1.56 **Figure6B**) content and CRC risk.

With regard to serum retinol, three studies were included and a total of four sets of data were combined. High serum retinol (OR = 0.62, 95% CI: 0.26 – 1.49 **Figure6C**) was inversely associated with CRC risk, but the association was not significant ($p_t = 0.284$). The results showed significant heterogeneity ($I^2 = 90.8\%$, $p=0.000$), and random effects model was used for combination. Subgroup analysis were also performed according to study type. Cohort studies (OR = 1.22, 95% CI: 0.80 – 1.86 **Figure6D**) showed no association between serum retinol and CRC risk, but case-control studies (OR = 0.29, 95% CI: 0.16 – 0.54 **Figure6D**) showed a significant inverse association between serum retinol and CRC risk.

3.5 Publication bias and Sensitivity analysis

Due to the reduction in serological studies included, bias testing and sensitivity analysis were not necessary. Therefore, we performed bias test and sensitivity analysis on the combined results of dietary retinol and carotenoids. We used Begg's test as well as Begg's funnel plot to assess publication bias. Begg's test results (**Figure7**): β -carotene ($Pr > |z| = 0.417$), α -carotene ($Pr > |z| = 0.721$), lycopene ($Pr > |z| = 0.464$), β -Cryptoxanthin ($Pr > |z| = 0.075$), Lutein/Zeaxanthin ($Pr > |z| = 0.304$), Carotenoids ($Pr > |z| = 0.234$), retinol ($Pr > |z| = 0.692$). The results of bias test showed that all funnel plots were symmetrical and ($Pr > |z| > 0.05$), indicating that no significant publication bias was found in the combined results.

Sensitivity analysis (**Figure8**) of the results was performed and the pooled OR varied in a limited range without significant change after removing each study, indicating that our results were stable. From this, it can be seen that the relevant conclusions we draw are stable and reliable.

4 Discussion

Although vitamin A (retinol) and carotenoids are widely present in a variety of vegetables and fruits, many people still lack the intake of these nutrients. Therefore, the impact of retinol and carotenoid intake on CRC risk has important public health implications. We included a total of 22 studies that pooled clinical studies on dietary and serum retinol and carotenoids and CRC risk. Subgroup analysis was performed according to tumor type, study category and sex.

The results showed that dietary β -carotene intake was weakly but not significantly negatively correlated with CRC risk, but β -carotene could significantly lower CRC risk in the male population, showing a protective and preventive effect. The consumption of β -carotene lowered the risk of CRC, however the link was not statistically significant. A high lycopene consumption lowered CRC risk marginally but not dramatically. There was no link seen between high lutein/zeaxanthin consumption and CRC risk. β -cryptoxanthin intake dramatically lowered the risk of CRC in both men and women. There was no link found between high carotenoid consumption and CRC risk. High retinol consumption had no significant connection with CRC risk, although it appeared to be protective in women, lowering CRC risk by 21%. In summary, high β -cryptoxanthin intake can significantly reduce CRC risk, and β -carotene, α -carotene, and lycopene have the potential to lower the risk of CRC, but there is uncertainty and it must be continued to be explored. β -carotene has a preventive effect on CRC in men and retinol seems to have a preventive effect in women, and this difference has caused us to have new ideas for making adjustments to meals by gender.

Our study surprised us by the finding that a high intake of β -cryptoxanthin (OR = 0.70, 95% CI: 0.54–0.90) was able to significantly reduce CRC risk. β -cryptoxanthin is one of the six primary carotenoids. It is mostly present in citrus fruits, although it is also found in corn, peas, and other yellow animal products (16, 28). β -cryptoxanthin has been demonstrated in animal experiments to have preventative and inhibitory effects on a number of malignancies, including colon cancer (29), gastric cancer (30), lung cancer (31–33), bladder cancer (34), and liver cancer (35) through a variety of molecular mechanisms. It has been demonstrated that β -cryptoxanthin in combination with oxaliplatin dramatically increased the apoptosis of colon cancer cells in vitro and in vivo, indicating anti-tumor and therapeutic actions on CRC (29). From this point of view, although there are few studies on β -cryptoxanthin, it may have a role in preventing and inhibiting tumors in a variety of cancers, especially CRC. The conclusions about β -cryptoxanthin in this meta-analysis should be paid attention to, and strengthening the study of β -cryptoxanthin may bring fruitful results.

In addition to focusing on the risk of dietary retinol and carotenoids on CRC, we also focused on serological aspects of the study. A significant inverse association was found between serum carotenoid concentrations and CRC risk. Serum β -carotene was shown to have a substantial negative relationship with CRC risk. Other carotenoids, while adversely associated, were not significant. Case-control studies have found a substantial negative link between serum retinol and CRC risk, while cohort studies have found no significant relationship, hence the relationship between serum retinol and CRC remains unknown and must be confirmed by large prospective investigations. Most previous studies have focused on dietary carotenoids, but in recent years attention has gradually shifted to serum carotenoids, possibly due to the development of serum detection techniques and more stable and accurate quantitative assessment of serum. Serum carotenoids are widely studied, in addition to CRC (36, 37), but also associated with the risk of breast cancer(38), lung cancer(39), prostate cancer(40, 41) and hepatocellular carcinoma(42), which can be used as a key research direction in the future. If the relationship between serum carotenoids and various cancers can be clearly understood, routine admission examination can be performed in high-risk cancer population to preliminarily evaluate and screen related tumors, which has certain application prospects in clinical practice.

We will further explore the mechanisms underlying the prevention and suppression of CRC by carotenoids. β -carotene has been found in animal studies to have anti-colon cancer properties through modulating M2 macrophages and activated fibroblasts(43). By regulating K-ras, PKB, and beta-catenin, dietary lutein can decrease colon carcinogenesis caused by p-dimethylhydrazine in rats(44). Carotenoids isolated from *Chlorella ellipsoidea* and *Chlorella vulgaris* have also been shown in cell tests to have antiproliferative and anticancer effects on human colon cancer cells(45). B-carotene has been demonstrated to decrease colon cancer cell development by reducing COX-2 production and down-regulating colon cancer cell homeostasis(46). A growing number of experimental investigations have also proven the mechanism and significance of carotenoids in anti-colorectal cancer.

There have also been several earlier meta-analyses investigating the relationship between carotene and CRC. Mannisto et al performed a meta-analysis of cohort studies on dietary carotenoids and CRC risk in 2006, and discovered no link between any carotenoids and CRC risk(47). Conclusion may be caused by several limitations. On the one hand, we believe that the relevant studies it includes are somewhat old and not suitable for the dietary pattern of modern humans. On the other hand, the studies it included were Caucasian studies in Europe and North America with certain geographical limitations; At the time, communication technology was limited, which easily led to a loss due to follow-up bias. Wang et al. performed a meta-analysis of observational data on lycopene consumption and CRC risk in 2016(48). The data indicate that lycopene consumption is not related with an increased risk of CRC, which is consistent with our findings. In 2016, Panic et al performed a meta-analysis of dietary carotenoid consumption and CRC risk, which found no significant link between dietary carotenoid intake and CRC(49).The reason for the inconsistency with our findings is that on the one hand we updated and added several new studies, on the other hand our study was performed in strict accordance with the quality assessment rules and removed several unqualified studies, and his study included these low-quality articles, which may affect the results. Third, we also conducted a gender subgroup analysis that may derive the effect of gender differences, and his study did not consider gender differences. Our findings are not consistent with the above the meta-analyses, but our study is highly credible.

We found clear heterogeneity in the entire summary results for retinol and carotenoids and CRC risk. Heterogeneity is typical in meta-analysis, and determining the source of the heterogeneity is an important step. First, where the heterogeneity of the data was considerable, we utilized a random-effects model to combine effect sizes. Second, we conducted a subgroup analysis by tumor type, research type, and gender. Most studies' heterogeneity was greatly decreased after subgroup analysis. Third, we conducted a sensitivity analysis to exclude the one that had the biggest influence on the research outcomes, hence lowering heterogeneity. In addition, there may be many factors that can increase heterogeneity, such as differences in race, region, dietary structure, ideology, and degree of economic development. As a result, the conclusions drawn should be treated with caution.

Our meta-analysis provides a number of advantages. First, for the first time, we not only evaluated the association between dietary carotenoids and retinol and CRC risk, but also performed serological aspects. Furthermore, each of the six major groups of carotenoids was thoroughly examined. Second, because this study included a large number of cases and participants, more reliable estimations of the connection between retinol and carotenoid consumption and CRC risk may be obtained. Third, there was no evidence of significant publication bias in our meta-analysis. Fourth, we conducted a detailed subgroup analysis according to tumor type, study type, and gender. Fifth, the results of our included studies were all adjusted for covariates. Sixth, we included studies from the last 20 years, avoiding that old dietary patterns influence the accuracy of study conclusions.

Our study has several limitations. First, we only included English articles, which may cause selection bias. Second, there is a large heterogeneity in the findings, although the sources of heterogeneity have been explored. Third, study results were not analyzed by region and race. Fourth, the specific doses of retinol and carotenoids were not stated, and no dose-response meta-analysis was performed. Fifth, detection and transformation tools for retinol and carotenoids contained in

ingested foods are not described. Sixth, although all results were adjusted for covariates, it is possible that there are other factors that affect the accuracy of the results.

5 Conclusion

Dietary β -carotene considerably decreased CRC risk in the male population, and dietary β -cryptoxanthin significantly reduced CRC risk. Alternatively, serum carotenoid concentrations were significantly inversely related to CRC risk. From this, it can be seen that carotenoids have some benefits in preventing CRC, especially β -carotene and β -cryptoxanthin. However, because of these limitations and the heterogeneity of this meta-analysis, large prospective studies with adequate sample size, well-controlled confounders, and long follow-up are warranted. In this process, the toxicity caused by high-dose retinol and carotenoids should be considered.

Declarations

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Author Contributions

Xiaoyong Han and Rangyin Zhao conceived the study; Guangming Zhang and Yajun Jiao performed the literature search; Da Wang and Yongfeng Wang extracted the required data; Xiaoyong Han performed the statistical analyses; Xiaoyong Han and Rangyin Zhao wrote a draft; Hui Cai and Kehu Yang reviewed the paper. All authors viewed and gave permission to publish this manuscript.

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Data Availability Statement

The data presented in this study are available in the inserted articles.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing financial interests.

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Tables

Table 1

Characteristics of included studies.

Author Year Country	type of Cancer	type of study	sample size	Diet/ Serum	Nutrient Type	adjustment for covariates.	NOS score
Roswall(27) 2010 Denmark	Colon and rectal cancer	Cohort study	56332/748	Diet	β -carotene	Education, alcohol consumption, consumption of red and processed meat, smoking status	7
Maureen(23) 2004 USA	rectal cancer	Case- control study	952/1205	Diet	Lycopene, β - carotene, Lutein	Age, body mass index, physical activity, energy intake, dietary fiber, dietary calcium, and smoking status	7
Dawn(50) 2010 USA	Colorectal Cancer	Case- control study	945/959	Diet	β -carotene	Age, gender, education, smoking status, BMI, physical activity, family history, history of alcohol use	6
Park(26) 2009 USA	Colon and rectal cancer	Cohort study	191004/2378	Diet	Lycopene, α - carotene, β - carotene, Carotenoids, β - cryptoxanthin, Lutein	Gender, age, family history of colorectal cancer, history of intestinal polyps, number of pack- years smoked, body mass index	8
Slattery(51) 2000 USA	Colon cancer	Case- control study	1993/2410	Diet	Lycopene, α - carotene, β - carotene, β - cryptoxanthin, Lutein, Zeaxanthin	Age, gender, smoking, alcohol consumption, BMI and long term strenuous physical activity	7
Leenders(22) 2014 Europe	Colon and rectal cancer	Case- control study	1399/1399	Diet	Lycopene, α - carotene, β - carotene, Carotenoids, Retinol	Smoking, alcohol consumption, BMI, physical activity, consumption level	7
Terry(52) 2015 Canada	Colon and rectal cancer	Cohort study	56837/5681	Diet	Lycopene, α - carotene, β - carotene, Carotenoids	Smoking status, relative body mass (body mass index), total fat intake, energy, alcohol, and folic acid, or menopausal status	7
Andre(53) 2004 Canada	Colon cancer	Case- control study	402/688	Diet	Lycopene, α - carotene, β - carotene, Carotenoids, Lutein/ Zeaxanthin, β - Cryptoxanthin	Age, history of CC in first-degree relatives, marital status, gender, physical activity, fiber and folate consumption, and total energy intake	7

Wang(54) 2014 Japan	Colon and rectal cancer	Case- control study	816/815	Diet	Lycopene, Carotenoids	Age, residence, family history of colorectal cancer, smoking, alcohol consumption, BMI, type of work, physical activity	6
Negri(55) 2002 Italy	Colorectal Cancer	Case- control study	1953/4154	Diet	Lycopene, Carotenoids, Retinol	Sociodemographic characteristics, smoking, physical activity, anthropometric measurements at different ages, family history of cancer	7
Levi(56) 2000 Switzerland	Colorectal Cancer	Case- control study	223/491	Diet	Carotenoids, Retinol	Age, sex, education, smoking, alcohol, body mass index, physical activity, and total energy and fiber intake	7
Lu(57) 2015 China	Colorectal Cancer	Case- control study	845/845	Diet	Lycopene, α - carotene, β - carotene, Carotenoids Lutein/Zeaxanthin β -Cryptoxanthin	Education, marital status, occupation, income, family history of cancer, smoking status, passive smoking, alcohol consumption, occupational activities, family and leisure activities, BMI	7

Table 1

Con.

Author Year Country	type of Cancer	type of study	sample size	Diet/ Serum	Nutrient Type	adjustment for covariates.	NOS score
Paiva(58) 2004 Portugal	Colorectal Cancer	Case- control study	100/211	Diet	Carotenoids	Age, sex, marital status, work physical activity, family history of cancer, body mass index, fiber, carotene, vitamin C, and total energy	7
Valentina(24) 2013 Switzerland	Colorectal Cancer	Case- control study	329/1361	Diet	β -carotene	Age, gender, family history, alcohol use, education, physical activity	6
Timothy(59) 2012 UK	Colorectal Cancer	Case- control study	565/1951	Diet	β -carotene	Height, weight, energy intake, alcohol intake, dietary fiber, smoking, alcohol consumption, physical activity, education, social class	7
Nancy(60) 2000 USA	Colon and rectal cancer	Cohort study	22071/267	Diet	β -carotene	Age, education, marital status, occupation, income, family history of cancer, smoking status, passive smoking, alcohol consumption, occupational activity, BMI	7
Wakai(61) 2006 Japan	Colon and rectal cancer	Case- control study	507/2535	Diet	Carotenoids, Retinol	Sex, age, family history, smoking, alcohol use, physical activity, energy intake	7
Shin(25) 2006 China	Colon and rectal cancer	Cohort study	73314/283	Diet	Carotenoids, Retinol	Age, menopausal status, education, smoking, alcohol consumption, physical activity, family history of colorectal cancer, use of vitamin supplements, and total energy intake	8
Kabat(62) 2012 USA	Colorectal Cancer	Cohort study	5477/88	serum	Lycopene, α - carotene, β - carotene, Lutein+ Zeaxanthin β - Cryptoxanthin, Retinol	Age, body mass index, waist circumference, alcohol intake, physical activity, family history of colorectal cancer, ethnicity	8
Huang(36) 2017 China	Colorectal Cancer	Case- control study	538/564	serum	Lycopene, α - carotene, β - carotene, Lutein/ Zeaxanthin β - Cryptoxanthin	Living conditions, educational level, occupation, income, study, alcohol consumption, family history of colorectal cancer, physical activity	7
Luo(63) 2019	Colon and rectal cancer	Case- control study	535/552	serum	Retinol	Age, sex, residence, educational level, marital status, income, family and leisure activities, passive	6

China						smoking, alcohol consumption, adult height and BMI	
Malila(64) 2002 Finland	Colorectal Cancer	Cohort study	26951/184	serum	Retinol, β -carotene	Age, body mass index (BMI), number of cigarettes smoked per day, occupational and leisure time physical activity, serum cholesterol concentration, alcohol intake	8

Table 2

Meta-results on intake of various nutrients and colorectal cancer risk

Nutrient Type	studies(n)	OR	95%CI	Pvalue	Model	Heterogeneity		
						Chi ²	I^2	PValue
β -carotene	20	0.89	0.78-1.03	0.113	random	51.61	63.2%	0.000
α -carotene	10	0.87	0.72-1.03	0.110	random	20.14	55.3%	0.017
Lycopene	13	0.93	0.81-1.07	0.329	random	34.83	65.6%	0.000
Lutein/Zeaxanthin	12	0.96	0.87-1.07	0.508	fix	12.31	10.6%	0.341
β -Cryptoxanthin	18	0.70	0.54-0.90	0.005	random	116.71	85.4%	0.000
Carotenoids	19	0.97	0.81-1.15	0.717	random	58.44	69.2%	0.000
Retinol	15	0.99	0.89-1.10	0.850	fix	21.37	34.5%	0.092
Carotenoids (serum)	11	0.73	0.58-0.93	0.010	random	30.79	67.5%	0.001
Retinol (serum)	4	0.62	0.26-1.49	0.284	random	30.51	90.8%	0.000

Figures

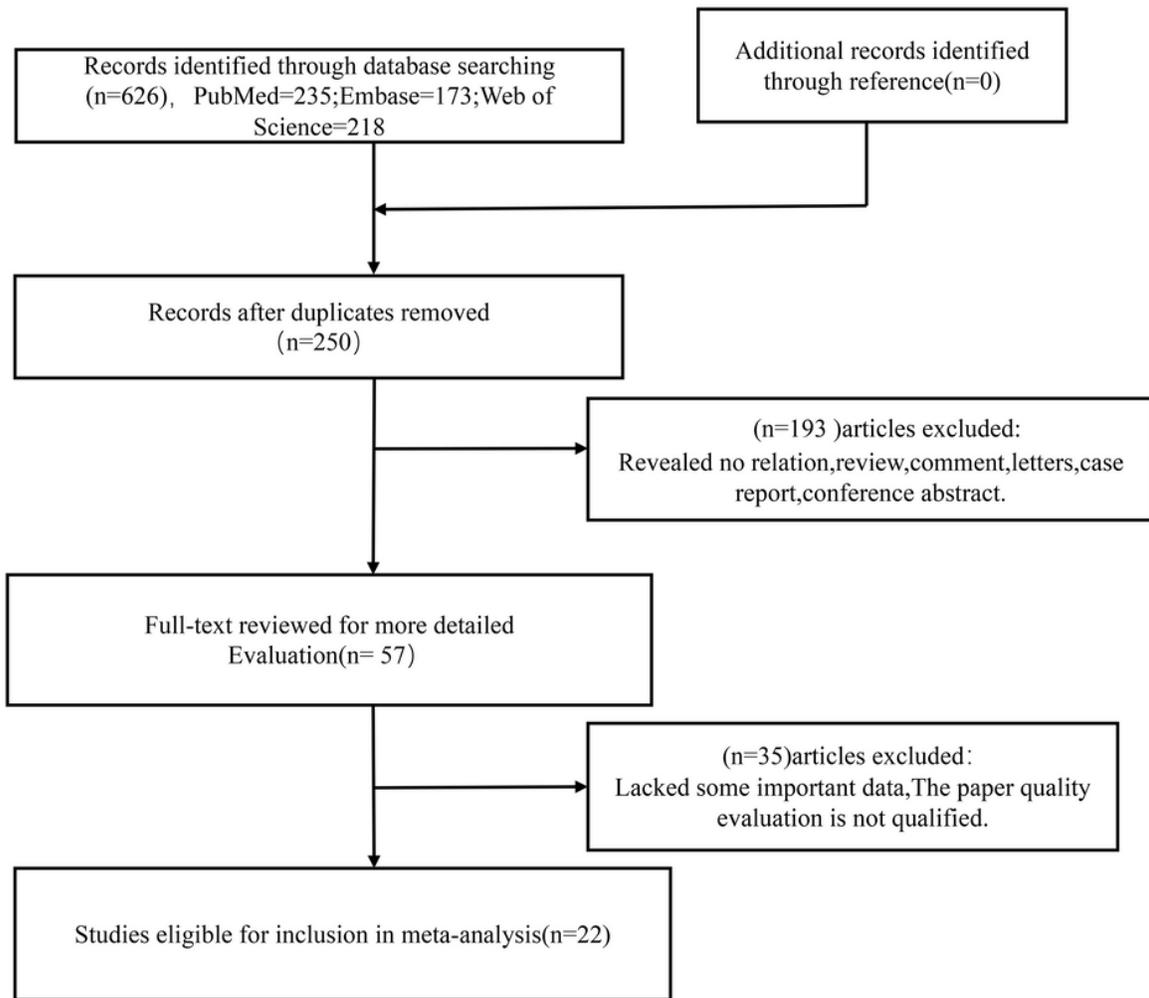


Figure 1

Flow diagram of this meta-analysis.

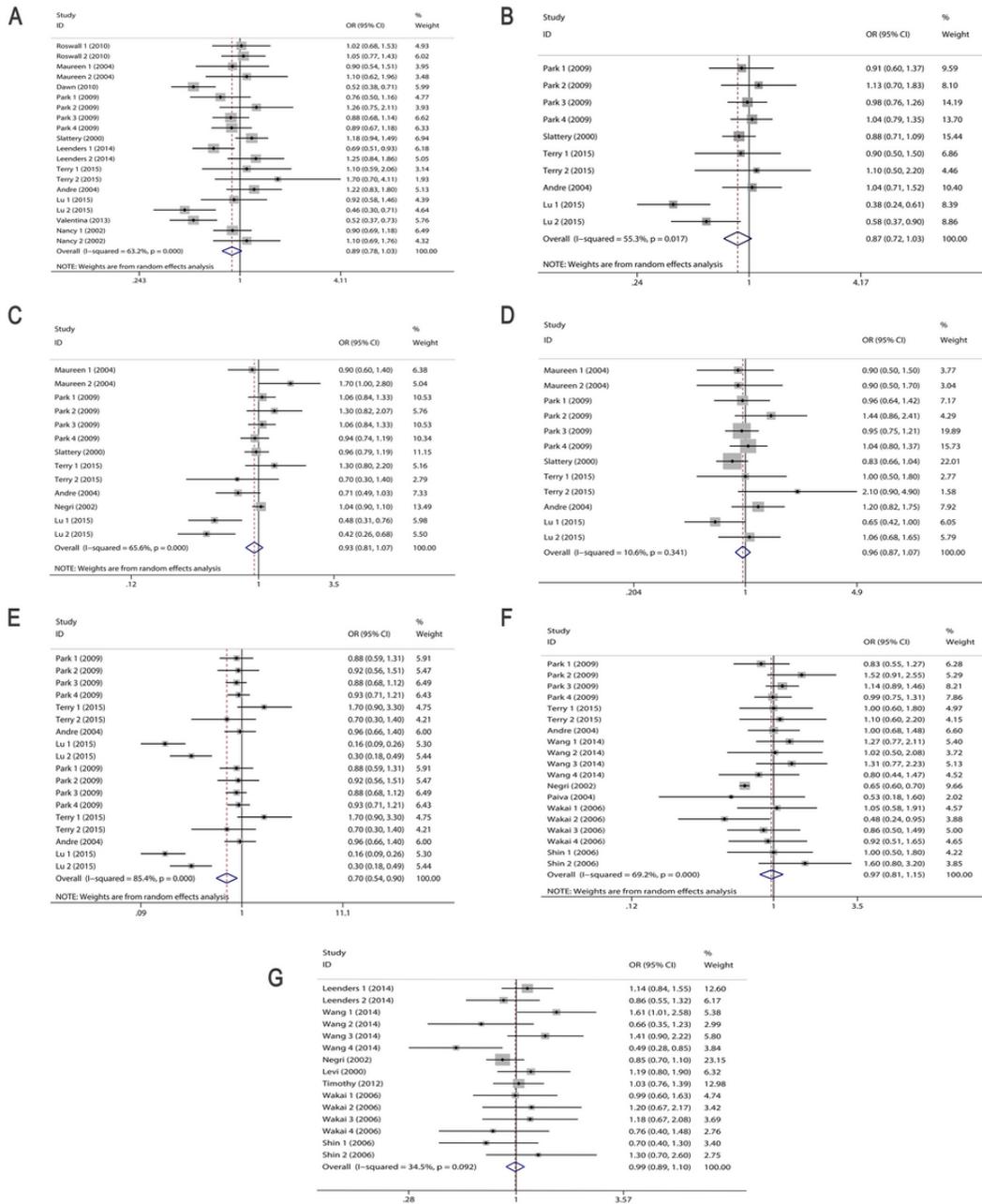


Figure 2

Forest plot on dietary intake of carotenoids and retinol and colorectal cancer risk. (A) β -carotene;(B) α -carotene; (C) Lycopene; (D) Lutein/Zeaxanthin;(E) β -Cryptoxanthin; (F) Carotenoids;(G) Retinol.

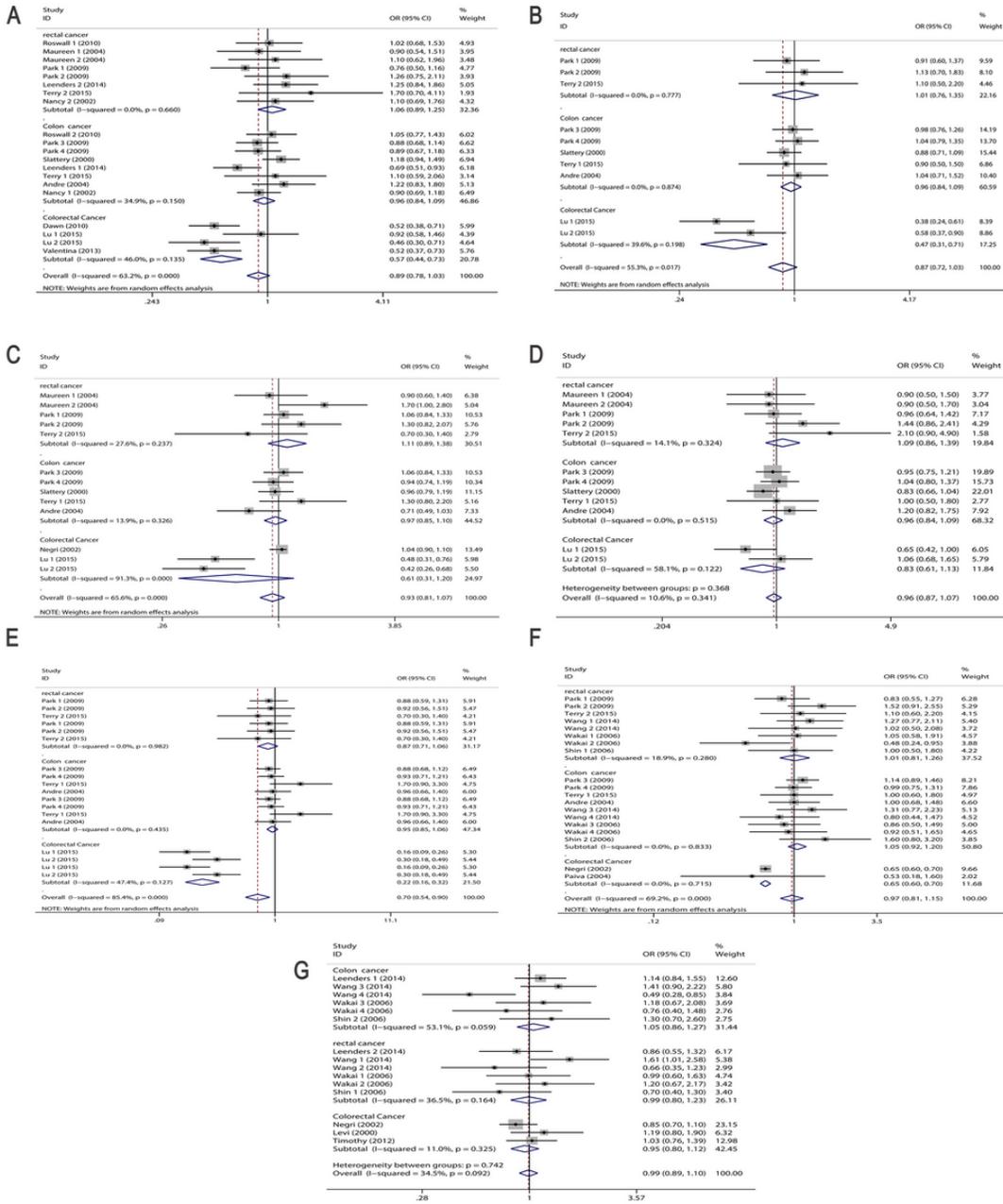


Figure 3

Tumor subgroup analysis of dietary carotenoid and retinol intake and colorectal cancer risk. (A) β -carotene;(B) α -carotene; (C) Lycopene; (D) Lutein/Zeaxanthin;(E) β -Cryptoxanthin; (F) Carotenoids;(G) Retinol.

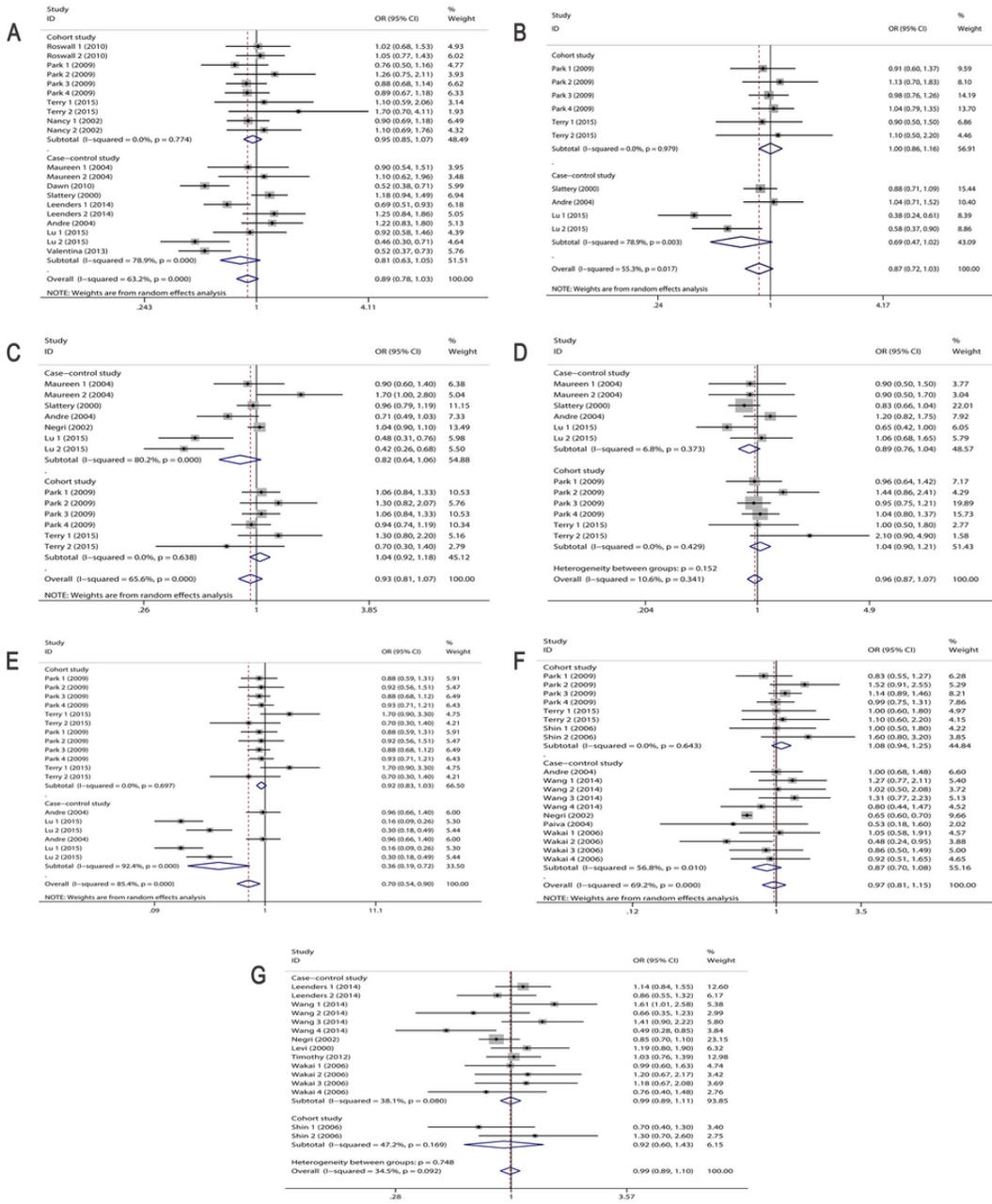


Figure 4

Study type subgroup analysis of dietary carotenoid and retinol intake and colorectal cancer risk. (A) β -carotene;(B) α -carotene; (C) Lycopene; (D) Lutein/Zeaxanthin;(E) β -Cryptoxanthin; (F) Carotenoids;(G) Retinol.

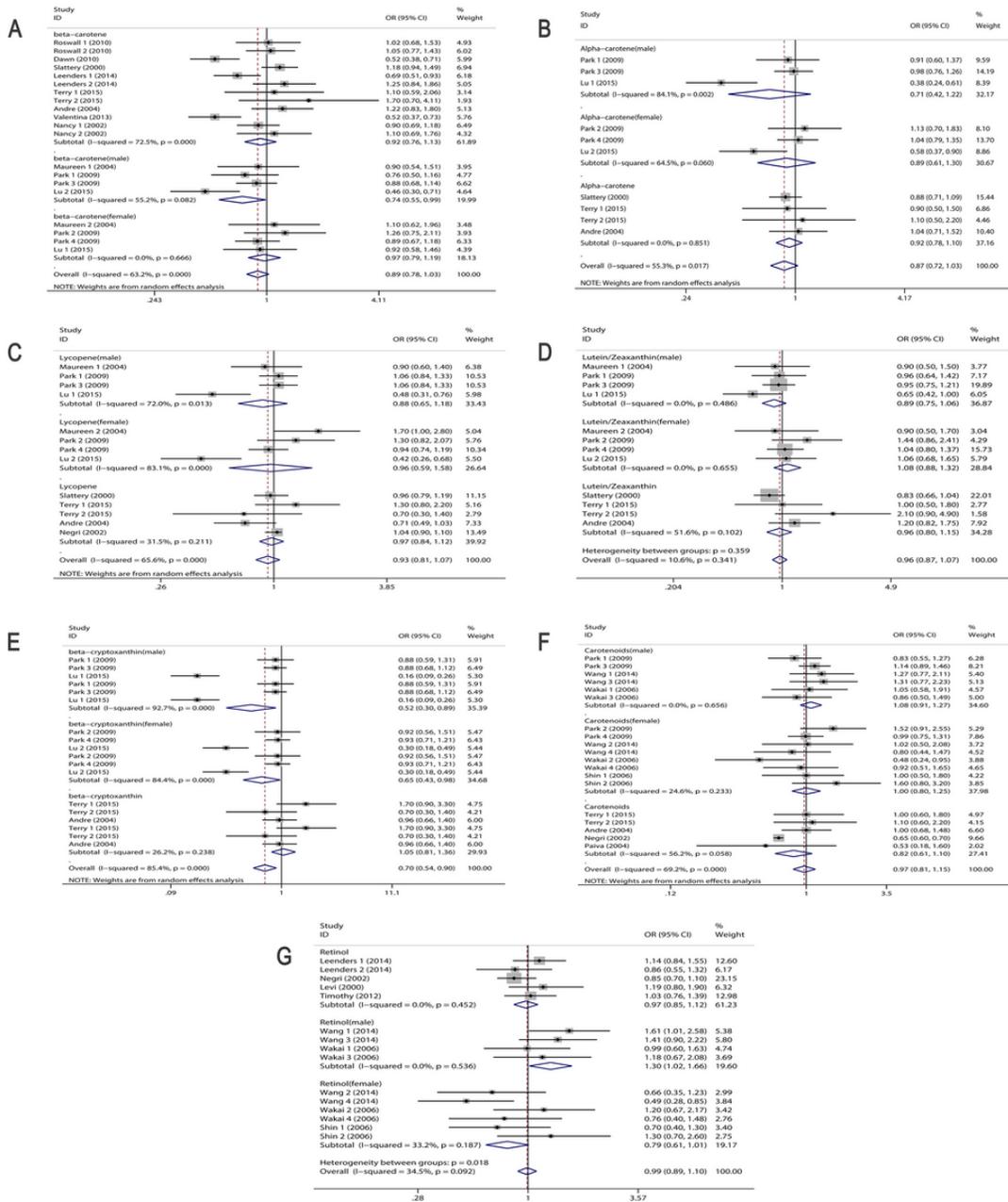


Figure 5

Sex subgroup analysis of dietary carotenoid and retinol intake and colorectal cancer risk. (A) β -carotene; (B) α -carotene; (C) Lycopene; (D) Lutein/Zeaxanthin; (E) β -Cryptoxanthin; (F) Carotenoids; (G) Retinol.

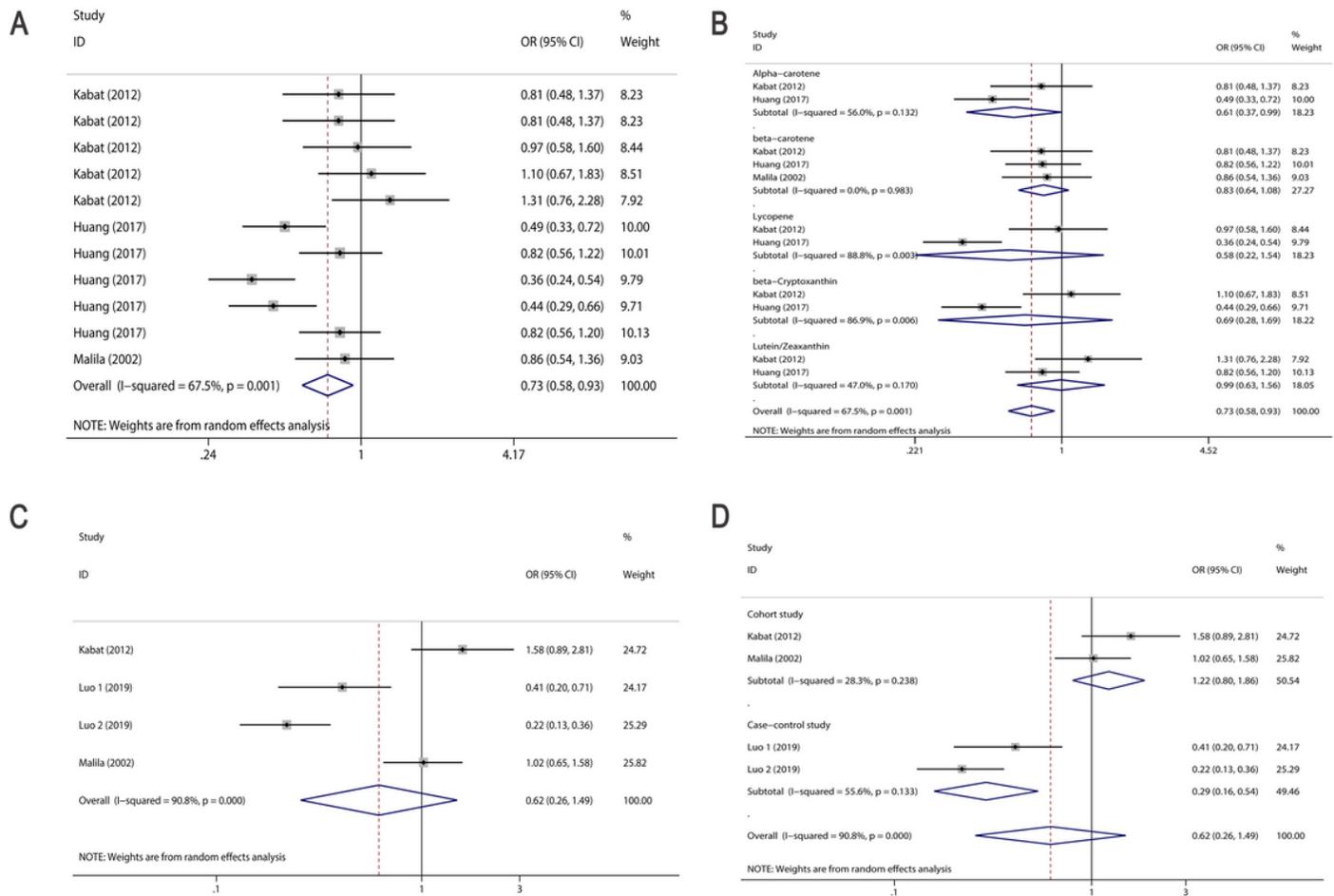


Figure 6

Forest plot of serum carotenoid and retinol concentrations and colorectal cancer risk. (A) serum carotenoid;(B) Subgroup analysis of serum carotenoids according to their types;(C) serum retinol;(D) Subgroup analysis of serum retinol by study type.

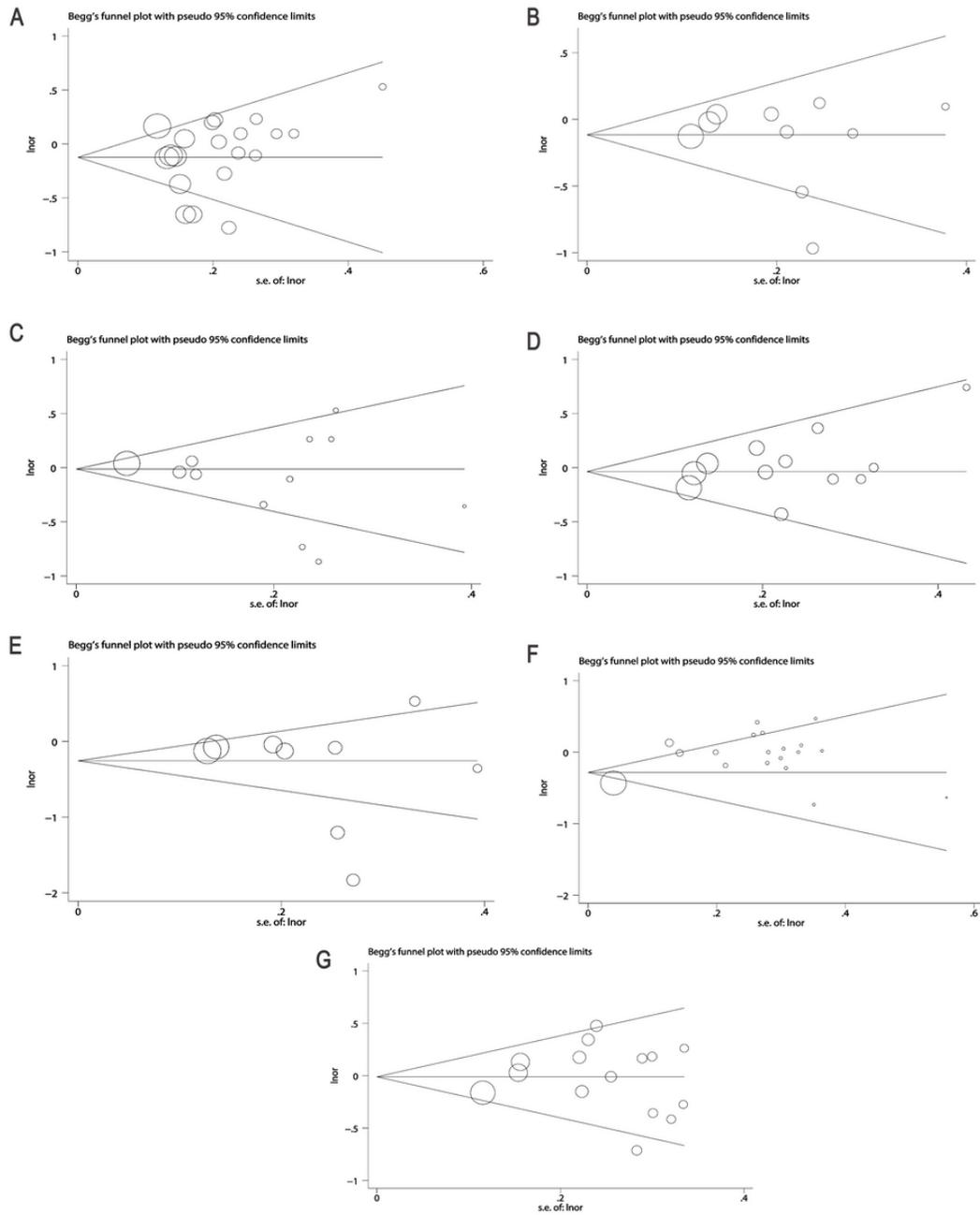


Figure 7

Begg's publication bias plots on dietary carotenoids and retinol and colorectal cancer risk. (A) β -carotene;(B) α -carotene; (C) Lycopene; (D) Lutein/Zeaxanthin;(E) β -Cryptoxanthin; (F) Carotenoids;(G) Retinol.

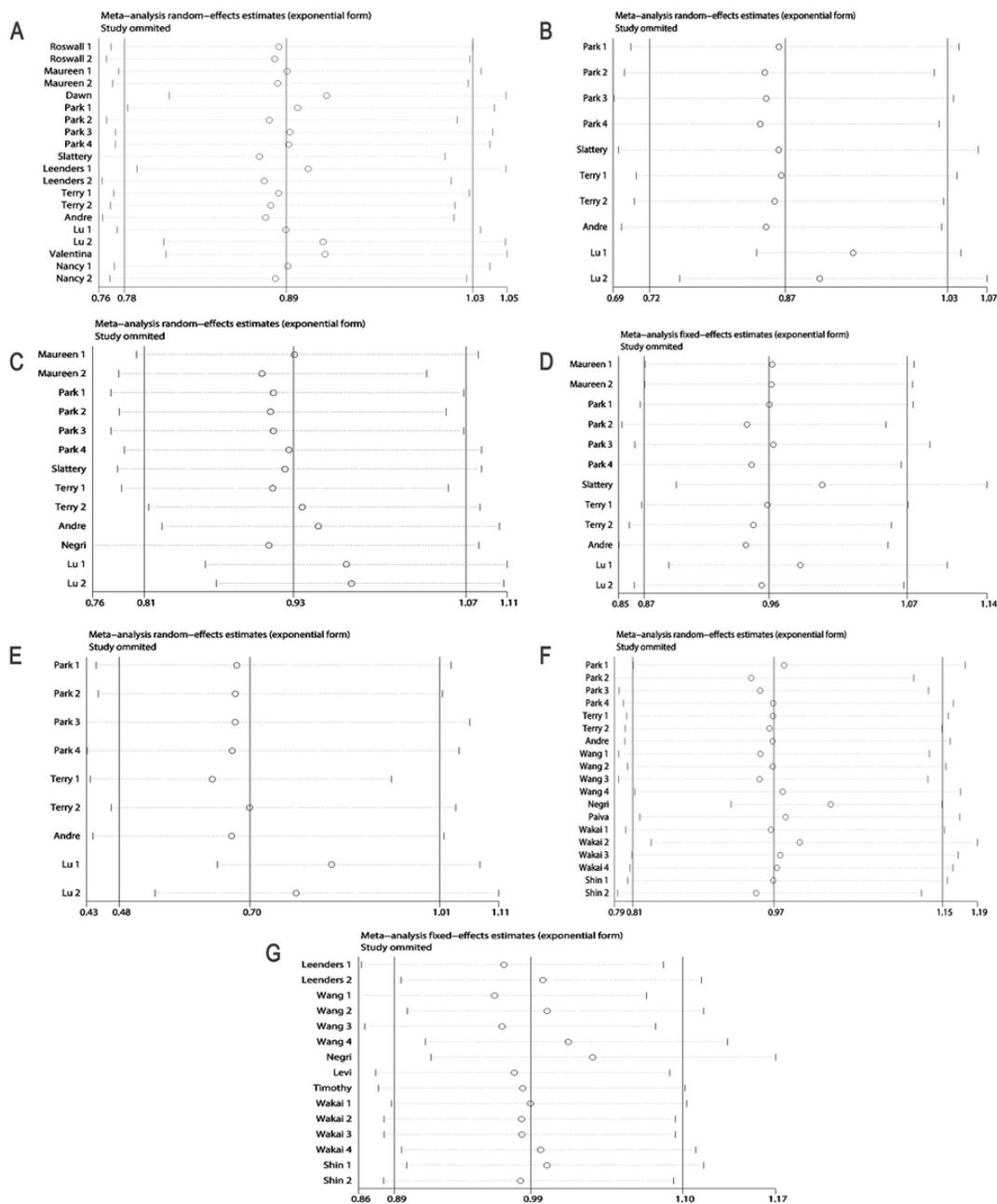


Figure 8

Sensitivity analysis plots on dietary carotenoids and retinol and colorectal cancer risk. (A) β -carotene;(B) α -carotene; (C) Lycopene; (D) Lutein/Zeaxanthin;(E) β -Cryptoxanthin; (F) Carotenoids;(G) Retinol.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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