Vegetable and Fruit Consumption and Prognosis Among Cancer Survivors: A Systematic Review and Meta-Analysis of Cohort Studies

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ABSTRACT

The number of cancer survivors is growing rapidly worldwide, especially long-term survivors. Although a healthy diet with a high vegetable and fruit consumption is a key factor in primary cancer prevention, there is a lack of specific dietary recommendations for cancer survivors, except in the case of breast cancer [World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) report]. We have therefore carried out a systematic review and meta-analysis of cohort studies reporting on the associations between vegetable and fruit intake with cancer recurrence and mortality and all-cause mortality in cancer patients. After a comprehensive search of PubMed and Scopus databases, the results of 28 selected articles were analyzed. A high vegetable intake before diagnosis was inversely associated with overall mortality in survivors of head and neck (HR: 0.75; 95% CI: 0.65, 0.87) and ovarian cancer (HR: 0.78; 95% CI: 0.66, 0.91). In ovarian cancer patients, prediagnosis fruit intake was also inversely associated with all-cause mortality (HR: 0.82; 95% CI: 0.70, 0.96). The evidence was insufficient for survivors of other cancers, although these associations generally tended to be protective. Therefore, more studies are needed to clarify the association between vegetable and fruit consumption and the prognosis of these different types of cancer. To date, the general recommendation to consume ≥5 servings of vegetables and fruit per day (∼400 g/d) could underestimate the needs of cancer survivors, particularly those with ovarian tumors, in which the recommendation could increase to ∼600 g/d (i.e., 300 g/d of vegetables and 300 g/d of fruit). *Adv Nutr* 2020;11:1569–1582.

Keywords: cancer, survival, mortality, recurrence, prognosis, vegetables, fruit, cohort, meta-analysis

Introduction

The global burden of cancer is increasing because of an aging and expanding population and a growing prevalence of unhealthy habits (1). In parallel, advances in early detection, treatment, and supportive care have led to a rapid and steady rise in the number of cancer survivors worldwide (2). The amount of people predicted to survive a diagnosis of cancer is increasing by ∼3% per year (3), the majority now surviving 5 y or more (4). Indeed, in 2011, 50% of UK cancer patients had a 10-y survival rate (5). However, there is considerable variation according to the cancer type, location, and stage (6). A cancer survivor is considered to be anyone who has been diagnosed with cancer, completed treatment with curative-intent (but not maintenance treatment), and is disease-free (no evidence of active cancer) (7).

One-third of deaths from cancer are due to lifestyle and dietary risk factors (e.g., high levels of adiposity, low vegetable and fruit intake, lack of physical activity, and tobacco and alcohol consumption) (8). The role of diet and nutrition in the cancer burden is well-established (9), ∼5% of cancers being exclusively attributed to dietary factors (10), without taking into account obesity (20%) and alcohol (4%). Islami et al. reported that 6.9% of cancers in the Chinese population and 1.9% of cancers in the US population were attributable to a low vegetable and fruit intake (11, 12). In European and US cohorts, adherence to a healthy diet, such as the Mediterranean diet and World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) dietary recommendations (13, 14), has been associated with a lower overall cancer risk (15, 16). In addition, an updated meta-analysis concluded that greater adherence to the Mediterranean diet was associated with a lower risk and mortality of several cancer types, especially colorectal cancer (17). Other dietary quality

indexes and dietary patterns have shown similar results (18, 19).

Healthy diets are largely based on plant-derived foods, predominantly vegetables and fruit, which are low in fat, especially saturated fat, high in fiber, and contain many vitamins, minerals, and phytochemical compounds (such as carotenoids, polyphenols, and sulfur compounds) (20). Vegetable consumption has been associated with a reduced overall cancer mortality among cancer survivors (19). Although vegetable and fruit intake was not related to cancer survival in breast cancer patients in 2 similar meta-analyses (21, 22); the WCRF/AICR report concluded that there is limited suggestive evidence linking a higher consumption of foods containing fiber with increased breast cancer survival (2). Among vegetable classes, the strongest associations with reduced cancer incidence have been found for green-yellow and cruciferous vegetables (23), which may be due to the chemopreventive properties of carotenoids and isothiocyanates, respectively (24). Among fruit, citrus fruits may have a relevant protective role against several cancers because of their high content of flavanones and vitamin C (25–29).

Apart from the WCRF/AICR recommendations for breast cancer survivors (2), there are no dietary guidelines for other cancer survivors beyond those recommended for primary cancer prevention. There is therefore a need for specific dietary recommendations for cancer survivors. In this context, the aim of this work was to review the literature and conduct a meta-analysis, wherever possible, of cohort studies reporting associations between vegetable and fruit intake and prognosis in cancer, evaluating cancer recurrence, site-specific cancer mortality, and overall mortality in cancer survivors. Our systematic review and meta-analysis is an update of the Schwedhelm et al. (19) article published in 2016. Whereas their review scope was broad, investigating all food classes and especially highlighting the relations with dietary patterns; our analysis has only focused on the intake of vegetables and fruit and their subclasses. Thus, we have had the opportunity to analyze in more detail the specific evidence by cancer subtype.

Methods

Data sources and search method

The literature search was independently performed by SH-B and MT-S using PubMed and Scopus databases (from their inception to March 2019). The following search terms were used: (cancer OR neoplasm OR carcinoma) AND (mortality OR survival OR recurrence OR prognosis OR outcome OR death) AND (vegetable OR fruit). Cancer prognosis was the main focus of this study, considering overall mortality, cancer-specific mortality, as well as cancer recurrence. Additionally, the term "tumor" was added to the search, but no changes were found in the results. The search was restricted to the English language. In addition, a human filter was used in the PubMed database. References to reviews and recovered articles were also checked. This work was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (30) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) (31) guidelines.

Inclusion and exclusion criteria

The study selection was independently carried out by 2 authors (SH-B and MT-S). Full-text articles were selected according to the following inclusion criteria: 1) cohort study design, 2) vegetable and fruit intake pre- and postdiagnosis as exposure, 3) overall mortality, site-specific cancer mortality, cancer recurrence, and prognosis as end-points, and 4) HR or risk ratio (RR) (with 95% CI) estimated and adjusted by confounding variables. Exclusion criteria were: 1) duplicated studies, 2) in vitro or animal studies, 3) clinical trials, ecological studies, editorials, reviews, and meta-analyses, 4) outcomes of cancer incidence, 5) nonvegetable and fruit foods and dietary patterns, 6) breast cancer survivors, and 7) no RR or HR (with 95% CI).

Data extraction

Discrepancies in data from the selected studies were analyzed by SH-B and MT-S. For each study, the model adjusted for the highest number of confounding variables was extracted. Studies were classified and aggregated by cancer site [bladder, colorectal, head and neck (including the oral cavity, pharynx, and larynx), gastric, lung, melanoma, non-Hodgkin lymphoma (NHL), esophagus, ovarian, pancreas, and prostate tumors]. Data from each study included in the systematic review and meta-analysis were the following: 1) cancer site, 2) outcome (cancer and overall mortality and recurrence), 3) identification of cohort (country, name of study), 4) follow-up (from the cancer diagnosis to the outcome), 5) sample characterization (size, number of cases, age and sex of subjects), 6) dietary assessment and timeframe, 7) exposures and their extreme categories (such as highest compared with lowest), 8) risk estimated as HR or RR (95% CI), 9) adjustments for confounding variables, and 10) author and year of study.

Study quality assessment

The quality of each study was independently checked and reviewed by SH-B and MT-S. Any discrepancies in the study inclusion, data extraction, and quality assessment were resolved with the support of a third person (RZ-R). To evaluate the risk of bias in individual studies, 2 validated scales were used: the STROBE-nut (extension of Strengthening the Reporting of Observational Studies in Epidemiology) (32) and the ROBINS-E (risk of bias in nonrandomized studies of exposures) checklists (33). STROBE-nut focuses on epidemiological studies relating to nutrition and shares some common items with the original STROBE Statement (32). In the present work, 30 items were used to evaluate study quality. The ROBINS-E tool evaluates the risk of bias assessment of nonrandomized trials, diagnostic test accuracy studies, and observational studies of exposures. The tool assesses 7 domains of bias: confounding, selection of participants into the study, classification of exposures, departures from intended exposures, missing data, measurement of outcomes, and selection of the reported result. Overall risk of bias assessment for each study is summarized within each domain. Low, moderate, serious, critical, or no information risk of bias was established in each study considering all domains (33).

Evidence quality assessment

The Hierarchies of Evidence Applied to Lifestyle Medicine (HEALM) scale was used to evaluate the overall strength of evidence for each outcome (34). HEALM items were evaluated for each association and classified into strong (Grade A), moderate/suggestive (Grade B), or insufficient/weak (Grade C) evidence.

Statistical analysis

Prior to the analyses, the studies were classified by cancer site and outcome (i.e., cancer recurrence, site-specific cancer mortality, and overall mortality). The meta-analysis was performed by pooling the multivariable-adjusted RRs or HRs of the highest dietary intake categories (e.g., total vegetables and fruit, total vegetables, and total fruit) compared with the lowest 1 if ≥3 studies reported data for the same exposure, cancer site, and outcome. When subtypes of the same food exposure group were described separately (e.g., citrus fruit and other fruit) in the same study, the pooled risk estimate (e.g., total fruit) was calculated by a meta-analysis fixed-effect model. Prediagnosis and postdiagnosis data were analyzed separately. The random-effect model was used because of the high variability in the study design among cohorts and the low number of studies meta-analyzed (35). The I^2 test, the Tau^2, and the 95% prediction intervals were used to evaluate the heterogeneity across studies. Meta-analyses were performed with the metan function of the Stata software, version 14 (Stata Corp).

Results

Literature search and study characteristics

A total of 8322 articles were identified from 2 databases (PubMed and Scopus). An additional 26 articles were included from other sources (reviews and manual searching). After removing the duplicates, 6035 potentially eligible articles remained. Among these, 5998 were excluded after title and abstract screening due to exclusion criteria (reviews/meta-analysis, editorials, ecological studies, in vitro or animal studies, other outcomes, and nonvegetable exposure). Thereafter, the full text of 86 articles was evaluated in detail (excluded articles are shown in **Supplemental Table 1**). Finally, a total of 28 articles were included in the systematic review and meta-analysis (**Figure 1**). Of these, 16 studies were used for the qualitative review (36–51) and 12 for the quantitative meta-analysis (52–63).

Cohort studies

A few cohort studies, mainly prospective, were identified for each outcome and classified by cancer site (**Supplemental Table 2**). The studies included in the systematic review and meta-analysis examining the association of total vegetable and fruit intake with cancer prognosis are summarized in **Tables 1–3**. The studies include aerodigestive, genital and urinary, and other cancer types. Results for vegetable and fruit subtypes are shown in **Supplemental Tables 3–5**. A total of 18,278 males and females aged between 16 and 84 y from European, North American, East Asian, and Australian cohorts were included in the systematic review and meta-analysis. The follow-up periods varied from 9.1 mo to 16 y. Dietary information assessment predominantly preceded cancer diagnosis. Regarding vegetable and fruit consumption, exposures were analyzed mainly by comparing the highest with the lowest categories (**Supplemental Table 6**).

Vegetable and fruit intake and prognosis in aerodigestive cancer patients.

Head and neck. After meta-analyzing 5 cohort studies (52, 53, 56–58), an inverse association between total vegetable consumption before diagnosis and overall mortality (HR: 0.75; 95% CI: 0.65, 0.87) was observed in head and neck cancer patients, including the oral cavity, pharynx, and larynx (**Figure 2**A). However, as the prediction interval is 0.54 to 1.04, the true effect size in 95% of all the population will fall in this range. A stronger association was detected for both all-cause and site-specific cancer mortality with postdiagnosis total vegetable intake than with prediagnosis intake in oral cavity and oropharynx cancer (56). However, no association between all-cause mortality and fruit (**Figure 2**B) or citrus fruit assessed before diagnosis was observed (58). No studies were found on the consumption of vegetable subtypes.

Digestive tract. The high consumption of fruit and berries was not related to lower colorectal cancer recurrence (45, 46). Total vegetable intakes before and after diagnosis
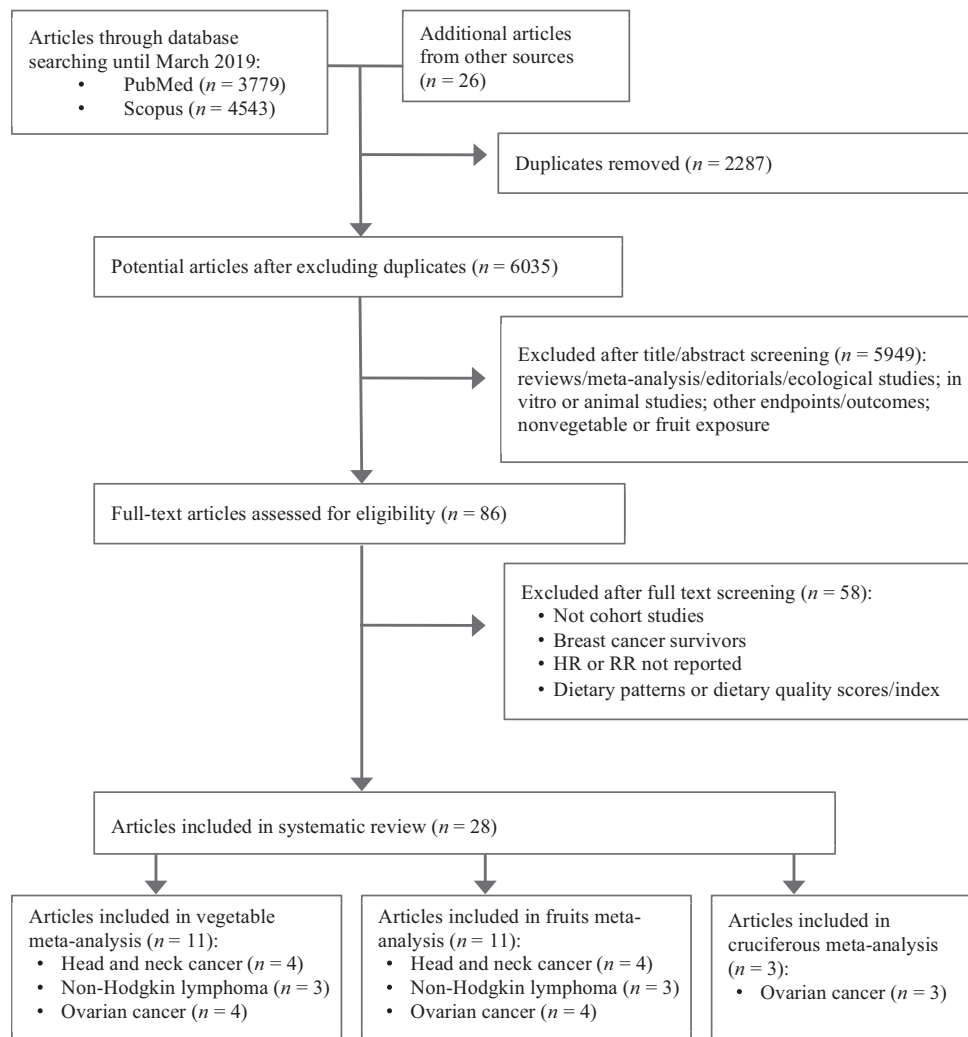
FIGURE 1 Flowchart of the study selection for the systematic review and meta-analysis. RR, risk ratio.

were not linked with prognosis in colorectal cancer survivors (45–47). Lower consumption of green leafy vegetables before diagnosis was associated with a higher risk of all-cause mortality in colon cancer patients (HR: 2.06; 95% CI: 1.10, 3.86), but not in rectal cancer patients (41). The consumption of 3 or more servings of raw vegetables per week (≥240 g/wk) before diagnosis was related to a lower risk of site-specific cancer mortality in gastric cancer patients (44). There was no association between prediagnosis green vegetable intake and overall mortality in pancreatic cancer patients (42). A Chinese study reported that the higher consumption of fermented preserved vegetables before diagnosis significantly correlated with a higher risk of all-cause mortality in esophagus cancer patients (40).

Respiratory tract. No association was found between vegetable and fruit consumption examined before diagnosis and overall mortality in lung cancer patients (48, 49). However, a high cruciferous vegetable intake before diagnosis was linked to a lower site-specific cancer mortality (HR: 0.69;

95% CI: 0.49, 0.95) in female lung cancer patients from the Shanghai Women's Health Study (43).

Vegetable and fruit intake and prognosis in genital and urinary cancer patients.

Ovary. The 4 meta-analyzed studies on ovarian cancer patients (59–62) showed an inverse association between total vegetable and total fruit intake before diagnosis and overall mortality (HR: 0.78; 95% CI: 0.66, 0.91 and HR: 0.82; 95% CI: 0.70, 0.96, respectively) (**Figure3**A and B). Although the results are significant, the prediction interval of both meta-analyses will be expected to be outside the protective HR range in 95% of all the population. Regarding vegetable subgroups, no association between cruciferous vegetable consumption and overall mortality was detected (**Supplemental Figure 1**). Null results were also found for the intake of other vegetable or fruit subgroups (e.g., green leafy, and yellow and red vegetables, and citrus fruit) (59–62).

TABLE 1 Summary of studies included in the systematic review and meta-analysis evaluating the association between total vegetable and fruit consumption and aerodigestive cancer prognosis[1]

Cancer site	Outcome n (cases)	Follow-up (years)	Gender age (years)	Dietary assessment	Exposure categorization	HR/RR (95% CI) timeframe[2,3]	Adjustments	Author, year (ref.) (country)
Head and neck	ACM 2202 (445)	3.2 ± 1.2 (mean ± SD)	M/F ≥16	FFQ	V: T3 (>1 p/d) vs. T1 (<5 p/wk); F: T3 (>1 p/d) vs. T1 (<1 p/wk)	[2]RR: 0.79 (0.61, 1.03); [2]RR: 0.91 (0.67, 1.23)	Age, sex, site, stage, comorbidity, treatment intent, education, relation status, income, smoking, alcohol, and fried food	Lang et al., 2019 (52) (UK)
Nasopharyngeal	ACM 1533 (243)	3.3 (<1,5) median (min, max)	M/F 46.1 (mean)	FFQ	F: daily or more vs. fewer than monthly servings	[2]HR: 0.78 (0.53, 1.14)	Age, sex, marital status, education level, clinical stage, smoking status, alcohol intake, and BMI	Shen et al., 2012 (53) (China)
Head and neck	ACM 504 (166)	2.7 (<1,5.5) median (min, max)	M/F 58.8 (mean)	FFQ	V: lowest (≤4 s/wk) vs. highest (≥5 s/wk); F: lowest (≤3 s/mo) vs. highest (≥1 s/wk)	[2]HR: 0.82 (0.59, 1.15); [2]HR: 1.26 (0.88, 1.81)	Age, sex, race, sleep score, educational level, marital status, cancer site, tumor stage, comorbidities, treatment received, smoking status, alcohol consumption, and physical activity	Duffy et al., 2009 (36) (USA)
Oral cavity and oropharynx	ACM 146 (74); CCSM 146 (49); R 146 (47)	3.1 (mean); 3.1 (mean); 3.6 (mean)	M/F categories: <50, 50–59, 60–69 and ≥70	FFQ	V: T3 (≥8) vs. T1 (≤4) s/wk; F: T3 (≥8) vs. T1 (≤4) s/wk; V: T3 (≥8) vs. T1 (≤4) s/wk; F: T3 (≥8) vs. T1 (≤4) s/wk; V: T3 (≥8) vs. T1 (≤4) s/wk; F:T3 (≥8) vs. T1 (≤4) s/wk	[2]RR: 0.54 (0.30, 0.98); [3]RR: 0.14 (0.04, 0.50); [2]RR: 1.26 (0.73, 2.18); [3]RR: 0.77 (0.36, 1.64); [1]RR: 0.61 (0.29, 1.31); [3]RR: 0.14 (0.03, 0.69); [2]RR: 1.04 (0.52, 2.10); [3]RR: 0.89 (0.34, 2.32); [2]RR: 0.56 (0.27, 1.15); [3]RR: 0.43 (0.16, 1.18); [2]RR: 0.75 (0.37, 1.52); [3]RR: 0.68 (0.29, 1.59)	Age, sex, clinical stage, and tumor site	Sandoval et al., 2009 (56) (Spain)
Laryngeal/ hypopharyngeal	ACM 931 (755)	8 (mean) 21 (max)	M/F categories: <50, 50–59, 60–69 and ≥70	DQ	V: Q4 (>328.6) vs. Q1 (<148.6) g/d; F: Q4 (>241) vs. Q1 (<56) g/d	[2]HR: 0.8 (0.6, 0.9); [2]HR: 1.0 (0.7, 1.2)	Age, sex, center, site of primary tumor, alcohol drinking, cigarette smoking, caloric intake without alcohol, and vegetable or fruit intake	Dikshit et al., 2005 (57) (Switzerland, France, Italy, and Spain)
Laryngeal	ACM 215 (136)	8–10	Males 59 (median)	DQ	V: T3 (<281.1) vs. T1 (<202.1) g/d	[2]HR: 0.57 (0.35, 0.94)	Age at diagnosis, clinical stage, occurrence of new primaries, and total calorie intake	Crosignani et al., 1996 (58) (Italy)
Gastric	ACM 568 (345)	1.2 (median) 10 (max)	M/F 63 (median)	FFQ	V+F: T1 (<2.7) vs. T3 (>4.3) s/d	[2]HR: 0.98 (0.75, 1.28)	Age, sex, education, extent of diseases, and total energy intake	Ferronha et al., 2012 (37) (Portugal)
Gastric	CCSM 877 (241)	10 (max)	M/F 40–79	DQ	F: highest (>3) vs. lowest (<3) times/wk	[2]HR: 0.98 (0.73, 1.31)	Age, sex, and pathological type and stage of cancer	Huang et al., 2000 (44) (Japan)[4]
Colorectal	R 1667 (738)	0.5–10	M/F 55–74	FFQ	V: T3 (≥1.5) vs. T1 (<1.1)[5]; F (excluding juice): T3 (≥0.9) vs. T1 (<0.5)[5]V+F: T3 (≥2.8) vs. T1 (<2.0)[5]	[2]HR: 0.93 (0.69, 1.25); [2]HR: 0.96 (0.70, 1.32); [2]HR: 0.87 (0.64, 1.20)	Age, sex, center, race, energy intake, year of follow-up screening, adenoma at T0, T3, or T5, adequate screening at T0, T3, or T5, processed meat intake, red meat intake, calcium intake, smoking status, education, exercise, family history of colorectal cancer, use of NSAIDs, HRT, BMI, alcohol intake	Kunzmann et al., 2016 (45) (USA)

(Continued)

TABLE 1 (Continued)

Cancer site	Outcome n (cases)	Follow-up (years)	Gender age (years)	Dietary assessment	Exposure categorization	HR/RR (95% CI) timeframe[2,3]	Adjustments	Author, year (ref.) (country)
Colorectal	R 87 (53)	3 (max)	M/F 65 (median)	5d DR	V: highest (>110) vs. lowest (<110) g/d F+berries: highest (>200) vs. lowest (<200) g/d	[3]RR: 1.2 (0.5, 2.9) [3]RR: 0.9 (0.3, 2.2)	Colorectal cancer in a first-degree relative, BMI, and type of intervention	Almendingen et al., 2004 (46) (Norway)
Colorectal	ACM 148 (46 at 5 y)	10 (max) 5 (RR ACM)	M/F 30–79	FFQ	V: T3 vs. T1 F: T3 vs. T1	[2]RR: 1.09 (0.49, 2.45) [2]RR: 0.84 (0.37, 1.88)	Age, sex, tumor stage, tumor location, and energy intake	Dray et al., 2003 (47) (France)
Lung	ACM 1052 (869)	<1 (median)	Male ≤80	FFQ	V+F: frequent (≥1 s/d) vs. occasional (<1 s/d)	[3]HR: 0.86 (0.72, 1.02)	District of residence, age at diagnosis, BMI, cancer history in first-degree relatives, education level, family income, stage at diagnosis, smoking status, smoking pack-years, and treatment	Li et al., 2017 (48) (China)
Lung	ACM 286 (ns) Current smokers	11 (max)	M/F 50–64	FFQ	V: T3 (160–536) vs. T1 (16–88)/d F: (excluding juices): T3 (143–671) vs. T1 (0–51) g/d	[2]HR: 0.84 (0.59, 1.21) [2]HR: 0.81 (0.58, 1.15)	Sex, age, extent of disease, duration of smoking, and potato and fruit/vegetable intake	Skuladottir et al., 2006 (49) (Denmark)

[1] Pre- and postdiagnosis dietary vegetables and fruit were not mixed in the meta-analysis. ACM, all-cause mortality; CCSM, cancer cause-specific mortality; DQ, dietary questionnaire; DR, dietary record; F, fruit; HRT, hormone replacement therapy; M/F, males and females; ns, not specified; NSAIDs, nonsteroidal anti-inflammatory drug; p/d, portion/day; p/wk, portion/week; R, cancer recurrence; ref, reference; RR, risk ratio; s/d, serving/day; s/mo, serving/month; s/wk, serving/week; V, vegetables; V+F, vegetables and fruit.

[2] Prediagnosis.

[3] Postdiagnosis.

[4] Retrospective cohort study.

[5] Food Patterns Equivalents Database (FPED) cup equivalents/1,000 kcal/d.

Prostate. In prostate cancer patients, prediagnosis consumption of total fruit was inversely associated with all-cause mortality, but not with site-specific cancer mortality (50). Raw vegetable intake was also inversely associated with all-cause and cancer-specific mortality, whereas no association was detected for the consumption of either total or cooked vegetables (50).

Bladder. In 2 studies on bladder cancer patients, the pre- and postdiagnosis intake of total vegetables, fruit, or both were not related to either all-cause mortality or cancer recurrence (38, 51). No association with the consumption of cruciferous vegetables before diagnosis was found either (38).

Vegetable and fruit intake and prognosis in patients with other cancer sites.

NHL. Three studies have evaluated the relation with overall mortality in patients with NHL (54, 55, 63), showing null results for the intake of vegetables (HR: 0.83; 95% CI: 0.59, 1.16) and fruit (HR: 1.00; 95% CI: 0.88, 1.13) in prediagnosis eating habits. The same exact results were previously obtained by Schwedhelm et al. (19). Han et al. (54) observed protective effects for green leafy vegetables and citrus fruit, but not for other vegetable subtypes, such as cruciferous, bean, and red and yellow vegetables.

Melanoma. The only study in melanoma patients, the Connecticut Skin Self-Examination Case-Control Study, found no association between the daily consumption of fruit or weekly consumption of green salad before diagnosis and site-specific cancer mortality (39).

Quality of studies and overall strength of evidence
The quality of all individual studies was categorized as moderate in all cases. The main cause for this classification was the concern of changes in exposure status among patients. In addition, minor reasons reducing the quality of studies were observed: bias due to confounding (40, 41, 57), bias in classification of exposures (39, 40, 42, 47, 48, 56), and bias in selection of the reported results (36, 39, 41, 42, 57, 61) (**Supplemental Table 7**). More details about the items considered in both the ROBINS-E and the STROBE-nut scale are provided as supplementary material (**Supplemental Tables 8** and **9**, respectively). According to the HEALM scale, the level of evidence of this systematic review was Grade C (insufficient/weak).

Discussion
Associations between vegetable and fruit intake and cancer mortality
The aim of this systematic review and meta-analysis was to examine the available evidence for the relation between vegetable and fruit consumption and cancer prognosis, excluding breast cancer (2). In summary, the current meta-analysis shows a lower mortality associated with vegetable

TABLE 2 Summary of studies included in the systematic review and meta-analysis evaluating association between total vegetable and fruit consumption and genital and urinary cancer prognosis[1]

Cancer site	Outcome n (cases)	Follow-up (years)	Gender age (years)	Dietary assessment	Exposure categorization	HR/RR (95% CI) timeframe[2,3]	Adjustments	Author, year (ref.) (country)
Ovarian	ACM 811 (547)	5.9 ± 3.8 (mean ± SD)	Female 18–79	FFQ	V: T3 (≥5) vs. T1 (<3) s/d. F: T3 (≥4) vs. T1 (none or <2) s/d	[2]RR: 0.88 (0.68, 1.13); [2]RR: 0.82 (0.63, 1.07)	Age at diagnosis, FIGO stage, amount of residual disease, grade, tumor subtype, smoking status, BMI, physical activity index, marital status, and daily caloric intake	Playdon et al., 2017 (59) (Australia)
Ovarian	ACM 636 (354); CCSM 636 (305)	17 (max)	Female 50–79	HEI	V: T3 (5) vs. T1 (2.5) points[4]; F: T3 (5) vs. T1 (2.5) points[5]; V: T3 (5) vs. T1 (2.5) points[4]; F: T3 (5) vs. T1 (2.5) points[5]	[2]HR: 0.70 (0.47, 1.04); [2]HR: 0.82 (0.55, 1.21); [2]HR: 0.76 (0.48, 1.20); [2]HR: 0.84 (0.54, 1.28)	Age at diagnosis, stage at diagnosis, race/ethnicity, diabetes, physical activity, total energy intake, waist circumference, family history of ovarian cancer, and clinical trial arms	Thomson et al., 2014 (60) (US)
Ovarian	ACM 341 (176)	10 (max)	Female 18–74	FFQ	V: T3 (≥2) vs. T1 (<1) s/d; F: T3 (≥2) vs. T1 (<1) s/d.; V+F: T3 (≥5) vs. T1 (<3) s/d	[2]HR: 0.66 (0.43, 1.01); [2]HR: 0.67 (0.44, 1.04); [2]HR: 0.61 (0.38, 0.98)	Age group, race, stage, grade, residual lesions, smoking status, BMI, oral contraceptive use, parity, and total energy intake	Dolecek et al., 2010 (61) (US)
Ovarian	ACM 609 (394)	7.3 (5, 8.3) mean (min, max)	Female 18–79	FFQ	V: T3 (>5.6) vs. T1 (<3.9) s/d; F: T3 (>4.5) vs. T1 (<2.8) s/d.	[2]HR: 0.75 (0.57, 0.99); [2]HR: 0.89 (0.67, 1.18)	FIGO stage, age, grade, total energy intake and BMI	Nagle et al., 2003 (62) (Australia)
Prostate	ACM 777 (263); CCSM 777 (81)	7.5 (median); 5.7 (median)	Male 66 (median)	FFQ	V: Q4 (≥203) vs. Q1 (<102) g/d; F: Q4 (≥380) vs. Q1 (<152) g/d; V (cut-off: 146) + F (cut-off: 247); V: Q4 (≥203) vs. Q1 (<102) g/d; F: Q4 (≥380) vs. Q1 (<152) g/d V (cut-off: 146) + F (cut-off: 247)	[2]HR: 0.81 (0.56, 1.16); [2]HR: 0.63 (0.44, 0.90); [2]HR: 0.66 (0.47, 0.93); [2]HR: 0.82 (0.42, 1.58); [2]HR: 0.78 (0.38, 1.61); [2]HR: 0.89 (0.48, 1.63)	Area of residence at diagnosis, calendar period, age at diagnosis, years of education, Gleason score, BMI, smoking habits and total energy intake	Taborelli et al., 2017 (50) (Italy)
Bladder	First R :728 (241); [2]389 (144); [3]Multiple R :728 (391)[2]; 389 (221)[3]	3.7 ± 1.5 (mean ± SD)	M/F 69 (mean)	FFQ	V: T3 (>2.5) vs. T1 (<1.5) p/d; F: T3 (>1.5) vs. T1 (<1) p/d; V+F: T3 (>4) vs. T1 (<2.5) p/d; V: T3 (>2.5) vs. T1 (<1.5) p/d; F: T3 (>1.5) vs. T1 (<1) p/d; V+F: T3 (>4) vs. T1 (<2.5) p/d	[2]HR: 1.02 (0.74, 1.41); [3]HR: 0.77 (0.50, 1.18); [2]HR: 0.85 (0.63, 1.14); [3]HR: 1.07 (0.78, 1.47); [2]HR:1.07 (0.78, 1.47); [3]HR: 0.65 (0.42, 1.01); [2]HR: 0.97 (0.86, 1.11); [3]HR: 0.96 (0.74, 1.09); [2]HR: 1.05 (0.91, 1.20); [3]HR: 1.02 (0.87, 1.20); [2]HR: 1.02 (0.90, 1.15); [3]HR: 1.00 (0.85, 1.18)	Age, sex, smoking status, tumor stage, grade, size, and multiplicity [and additionally adjusted for re-resection of a bladder tumor (second transurethral resection) in the time to multiple recurrences analysis]	Jochems et al., 2018 (51) (UK)
Bladder	ACM 239 (179); CCSM 239 (101)	8 (mean); 6.4 (<1,25.1) median (min, max)	M/F categories: <60, 60–70 and >70	FFQ	V: T3 (>85.5) vs. T1 (<52) s/mo; F: T3 (>51) vs. T1 (<27.5) s/mo; V: T3 (>85.5) vs. T1 (<52) s/mo; F: T3 (>51) vs. T1 (<27.5) s/mo	[2]HR: 0.91 (0.62, 1.36); [2]HR: 0.91 (0.62, 1.33); [2]HR: 1.06 (0.63, 1.78); [2]HR: 1.09 (0.66, 1.81)	Age at diagnosis, total meat intake, pack-years of smoking, tumor stage and radiation therapy	Tang et al., 2010 (38) (US)

[1] Pre- and postdiagnosis dietary vegetables and fruit were not mixed in the meta-analysis. ACM, all-cause mortality; CCSM, cancer cause-specific mortality; F, fruit; FIGO, International Federation of Gynecology and Obstetrics; HEI, healthy eating index; M/F, males and females; p/d, portion/day; R, cancer recurrence; ref, reference; RR, risk ratio; s/d, serving/day; s/mo, serving/month; V, vegetables; V+F, vegetables and fruit.

[2] Prediagnosis.

[3] Postdiagnosis.

[4] 1.1 compared with 0.6 cup eq/1000 kcal.

[5] 0.8 compared with 0.4 cup eq/1000 kcal.

TABLE 3 Summary of studies included in the systematic review and meta-analysis evaluating the association between total vegetable and fruit consumption and other cancer prognosis[1]

Cancer site	Outcome n (cases)	Follow-up (years)	Gender age (years)	Dietary assessment	Exposure categorization	HR/RR (95% CI) timeframe[2]	Adjustments	Author, year (ref.) (country)
NHL	ACM 301 (91)	8.2 (median)	M/F 20–75	FFQ	V: T3 (>102.1) vs. T1 (<66.1) g/1000 kcal∗d F: T3 (>138.1) vs. T1 (<69.5) g/1000 kcal∗d V+F:T3 (>239.7) vs. T1 (<147.8) g/1000 kcal∗d	[2]HR: 0.9 (0.5, 1.5) [2]HR: 0.9 (0.5, 1.6) [2]HR: 1.1 (0.6, 2.1)	Age, sex, education, smoking status, and total energy intake	Ollberding et al., 2013 (63) (USA)
NHL	ACM 568 (250) CCSM 568 (148)	7.7 (median) 11.8 (max)	Female 21–84	FFQ	V: ≥3 s/d vs. <3 s/d (cut-off) F: ≥2 s/d vs. <2 s/d (cut-off) V+F:≥5 s/d vs. <5 s/d (cut-off) V: ≥3 s/d vs. <3 s/d (cut-off) F: ≥2 s/d vs. <2 s/d (cut-off) V+F:≥5 s/d vs. <5 s/d (cut-off)	[2]HR: 0.58 (0.38, 0.89) [2]HR: 0.91 (0.70, 1.18) [2]HR: 0.68 (0.49, 0.95) [2]HR: 0.58 (0.33, 1.03) [2]HR: 1.04 (0.74, 1.45) [2]HR: 0.58 (0.33, 1.03)	Age, education, stage, B-symptom, initial treatment, and total energy intake	Han et al., 2010 (54)(USA)
NHL	ACM 2339 (1348) CCSM 2339 (903)	4.5 ± 4.1 (mean ± SD)	M/F 45–75 (mean at diagnosis: 71.8)	FFQ	V: T3 (≥179.9) vs. T1 (<120.8) g/1000 kcal/d F: T3 (≥201.3) vs. T1 (<98.6) g/1000 kcal/d V: T3 (≥179.9) vs. T1 (<120.8) g/1000 kcal/d F: T3 (≥201.3) vs. T1 (<98.6) g/1000 kcal/d	[2]HR: 0.98 (0.85, 1.12) [2]HR: 1.03 (0.90, 1.19) [2]HR: 0.98 (0.83, 1.16) [2]HR: 1.04 (0.88, 1.24)	Age at cohort entry, age at diagnosis, 5-y survival, sex, BMI, education, comorbidity, NHL type, stage, treatment, smoking status, and alcohol intake	Leo et al., 2016 (55) (USA)
Melanoma	CCSM 249 (92)	16 (median)	M/F Categories: ≤65 and >65	DQ	F: at least daily vs. less than daily	[2]HR: 0.66 (0.42, 1.04)	Breslow thickness, age at diagnosis, sex, ulceration, and microsatellitosis	Gould Rothberga et al., 2014 (39) (USA)

[1] ACM, all-cause mortality; CCSM, cancer cause-specific mortality; DQ, dietary questionnaire; F, fruit; M/F, males and females; NHL, non-Hodgkin lymphoma; ref., reference; RR, risk ratio; s/d, servings/day; V, vegetables; V+F, vegetables and fruit.
[2] Prediagnosis.

and fruit intake in ovarian cancer patients, and with vegetable intake in head and neck cancer patients.

A 25% lower risk in all-cause mortality was observed in survivors of head and neck cancer consuming more vegetables, with the highest risk reduction for total vegetable intake (∼300 g/d) (56–58). Sandoval et al. (56) observed a more pronounced inverse risk in all-cause and oral and oropharynx cancer mortality when considering the post-diagnosis vegetable intake compared with the prediagnosis intake. This suggests that it is more useful to assess the diet after cancer diagnosis and treatment as it has more impact on prognosis. Although no significant association was found when comparing the highest and lowest categories of total vegetable intake with oral and oropharynx cancer recurrence, a 73% lower risk was observed among moderate consumers of vegetables (5–7 servings/wk reported after diagnosis, equivalent to ∼400 g/d) (56). In addition, a protective effect has been described for a whole-food diet rich in vegetables and fruit regarding overall mortality in head and neck cancer patients (64). However, in the present meta-analysis, no association was found between head and neck cancer prognosis and fruit intake, in contrast with Crosignani et al. (58), who reported a lower all-cause mortality in men consuming ≥200 g/wk compared with 80 g/wk or lower of noncitrus fruit. Similar inverse associations have been observed between the intake of nonstarchy vegetables and oral cancer risk (including mouth, pharynx, larynx, and nasopharynx sites) in healthy populations, but not with fruit consumption (65).

There are few studies on prognosis in digestive tract cancer survivors [esophagus (40), stomach (37, 44), pancreas (42), and colorectum (41, 45–47)], suggesting basically null results. However, the lowest consumption of green leafy vegetables (almost never compared with almost every day) was directly associated with a higher all-cause mortality in male colorectal cancer patients, particularly with colon cancer (41). Furthermore, results of the WCRF/AICR report were also suggestive of an inverse relation between a low vegetable and fruit intake and both incident colorectal and gastric cancer risks (65).

Vegetable and fruit consumption may be inversely related to the incidence of lung cancer (66, 67), particularly in smoker populations (65, 68). Although an uncertain relation was found between lung cancer prognosis and total vegetable and fruit intake (48, 49), Wu et al. (43) reported a 31% lower site-specific cancer mortality in female nonsmoker lung cancer patients consuming ∼120 g of cruciferous vegetables per day. Similarly, the risk of lung cancer incidence was lower among high consumers of cruciferous vegetables (68).

Our meta-analysis revealed that a higher vegetable (∼300 g/d) and fruit (∼300 g/d) intake was associated with a 22% and 18% lower overall mortality, respectively, in ovarian cancer patients. The strongest associations were observed in ovarian cancer patients consuming ≥5 portions of vegetables and fruit per day (>400 g) (61). Almost identical protective effects were found with a higher adherence to the Healthy Eating Index (60). However, the results for the relations
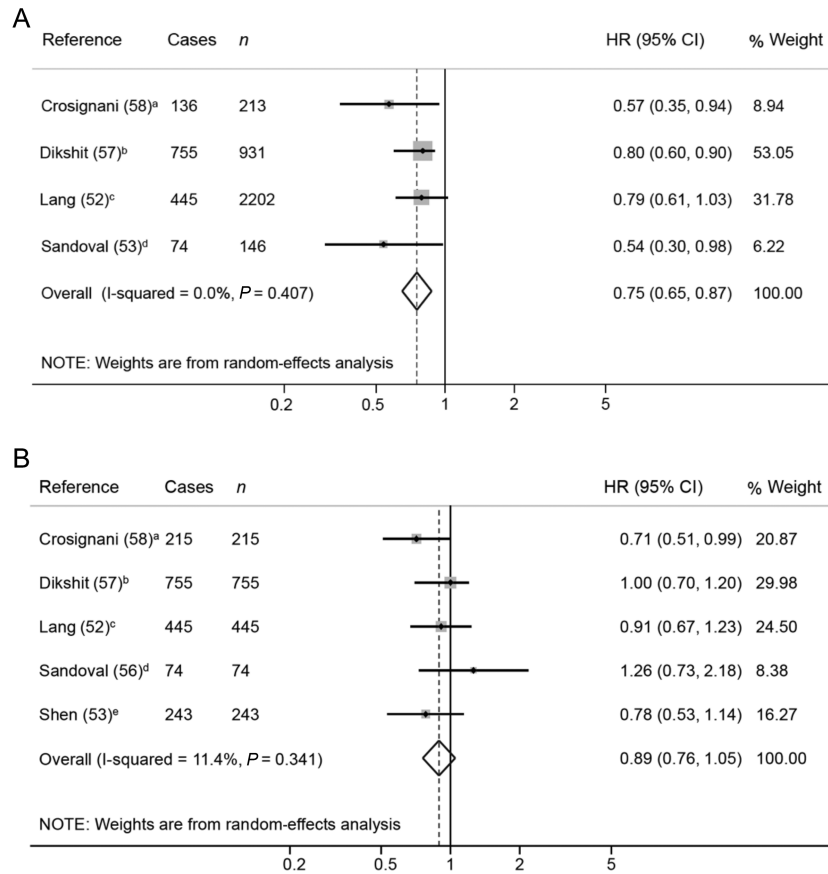
FIGURE 2 Forest plot showing pooled HRs with 95% CI for overall mortality risk in head and neck cancer patients, comparing the prediagnosis highest compared with lowest vegetable (A) and fruit (B) intake category. Quantification of the exposures: a) >281.1 g/d compared with <202.1 g/d; b) >328.6 compared with <148.6 g/d; c) <1 portions/d compared with <5 portions/wk; d) ≥8 compared with ≤4 servings/wk; e) ≥321.4 compared with 0 g/d.

between vegetable and fruit subgroup intakes and ovarian cancer prognosis were inconclusive (59–62). Similarly, null results were described between vegetable and fruit intake and incident ovarian cancer risk in the WCRF/AICR report (65).

In an Italian cohort of prostate cancer patients, diets rich in fruit, mainly noncitrus fruit, and in both vegetables and fruit were associated with a lower risk of all-cause mortality (50). Regarding dietary patterns, Western diets were directly associated with overall and cause-specific cancer mortality, whereas Prudent and Mediterranean diets were not significantly related to overall mortality (69, 70). No association was found between vegetable and fruit intake and the incidence of prostate cancer in earlier studies (71, 72). Despite that, since cardiovascular disease is the major cause of death in prostate cancer survivors (73), a dietary pattern rich in vegetables, fruit, and whole grains is also typically recommended for cardiovascular disease prevention (74).

Vegetable and fruit consumption was not associated with prognosis in bladder cancer (38, 51). The WCRF/AICR report shows that the risk of bladder cancer is inversely related to the intake of nonstarchy vegetables and fruit, although with limited evidence (65). Several meta-analyses

have addressed this topic, also with inconsistent results (71, 75–78).

The overall results in NHL cancer survivors were null (19); however, a US-based study found an inverse association between the combined consumption of vegetables and fruit and total mortality in NHL cancer survivors (54). Likewise, uncertain results were obtained for the intake of green leafy vegetables and citrus fruit separately (54, 63). Regarding NHL incidence, previous meta-analyses suggest that a high intake of vegetables, as well as vegetables and fruit, was significantly related to a 20% lower NHL risk in healthy subjects (79, 80). Although fruit intake was not associated with NHL risk (79, 80), a diet rich in citrus fruit resulted in a 15% lower risk (80).

Although in our review we did not include breast cancer survivors, it is important to highlight that a previous meta-analysis in 2017, including 12 studies, showed null results with the intake of total fruit and vegetables combined (HR: 1.01; 95% CI: 0.72, 1.42), total vegetables (HR: 0.99; 95% CI: 0.89, 1.11), and total fruit (HR: 0.88; 95% CI: 0.74, 1.05) (21). Similar results were also reported in another meta-analysis, including 10 studies (22). However, in the
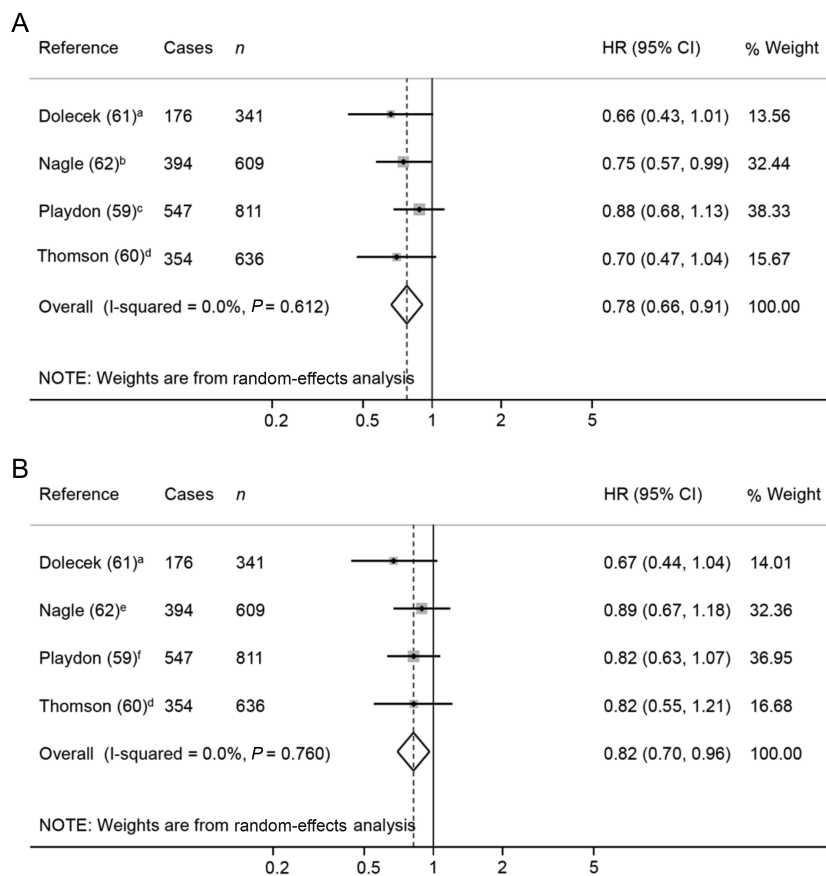
FIGURE 3 Forest plot showing pooled HRs with 95% CI for overall mortality risk in ovarian cancer patients, comparing the prediagnosis highest compared with lowest vegetable (A) and fruit (B) intake categories. Quantification of the exposures: a) 2 compared with 1 servings/d; b) ≥5.6 compared with <3.0 servings/wk; c) ≥5 compared with <3 servings/d; d) 5 compared with 2.5 points (1.1 compared with 0.6 cup eq/1000 kcal in vegetables and 0.8 compared with 0.4 cup eq/1000 kcal in fruit); e) ≥4.5 compared with 2.8 servings/wk; f) ≥4 compared with <2 servings/d.

WCRF/AICR report, an association between the higher consumption of foods containing fiber and increased breast cancer survival was presented (2). Moreover, an inverse association, classified as probable strong evidence, was observed between nonstarchy vegetables and breast cancer incidence in the WCRF/AICR report (65).

Food processing and cooking or its absence is another factor to be considered when assessing the effect of vegetable intake. Among studies assessing the relation between raw vegetable consumption and cancer prognosis (38, 44, 50), 2 retrospective studies observed an association with 26% and 36% lower overall mortality in patients with gastric and prostate cancer, respectively (44, 50). These results are similar to those reported for the incidence of upper gastrointestinal cancer, but not prostate cancer (81). The consumption of ≥1 serving/wk (≥70 g/wk) of fermented preserved vegetables was associated with a higher all-cause mortality in all patients, in ever smokers (smoking >100 cigarettes or equivalent use of pipes in their lifetime) and in ever alcohol drinkers (individuals that drank alcohol at least

once per month) with esophagus cancer, but not in those who have never smoked or drunk (40). Likewise, the consumption of salt-preserved foods correlates with a higher risk incidence of gastric and nasopharynx cancer (65).

Comparing results by cancer site, vegetable intake protected against overall mortality in patients with cancer of the ovary and head and neck. Similar results were observed with fruit consumption and overall mortality in patients with cancer of the ovary and prostate. Raw vegetable consumption has been associated with a lower mortality in survivors of prostate and gastric cancer, whereas the intake of fermented preserved vegetables has been associated with a higher mortality in esophagus cancer survivors. No significant relations between the intake of vegetables or fruit and cancer prognosis have been observed in the rest of investigated tumor sites (breast, NHL, colorectal, lung, bladder, and melanoma). Although more studies are needed to validate these observations, cancer sites seem to respond differently to dietary intake and specific recommendations should be addressed for each case.

Limitations of the current data

The protocol of this systematic review and meta-analysis was not registered in the International Prospective Register of Systematic Reviews (PROSPERO) because data extraction was completed before intending to register it. Another limitation of the present study is that it is based on insufficient/weak evidence according to the HEALM scale, due to the noncontrolled trial design of the studies included in this meta-analysis and the vague explanation of the mechanisms of action. In spite of this, the included studies allow generalizability of the results to large populations thanks to the sample size and the long-term or lifetime periods measured. Only cohort studies, mainly prospective, were included in our systematic review and meta-analysis. The low number of studies quantified in each subgroup (maximum of 4) precluded the performance of analyses of sensitivity. In general, studies were adjusted for the main potential confounders and the follow-up length was usually adequate; although some publications only provided the maximum period, but not the mean or median (44, 46, 47, 49, 58, 60, 61). Moreover, the population sample in most of the studies was representative of the general population, and the events were registered with medical certificates or report linkage. Another potential limitation is dietary measurement error, although vegetable and fruit consumption was assessed by validated questionnaires, mainly using dietary food frequency. Consumption categories (quantiles) were based on the intake of each cohort, with considerable variability between studies, which complicates the comparison of results. Moreover, dietary data was collected in servings or in cups, but each study used different sizes, especially for servings (without including this information in the publication), and therefore it impeded the possibility of performing accurate dose-response analyses. Another drawback is that in most of the studies, data of postdiagnosis diet was not considered. Therefore, in these studies, potential dietary changes after cancer diagnosis and treatment were not accounted for. This was the main cause of risk of bias in most of the studies, obtaining the moderate qualification in the ROBINS-E tool. In order to take into account this limitation, we did not mix prediagnosis with postdiagnosis data in our meta-analyses. In addition, some studies limited the analysis to smokers or nonsmokers, or to males or females, and the results from these specific cohorts cannot be directly generalized. Another limitation was the disparity in the classification of vegetables when evaluating subgroup intake, in contrast with fruit, which are clearly divided into citrus and noncitrus. A homogeneous classification of vegetables should be established to facilitate interpretation of study results. In addition, fruit juices were included as total fruit exposure by some authors. Five studies in particular took into account fruit juice consumption, some of them limiting only natural fruit juices. On the other hand, 4 out of the total studies excluded juices and 14 did not specify the criteria. The 2010 Dietary Guidelines for Americans considered 100% fruit juices a serving of fruit (82). However, the implications of consuming fruit juice remain controversial, in terms of its nutritional value and health impacts (83–85). Nevertheless, this meta-analysis adds valuable information to previous studies. This investigation focuses on the associations between the intake of vegetables and fruit, as well as their subgroups, and cancer prognosis. To date, only recommendations of vegetable and fruit intake for breast cancer survivors have been published (2).

Future directions

Although there is a growing body of evidence on the associations between vegetable and fruit consumption and cancer incidence risk, the evidence on cancer prognosis is still limited. Much of the available data is based on prediagnosis exposure instead of postdiagnosis exposure, and it is known that cancer diagnosis can trigger significant changes of vegetables and fruit intake (86), but not in all cases (87). Therefore, further studies on postdiagnosis consumption data are needed. Furthermore, the types of fruit and vegetables included in the studies should be standardized with the exclusion of fruit juices and starchy vegetables, as their composition is different. Additionally, more studies on subgroups are needed with a predefined classification. Preparation types and processing methods, e.g., cooked compared with raw vegetables should also be analyzed in future studies. Finally, more studies using biomarkers of vegetable and fruit consumption (88) are also warranted to improve dietary assessment.

Conclusions

In the last decades, dietary recommendations have mainly focused on the primary prevention of noncommunicable diseases, for which the WHO suggests a minimum consumption of 400 g/d (5 servings/d) of vegetables and fruit (89). In addition, a systematic and dose-response meta-analysis concluded that the consumption of 550–600 g/d (7–7.5 servings/d) of vegetables and fruit was associated with a ∼14% lower risk of total incident cancer (90). To date, dietary recommendations for cancer prevention are also given to survivors, despite possible differences in the associations with cancer incidence and cancer prognosis. Both the American Cancer Society (ACS) nutritional and physical activity guidelines for cancer survivors and the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on nutrition in cancer patients, are in parallel with the current public health guidelines for adults, which recommend following a diet high in vegetables, fruit, and whole grains (65, 73, 91, 92). Those recommendations are based on the consideration that survivors have a high risk of suffering a second primary cancer or other chronic diseases (73, 91).

Our results suggest that diets high in fruit and vegetables, especially rich in vegetables, are associated with lower cancer mortality among head and neck and ovarian cancer survivors. Thus, the consumption of ∼300 g/d of vegetables by head and neck cancer patients and ∼300 g/d of vegetables and ∼300 g/d fruit separately by ovarian cancer patients decreased overall mortality. Moreover, it is important to bear

in mind that none of the studies have detected a harmful relation with the consumption of fruit and vegetables in cancer patients. According to our findings, the current general recommendation based on the consumption of 5 or more servings of vegetables or fruit per day (400 g/d) seems to be partially underestimating the needs in cancer survivors, at least for ovarian cancer survivors that could increase to ~600 g/d (i.e., 300 g/d of vegetables and 300 g/d of fruit).

Acknowledgments

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