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Review

Cancer Epidemiology, Biomarkers & Prevention

Carotenoid Intake from Natural Sources and Head and Neck Cancer: A Systematic Review and Meta-analysis of Epidemiological Studies

Emanuele Leoncini[1], Darko Nedovic[1], Nikola Panic[1], Roberta Pastorino[1], Valeria Edefonti[2], and Stefania Boccia[1]

Abstract

Because of their role as antioxidants, the intake of carotenoids has been hypothesized to reduce the risk of head and neck cancer (HNC). We conducted a systematic review and meta-analysis of the epidemiological studies to investigate whether the intake of specific carotenoids from dietary sources, as well as combined carotenoids, is associated with the risk of HNC according to cancer subsites. A comprehensive literature search of the Medline and Scopus databases was conducted. Sixteen articles were identified from the literature search, of which 15 were case–control studies and one prospective cohort study. The risk reduction associated with β-carotene equivalents intake was 46% (95% CI, 20%–63%) for cancer of oral cavity and 57% (95% CI, 23%–76%) for laryngeal cancer. Lycopene and β-cryptoxanthin also reduced the risk for laryngeal cancer; the ORs for the highest category compared with the lowest one of carotenoid intake were 50% (95% CI, 11%–72%) and 59% (95% CI, 49%–67%), respectively. Lycopene, α-carotene, and β-cryptoxanthin were associated with at least 26% reduction in the rate of oral and pharyngeal cancer (95% CI, 2%–44%). Our systematic review and meta-analysis on dietary carotenoids intake and HNC showed carotenoids to act protectively against HNC, in relation to most of single nutrients and subsites. *Cancer Epidemiol Biomarkers Prev; 24(7); 1003–11. ©2015 AACR.*

Introduction

Head and neck cancer (HNC) encompasses tumors that occur in several sites of the head and neck region, including the oral cavity, pharynx, and larynx, with 90% being squamous cell carcinomas (1). Worldwide, cancers of the head and neck are the sixth most common cancer, with an estimated half million new cases and over 450,000 deaths in 2012 (2). Carotenoids represent a diverse group of natural pigments of the polyene type (3) and are present in non-starchy vegetables and fruit. Carotenoids can be classified into oxygenated carotenoids (β-cryptoxanthin, lutein, and zeaxanthin), called xanthophylls, and hydrocarbon carotenoids (e.g., α-carotene, β-carotene, and lycopene), called carotenes (4). They are known to be very efficient physical and chemical quenchers of singlet oxygen, and potent scavengers of other reactive oxygen species (5, 6). Because of their role, the intake of carotenoids has been hypothesized to reduce the risk of HNC (7). However, carotenoids from natural sources might have a different effect on HNC, depending on the degree of their biologic activity and antioxidant capacities (8).

Several epidemiological studies have examined the association between carotenoid intake from dietary sources and HNC risk (9–18); however, only a few assessed the association between single-nutrient intake and HNC, with conflicting results (17, 19–24).

Although some reviews report that carotenoids intake have a protective effect on overall HNC (25, 26), the effect on specific cancer subsites and that of single carotenoids so far were not addressed. The aim of this study is to conduct a systematic review and meta-analysis of the epidemiological studies to investigate whether the intake of specific carotenoids from dietary sources, as well as combined carotenoids, reduces the risk of HNC according to specific cancer subsites.

Materials and Methods

Search strategy

We conducted a comprehensive literature search of the MEDLINE and Scopus databases. We selected the following keywords for the literature search: "diet", "nutrients", "carotenoids", "cryptoxanthin", "lycopene", "lutein", "zeaxanthin", "oral carcinoma", "oral cancer", "pharyngeal cancer", "laryngeal cancer", "hypopharyngeal cancer", "oropharyngeal cancer", and "head and neck cancer". The search was limited to human subjects with language restriction to English studies until May 1, 2014. The snowball strategy, including manual search of the references listed by studies retrieved from the online databases, was also adopted to identify additional studies. Abstracts, systematic reviews, editorials, and case reports were not included.

Inclusion and exclusion criteria

The eligibility criteria for inclusion in the review required that the study: (i) refers to one or more conditions corresponding with HNC clinical entity; (ii) examines the association of HNC risk with carotenoid intakes from natural sources either when considered separately or when combined; (iii) provides effect

[1]Section of Hygiene, Institute of Public Health, Università Cattolica del Sacro Cuore, Rome, Italy. [2]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy.

Corresponding Author: Stefania Boccia, Università Cattolica del Sacro Cuore, Largo F. Vito 1, 00168 Rome, Italy. Phone: 39-06-30154396/35001527; Fax: 39-06-35001522; E-mail: sboccia@rm.unicatt.it

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measures, such as a risk ratio (RR) or odds ratio (OR), and associated 95% confidence interval (CI). We excluded comments, letters, ecological studies, and animal studies. Studies were also included if they were case–control or cohort studies, studied the effects of levels of carotenoid intakes, and reported HNC cancer as the outcomes of interest. For articles including the same population resources or overlapping datasets, the study with the largest number of cases was included.

Data extraction

Two investigators (N. Panic and E. Leoncini) independently extracted information from the included studies and entered into an Excel 2010 (Microsoft Corp.) spreadsheet. Any discrepancies regarding individual study inclusion, data extraction, and interpretation were resolved by consulting a third investigator (D. Nedovic). We extracted data related to study characteristics, including first author name, year of publication, location of the study, study period, study design, number of cases and controls, site of cancer, and carotenoid examined.

Exposure to different carotenoids was investigated by extracting information on both combined carotenoids and on the intakes of individual carotenoids: α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein, and zeaxanthin.

When the general term "carotene" is used in the article, we contacted the corresponding author to ask what is meant by carotene. The term carotene has been used to indicate β-carotene equivalents in four articles (17, 18, 23, 27). We were not able to track down an updated email address for two authors (12, 15). We hypothesized that the term carotene has also been used to indicate β-carotene equivalents.

As the level of carotenoids was often categorized into quantiles, the highest intake group for HNC compared with the lowest intake group was reported in each study.

Quality assessment

We performed the quality assessment of the included studies by using Newcastle–Ottawa quality assessment scale. This scale varies from 0 (lowest quality score) to a maximum possible score of 9 (highest quality score) and incorporates information on participant selection, outcome and exposure ascertainment, and the potential for confounding (28). The systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement (29).

Statistical analysis

The association between carotenoid intake and HNC risk overall and by cancer subsites was estimated by calculating pooled OR and 95% CI, comparing the highest with the lowest category of carotenoid intake. We used random-effects models to account for variation between studies as this can provide more conservative results than a fixed-effects model (30). We quantified the proportion of the total variation due to that heterogeneity by using the I^2 statistic (31). Analyses were conducted using Stata software (StataCorp. 2013. Stata Statistical Software: Release 13: StataCorp LP).

Results

Figure 1 reports the flowchart of the bibliographic search strategy and the results. We identified a total of 432 articles in our initial search. Of these, 395 articles were excluded as duplicates, reviews, or unrelated to the research topic. The remaining 37 articles were assessed for eligibility, and 13 articles were excluded because they did not meet the inclusion criteria. An additional 8 articles were excluded as they did not report a measure of association between carotenoid intakes and HNC risk (9–11, 13, 14, 16, 19, 32). Finally, 16 articles were included, of which 15 were case–control studies (12, 15, 17, 18, 20–24, 27, 33–37) and one prospective cohort study (38).

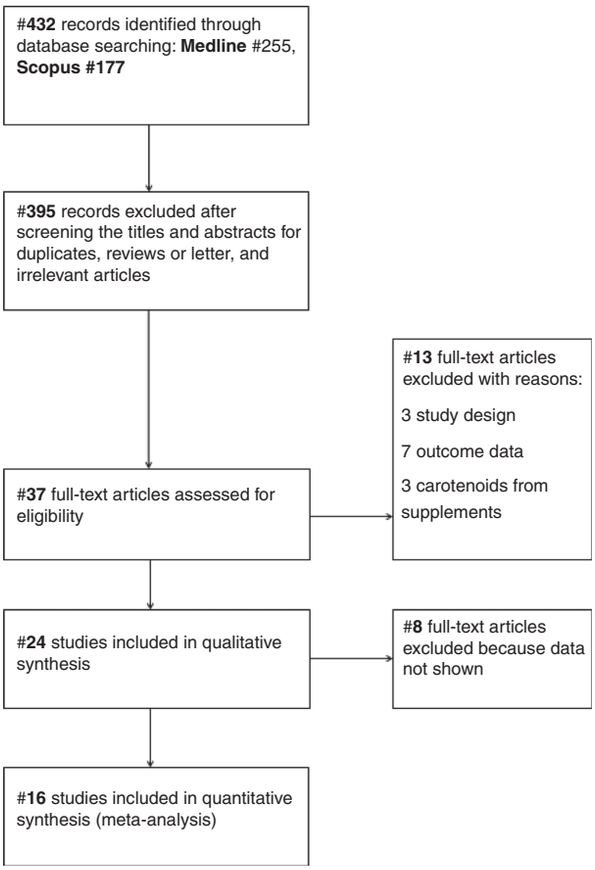

Figure 1.
The search strategy and flow diagram for database search.

Table 1 shows the main characteristics of the 16 studies included. Case–control studies were published between 1991 and 2013 and involved a total of 5,482 cases and 14,130 controls. The prospective cohort study included 34,691 postmenopausal Iowa women over the period 1986 to 1992. Eight studies were conducted in Europe (17, 22–24, 27, 33, 34, 36), four in North America (12, 35, 37, 39), two in South America (20, 21), and two in Asia (15, 18). Most of the studies included provided effect measures estimates adjusted at least for age, gender, energy intake, and smoking (12, 15, 17, 18, 20, 21, 23, 24).

Regarding the methodological quality of the included studies, six (37.5%) were scored 8 (12, 15, 20, 21, 35, 37) according to the Newcastle–Ottawa scale, five (31.3%) were scored 7 (22, 23, 27, 33, 36), three (18.7%) were scored 6 (17, 18, 34), and two (12.5%) were scored 5 (25, 38).

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Table 1. Characteristics of the studies of carotenoid intake and head and neck cancer (HNC) risk included in the final analysis ($n = 16$)

First author, year (ref.)	Study location	Year	Population (cases/controls)	OR (95% CI) for the highest vs. the lowest category of consumption by site of cancer	Adjusted for	Newcastle–Ottawa score
Bravi, 2013 (24)	Italy, Switzerland	1997–2009	768 OCP/2,078	α-Carotene 0.51 (0.34–0.76), β-carotene 0.28 (0.18–0.43), β-cryptoxanthin 0.37 (0.24–0.56), lycopene 0.92 (0.54–1.55), lutein plus zeaxanthin 0.34 (0.23–0.51)	Age, gender, center, education, year of interview, BMI, tobacco smoking, alcohol drinking, nonalcohol energy intake	5
Suzuki, 2006 (18)	Japan	2001–2004	385 (193 OC, 132 P, 60 L)/1,925	HNC: 0.59 (0.42–0.84); OC: carotene 0.56 (0.35–0.91); P: carotene 0.61 (0.31–1.20); L: carotene 0.51 (0.21–1.25)	Smoking status, drinking status, multivitamin use, nonalcohol energy intake, dental brushing, year of first visit (matched for age and gender)	6
Gallus, 2003 (27)	Italy, Switzerland	1986–2000	68 L/340	Carotene 0.74 (0.32–1.74), lycopene 0.5 (0.10–2.10)	Education, BMI, tobacco and alcohol consumption, nonalcohol energy intake (conditioned on age, year of interview, study center)	7
Bidoli, 2003 (23)	Italy, Switzerland	1992–2000	527 L/1,297	Carotene 0.30 (0.20–0.40), α-carotene 0.30 (0.20–0.50), β-carotene 0.20 (0.20–0.40), β-cryptoxanthin 0.40 (0.20–0.50), lycopene 0.70 (0.50–1.10), lutein plus zeaxanthin 0.40 (0.30–0.60)	Education, BMI, alcohol drinking, smoking habits, nonalcohol energy (conditioned on age, gender, center)	7
Petridou, 2002 (22)	Greece	nr	106 OC/106	β-Carotene 1.01 (0.67–1.51)	BMI, height, education, oral hygiene, tobacco and alcohol consumption, coffee consumption, total energy intake	7
Negri, 2000 (17)	Italy	1992–1997	754 OCP/1,775	Carotene 0.43 (0.28–0.66), lycopene 0.67 (0.44–1.02)	Age, gender, study center, education, occupation, BMI, tobacco smoking, alcohol drinking, nonalcohol energy	6
De Stefani, 2000 (27)	Uruguay	1996–1998	142 (66 OCP, 76 L)/491	OCP: lycopene 0.42 (0.19–0.91); L: lycopene 0.21 (0.10–0.43)	Age, gender, residence, urban/rural status, education, BMI, tobacco smoking, alcohol drinking, total energy intake	8
De Stefani, 1999 (20)	Uruguay	1996–1997	67 (33 OCP, 34 L)/393	OCP: α-carotene 0.70 (0.40–1.20), β-carotene 1.20 (0.70–2.10), lycopene 0.90 (0.50–1.50), lutein 0.80 (0.40–1.40), cryptoxanthin 0.60 (0.30–1.00); L: α-carotene 0.70 (0.40–1.10), β-carotene 1.50 (0.90–2.40), lycopene 0.70 (0.50–1.20), lutein 0.90 (0.50–1.40), cryptoxanthin 0.50 (0.30–0.90)	Age, gender, residence, urban/rural status, education, BMI, tobacco smoking (pack-years), total alcohol intake, total energy intake	8
Schantz, 1997 (37)	USA	1992–1994	167 HNC/177	α-Carotene 1.30 (0.67–2.55), β-carotene 1.39 (0.73–2.67), β-cryptoxanthin 0.30 (0.15–0.60), lycopene 0.60 (0.32–1.11), lutein 0.95 (0.52–1.73)	Age, gender, ethnicity, caloric intake	8

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Table 1. Characteristics of the studies of carotenoid intake and head and neck cancer (HNC) risk included in the final analysis ($n = 16$) (Cont'd)

First author, year (ref.)	Study location	Year	Population (cases/controls)	OR (95% CI) for the highest vs. the lowest category of consumption by site of cancer	Adjusted for	Newcastle–Ottawa score
Esteve, 1996 (36)	Spain, Itay, Switzerland, France	1977–1983	1147 (727 L, 399 HE)/2,736	L: β-carotene 1.66 (1.13–2.43)[a]; HE: β-carotene 1.31 (0.81–2.10)[a]	Age, study center, energy intake, tobacco, alcohol	7
Zheng, 1995[b] (38)	USA	1986–1992	34,691 subjects, 33 MPE cases	MPE: carotene 0.70 (0.30–1.80)[c]	Age, smoking status, pack-years of cigarettes, total energy intake	5
Zheng, 1993 (15)	China	1989	404 OC/404	Carotene 0.51 (0.27–0.96)	Age, gender, education, inadequate dentition, tobacco smoking, alcohol drinking, Quetelet index, total energy intake	8
Marshall, 1992 (12)	USA	1975–1983	290 OCP/290	Carotene 1.00 (0.80–1.20)	Age, gender, total calories, Quetelet index, smoking, alcohol risk imposed by teeth lost but not replaced (matched for age, gender, social class)	8
Freudenheim, 1992 (35)	USA	1975–1985	250 L/250	Carotenoids 0.40 (0.20–0.83)	Kilocalories, cigarettes, alcohol, education	8
La Vecchia, 1991 (34)	Italy	1987–1989	105 OCP/1,169	Carotenoids 0.30 (0.20–0.40)	Age, gender, area of residence, education, social class, smoking	6
Franceschi, 1991 (33)	Italy	1985–1991	302 OCP/699	Carotenoids 0.80 (0.60–1.20)	Age, gender, occupation, smoking and drinking habits	7

Abbreviations: BMI, body mass index; E, endolarynx; HE, hypopharynx and epilarynx; L, larynx; MPE, mouth, pharynx, and esophagus; na, not applicable; nr, not reported; OC, oral cavity; OCP, oral cavity and pharynx; P, pharynx.

[a]The reference group is the highest category.

[b]Prospective cohort study.

[c]Relative risk was reported.

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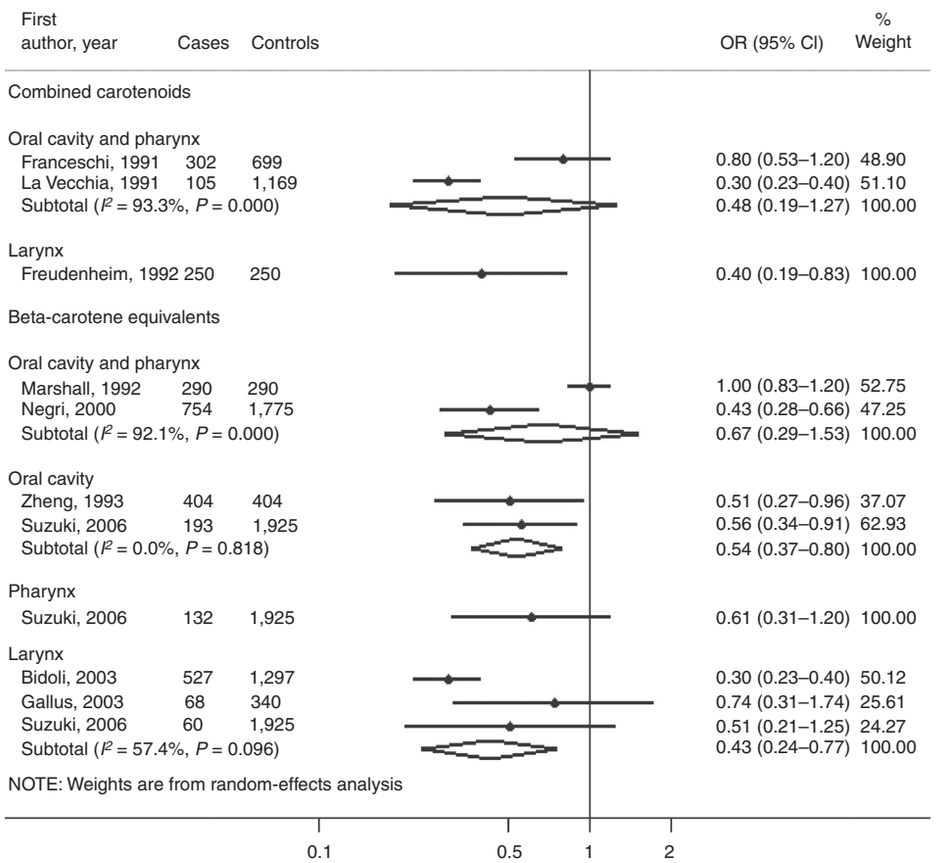

Figure 2.
Meta-analysis of studies reporting HNC risk in relation to natural intake of combined carotenoids and β-carotene equivalents. Quantile cutoff points (or average intake): Franceschi, 1991: not reported; La Vecchia, 1991: not reported; Freudenheim, 1992: ≥8,126 vs. ≤3,119 IU/day; Negri, 2000: mean (SD) = 4,067.5 (2,398.1) μg/day among controls; Marshall, 1992: not reported; Suzuki, 2006: >4,029 vs. <1,906 μg/day; Zheng, 1993: ≥3,486 vs. <2,054 IU/day; Bidoli, 2003: mean (SD) = 3,700 (2,400) μg/day among controls; Gallus, 2003: not reported.

Association between carotenoid intake and HNC

Combined carotenoids. Three studies addressed the association between the intake of combined carotenoids in general and HNC (33–35). We reported a nonsignificant inverse association for the highest level of intake of carotenoids for cancer of oral cavity and pharynx (OR, 0.48; 95% CI, 0.19–1.27; I^2 = 93.3%; P<0.001) (Fig. 2). Only a case–control study from the United States addressed the association between combined carotenoids intake and larynx, and observed a consistent protective effect (OR, 0.40; 95% CI, 0.19–0.83; ref. 35).

β-*Carotene equivalents.* Six case–control studies investigated the association between β-carotene equivalents intake and HNC (12, 15, 17, 18, 23, 27). The meta-analysis identified β-carotene equivalents to act protectively against oral cavity cancer (OR, 0.54; 95% CI, 0.37–0.80; I^2 = 0.0%; P = 0.82) and laryngeal cancer (OR, 0.43; 95% CI, 0.24–0.77; I^2 = 57.4%; P = 0.10; Fig. 2). In a case–control study conducted in Japan, a nonsignificant association was observed between β-carotene equivalents intakes and pharynx (OR, 0.61; 95% CI, 0.31–1.20). When oral cancer and pharynx cancer were considered together, an inverse nonsignificant association was observed (OR, 0.67; 95% CI, 0.29–1.53; I^2 = 92.1%; P < 0.001).

Moreover, one prospective cohort study of 34,691 postmenopausal women in Iowa examined the association between β-carotene equivalents intake and the risk of cancers of the upper digestive tract (mouth, pharynx, and esophagus), with no significant association found (RR, 0.70; 95% CI, 0.30–1.80; ref. 38).

α-*Carotene.* Three studies examined the association between α-carotene intake and subsites of HNC (20, 23, 24). A strong inverse association was found for a high intake of α-carotene for cancer of the oral cavity and pharynx (OR, 0.57; 95% CI, 0.41–0.79; I^2 = 0.0%; P = 0.35), whereas a nonsignificant inverse association was reported for cancer of the larynx (OR, 0.46; 95% CI, 0.20–1.06; I^2 = 83.1%; P < 0.05; Fig. 3). Only one case–control study from the United States examined the association between α-carotene intake and the risk of HNC in general, with no significant association found (OR, 1.30; 95% CI, 0.66–0.2.55; ref. 37).

β-*Carotene.* Six studies reported data on β-carotene intake and HNC (20, 22–24, 36, 37). The meta-analysis showed a nonsignificant inverse association for a high intake of β-carotene, both for cancer of the oral cavity and pharynx (OR, 0.57; 95% CI, 0.14–2.38, I^2 = 93.9%, P<0.001) and for that of the larynx (OR, 0.58; 95% CI, 0.22–1.55; I^2 = 91.4%; P<0.001; Fig. 3).

Results from studies on β-carotene intake in relation to risk of HNC in general (OR, 1.39; 95% CI, 0.72–2.67; ref. 37), epilaryngeal and hypopharyngeal cancer (OR, 0.76; 95% CI, 0.47–1.23; ref. 36), and oral cancer (OR, 1.01; 95% CI, 0.68–1.51; ref. 22) were inconsistent, with both inverse and positive associations reported.

β-*Cryptoxanthin.* Four studies reported data on β-cryptoxanthin in relation to HNC (20, 23, 24, 37). We observed a protective effect of the highest versus the lowest category

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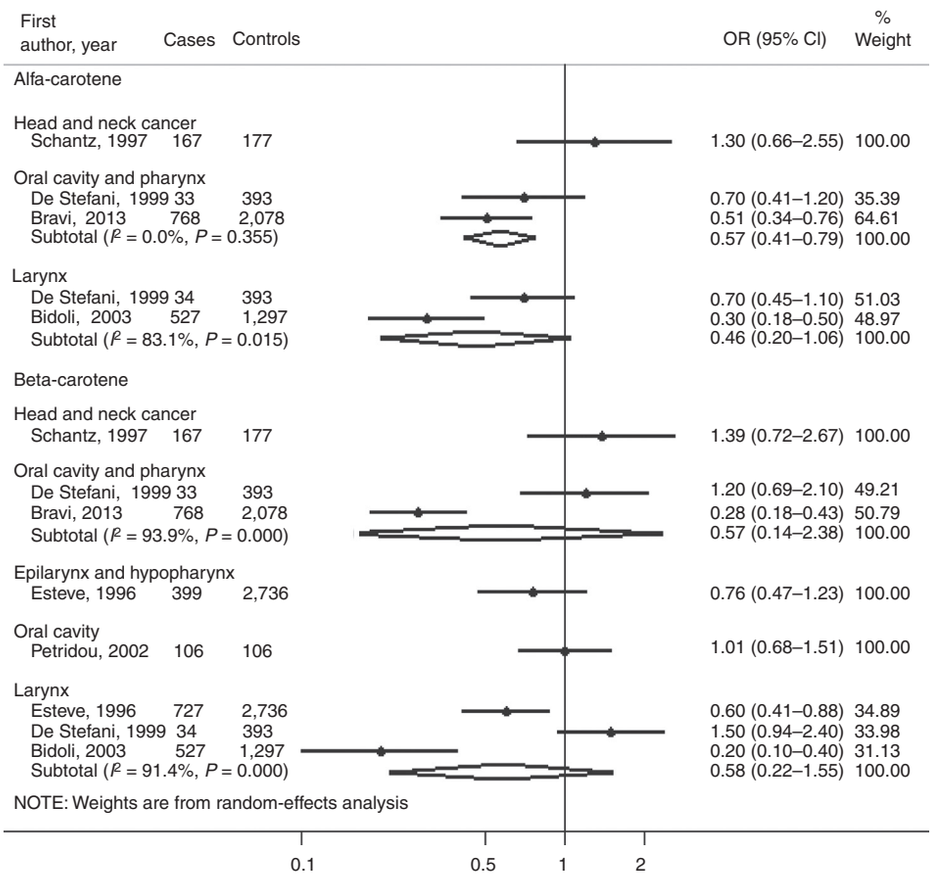

Figure 3.
Meta-analysis of studies reporting HNC risk in relation to natural intake of α-carotene and β-carotene. Quantile cutoff points (or average intake): Schantz, 1997: >609.5 vs. <181.9 μg/day; Bravi, 2013: mean (SD) = 696.6 (607.3) μg/day among controls; De Stefani, 1999: not reported; Bidoli, 2003: mean (SD) = 800 (900) μg/day among controls; Schantz, 1997: >4,421 vs. <2,064 μg/day; Bravi, 2013: mean (SD) = 4,457.1 (2,303.3) μg/day among controls; De Stefani, 1999: not reported; Esteve, 1996: >1,300 vs. ≤400 μg/day; Petridou, 2002: mean (SD) = 3,642 (1,920) μg/day among cases, mean (SD) = 3,410 (1,870) μg/day among controls; Bidoli, 2003: mean (SD) = 4,100 (2,600) μg/day among controls.

of β-cryptoxanthin intake for oral and pharyngeal cancer (OR, 0.46; 95% CI, 0.29–0.74; I^2 = 51.8%; P = 0.15) and for laryngeal cancer (OR, 0.41; 95% CI, 0.33–0.51; I^2 = 0.0%; P = 0.49; Fig. 4). Only a case–control study from the United States addressed the association between β-cryptoxanthin intake and HNC in general, and observed a consistent protective effect (OR, 0.30; 95% CI, 0.15–0.60; ref. 37).

Lycopene. Seven studies reported data on lycopene intake and HNC (17, 20, 21, 23, 24, 27, 37). The meta-analysis identified lycopene to act protectively against oral and pharyngeal cancer (OR, 0.74; 95% CI, 0.56–0.98; I^2 = 14.5%; P = 0.32), as well as against laryngeal cancer (OR, 0.50; 95% CI, 0.28–0.89; I^2 = 65.9%; P < 0.05; ref. Fig. 4). Oppositely, a case–control study from the United States did not report a consistent association between lycopene intake and HNC in general (OR, 0.60; 95% CI, 0.32–1.11; ref. 37).

Lutein and zeaxanthin. Four studies reported data of lutein and zeaxanthin in relation to HNC (20, 23, 24, 37). A nonsignificant inverse association was observed for the highest level of intake of lutein and zeaxanthin, both for cancer of the oral cavity and pharynx (OR, 0.51; 95% CI, 0.22–1.18; I^2 = 83.0%; P < 0.05) and for that of the larynx (OR, 0.60; 95% CI, 0.27–1.32; I^2 = 85.8%; P < 0.01; Fig. 5). Similarly, a case–control study from the United States did not find any significant association between lutein intake and HNC in general (OR, 0.95; 95% CI, 0.52–1.73).

Discussion

Our review reports that the intake of carotenoids from natural sources protects against the development of HNC in relation to most individual carotenoids, with some differences between cancer subsites. We observed that a high intake of β-carotene equivalents significantly decreases the risk for cancer of oral cavity as well as for laryngeal cancer. Lycopene and β-cryptoxanthin also reduced the risk of laryngeal cancer. Lycopene, α-carotene, and β-cryptoxanthin appear to significantly reduce the risk of oral and pharyngeal cancer.

The effect of carotenoid intake was investigated in relation to several cancer sites (39–43). A consistent protective effect was reported so far for cancers of the lung (41), prostate (42), colon (43), cervix (44), and esophagus (40).

Carotenoids represent a diverse group of natural pigments of the polyene type (3). There are several possible cancer prevention mechanisms that can explain the favorable effect of carotenoids toward cancer development (7, 45). Carotenoids can function as a provitamin A having effect on cellular differentiation and proliferation (46, 47). Moreover their anticarcinogenic effect lies in the ability to act as antioxidants, quenching free radicals, reducing damage from reactive oxidant species, and inhibiting lipid peroxidation (45).

Although the bioavailability and absorption of the synthetic form of carotenoids are different with respect to carotenoids from natural sources (48), several studies have reported an increased risk of cancer development in individuals taking

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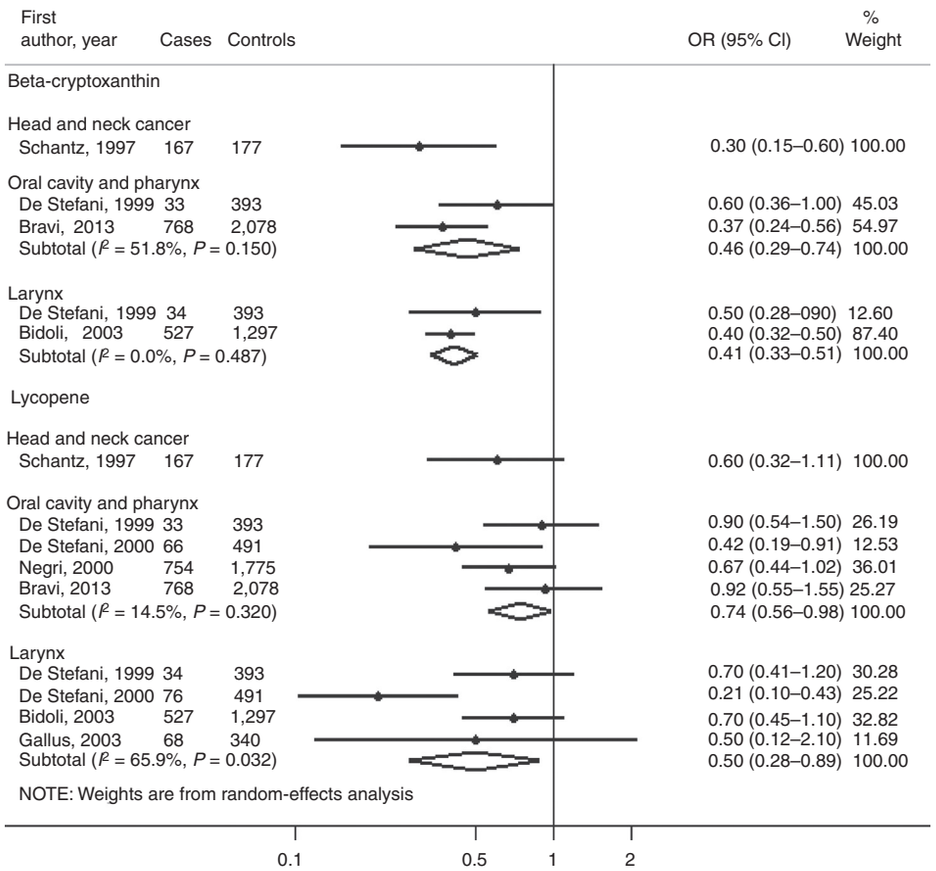

Figure 4.
Meta-analysis of studies reporting HNC risk in relation to natural intake of β-cryptoxanthin and lycopene. Quantile cutoff points (or average intake): Schantz, 1997: >148 vs. <61.4 μg/day; Bravi, 2013: mean (SD) = 463.0 (559.1) μg/day among controls; De Stefani, 1999: not reported; Bidoli, 2003: mean (SD) = 200 (300) μg/day among controls; Schantz, 1997: >1,898.4 vs. <910.7 μg/day; Bravi, 2013: mean (SD) = 4,873.2 (3,418.4) μg/day among controls; De Stefani, 1999: not reported; Negri, 2000: mean (SD) = 7,084.0 (3,763.1) μg/day among controls; De Stefani, 2000: ≥3,388 vs. ≤2,240 μg/day; Bidoli, 2003: mean (SD) = 6,400 (3,700) μg/day among controls; Gallus, 2003: not reported.

β-carotene preventively. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC) indicated a significantly higher occurrence of lung cancer among heavy cigarette-smoking men who were taking α-tocopherol and β-carotene in comparison to individuals taking the placebo (49). The Beta-Carotene and Retinol Efficacy Trial (CARET) study, as well as others, also reported that the combination of β-carotene and vitamin A supplementation was associated with increased lung cancer

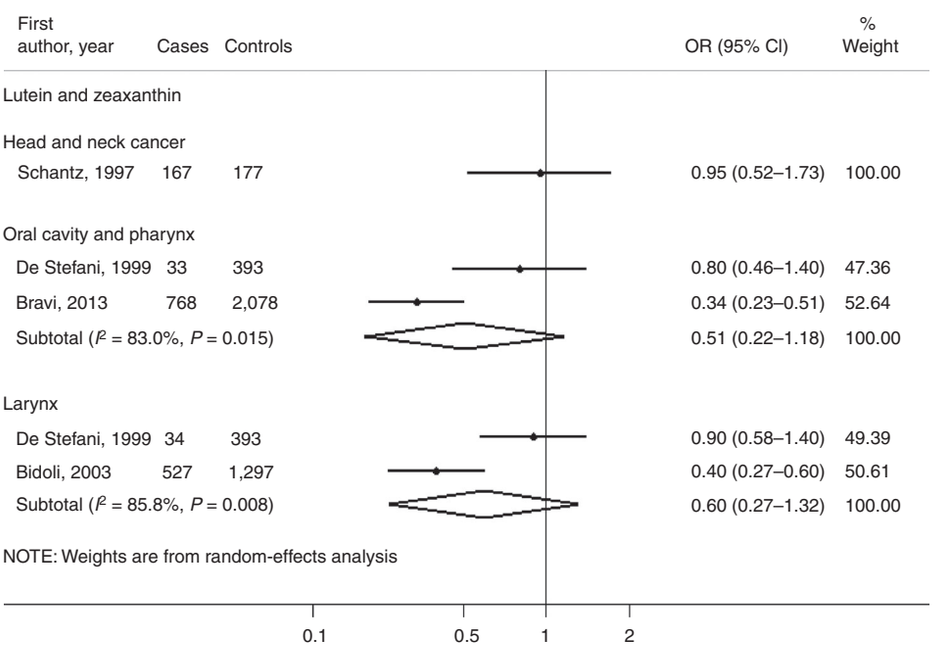

Figure 5.
Meta-analysis of studies reporting HNC risk in relation to natural intake of lutein and zeaxanthin. Quantile cutoff points (or average intake): Schantz, 1997: >3,732 vs. <1,678 μg/day; Bravi, 2013: mean (SD) = 4,381.5 (2,286.3) μg/day among controls; De Stefani, 1999: not reported; Bidoli, 2003: mean (SD) = 4,300 (2,500) μg/day among controls; De Stefani, 1999: not reported.

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risk among men and women at a high risk, such as asbestos workers and smokers, and in subjects who consumed larger amounts of alcohol (50–52). Furthermore, it has been reported that β-carotene could also be susceptible to an alternative mechanism, not having an anti-oxygenic, but a pro-oxygenic, effect (5). These studies suggest that the pro-oxidant effects of carotenoids may be explained in terms of their strong interference with unhealthy lifestyle factors (53).

Few systematic reviews and meta-analyses have investigated the relationship between dietary habits and the risk of HNC. Two of them have reviewed the findings of studies that have examined the association between HNC and carotenoid intake (25, 26). The first review, examining the association of cancers of the upper digestive tract with diet, found that carotene, vitamin C, and vitamin E are protective, most likely in combination with each other and with other micronutrients (25). In the second review, β-carotene has been inversely related to the risk of oral and pharyngeal cancer, although it remains difficult to disentangle its potential effect from that of fruit and vegetables (26). However, in both studies, the effect on specific cancer subsites and the single carotenoids so far was not addressed.

The strength of our review is that we have investigated the effect of individual and combined carotenoids from diet on overall and specific subsites of HNC. In interpreting our results, we acknowledge a few limitations. First, although most of the included studies provided estimates adjusted for major recognized risk factors for HNC, residual confounding from other dietary factors (or other factors, e.g., HPV) cannot be excluded. In fact, carotenoids intake tends to be associated with healthy behaviors that may be protective against HNC, such as a better educational background. Second, although cigarette smoking is known to be a major risk factor for HNC, we were unable to conduct stratified meta-analyses according to smoking status (54). Lastly, heterogeneity may have inadvertently been introduced because of the methodological differences among studies, including different ranges of exposure used to define categories.

In conclusion, our systematic review and meta-analysis on dietary carotenoids intake and HNC suggests that high levels of carotenoid intake may protect against the risk of HNC, in relation to most of single nutrients and HNC subsites.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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