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REVIEW

Fruits and vegetables and cervical cancer: a systematic review and meta-analysis

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ABSTRACT

We conducted a meta-analysis to examine the association of fruits and vegetables intake with the occurrence of cervical intraepithelial neoplasia (CIN) and invasive cancer. MEDLINE, LILACS, Scopus, Cochrane Library, and Web of Science databases and gray literature on Google Scholar were searched before December 17, 2018. Odds ratio (OR) or relative risk (RR) estimates for the highest vs. the lowest intake of intake and 95% confidence intervals (CI) from the included studies were pooled using fixed and random-effects models. We found 18 studies: 17 case–control studies ($n = 9{,}014$ cases, $n = 29{,}088$ controls) and one cohort study ($n = 299{,}651$). No association was observed for CIN. The pooled adjusted ORs (95% CI) for cervical cancer were 0.61 (95% CI 0.52–0.73) for vegetables and 0.80 (95% CI 0.70–0.93) for fruits. However, no association was observed when the pooled effect was estimated among studies that adjusted for human papillomavirus (HPV). Consumption of vegetables and fruits was not associated with incidence of cervical cancer among studies that controlled for HPV infection. The level of evidence is limited because only one cohort study was included in the analysis.

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Introduction

Cervical cancer is the second most common cancer and the third leading cause of death from cancer among females in less developed countries (1). Worldwide, among women aged between 20 and 39 years, cervical cancer is the second most common cancer (2). Overall, 527,600 new cervical cancer cases and 265,700 deaths worldwide were estimated in 2012. Nearly half of these cases were diagnosed in women aged <50 years (1, 3), and almost 90% of cervical cancer deaths occur in developing countries in Africa, Latin America, the Caribbean, and Asia, which reflects differences in availability of screening for the detection and removal of precancerous lesions (1).

Cervical squamous carcinoma results from persistent infection with carcinogenic genotypes of human papillomavirus (HPV), a necessary condition for the disease to occur. Persistently infected cells progress to precancerous lesions called cervical intraepithelial neoplasia (CIN), from grade one to grade 3, or carcinoma *in situ* and, finally to invasive squamous carcinoma (4). Most HPV infections clear within 3 years; the 10% that persist for 2 years or more are highly likely to become precancerous (4).

The International Agency for Research on Cancer classified 12 types of HPV as group 1 carcinogenic agents in humans, including HPV 16 and HPV 18. These two types are the most carcinogenic, together causing 70% of cervical cancers. Since 2006, two vaccines have been available for HPV 16 and 18, and since 2014, a 9-valent HPV vaccine that can prevent approximately 90% of cervical cancers has been available (5).

Cofactors to HPV infection include tobacco smoking, long-term oral contraceptive use, and high parity (6–9). Diet could be an important cofactor influencing susceptibility to infection, its persistence, and its likelihood of altering DNA stability and repair.

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Study of the relationship between nutritional factors and cervical neoplasia is complicated by its multifactorial etiology, with many of the identified risk factors being correlated with nutritional and socioeconomic status (10). Therefore, an association between diet and cervical neoplasia could be due to residual confounding by socioeconomic status. Dietary inadequacy consequent to poverty may contribute to the high incidence rates in developing countries (11).

A review published in 2005 (12) classified scientific evidence as a possible protective effect of fruits and vegetables on HPV persistence, based on two prospective studies (13, 14), and the possible protective effect of vegetables in cervical neoplasia based on one case–control study (15). The World Cancer Research Fund (WCRF) Network's Second Expert Report, Diet, Nutrition, Physical Activity and cancer in 2007, concluded that there was no strong evidence for protective effects of food and nutrition against cervical cancer, except in the case of carrots, which were classified as having limited evidence of protective effects. In May 2018, the WCRFs Third Expert Report regarding dietary fruit and vegetable intake suggests a decreased risk of mouth, pharynx, larynx, esophageal, stomach, bladder, lung, breast, and colon cancer. However, no meta-analysis was conducted for cervical cancer because of the limited number of cohorts, and in the WCRFs systematic literature review, studies with pre-invasive neoplastic lesions as outcome were not included (16). An umbrella review published in 2019 reported no evidence and insufficient evidence for the association between endometrial cancer and vegetable and fruit intake, respectively (17).

This systematic review and meta-analysis aimed to examine associations between the intake of fruits and vegetables and the risk of CIN and invasive cervical cancer by considering the effect of HPV infection status.

Methods

We conducted this systematic literature review using a registered protocol CRD42016036792 (https://www.crd.york.ac.uk/PROSPERO), and in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A protocol was written before starting the literature search (Supplement Data).

Data sources

The MEDLINE, LILACS, Scopus, the Cochrane Library and Web of Science databases were searched for articles published before 17 December 2018. We also searched for gray literature using Google Scholar. The following keywords were used: fruits OR vegetables OR dietary OR eating OR food OR food consumption OR nutrition AND cervical intraepithelial neoplasia OR uterine cervical dysplasia OR uterine cervical neoplasms OR cervical cancer. Further details regarding the search strategy for each database are presented in Supporting Information Appendix 1. Two authors conducted independent searches.

Study eligibility

To be eligible for inclusion, studies had to fulfill the following criteria: (i) present histological confirmation of cervical dysplasia or invasive cancer; (ii) present original data (excluding reviews, editorials, and meta-analysis); (iii) make available estimates of fruit and/or vegetable intake; (iv) be conducted in humans, i.e., excluding animal and in vitro studies; (v) be cross-sectional, case–control, prospective cohort studies, and clinical trials; and (vi) make adjustment for potential confounders: socioeconomic and demographic (age, race/ethnicity, income, education, marital status, income), proxy of HPV acquisition (sexual debut, number of sexual partners, age at first marriage, frequency of sexual intercourse), and cofactors that influence the risk of progression from HPV infection to persistence (tobacco smoking, oral contraceptive use, and parity (6–9)); and (vii) availability of effect estimates, such as odds ratio (OR), relative risk (RR), or hazard ratio (HR), with their corresponding estimates of precision. Studies that did not meet the inclusion criteria were excluded during the initial review. When uncertainty existed, we retrieved and assessed the full text article; if this was not available, we requested it from authors by e-mail (18). No limit for age interval was established, nor for study design in the original studies.

Study selection

The relevance of studies was assessed through a hierarchical approach on the basis of title and abstract. After initial screening of titles and abstracts, the studies included by both reviewers were compared. Disagreement was resolved by consensus, and any differences were settled by the third author.

Data extraction and quality assessment

Data extraction was performed independently by two authors. The following information was extracted

from each study: author; publication year; country; number of participants; outcome; exposure; methods used to measure exposure; confounding variables; methods used to determine HPV infection; the most fully adjusted OR, RR or HR of CIN or cancer, and corresponding 95% confidence interval (CI) for the highest vs. lowest level of intake, with the greatest number of adjustments. Study quality was independently assessed by two authors according to the Newcastle–Ottawa Quality Assessment Scale (NOS) for cohort and case–control studies (19) or adapted for cross-sectional studies (20). The NOS contains eight items for case–control and cohort studies and nine items for cross-sectional studies, categorized into three dimensions: selection, comparability, and ascertainment of either the exposure or outcome of interest for case–control or cohort studies, respectively (19). This scale identifies high-quality choices with a star: a maximum of one star for each item within the selection (four items) and exposure/outcome categories (three items), and a maximum of two stars for comparability (one item). The NOS cutoffs for good quality were defined as those that scored the maximum stars for all items ($\geq$3 stars for selection, $\geq$2 for comparability and $\geq$2 for outcome); studies of fair quality scored two stars for selection, $\geq$1 for comparability and $\geq$2 for outcome; and poor quality studies scored 0–1 for selection, 0 for comparability and 0–1 for outcome (21).

Statistical analysis

The most fully adjusted OR, RR, or HR were used to measure the association between intake of fruits and vegetables combined, fruits only, and vegetables only, and the risk of CIN or cervical cancer. Measures of relative effect (OR, RR, or HR) and respective CI were combined on the log scale. We then estimated the pooled OR and 95% CIs for the highest vs. lowest level of intake. The reference category of vegetable and fruit intake was that with the lowest intake. In studies with the higher intake as reference category, the estimated risk was taken as one over the estimate. We considered the intake of the most frequently consumed type of vegetable.

The analyses were stratified by HPV adjustment (yes or no), study design, study sample size ($n \leq 199$ cases vs. >200 cases), study settings (hospital or population-based), designed *a priori*.

We estimated the pooled effect using a random-effects model to account for differences in the size of the effects among studies, depending on population characteristics (age, education, smoking, and sexual habits), country and HPV infection assessment method. We also estimated the fixed-effect model, considering that all studies in the analysis could share a common effect size. Pooling of effect sizes was used to compare how both models affect results (22).

Statistical heterogeneity among the studies was assessed by the Cochran Q and the I^2 statistics, which describe the percentage of total variation across studies that was attributable to heterogeneity rather than to chance or random error (23). If $I^2 < 25\%$, there is no heterogeneity; if $I^2 = 25$–50%, there is moderate heterogeneity; $I^2 = 50$–75% represents great heterogeneity; and $I^2 > 75\%$ indicates extreme heterogeneity (24). The heterogeneity was considered significant if $I^2 > 50$ or $p < 0.10$. Influence analysis was used to examine the influence of each study on the overall results. Publication bias was assessed by stratifying between study sample size ($n < 199$ or $n > 200$ cases), which selected cutoff was *a priori* and tentative, without any specific reason. All statistical analyses were performed with Stata/SE software (version 14.0; StataCorp, College Station, TX, USA).

Results

Figure 1 summarizes the selection of studies following PRISMA guidelines. We identified 5,867 potential studies in our search, as follows: PubMed 1,876, Scopus 2,260, Web of Science 1,555, Cochrane 116, LILACS 32, and Google Scholar 28. After removing duplicates using Endnote, and manual selection based on title and author name ($n = 1{,}612$), 4,255 entries were screened based on title and abstract, 4,174 were classified as irrelevant, and 81 potentially valid reports were left.

Among the 81 remaining studies, 63 were excluded: five without histological confirmation, 43 did not evaluate the exposure of interest, six did not provide a measure of association, two studies did not adjust for confounders, three did not provide information on the 95% CI, three articles reported the same population (i.e., selection for study was based on more broad outcomes (25), two outcomes of interest were present (26), and there were multiple adjusted risks (27)), and one cross-sectional study. Cross-sectional study was not an exclusion criterion, but we decided not to include because dietary habits were not assessed previously to diagnose. Finally, a total of 18 studies were deemed eligible for inclusion (Figure 1): 17 case–control studies ($n = 9{,}014$ cases, $n = 29{,}088$ controls) and one cohort ($n = 299{,}651$ participants). The majority of

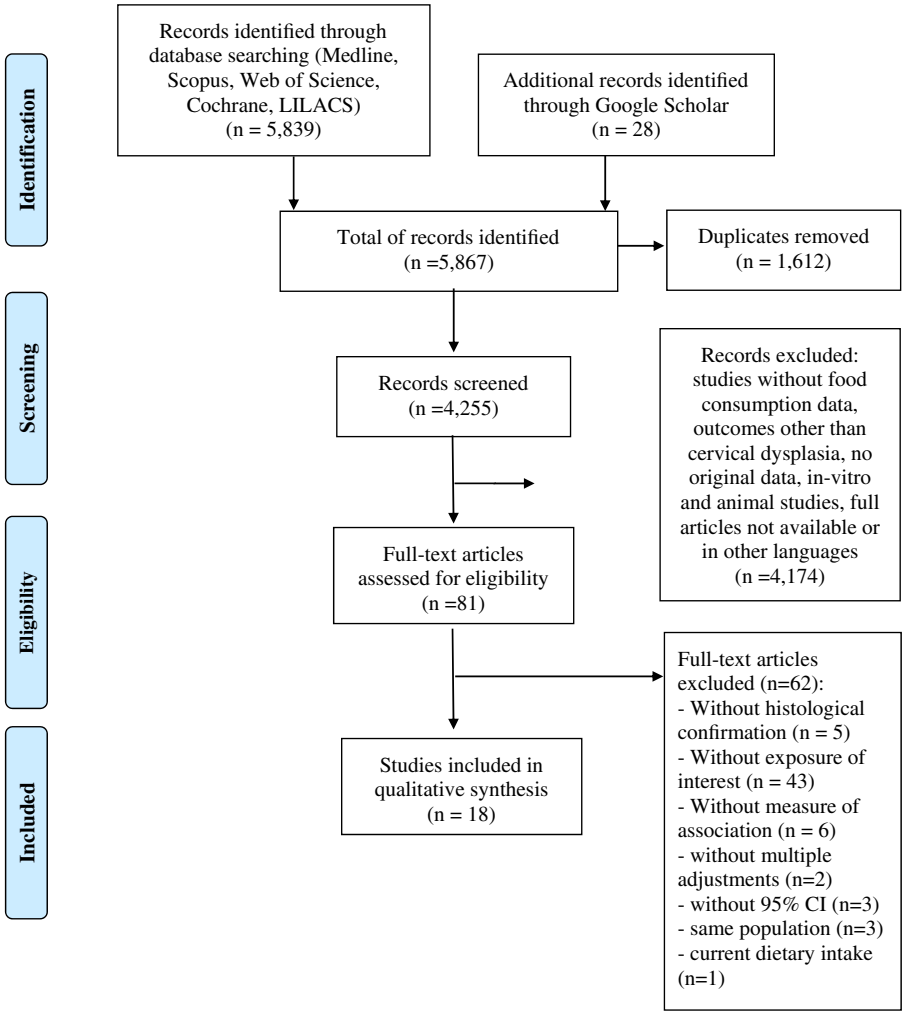

Figure 1. Flow chart of published studies for inclusion in the systematic review.

studies were identified in PubMed, Web of Science and one (28) from LILACS.

Study characteristics

Table 1 shows the main characteristics of the selected studies that were published between 1988 and 2011. Two of the included studies were performed in the United States of America (25, 29), four in Latin and Central America (11, 18, 28, 30), five in Asia (15, 31–34), two in China (35, 36), four in Europe (26, 37–39), and one in Australia (40). Seventeen studies were case–control and one a cohort study (37). Risk for cervical lesions in the cohort study was estimated by the Cox proportional hazard to calculate HR (37). We assumed that HR is an estimative of risk equivalent to OR in the case of a rare event (41), as observed by Gonzalez et al. (37). Dietary intake was ascertained via food frequency questionnaires (FFQs), including 28–266 food items.

The reference category for vegetable and fruit intake was that of the lowest intake. Thus, we converted the OR in three studies (26, 28, 38). In these studies, the risk was one over the estimate, for example, in La Vecchia et al. (26), the reference category was green vegetable intake ($\geq$14 portions/week) and the lowest group ($<$7 portions/week) and risk for invasive cancer was OR = 4.67 (estimated risk 1/4.67 = 0.21).

Seven studies investigated the association of different vegetables (e.g., kale, spinach, cruciferous vegetables, carrots, and tomatoes) (15, 18, 27, 29, 31, 34, 42) with CIN. We considered the intake of the most frequently consumed type of vegetables. For example, La Vecchia et al. (42) investigated the association for two exposures of interest and respective frequency of consumption for green vegetable intake ($\geq$14 times/week vs. $<$7 times/week), and carrots ($\geq$2 times/week vs. $<$1 time/week); in this case, we considered the estimated risk associated with the intake of green vegetables.

Table 1. Characteristics of selected studies on fruit and vegetable intake and risk of cervical dysplasia and cancer ($n = 18$).

Author	Country. study design	Cases/controls or cases/study size or follow-up (years)	Outcome	Exposure	Comparisons	Maximum adjusted OR (95%CI)	Confounding variables
Atalah et al. (18)	Chile case–control	170/340	Carcinoma	Leafy vegetables	Not informed	0.70 (0.57–0.87)	BMI
Brock et al. (40)	Australia, case–control	117/196	CIS	Fruits, salads	≥1.2 vs. <0.3 fruits times/day; ≥1.9 vs. <0.7 vegetables times/day	0.4 (0.1–1.0) 0.4 (0.1–0.9)	Total sexual partner, sexual debut, smoking, OC, other food groups
Cuzick et al. (39)	London, case–control	121/241	Cervical cancer	Leafy vegetables, fruits	≥8 vs. ≤2 leafy vegetables pieces/day; ≥8 vs. 0 pieces fruits/week	0.59 (0.24–1.48) 0.67 (0.19–2.35)	Age, total sexual partner, age 1st intercourse
de Vet et al. (38)	Netherlands, case–control	257/705	Cervical dysplasia	Spinach, fruits, tomatoes	≥3 vs. 0 times/month spinach ≥3 vs. 0 fruits times/month ≥3 vs. 0 tomatoes times/month	1.59 (0.97–2.61) 0.29 (0.13–0.63) 0.58 (0.33–1.02)	Age, demographic, marital status, education, smoking, parity,OC, sexual debut, frequency of intercourse, number preventive smears, intake
Ghosh et al. (36)	China, case–control	239/979	Cervical cancer	Fruits and juices, vegetables, vegetables + fruit s	>60g vs. ≤31g fruits >80g vs. ≤48g vegetables >22g vs. ≤86g vegetables + fruits	0.80 (0.53–1.10) 0.58 (0.38–0.89) 0.52 (0.34–0.77)	Age, education, smoking, OC, family history, parity,age first pregnancy, total energy intake
Gonzalez et al. (37)	EPIC, cohort	299,649 or 2,700,667 person-year	CIS, cervical cancer	Total vegetables, total fruits, leafy vegetables	>286 vs. <117 total vegetables g/day; >337 vs. <125 total fruits g/day; 4th quartile vs. 1st	0.92 (0.74–1.14) 0.99 (0.82–1.20) 0.78 (0.56–1.08)	Education, smoking, marital status, parity, alcohol, BMI, energy
Hernandez et al. (25)	USA, case–control	122/183	SIL	Vegetables, fruits, spinach	>331.9g vs. ≤152.4g all vegetables; >253g vs. ≤ 68.6g all fruits ; >7g vs. ≤0.24g spinach	1.6 (0.6–4.7) 0.6 (0.2–1.6) 1.2 (0.5–2.9)	Age, ethnicity, energy, smoking, alcohol, sexual partner, HPV, calorie
Herrero et al. (43)	Central America, case–control	748/1411	Cervical cancer	Fruit, vegetables, leafy vegetables,	≥119g vs. <43g fruits, ≥207g vs. <121g vegetables, ≥111g vs. <56g leafy vegetables	0.86 (0.60–1.20) 0.97 (0.70–1.30) 0.95 (0.70–1.30)	Age, study site, lifetime sexual partner, parity, HPV 16/18
Hirose et al. (27)	Japan, case–control	416/20,985	Cervical cancer	Green vegetables, carrot, fruits	≥5 vs. ≤2 green vegetables times/week, ≥5 vs. ≤2 carrots times/week, daily fruits vs. ≤3–4 times/week	0.56 (0.43–0.74) 0.70 (0.52–0.94) 0.92 (0.72–1.16)	Age, marital status, sexual debut, parity, smoking
Hosono et al. (34)	Japan, case–control	333/1665	CIN3, invasive cancer	Green vegetables	>5 vs. <1 times/week	CIN3: 0.40 (0.06–2.55) Invasive: 0.61 (0.29–1.27)	Age, smoking, alcohol, OC, supplement, gravidity
Hwang et al. (33)	Korea, Nested case–control	90 CIN1, 72 CIN2/3/, 166 controls	CIN 2/3 only HPV+	Vegetables, fruits	≥342 vs. ≤260 vegetables g/day;≥153 vs. ≤70 fruits g/day	1.11 (0.53–2.36) 0.97 (0.93–1.02)	Age, income, education, OC, menopausal status, parity, smoking, alcohol
Larrinaga et al. (28)	Uruguay, case–control	53/208	Cervical cancer	Vegetables	<1 vs. >5 times/week	2.8 (0.9–8.2)	Age, outpatient department, residence, sexual debut, total sexual partner
La Vecchia et al. (26)	Italy, case–control	392/392	Cervical cancer, CIN1/2/3	Carrots, green vegetables	≥2 vs. <1 carrots portion/week; ≥14 vs. <7 green vegetables portions/week	Cancer: 3.18 (2.10–4.82) CIN: 1.01 (0.59–1.74) Cancer: 4.67 (2.23–9.81) CIN: 0.90 (0.39–2.04)	Age, interviewer, marital status, education, parity, sexual debut, menopause, BMI, lifetime sexual partner, smoking, OC, hormone use

(*Continued*)

Table 1. Continued.

Author	Country. study design	Cases/controls or cases/study size or follow-up (years)	Outcome	Exposure	Comparisons	Maximum adjusted OR (95%CI)	Confounding variables
Peng et al. (56)	China, case–control	101/146	Cervical cancer	Vegetables	Daily vs. once/week	0.5 (0.2–1.6)	Age, income, residence, age at first marriage, smoking, HPV16/33
Rajkumar et al. (31)	India, case–control	205/213	Cervical cancer	Vegetables + fruits, green vegetables, fresh tomatoes, carrots, cruciferous	≥7 vs. <6 vegetables + fruits servings/week, ≥2 vs. 0 green vegetables, ≥5 vs. vs. <3 tomatoes servings/week, ≥5 vs. <3 carrots servings/ week, ≥5 vs. <3 cruciferous servings/week	0.37 (0.11–1.22) 0.59 (0.22–1.59) 0.64 (0.25–1.66) 0.64 (0.31–1.35) 0.73 (0.36–1.49)	Age, residence, education, occupation, marital status, age first marriage, parity, husband extramarital status
Shannon et al. (15)	Thailand, case–control	50/125	Cervical cancer	Cruciferous vegetables	>1.20 vs. ≤0.17 servings/day	1.30 (0.51–3.30)	Age, energy, interviewer, parity
Tomita et al. (30)	Brazil, case–control	231/453 108/453	CIN3, cervical cancer	Dark green and deep yellow vegetables + fruits, carrots	≥45.7g vs. <16.7g dark green and deep yellow vegetables and fruits, ≥203g vs. <69g carrots	CIN3: 0.52 (0.27–1.00) Cancer: 1.55 (0.73–3.29) CIN3: 0.50 (0.27–0.95) Cancer: 0.56 (0.34–0.92)	Age, hospital, ethnicity, education, smoking, sexual debut, lifetime sexual partner, parity, HPV
Verreault et al. (29)	USA case–control	189/227	Cervical carcinoma	Fruits, dark green and yellow vegetables	≥7 vs. <2 times/week fruits, ≥10 vs. <5.2 times/week	0.3 (0.2–0.6) 0.6 (0.3–1.1)	Age, race, education, smoking, number of pap, OC, barrier contraceptive use, history cervical infection, sexual debut, lifetime sexual partners

OC: oral contraceptive, HPV: human papillomavirus, HC2: hybrid capture.

Six studies presented estimates that were adjusted for potential confounding variables and also for HPV infection using *in situ* hybridization (43), hybrid capture 2 (HC2) (33), and polymerase chain reaction (PCR) (25, 30, 31, 35).

Most of the studies adjusted the estimates for age, education, sexual debut, lifetime sexual partners, smoking, and oral contraceptive use. Additional adjustment for HPV infection was done in five studies for infection by HPV 16/18 detected by *in situ* hybridization (43), and by HPV genotyped by PCR (30, 35, 44). Hwang (33) assessed risk only among HPV-positive women.

In their original article, Tomita et al. (30) investigated dark green and deep yellow vegetables and fruits, and carrots. However, information about the intake of fruits and vegetables combined, fruits only, and vegetables only were available and considered in the pooled analysis.

Meta-analysis results

Cervical dysplasia

The study-specific maximally adjusted OR for all available data, for the highest intake of vegetables only or fruits only vs. the lowest intake, were pooled to examine association with CIN (Figure 2). Based on eight studies of vegetable intake and six studies on fruits, no associations were observed; there was still no association after stratification by adjustment for HPV infection. No heterogeneity across studies was observed for vegetables, but heterogeneity was higher among studies investigating fruit intake with no adjustment for HPV.

Table 2 shows the pooled estimates stratified by study type, study setting (hospital or population-based), case sample size, study quality (Supplement 1 shows the quality classification for each study), and specific groups of vegetables, like leafy vegetables, or dark green and deep yellow vegetables and fruit, or carrots only. No association with precancerous lesions was observed (Table 2).

The influence of individual studies on the pooled effect was assessed by omitting each of the included studies. When the study by Hernandez et al. (25) was omitted from the meta-analysis, moderate heterogeneity was observed for vegetable intake and CIN risk, but without association. And after omitting Gonzalez et al. (37), the prospective study, a significant and reduced risk for CIN related to fruit and vegetable intake was observed.

Cervical cancer

The pooled OR for the association of vegetables only and fruits only with cervical cancer is shown in Figure 3. We identified 14 studies that reported on vegetable intake and eight studies on fruits, with a decrease of 40 and 20% in cervical cancer among women with the highest intakes of vegetables and fruits, respectively. After stratifying according to HPV infection, an association was observed only among studies without HPV adjustment (Table 2). We identified two studies (31, 36) on the association between the intake of vegetables and fruits combined, and the pooled OR using the random-effects model was 0.51 (95% CI 0.36–0.73), with no heterogeneity ($I^2 = 0\%$, $p = 0.85$) (data not shown).

Table 2 shows stratified analysis. Most studies were hospital-based, and the pooled effects based on studies with good quality presented more precise and significant results. Concerning sample size, statistically significant associations for cervical dysplasia were observed only for small studies.

Discussion

This systematic review showed that intake of fruits and vegetables, carrots, and leafy and dark green and deep yellow vegetables and fruits, are associated with a reduced risk of cervical cancer, but not associated with precancerous lesions. However, when stratified by HPV, no association was observed among studies that adjusted for HPV infection. Therefore, it is possible that HPV infection may have confounded the observed associations.

Diet would be a proxy of healthy behavior or mediated by lifestyle factors (17), and women with a diet rich in fruits and vegetables would be more likely to be nonsmokers and condom users, and highly educated, all variables associated with HPV infection (17, 45–47). Moreover, compared to nonsmokers, smokers eat less vegetables and fruits and present lower circulating antioxidants (48). An additive interaction of low intake of dark green and deep yellow vegetables and fruits and smoking was observed for cervical dysplasia risk (49).

In this review, five studies adjusted for HPV infection status, which was assessed using different methods, such as *in situ* hybridization (43), HC2 (33) or a more sensitive method, PCR (30, 35, 44). It is conceivable that studies that used less-sensitive methods for HPV diagnosis (i.e., *in situ* hybridization or HC2) could be affected by residual confounding. However,

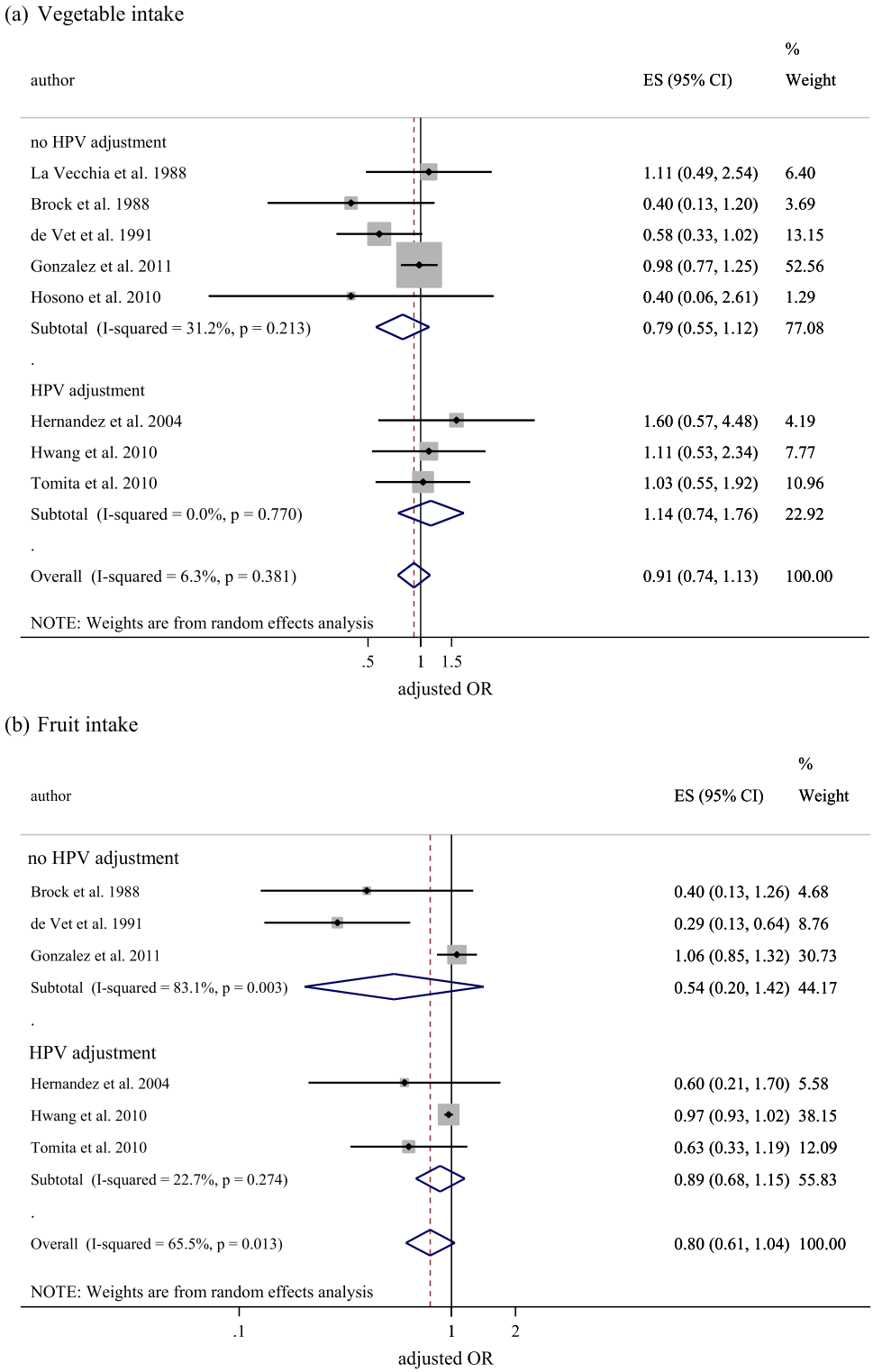

Figure 2. Forest plot of (a) vegetables and (b) fruits intake and cervical dysplasia risk according to without or with HPV adjustment.

results from these studies were similar to those that adjusted for HPV detected by PCR.

The pooled effects using random and fixed-effects models were similar, and we presented results for random-effects models. For most of the analysis, pooled estimates were not modified by sample size, suggesting that publication bias is unlikely.

Reduced risk for cervical cancer was observed in case–control studies, but not in the cohort study. In the Gonzalez et al. study (37), different dietary intake

Table 2. Fruit and vegetable intake and risk of cervical dysplasia and cancer by subgroups.

	Cervical dysplasia		Cervical cancer	
Subgroups analysis	*n*	Pooled effect (95%CI)	*n*	Pooled effect (95%CI)
Vegetables	**8**	**0.91 (0.74–1.13)**	**14**	**0.61 (0.52–0.73)**
Study design				
Cohort	1	0.98 (0.77–1.25)	1	0.73 (0.46–1.16)
Case–control	7	0.85 (0.61–1.18)	13	0.60 (0.50–0.72)
Study size				
≤199 cases	3	0.71 (0.26–1.93)	6	0.64 (0.54–0.76)
>200 cases	5	0.94 (0.77–1.14)	7	0.59 (0.49–0.72)
Study settings				
Population based	3	0.72 (0.44–1.18)	1	0.60 (0.31–1.15)
Hospital based	5	1.09 (0.75–1.59)	12	0.62 (0.55–0.71)
Quality				
Good	8	0.91 (0.74–1.13)	10	0.65 (0.59–0.77)
Fair		–	4	0.59 (0.49–0.71)
Control for confounding				
adjusted for HPV	3	1.04 (0.74–1.76)	3	0.90 (0.68–1.19)
Fruits	**5**	**0.96 (0.92–1.01)**	**8**	**0.80 (0.70–0.93)**
Study design				
Cohort	1	1.06 (0. 85–1.32)	1	0.79 (0.53–1.18)
Case–control	4	0.59 (0.35–0.99)	7	0.81 (0.69–0.94)
Study size				
≤199 cases	2	0.54 (0.20–1.42)	4	0.78 (0.67–0.92)
>200 cases	3	0.89 (0.68–1.15)	3	1.04 (0.64–1.67)
Study settings				
Population based	3	0.54 (0.20–1.42)	1	1.30 (0.64–2.65)
Hospital based	2	0.89 (0.68–1.15)	6	0.79 (0.67–0.92)
Quality				
Good	5	0.96 (0.92–1.01)	6	0.81 (0.69–0.94)
Fair		–	2	0.79 (0.53–1.16)
Control for confounding				
adjusted for HPV	3	0.89 (0.68–1.15)	6	0.87 (0.64–1.20)
Leafy vegetables	**6**	**1.02 (0.79–1.32)**	**10**	**0.63 (0.55–0.73)**
Study design				
Cohort	1	0.90 (0.61–1.33)		–
Case–control	5	1.05 (0.76–1.46)	10	0.63 (0.55–0.73)
Study size				
≤199 cases	2	0.98 (0.43–2.18)	5	0.60 (0.48–0.74)
>200 cases	4	0.99 (0.76–1.29)	4	0.66 (0.55–0.78)
Study settings				
Population based	2	1.12 (0.82–1.52)	1	0.60 (0.33–1.15)
Hospital based	4	0.77 (0.50–1.19)	8	0.64 (0.56–0.74)
Quality				
Good	6	0.99 (0.77–1.27)	8	0.65 (0.55–0.77)
Fair		–	2	0.60 (0.48–0.75)
Control for confounding				
adjusted for HPV	3	0.85 (0.61–1.18)	2	1.00 (0.75–1.33)
Carrots	**3**	**1.03 (0.74–1.44)**	**4**	**0.58 (0.47–0.72)**
Study size				
≤199 cases		–		–
>200 cases	3	1.03 (0.74–1.44)	4	0.58 (0.47–0.72)
Study settings				
Population based	1	2.00 (1.12–3.57)		–
Hospital based	2	0.74 (0.49–1.12)	4	0.58 (0.47–0.72)
Quality				
Good	3	1.03 (0.74–1.44)	4	0.58 (0.47–0.72)
Fair		–		–
Control for confounding				
Adjusted for HPV	1	0.50 (0.27–0.94)	1	0.96 (0.52–1.77)

methods from each study setting was used – FFQs with different numbers of food items, semi-quantitative assessment or diet history – that could have impacted in the accuracy of dietary intake, but was assessed prospectively. Important bias in case–control studies are recall and selection bias. It is likely that recall bias was present particularly among cases that may have changed dietary intake as a result of diagnose or the impact of disease and its treatment (50). And for selection bias, only three studies reported refusal rate (39, 42, 49) that was minimum (<5%). An additional methodological problem is the fact that case–control studies fail to capture the early stages of the natural history of cervical neoplasia that precede the onset of invasive lesions. Moreover, differential misclassification of HPV status especially among controls may bias the estimated relative risk (51, 52).

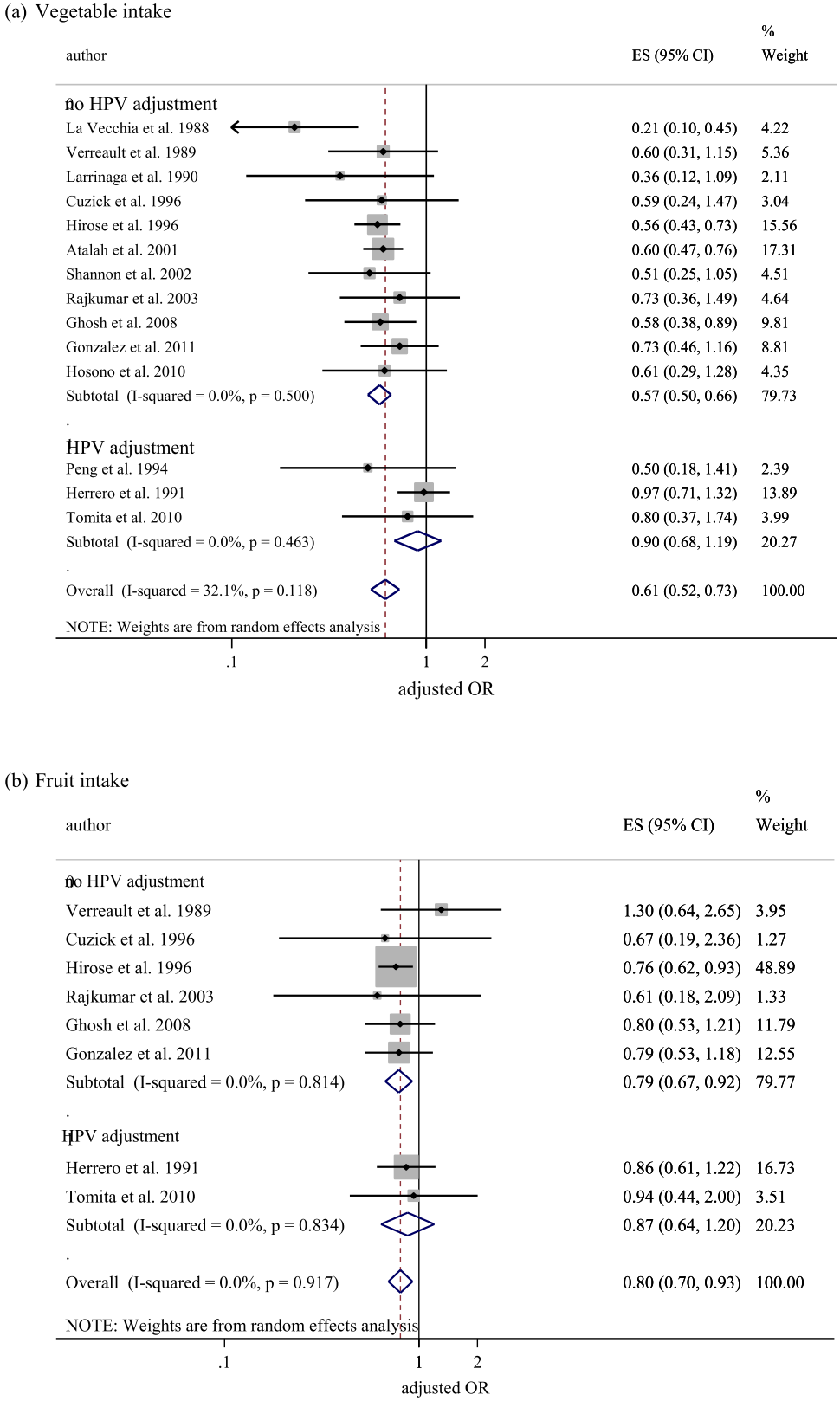

Figure 3. Forest plot of (a) vegetables and (b) fruits intake and cervical cancer risk according to without or with HPV adjustment.

Another limitation of the present meta-analysis is the significant statistical heterogeneity observed in investigation of the association of fruit intake and cervical dysplasia among studies without HPV adjustment.

Although the present review did not find evidence of an association of fruit and vegetable intake with cervical cancer after adjustment for HPV infection, prospective studies showed clearance of HPV infection

among women with diets rich in these food groups (14, 53, 54). The benefit against cervical cancer of the intake of fruits and vegetables could be because of the presence of vitamins, which might contribute to potential antioxidant, immunity, genomic stability, and gene expression effects. Antioxidants from β-carotene, lycopene, and vitamin C can scavenge reactive oxygen species, and guarantee fluidity and integrity of the immunologic cell membrane (55). At early stages of carcinogenesis, a high intake of foods rich in β-carotene and lutein may play a role in immune response, which may counter persistence of HPV infection (56). Folate found in dark green and deep yellow vegetables and fruit has an important role in guaranteeing genomic stability and gene expression, and precursors of DNA and RNA (57). Hence, recommendations from the World Health Organization, World Cancer Research Fund and American Institute for Cancer Research for daily consumption of 400 g of vegetables and fruits could also be important for cervical cancer prevention (16). A recent summary of the available evidence regarding dietary fruit and vegetable intake demonstrated the beneficial effects of higher intakes in chronic conditions like cardiovascular disease, age-related cataracts, colon cancer prevention, and pancreatic diseases (17).

In conclusion, vegetable and fruit intakes were not associated with cervical cancer among studies that controlled for HPV infection. The level of this evidence is limited, since only one cohort study was included in the analysis. More prospective studies are necessary to investigate the role of fruit and vegetable consumption in the clearance of oncogenic HPV infections, targeting the early stage of carcinogenesis.

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