



Association between carotenoids and prostate cancer risk: A Meta-Analysis

Hadjer BENKHADDA ¹, Manel BOUCHENTOUF ¹, **Salah Eddine EL HERRAG ^{1*}**

¹ Department of Biology, Faculty of Natural and Life Sciences, Djillali Liabes University, PO Box 89, Sidi-Bel-Abbes (22000), Algeria

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ABSTRACT

Background: Carotenoids have been hypothesized to promote the prevention and treatment of prostate cancer (PC). Aims: Conducting a meta-analysis to assess whether the association differs by the type of carotenoids and to compare the relationships of each type of carotenoid with PC risk. Methods and Material: A literature search was conducted using the PubMed database. Pertinent studies were included in the meta-analysis of higher versus lower categories of dietary intakes or serum concentrations of carotenoids in relation to PC. A random-effects model was used to obtain the pooled odds ratios (ORs) and their confidence intervals (95%) of the case-control and cohort studies, for generic inverse variance data. Results: 13 identified studies involved 44,861 participants. The meta-analysis determined, for total carotenoids and lycopene, a statistically significant relationship with PC risk; OR: 0.88; 95% CI 0.81-0.96 and 0.87; 95% CI 0.77-0.99 respectively. However, no other carotenoid was noticed to have a statistically significant association with PC risk. Comparison of the effect of each type of carotenoid on PC risk showed that lycopene, lutein-zeaxanthin, and β -cryptoxanthin had a moderate inverse but not statistically significant relationship with PC risk. Compared to β -carotene, and α -carotene results, their effect estimates were higher than the previous carotenoids. Conclusions: Our findings indicate that PC was inversely associated with total carotenoids and lycopene dietary intake and serum concentrations. These data provide support for the utilization of carotenoids for the treatment and prevention of PC.

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* Corresponding author  Tel: +213 697813902

 salaheddine.elherrag@univ-sba.dz

1. INTRODUCTION

Prostate cancer (PC) or carcinoma of the prostate is ranked as the second most common cancer within men worldwide [1]. An estimated number of 1.3 million cases were diagnosed worldwide with PC in 2018, accounting for 13.5 % of the cancers diagnosed in men, with almost 63 % of them (802.294) occurring in more developed regions [2]. The development of PC is complex and influenced by a combination of genetic, hormonal, and social factors. Carotenoids represent biologically active phytochemicals which are present as micro-components in fruits and

vegetables and are responsible for their yellow, orange and red colors [3]. These micronutrients are thought to be responsible for the beneficial properties of fruits and vegetables in preventing human diseases including cardiovascular diseases [4], cancer [5-7], and other chronic diseases, and have distinct anti-oxidative properties, including protecting DNA and other important biomolecules from free radicals [8]. In recent years the antioxidant properties of carotenoids have been the major focus of research. More than 600 carotenoids have so far

been identified in nature. However, only about 40 are present in a typical human diet. Among these 40, about 20 carotenoids have been identified in human blood and tissues. Close to 90% of the carotenoids, in the diet and the human body, is represented by alpha-carotene, beta-carotene, lutein, beta-cryptoxanthin, and lycopene [9]. Higher consumption of tomato products, dietary lycopene intake, and circulating lycopene concentrations were found to be inversely associated with prostate cancer risk [10,11]. Many epidemiological studies have investigated the association between prostate cancer and carotenoids, however, results have been inconsistent [12,13]. Consequently, In the current study, we aimed to investigate the relationship between dietary intake or blood concentrations of these carotenoids and their potential preventive effect on PC.

2. MATERIAL AND METHODS

2.1 Search strategy

The current meta-analysis was performed in accordance with PRISMA guidelines [14]. The literature search was independently undertaken by two authors (H.B and M.B). The author (S.E) made the final decision in case of any discrepancy. A comprehensive literature search was conducted using the PubMed database [<https://www.ncbi.nlm.nih.gov/pubmed>] to identify relevant English published articles on the relationship between carotenoids dietary intake or supplementation and the risk of PC. Using medical subject heading (Mesh), with the key terms: "carotenoids" and "prostatic neoplasms". English full texts were searched with no population restriction (the final search was performed on 13 May 2018).

2.2 Study selection

Studies that met the following criteria were included in the meta-analysis: (a) the study design was a cohort, and case-control ; (b) the primary outcome was clearly defined as prostate cancer ; (c) studies that assessed the relationship between carotenoids (lycopene, β -carotene, α -carotene, β -cryptoxanthin, and lutein/zeaxanthin) and PC risk ; (d) the exposure of interest was carotenoids intake and supplementation ; (e) the study provided Odds Ratios (OR) with 95% confidence intervals (CI) for exposure categories. Furthermore, letters, comments, and articles, not published as full text, reviews, meta-analyses, animal studies, cellular culture, reports, and articles with missing or not appropriate data, were excluded.

2.3 Data extraction

Data collection form, for each publication, was as follow: first author's name, year of publication, country of origin,

outcomes, recruitment and intervention periods, study type, number of cases, controls, total number, and age of participants in the study, exposure values of carotenoids (serum and/or intake), and the adjusted confounders.

2.4 Summary measures

Review Manager 5.3 was utilized to analyze the data [15]. The pooled OR with 95% CI is given both for the fixed effects model and the random effects model. If value 1 is not within the 95% CI, then the OR is statistically significant at the 5% level ($P \leq 0.05$) [16]. We used the study-specific OR for the highest versus lowest categories of dietary carotenoids intake or carotenoids concentration exposure for the meta-analysis. The study selection, data extraction, and statistical analysis were independently undertaken by two authors (H.B and M.B), a third author (S.E) made the final decision in case of any disagreement.

2.5 Publication bias

Publication bias and the small study effect were assessed using Begg's [17] rank correlation test and Egger's regression test [18], following a visual assessment of funnel plots. The R program was used for assessing the bias risk across studies [19].

2.6 Sensitivity and subgroup analyses

Pre-Specified subgroup analyses were performed allowing for study types, location, methods used, and the adjusted confounders. Furthermore, sensitivity analyses were performed by excluding one dataset at a time with the purpose of analyzing the influence of each study on the effect estimates and the heterogeneity.

3 RESULTS

3.1 Study selection

The literature search yielded a total of 754 publications. After screening, 13 studies were included and 741 were excluded, among the 741 excluded articles, 470 did not meet the criteria, 194 reviews, and meta-analysis, and 34 letters to editorial and comments, and 43 not appropriate or missing data (Figure 1).

3.2 Study characteristics

Table 1 summarizes properties of the included studies. Two cohort and 11 case-control studies were included. Seven studies were carried out in the USA [12, 13, 20–24], three in Australia [25–27], two in Europe [28, 29], and one in Asia[30]. Among the included studies, eleven studies reported the effects of dietary intake or serum concentrations of lycopene and β -Carotene on PC. With the exception of five studies, almost all adjusted analyses

included age as a potential confounder and four studies controlled for family history of PC and body mass index (BMI).

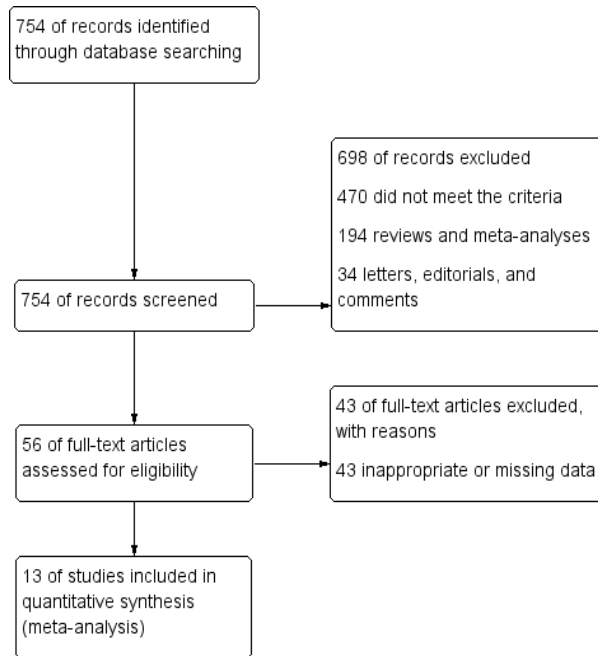


Figure 1: Flowchart of study selection

3.3 Relationship between carotenoids and risk of PC

The results of the meta-analysis, of highest versus lowest categories of carotenoids intake and serum concentrations, are summarized in table 2 and figure 2. A total of 44,861 participants from these studies were assigned to intervention or control groups. The number of participants in each case-control and cohort ranged from 321 to 29,361. The effects of lycopene and β -carotene were examined singly or in combination in six studies and in combination with other carotenoids in seven studies.

The summary effect of the main analysis on PC was statistically significant with an OR of 0.88 (95% CI 0.81-0.96), with moderate heterogeneity ($I^2 = 56\%$). Thus, we conclude that carotenoids intake decreased the overall relative risk of PC.

Nonetheless, we observed, after performing a sensitivity analysis, that one study (Jian *et al.*, 2004) [30] constituted the major source of heterogeneity in our meta-analysis and after neglecting this study, I^2 dropped to only 2%.

3.3.1 Lycopene

A total of 11 studies with 15 datasets, on the relationship between lycopene and prostate cancer, were included. Our results showed that lycopene significantly reduced the prostate cancer risk (OR = 0.88; 95% CI 0.78-1.00), with moderate heterogeneity ($I^2 = 44\%$).

According to further subgroup analysis, as shown in Table 3, we did not identify significant associations between PC risk and lycopene for cohort studies ($P = 0.56$). However, case-control studies indicated that lycopene significantly decreased PC risk (OR = 0.87; 95% CI 0.77-0.99). Moreover, studies conducted in Australia and North American countries showed a stronger inverse relationship than European studies (OR = 0.76; 95% CI 0.53-1.09), (OR = 0.90; 95% CI 0.83-0.99, P (Z-test) = 0.03), and (OR = 0.94; 95% CI 0.75-1.16) respectively. Five studies with seven datasets reported data about dietary lycopene supplementation and PC risk. A statistically significant negative association was observed (OR = 0.83; 95% CI 0.70-0.99). A less strong and yet statistically non-significant inverse relationship was found between serum lycopene concentrations and PC (OR = 0.96; 95% CI 0.81-1.15).

3.3.2 α -Carotene

Regarding the overall pooled estimates of the association between α -carotene and PC risk, we noticed a statistically non-significant negative association with an OR of 0.80 (95% CI 0.60-1.07) and a moderate heterogeneity ($I^2 = 59\%$). Alpha carotene was found to decrease PC risk in case-control studies and in studies conducted in North American countries (OR = 0.86; 95% CI 0.64-1.15) and (OR = 0.87; 95% CI 0.59-1.29) respectively, although the associations were not statistically significant. The same pattern was noticed for studies investigating the effect of highest versus lowest categories of α -carotene intake (OR = 0.87; 95% CI 0.59-1.29) and serum concentrations (OR = 0.65; 95% CI 0.33-1.27).

3.3.3 β -Carotene

A total of 11 studies, including 15 datasets, reported data on β -carotene and PC risk. Comparing the highest with the lowest dietary intake or blood concentrations, a statistically non-significant inverse association was found with an OR of 0.95 (95% CI 0.78-1.11) and moderate heterogeneity ($I^2 = 54\%$). The main analysis was stratified according to study type, population, and methods used to assess the relationship. Therefore, nine studies with 13 datasets of case-control studies were pooled (OR = 0.95; 95% CI 0.78-1.16), and two cohort studies (OR = 0.79; 95% CI 0.46-1.35), suggesting a statistically non-significant negative association between β -carotene and PC risk. Our findings suggest that β -carotene has no effect on PC risk among North American (OR = 1.02; 95% CI 0.83-1.26), and Australian populations (OR = 1.00; 95% CI 0.76-1.31) and studies examining the effect of highest versus lowest categories of serum concentrations of β -carotene on PC (OR = 1.01; 95% CI 0.84-1.23).

Table 1: Characteristics of included studies

Case-control studies						
Author, year [ref]	Country	Follow up	Cases / controls	Methods	Type of carotenoids	Adjusted confounders
Beilby <i>et al.</i> 2010 [29]	Australia	1990-2004	96/225	Serum	Lycopene	Age, administered vitamin A supplement.
Bosetti <i>et al.</i> 2004 [32]	Italy	1991-2002	1294/1451	Dietary	Lycopene, β -carotene, Lutein	Age, study center, education, physical activity, body mass index, family history of prostate cancer and total calorie intake
Gill <i>et al.</i> 2009 [22]	The USA	1993-1996	467/936	Serum	Lycopene, β -carotene, Lutein, β -cryptoxanthin	Age at specimen collection, fasting hours prior to blood draw, body mass index, family history of prostate cancer, and education.
Goodman <i>et al.</i> 2003 [23]	The USA	1983-1996	205/205	Serum	Lycopene, β -carotene, α -Carotene, β -Cryptoxanthin, Lutein	Exposure population, study center at randomization, age at randomization within 5-year intervals, sex, smoking status at randomization, and year of randomization.
Jian <i>et al.</i> 2004 [34]	China	2001- 2002	130/274	Dietary	Lycopene, β -carotene, α -carotene, β -cryptoxanthin, Lutein	Age, locality, education, family income marital status, number of children, family history of prostate cancer, BMI, tea drinking, caloric intake, and fat intake.
Key <i>et al.</i> 1997 [33]	UK	1989-1992	328/328	Dietary	Lycopene	Social class.
Norrish <i>et al.</i> 2000 [31]	New Zealand	1996-1997	317/480	Dietary	Lycopene	Age, height, total nonsteroidal anti-inflammatory drugs, and socioeconomic status.
Peters <i>et al.</i> 2007 [24]	The USA	2000-2003	692/844	Serum	Lycopene, α -Carotene, β -Carotene, β -Cryptoxanthin, Lutein	Age, time since initial screening, year of blood draw, and study center.
Cook <i>et al.</i> 1999 [25]	The USA	1982-1988	1439/2204	Serum	β -carotene	Smoking, age, and randomized aspirin assignment.
Kirsh <i>et al.</i> 2006 [27]	The USA	1993-2001	1338/29361	Dietary	Lycopene	N/A
Wu <i>et al.</i> 2004 [26]	The USA	1993-1998	450/450	Serum	β -carotene, Lycopene, β -cryptoxanthin, Lutein/zeaxanthin	Matching variables plus cholesterol levels, selenium supplementation, vitamin E supplementation, family history of prostate cancer, body mass index, height, vigorous exercise, history of vasectomy and current smoking.
Cohort studies						
Author, year [ref]	Country	Follow up	No events / total	Methods	Type of carotenoids	Adjusted confounders
Nordström <i>et al.</i> 2016 [28]	The USA	2000-2007	112/559	Serum	β -carotene, Lycopene, α -carotene	N/A
Ambrosini <i>et al.</i> 2007 [30]	Australia	1943-1966	97/1888	Dietary	β -carotene	N/A

Table 2: Summary of results

Analysis	No of studies (datasets) [ref]	Model	OR [95% CI]	Z-test	Heterogeneity			Publication bias (P value)	
					I ² (%)	Tau ²	Chi ²	Begg's test	Egger's test
Lycopene	11 (15) [22-24, 26-29, 31-34]	RE	0.88 [0.78-1.00]	1.97 (P = 0.05)	70	0.12	19.74, df=6 (P = 0.003)	0.9605	0.678
β-Carotene	11 (15) [22-26, 28-32, 34]	RE	0.93 [0.78-1.11]	0.78 (P = 0.43)	54	0.06	30.12, df=14 (P = 0.007)	0.216	0.522
Lutein/Zeaxanthin	6 (9) [22-24, 26, 32, 34]	RE	0.86 [0.64-1.15]	1.01 (P = 0.31)	72	0.13	28.26, df=8 (P = 0.0004)	NA	NA
β-cryptoxanthin	6 (7) [22-24, 26, 32, 34]	RE	0.80 [0.58-1.09]	1.42 (P = 0.16)	70	0.12	19.74, df=6 (P = 0.003)	NA	NA
α-Carotene	6 (6) [23, 24, 26, 28, 32, 34]	RE	0.80 [0.60-1.07]	1.47 (P = 0.14)	59	0.07	12.16, df=5 (P = 0.03)	NA	NA

NA not applicable, OR odds ratio, RE random effects.

Table 3: Subgroup analysis results of the association between Lycopene and prostate cancer

Subgroups	No of studies (No of datasets)	References	Model	OR [95% CI]	Z- test	Heterogeneity		
						I ² (%)	T ²	χ ²
All studies	11 (15)	[22-24, 26-29, 31-34]	RE	0.88 [0.78-1.00]	1.97 (P = 0.05)	44	0.02	24.93, df = 14 (P = 0.04)
Study type								
Cohort	1 (1)	[28]	RE	1.22 [0.62-2.40]	0.58 (P = 0.56)			N/A
Case-control	12 (14)	[22-24, 26, 27, 29, 31-34]	RE	0.87 [0.77-0.99]	2.08 (P = 0.04)	46	0.02	24.06, df = 13 (P = 0.03)
Study location								
Asia	1 (1)	[34]	RE	0.18 [0.08-0.40]	4.08 (P < 0.0001)			N/A
Europe	2 (2)	[32, 33]	FE	0.94 [0.75-1.16]	0.59 (P = 0.56)	0	N/A	0.00, df = 1 (P = 0.96)
North America	6 (10)	[22-24, 26-28]	FE	0.90 [0.83-0.99]	2.22 (P = 0.03)	5	N/A	9.43, df = 9 (P = 0.40)
Australia	2 (2)	[29, 31]	FE	0.76 [0.53-1.09]	1.47 (P = 0.14)	0	N/A	0.00, df = 1 (P = 0.98)
Methods								
Serum	6 (8)	[22-24, 26, 28, 29]	FE	0.96 [0.81-1.15]	0.41 (P = 0.68)	0	N/A	6.31, df = 7 (P = 0.50)
Dietary	5 (7)	[27, 31-34]	RE	0.83 [0.70-0.99]	2.05 (P = 0.04)	66	0.03	17.49, df = 6 (P = 0.008)
Adjusted confounders								
Age	8 (12)	[22-24, 27, 29, 31, 32, 34]	RE	0.88 [0.76-1.01]	1.77 (P = 0.08)	52	0.03	22.85, df = 11 (P = 0.02)
Family history of PC	4 (5)	[22, 26, 32, 34]	RE	0.70 [0.44-1.13]	1.45 (P = 0.15)	76	0.20	16.96, df = 4 (P = 0.005)
BMI	4 (5)	[22, 26, 32, 34]	RE	0.70 [0.44-1.13]	1.45 (P = 0.15)	76	0.20	16.96, df = 4 (P = 0.005)
Education	3 (4)	[22, 32, 34]	RE	0.71 [0.39-1.30]	1.10 (P = 0.27)	82	0.28	16.37, df = 3 (P = 0.0010)
Study Center	3 (3)	[23, 24, 32]	FE	1.01 [0.85-1.21]	0.16 (P = 0.87)	0	N/A	0.82, df = 2 (P = 0.67)
Smoking	2 (2)	[23, 26]	FE	0.83 [0.57, 1.21]	0.96 (P = 0.34)	28	N/A	1.38, df = 1 (P = 0.24)
Height	2 (2)	[26, 31]	FE	0.72 [0.51, 1.01]	1.91 (P = 0.06)	0	N/A	0.17, df = 1 (P = 0.68)
Caloric intake	2 (2)	[32, 34]	RE	0.43 [0.09, 2.17]	1.02 (P = 0.31)	93	1.27	13.99, df = 1 (P = 0.0002)

BMI Body mass index, df degree of freedom, FE fixed effects, N/A not-applicable, PC prostate cancer, OR odds ratio, RE random effects.

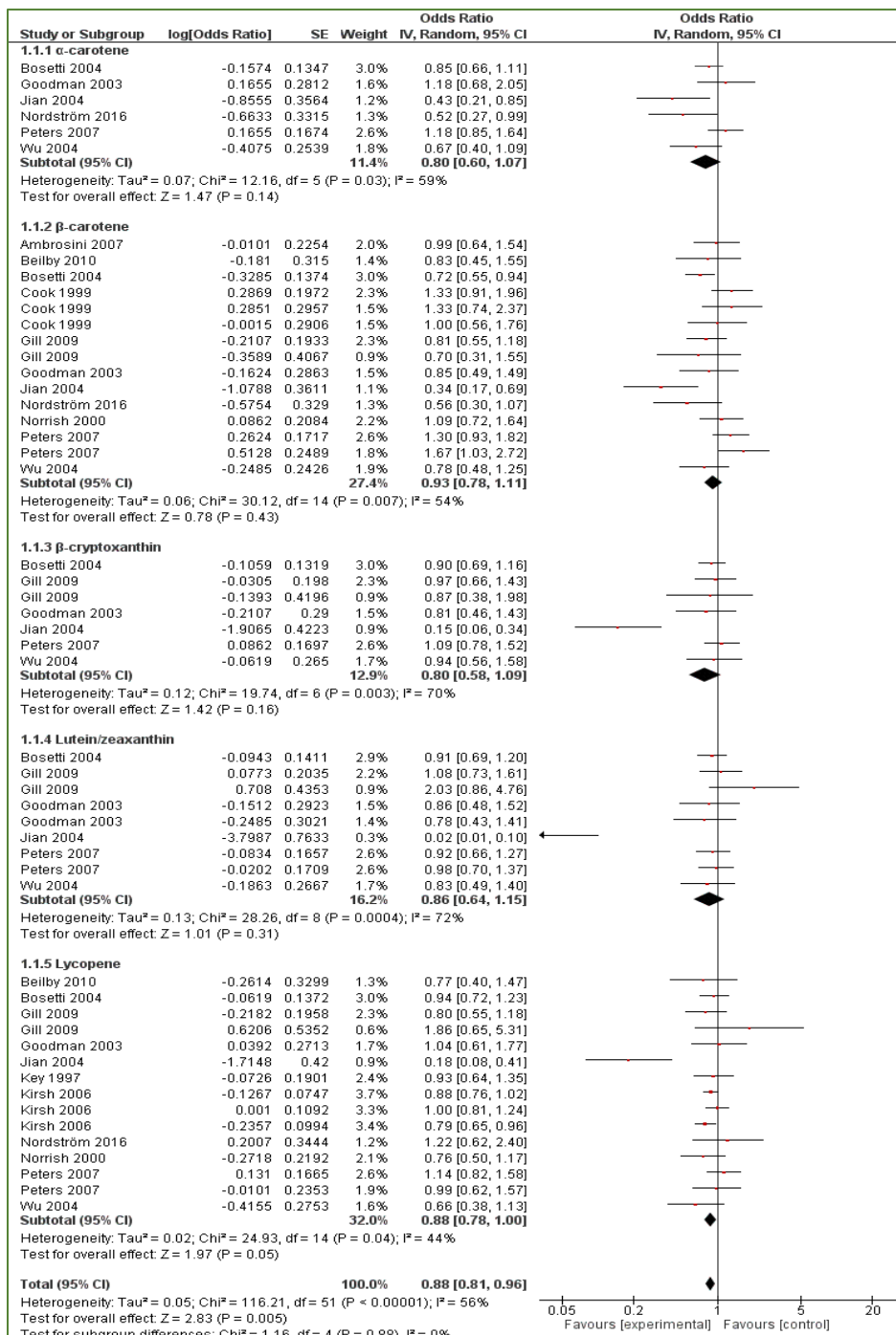


Figure 2: Forest plot for the association between Carotenoids and PC risk

3.3.4 Lutein/Zeaxanthin

Aiming to investigate the relationship between lutein/zeaxanthin and PC risk, the summary of ORs of six case-control studies with nine datasets was estimated. We observed a statistically non-significant decrease in PC risk

with an OR of 0.86 (95% CI 0.64-1.15) with high heterogeneity (I² = 72%). A slight decrease and yet statistically not-significant was noticed within North American populations and for studies using serum concentrations of lutein/zeaxanthin to investigate the association (OR = 0.96; 95% CI 0.81-1.14).

3.3.5 β -cryptoxanthin

In a pooled analysis of six case-control studies reporting data about the effect of β -cryptoxanthin on PC risk, an OR of 0.80 (95% CI 0.58-1.09, $I^2 = 70\%$) was found, indicating a statistically non-significant inverse association. A slight decrease and yet statistically not-significant was noticed within North American populations and for studies using serum concentrations of β -cryptoxanthin to investigate the association (OR = 0.98; 95% CI 0.80-1.20).

3.4 Publication bias

The funnel plots put in the Supplementary figures show no sign of asymmetry. Among the five meta-analyses, the risk of bias assessment was available for two analyses since they included a number of datasets ≥ 10 . Both analyses showed no evidence of small study effect. The analysis of lycopene and PC (Begg's test $P = 0.9605$, Egger's test $P = 0.678$) and the analysis of β -Carotene and PC (Begg's test $P = 0.216$, Egger's test $P = 0.522$).

4 DISCUSSION

The current meta-analysis, which included 13 studies, provided evidence that carotenoids could prevent against PC. To sum up, the overall analysis demonstrated a significant decrease in PC incidence. The same pattern was noticed for all types of carotenoids investigated in our study i.e. lycopene β -carotene, α -carotene, β -cryptoxanthin, and lutein/zeaxanthin.

In vitro and animal studies have provided evidence that carotenoids may protect against several types of cancer [31–34]. Additionally, the World Cancer Research Fund (WCRF) released a comprehensive report on food and cancer prevention in 2007 highlighting that foods containing carotenoids are probably protective against lung, mouth, pharynx, and larynx cancers [35].

Stahl and Sies [36] stated that carotenoids and/or their metabolites influence the expression of certain genes or may act as regulatory enzymes inhibitors in context with cancer preventive properties of these compounds.

The mechanism underlying the beneficial effect of lycopene on PC risk can be explained by this carotenoid high biological activity through antioxidant properties as preventing DNA damage by scavenging free radicals [8] and modulating gene expression related to PC growth [37]. Furthermore, Yang *et al.*, [38] showed that this non-provitamin A carotenoid inhibits PC cell proliferation via the PPAR γ -LXR α – ABCA1 pathway. According to Stahl and Sies [36] and Gerster [39], lycopene was found to hamper the progression of PC via apoptosis induction and angiogenesis suppression.

The current analysis provides support for future studies using carotenoid-based dietary or supplementation interventions and plays a key role in PC survivorship including treatment.

Concerning the risk of PC, our results agree with some previous studies. Wang *et al.* [40], reported in a meta-analysis of 34 studies, that lycopene (RR = 0.88; 95% CI 0.76-1.02), but not β -carotene (RR = 0.90; 95% CI 0.81-1.01), were inversely associated with the risk of PC.

Nonetheless, both Chen *et al.* (2015) [41], Ilic *et al.* [42] found a positive association between lycopene consumption (RR = 0.91; 95% CI 0.81-1.01) and (OR = - 0.34; 95% CI - 2.01-1.32) respectively with the risk of PC.

Controversially to our analysis, Wang *et al.* [40] stated that α -carotene (RR = 0.87; 95% CI 0.76-0.99) was positively associated with the risk of developing PC.

However, similar to dietary carotene intake, Van Hoang *et al.* [43] observed in a case-control study no relationship between β -cryptoxanthin intake as well as lutein and zeaxanthin with adjusted ORs of 1.29 (95% CI 0.79-2.09) and 0.73 (95% CI 0.44-1.20) respectively with PC risk.

The type of studies (cohort and case-control), populations (Asia, Europe, Australia, and the USA) slightly influenced the odds estimate. However, sensitivity analysis further showed that when omitting the studies conducted by (Jian *et al.*, 2004) [30], the results noticeably changed.

To the best of our knowledge, this is the first meta-analysis undertaken to highlight the relationship between carotenoids and PC risk. However, some limitations should be considered as the limited number of articles included in our analysis. Moreover, our analyses showed heterogeneity evidence. However, subgroup analysis demonstrated sources of heterogeneity that could be attributable to including different study designs in the analyses.

5 CONCLUSION

The current meta-analysis has been undertaken to assess available evidence for treatment and prevention of PC, to show the contribution of carotenoids, their intake or supplementation, and to perform a comparison between their relationships with PC risk.

Our results showed that all types of carotenoids investigated in our study may contribute to the prevention of PC. To determine whether they are clinically relevant, more laboratory and clinical trials are needed on the effects of these compounds on the behavior of prostate cancer cells and tissues. Moreover, the lack of evidence and data supports the call for publishing more research in this area to investigate the effectiveness of carotenoids for the prevention and treatment of PC.

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