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REVIEW ARTICLE

The influence of dietary vegetables and fruits on endometrial cancer risk: a meta-analysis of observational studies

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Fruits and vegetables store many bioactive compounds and micronutrients, making their consumption ideal for maintaining good health. A previous meta-analysis in 2007 provided evidence that high vegetable and cruciferous vegetable intake might help prevent endometrial cancer (EC) development. The current study purposely explored the favorable effects of vegetables, fruits, and their other specific types using a review of the most recent papers. We conducted a systematic search through August 2021 in the PubMed and EMBASE databases on this topic, through which twenty-seven studies, consisting of 21 case-control and 6 cohort studies, were obtained. The results showed that vegetables (pooled odds ratio [OR], relative risk [RR], hazard ratio [HR] = 0.76, 95% confidence interval [CI] 0.63–0.91), cruciferous vegetables (pooled OR = 0.81, 95% CI 0.70–0.94), dark green and yellow/orange combined vegetables (pooled OR = 0.64, 95% CI 0.42–0.97), and fruits (pooled OR = 0.81, 95% CI 0.70–0.92) were strongly associated with a reduced risk of EC. These results were primarily based on studies of high quality and exhibited either by case-control only or a combination of case-control and cohort studies. Additionally, the results varied by geographic location, such as Western areas, the US, and Italy. This meta-analysis suggested that the consumption of fruits and vegetables has beneficial effects on EC risk and that specific kinds of fruits and vegetables should be recommended differently due to their outstanding bioactive components.

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INTRODUCTION

Endometrial cancer (EC) is the 2nd most common gynaecologic cancer. In 2020, it accounted for around 400,000 new cases, which is approximately 2.2% of all cancer cases globally [1]. The incidence seems to vary by geographical area and is higher specifically in Western and high-income countries while lower in Asian countries. EC is frequently diagnosed at the early stage of the disease and has a favorable prognosis of 5-year survival rate [2]. The mortality rate was approximately 1% among all cancers in 2020; however, high-grade EC tends to recur, and recurrent EC has a dismal prognosis [3].

From 2000 to 2010, the EC incidence experienced a double increase [4]. It has been emphasized that EC development is mainly caused by hormonal conditions, such as an excess of oestrogen and/or a lack of progesterone [5]. In detail, the hormonal aetiology of EC could be attributed to the early menarche, late menopause, nulliparity, hormone replacement therapy (HRT), and obesity in women [4]. Among them, increasing trends of HRT use in perimenopausal and postmenopausal women in the late 20th century might partly explain the increasing trends in EC incidence. In some countries, socioeconomic transitions have contributed to changes in reproductive factors, such as a decline in the high parity, which protects women from EC.

Besides, studies have shown that EC risk is also associated with changes in dietary and lifestyle habits. According to an updated report by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AIRC) in 2018, body fatness was classified as a convincing risk factor for EC, whereas high glycaemic load and adult attained height were probable risk factors for EC [2]. In contrast, physical activity and coffee consumption were considered probable protective factors against EC. Moreover, vegetables, fruits, and other plant foods have been concerned to be suggestive factors, although epidemiological evidence of their protective effects against EC has yet to be determined.

Vegetables and fruits are essential foods that contain many nutrients that are thought to have a beneficial effect on the human body. Prior studies have investigated the possible linkage between eating fruits and vegetable and the development of EC; however, these links are controversial. One meta-analysis of this association was performed in 2007 and included sixteen case-control studies and one cohort study [6]. The results suggested a possible protective effect of vegetables, particularly cruciferous vegetables, against EC risk. The summarized result was slightly statistically significant for fruit consumption. The study has encountered some limitations as follows: (1) a limited number of studies, (2) inadequate assessment of study quality with a systematic scale, (3) lack of stratification analysis for the type of specific fruits and vegetables, and (4) the inability to explore differences among study locations and ethnic groups.

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This study aimed to identify the protective impact of vegetables and fruits on the development of EC, exploring the effect of specific subgroups of vegetable and fruit types among study populations and locations, the details of which were not clarified in the previous study.

MATERIALS AND METHODS

The current study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), registration number (CRD42021278433).

Literature search

We used two different data sources, PubMed and EMBASE, to systematically search all eligible studies through August 2021. The following Medical Subject Headings (MeSH) terms related to vegetable and fruit intake and EC outcome were applied: "fruit" or "fruits" or "vegetable" or "vegetables" or "food plants" and "endometrial neoplasms" or "endometrial cancer". The publication language of all studies was not limited.

Study selection and eligibility criteria

Articles were screened with the following criteria, which were applied to each study: (1) observational epidemiological studies (case-control, nested case-control, and cohort designs), (2) studies investigating the association of fruit and vegetable intake with the risk of EC, and (3) study outcomes estimated by adjusted odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs), and apparently identified 95% confidence intervals (CIs). In situations of an overlapping sample, the study with the higher quality was preferentially included. Following the selection criteria, two investigators (YTL and MG) independently extracted the potential studies for final analyses.

Methodological quality assessment

The methodological quality of each study was evaluated using the Newcastle Ottawa Scale (NOS) for case-control and cohort studies [7]. The three main components of the scale are (1) the selection of the study population, (2) comparability, and (3) identification of the exposure or outcome. The maximum score is indicated by 9 stars for those components after assessment. In this study, we categorized the scores into 3 groups: high quality (≥7 stars), high risk (4–6 stars), and very high risk (≤3 stars).

Main analysis and subgroup analyses

The association of fruit and vegetable intake with EC risk was investigated (comparing the highest level versus lowest level of intake) and is outlined in the main analysis. In subgroup analyses, we performed pooled estimations for groups by study design (case-control, cohort), quality of the study (high, low), study location (Western countries, the US, or Asian countries), vegetables and fruits combined, vegetables only, fruits only, and types of fruits and vegetables (citrus fruits, cruciferous vegetables, dark green leafy and yellow vegetables combined, and allium vegetables).

Statistical analyses

The strength of the association between intake of types across vegetables and/or fruits and EC risk was almost measured by the OR, RR, HR. The effect estimates were individually figured out, combined, and weighted in the main data analysis along with their 95% CIs, followed by the calculation of the pooled effect sizes (pORs, pRRs, pHRs) with the respective 95% CIs. The variety of study locations and populations led to the use of a random-effects model using the Der Simonian and Laird method [8]. The heterogeneity of all the included studies was assessed by the Higgins I^2 index, which was percentage of total variation among those studies. An I^2 value of zero or lesser than zero was then set as zero (no heterogeneity across studies), and the maximum value of I^2 was up to 100% (maximal heterogeneity). An I^2 value over 50% indicates substantial heterogeneity [9].

We evaluated publication bias using Begg's funnel plot and Egger's test [10, 11]. Publication bias is displayed by asymmetry of the funnel plot or a *p*-value under 0.05 for Egger's test. A disagreement between these two outcomes was resolved according to the *p*-value of Egger's test due to the possibility of visual judgment of Begg's funnel plot being misleading [12]. Later, the trim-and-fill method was used when significant publication bias was identified by Egger's test. All statistical analyses were performed using the Stata SE software package, version 17.0 (Stata Corp., College Station, TX).

RESULTS

Identification of relevant studies

The study selection process is described in Fig. 1. A total of 962 articles were identified by searching two databases and hand searching. Based on title evaluation, 126 duplicates and 750 unrelated articles were excluded. The remaining 86 articles were evaluated by their abstracts, and then 40 studies were omitted for the detailed reasons shown in Fig. 1. After full-text evaluation of the remaining 46 studies, a total of 27 studies were eligible for final analysis [13–39].

Although the variables seemed to be relevant, the 1993 study by Barbone et al. [40] investigated specific vegetables (broccoli, cauliflower, carrot, spinach, iceberg lettuce, and tomato), but not vegetables overall, leading to an inability of subgroup categorization. Therefore, this study was excluded from the comprehensive analyses.

Studies by Dalvi et al. [26] in 2007 and Canchola et al. [17] in 2015 investigated the association of plant-based patterns and EC risk and defined plant-based patterns by the predominant load of an array of fruits and vegetables. Consequently, the plant-based pattern effects on EC risk in these two studies were used in our study as a representative for the combined analysis of fruits and vegetables.

General characteristics of studies and quality assessment

A summary of the study characteristics is shown in Table 1. We included 21 case-control studies published from 1986 to 2021, with 6249 EC patients and 38,068 controls. Four case-control studies were conducted with the same study population but focused on different types of fruits and vegetables [13, 23, 38, 39]. Six cohort studies published between 1999 and 2019 recruited 573,636 participants. After the follow-up time, 4188 subjects were confirmed to have EC. Cohort studies had a long follow-up period, ranging from 8 years to 20.4 years. Overall, ten studies were conducted in the US, and seven studies were in Italy. Other studies were from China ($n = 1$), Japan ($n = 2$), European countries ($n = 1$), England ($n = 1$), Greece ($n = 2$), Mexico ($n = 1$), Poland ($n = 1$), and Sweden ($n = 1$).

The methodological quality of the studies was evaluated using the Newcastle Ottawa Scale for both case-control and cohort designs and is displayed in Table 2. The quality scores for the case-control studies ranged from 3 to 8 stars, in which 15 studies were judged to be of high quality. The scores of the cohort studies ranged from 5 to 8 stars, with four of six studies considered to be of high quality.

Combined intake of fruits and vegetables and risk of EC

First, based on the available data on the combined intake of fruits and vegetables, we investigated the association with EC risk. The results of the combination of fruit and vegetable intake were not significant even in subgroup analyses by study design (3 cohort and 4 case-control studies) [16, 17, 21, 26, 30, 31, 33] (Supplementary Fig. S1.1). All seven studies were conducted in Western

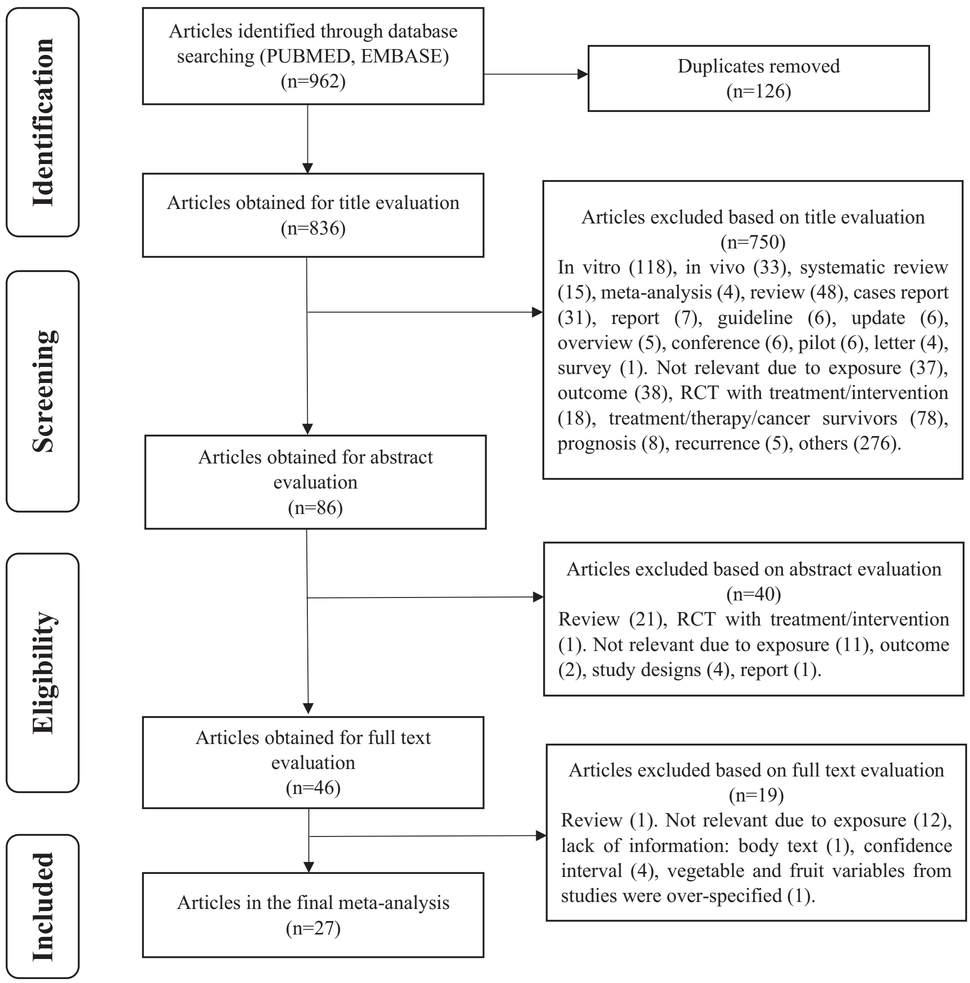

Fig. 1 Flow diagram for study selection. The main process included 4 parts: (1) identification, (2) screening, (3) eligibility, and (4) included articles.

areas. The subgroup analysis based on study quality also showed no significant association between combined fruits and vegetables and EC risk (Supplementary Fig. S1.2). No publication bias was found for the total selected studies ($n = 7$) (Begg's funnel plot followed a symmetric shape; Egger's test had a p for bias of 0.279; Supplementary Fig. S1.3).

Fruit intake and EC risk

In total, 19 studies assessed the relationship between fruit intake and EC risk [13–15, 18, 21–25, 27–32, 34–37]. Fruits were observed to have a protective effect against EC in a summarized analysis of 11 case-control studies evaluated to be of high quality (pOR=0.81, 95% CI 0.70–0.92), but a significant association was not observed based on the cohort studies (Fig. 2). The pooled analyses of case-control studies conducted in Western areas ($n = 13$), especially Italy ($n = 4$), showed more or less similar results to the overall analysis (pOR=0.83, 95% CI 0.74–0.94 in Western areas, OR = 0.71 95% CI 0.56–0.90 in Italy). However, the results were borderline significant in US countries (pOR=0.78, 95% CI 0.59–1.03) and not significant in the cohort studies (Supplementary Fig. S2.1, S2.2). No publication bias was found for the total selected studies ($n = 19$) (Begg's funnel plot followed a symmetric shape; Egger's test had a p for bias of 0.280; Supplementary Fig. S2.3).

Vegetable intake and EC risk

Twenty studies mentioned the association between vegetable intake and EC risk [14, 15, 18–25, 27–32, 34–37]. In an analysis of fourteen high-quality studies including 3 cohort and 11 case-control studies, vegetable intake (highest vs. lowest level of intake) was found to significantly contribute to a 24% reduction in the risk of EC (pOR/RR/HR = 0.76, 95% CI 0.63–0.91). The result was consistent with a subgroup analysis of case-control studies (pOR = 0.66, 95% CI 0.52–0.84) but not a subgroup analysis of 3 cohort studies (pRR/HR = 1.03, 95% CI 0.89–1.19) (Fig. 3). Subgroup analysis of study locations, such as Western areas, the US, and Italy, also showed a similar result (Supplementary Fig. S3.1, S3.2). Publication bias was observed for the total selected studies ($n = 20$) (Begg's funnel plot was asymmetric; Egger's test had a p for bias of 0.009; Supplementary Fig. S3.3). Then, the trim-and-fill method was conducted; however, the analysis showed no trimming performed, and the data were unchanged.

For the sensitivity analysis, three studies among a total of twenty-study were excluded [15, 24, 37]. The outcomes remained significant and followed the same direction as the abovementioned results (Supplementary Fig. S3.4, S3.5). No publication bias was found for this group ($n = 17$) (Begg's funnel plot followed a symmetric shape; Egger's test had a p for bias of 0.102; Supplementary Fig. S3.6).

Subgroups of specific vegetables and fruits

The summarized results of the association of citrus fruits, cruciferous vegetables, combined dark green and yellow/orange vegetables, and allium vegetables with EC risk are presented in Table 3.

Table 1. General characteristics of 27 observational studies included in the analysis.

Study	Study population	Time frame/ Follow-up period	Cancer diagnosis	Type of fruits, vegetables	OR/RR/HR (95% CI)	Matched and adjusted variables
Case-control studies (N = 21)						
Esposito et al, 2021 [13]	454 cases/ 908 controls in Italy (hospital-based)	1992–2006	Endometrial cancer	Fruits	OR = 0.75 (0.50–1.14)	Age-, center-matched Adjusted for year of interview, education, total energy intake, BMI, occupational physical activity, smoking status, alcohol intake, history of diabetes, age at menarche, parity, OC use, HRT use, and menopausal status.
Ricceri et al, 2017 [15]	297 cases/ 307 controls Italy (hospital-based)	2008	Endometrial cancer	Fruits Vegetables	OR = 0.55 (0.28–1.06) OR = 0.34 (0.17–0.68)	Adjusted for age, parity, menopausal status, HRT use, OC use, BMI, age at menarche, physical activity, education, smoking status, and total energy intake.
Plagens-Rotman et al, 2016 [16]	68 cases/ 480 controls in Poland (hospital-based)	2011–2013	Endometrial cancer	Fruits/ vegetables combined	OR = 0.85 (0.18–4.09)	No information.
Takayama et al, 2013 [19]	161 cases/ 380 controls in Japan (hospital-based)	2002–2007	Endometrial endometrioid adenocarcinoma (EEA)	Vegetables	OR = 0.47 (0.26–0.83)	Adjusted for age, weight, BMI, educational background, medical history, smoking habits, and reproductive factors (number of deliveries, breast feeding experience, OC use, and menopausal status), total energy intake.
Bosetti et al, 2012 [20]	367 cases/ 798 controls in Italy (hospital-based)	1991–2009	Endometrial cancer	Cruciferous vegetables	OR = 0.93 (0.68–1.27)	Adjusted for age, study center, year of interview, education, alcohol drinking, tobacco smoking, BMI, and total energy intake, parity, menopausal status, age at menopause, and OC and HRT use.
Foschi et al, 2010 [39]	454 cases/ 908 controls in Italy and Switzerland (hospital-based)	1991–2007	Endometrial cancer	Citrus fruit/ juice	OR = 0.95 (0.67–1.34)	Age-, study center-matched Adjusted for tobacco smoking, alcohol, education, BMI, physical activity, and energy intake.
Chandran et al, 2010 [22]	424 cases/ 398 controls in US (population-based)	2001–2005	Epithelial endometrial cancer	Fruits Vegetables Dark green/ orange vegetables	OR = 0.87 (0.55–1.39) OR = 0.93 (0.59–1.48) OR = 1.02 (0.65–1.60)	Adjusted for age, education, race, age at menarche, menopausal status, age at menopause for postmenopausal women, parity, OC use, HRT use, BMI, and total calories physical activity, smoking status, and alcohol.
Bravi et al, 2009 [23]	454 cases/ 908 controls in Italy and Switzerland (hospital-based)	1992–2006	Endometrial cancer	Fruits Vegetables	OR = 0.83 (0.55–1.24) OR = 0.59 (0.37–0.94)	Age-, center-matched Adjusted for year of interview, education, total energy intake, BMI, history of diabetes, age at menarche, parity, OC use, HRT, and menopausal status.
Yeh et al, 2009 [24]	541 cases/ 541 controls in US (hospital-based)	1982–1998	Endometrial cancer	Fruits Vegetables Cruciferous vegetables	OR = 1.10 (0.74–1.62) OR = 0.51 (0.34–0.75) OR = 0.77 (0.52–1.13)	Adjusted for age, BMI, exogenous estrogen use, smoking, total menstrual months, and total energy.
Galeone et al, 2009 [38]	454 cases/908 controls in three Italian areas (hospital-based)	1992–2006	Endometrial cancer	Allium vegetables	OR = 0.40 (0.22–0.72)	Age-, study center-matched Adjusted for total energy intake, education, BMI, age at menarche, parity, OC use, HRT use, and menopausal status.

Table 1. continued

Study	Study population	Time frame/ Follow-up period	Cancer diagnosis	Type of fruits, vegetables	OR/RR/HR (95% CI)	Matched and adjusted variables
Dalvi et al, 2007 [26]	488 cases/ 461 controls in US (population-based)	1996–1999	Endometrial cancer	Fruits/ vegetables combined[a]	OR = 1.20 (0.72–2.00)	Adjusted for age, race/ethnicity, age at menarche, OC use, parity, average daily caloric intake, average weekly physical activity, and the joint effects of menopausal status, HT use, and BMI.
Salazar-Martinez et al, 2005 [27]	85 cases/ 629 controls in Mexico (hospital-based)	1995–1997	Endometrial cancer	Fruits Green leafy vegetables	OR = 0.88 (0.43–1.79) OR = 1.11 (0.56–2.21)	Adjusted for age, total energy intake, number of live births, BMI, physical activity, and diabetes.
Tao et al, 2005 [28]	832 cases/ 846 controls in China (population-based)	1997–2001	Endometrial cancer	Fruits Vegetables Dark green/ yellow vegetables Cruciferous vegetables	OR = 0.97 (0.72–1.31) OR = 0.69 (0.50–0.96) OR = 0.70 (0.52–0.95) OR = 0.83 (0.62–1.12)	Adjusted for age, education, menopausal status, years of menstruation, first-degree family history of breast, colorectal, endometrial cancer, OC use, number of pregnancies, history of diabetes, BMI, total meat and fish intake and caloric intake.
Petridou et al, 2002 [29]	84 cases/ 84 controls in Greece (hospital-based)	1999	Endometrial cancer	Fruits Vegetables	OR = 1.03 (0.74–1.43) OR = 1.25 (0.89–1.74)	Age-matched Adjusted for education, BMI, pregnancy, and total energy intake
Terry et al, 2002 [30]	709 cases/ 2887 controls in Sweden (population-based)	1994–1995	Endometrial cancer in postmenopausal women	Fruits/ vegetables combined Fruits Brassica vegetables	OR = 0.90 (0.70–1.20) OR = 0.90 (0.70–1.20) OR = 0.80 (0.60–1.10)	Adjusted for age, BMI, smoking, physical activity, prevalence of diabetes, fatty fish consumption, and quintiles of total food consumption.
Littman et al, 2001 [31]	679 cases/ 944 controls in US (population-based)	1985–1991 (case), 1986–1993 (control)	Endometrial cancer in postmenopausal women	Fruits/ vegetables combined Fruits Vegetables Dark green/ yellow vegetables Cruciferous vegetables Citrus fruit/ juice	OR = 0.73 (0.50–1.10) OR = 0.67 (0.47–0.95) OR = 0.69 (0.48–1.00) OR = 0.75 (0.56–1.00) OR = 0.71 (0.54–0.95) OR = 0.85 (0.65–1.10)	Adjusted for age, county, total energy intake, smoking status, BMI, unopposed estrogen use
McCann et al, 2000 [32]	232 cases/ 639 controls in US (population-based)	1986–1991	Endometrial cancer	Fruits Vegetables Citrus fruits	OR = 0.90 (0.50–1.70) OR = 0.50 (0.30–0.90) OR = 1.00 (0.50–1.90)	Adjusted for age, education, BMI, diabetes, hypertension, pack-years cigarette smoking, age at menarche, parity, OC use, menopause status, and postmenopausal estrogen use. Each food group further adjusted for the remaining food groups.
Goodman et al, 1997 [34]	332 cases/ 511 controls in US (population-based)	1985-1993	Endometrial cancer	Fruits Vegetables	OR = 0.48 (0.28–0.80)	Adjusted for pregnancy history, birth control pill use, estrogen use, history of diabetes mellitus, Quetelet's index, and total calories

Table 1. continued

Study	Study population	Time frame/ Follow-up period	Cancer diagnosis	Type of fruits, vegetables	OR/RR/HR (95% CI)	Matched and adjusted variables
					OR = 0.51 (0.29–0.90)	
Hirose et al, 1996 [35]	145 cases/ 26,751 controls in Japan (hospital-based)	1988	Endometrial cancer	Fruits Vegetables Green vegetables	OR = 1.97 (1.37–2.82) OR = 1.54 (1.11–2.13) OR = 1.12 (0.74–1.70)	Adjusted for age, first-visit year.
Tzonou et al, 1996 [36]	145 cases/ 298 controls in Greece (hospital-based)	1992–1994	Endometrial cancer	Fruits Vegetables	OR = 0.96 (0.76–1.21) OR = 0.85 (0.66–1.11)	Adjusted for age, schooling years, age at menopause, age at menarche, number of liveborn children, number of miscarriages, number of abortions, history of OC use, history of use of menopausal oestrogens, smoking, alcohol intake, coffee drinking, height, BMI, and energy intake.
La Vecchia et al, 1986 [37]	206 cases/ 206 controls in Italy (hospital based)	1979	Endometrial cancer	Fruits Green vegetables	OR = 0.57 (0.33–0.99) OR = 0.24 (0.13–0.45)	Adjusted for interviewer, age, marital status, years of education, BMI, parity, positive history for diabetes or hypertension, age at menarche and at menopause, OC, and other female hormone use.
Cohort study (N = 6)						
Dunneram et al, 2019 [14]	32,289 women from UK Women's Cohort study, 238 cases (England, Wales, and Scotland)	1995–1998 (18 years)	Endometrial cancer	Fruits Vegetables Cruciferous vegetables Citrus fruits	HR = 0.90 (0.79–1.03) HR = 0.93 (0.80–1.08) HR = 0.94 (0.76–1.16) HR = 0.77 (0.54–1.10)	Adjusted for age, physical activity, ethanol intake, smoking status, cumulative duration of breastfeeding, menopausal status, and socio-economic status, history of diabetes, and hypertension.
Canchola et al, 2015 [17]	75,093 active and retired females teachers and administrators, 937 cases (US)	1995–2011 (16.1 years)	Endometrial cancer	Fruits/ vegetables combined[b]	RR = 0.91 (0.72–1.15)	Adjusted for age, race, age at menarche, gravidity, OC use, average annual long-term, moderate plus strenuous physical activity, smoking status, height, and average daily caloric intake. Models were additionally adjusted for the following time-dependent exposures: BMI at baseline and updated at the 10-year follow-up, menopausal status/HRT use at baseline and updated at the 5-year and 10-year follow-ups.
Merritt et al, 2015 [18]	301,107 from the European Prospective Investigation into Cancer and Nutrition (EPIC), 1303 cases (10 European countries and 11 US states)	1992–2000 (11 years)	Endometrial cancer	Fruits Vegetables Citrus fruits	HR = 1.06 (0.90–1.27) HR = 1.09 (0.84–1.42) HR = 1.05 (0.89–1.24)	Adjusted for BMI, total energy intake, smoking status, age at menarche, OC use, a combined variable for menopausal status and PMH use, parity. Stratified by the age of recruitment and the study center.
Kabat et al, 2010 [21]	112,088 women from the NIH-AARP (National Institutes of Health-American Association of Retired Persons) Diet and Health Study, 1142 cases (US)	1995–1996 (8 years)	Endometrial cancer	Fruits/ vegetables combined Fruits Vegetables	HR = 1.12 (0.90–1.39) HR = 1.30 (1.04–1.61) HR = 1.09 (0.90–1.33)	Adjusted for age at baseline, education, age at menarche, parity, OC use, HRT use, age at menopause, BMI, smoking, frequency of vigorous physical activity, total fat intake, and caloric intake.

Table 1. continued

Study	Study population	Time frame/ Follow-up period	Cancer diagnosis	Type of fruits, vegetables	OR/RR/HR (95% CI)	Matched and adjusted variables
McCullough et al, 2007 [25]	41,400 women from Cancer Prevention Study II (CPS-II) Nutrition Cohort, established by the American Cancer Society, 435 cases (US)	1992–1993 (10 years)	Endometrial cancer	Fruits Vegetables Cruciferous vegetables Citrus fruits	RR = 1.24 (0.90–1.70) RR = 1.21 (0.89–1.65) RR = 1.15 (0.85–1.57) RR = 1.14 (0.84–1.55)	Adjusted for age, age at menarche, age at menopause, number of livebirths, age at first birth, HRT use, combined HRT, cigarette smoking, recreational physical activity, total energy intake, BMI.
Terry et al, 1999 [33]	11,659 women from the Swedish Twin Registry, 133 cases (US)	From 1961 (20.4 years)	Endometrial cancer	Fruits/ vegetables combined	RR = 0.40 (0.20–0.90)	Adjusted for age, physical activity, weight at enrollment and parity.

([a]Dietary pattern "plant-based" was predominately characterized by consumption of fruits and vegetables).
([b]Dietary pattern "plant-based" was characterized by high factor loadings on an array of fruits and vegetables).
BMI body mass index, *OC* oral contraceptive, *HRT* Hormone replacement therapy, *PMH* postmenopausal hormone, *ORs* odds ratio, *RR* relative risk, *HR* hazard ratio.

Six studies investigated the association of citrus fruits with EC risk [14, 18, 25, 31, 32, 39], but the pooled analyses showed no significant association based on either study quality (pOR/RR/HR = 0.92, 95% CI 0.79–1.08) or Western area (pOR/RR/HR = 0.98, 95% CI 0.88–1.10). No publication bias was found for the total selected studies ($n = 6$) (Begg's funnel plot followed a symmetric shape; Egger's test had a p for bias of 0.491; Supplementary Fig. S4).

Seven studies explored the beneficial effect of cruciferous vegetables on EC risk [14, 20, 24, 25, 28, 30, 31]. Among them, six high-quality studies were found (4 case-control studies, 2 cohort studies). The overall analysis including these six studies showed a marginally significant association between cruciferous vegetables and EC risk (pOR/RR/HR = 0.88, 95% CI 0.78–1.00). However, after stratifying by study design, the outcome from a pooled analysis of 4 case-control studies showed a significant association with 19% reduced odds of EC risk (pOR=0.81, 95% CI 0.70–0.94). The case-control studies conducted in Western areas ($n = 4$) were separately analyzed and showed similar results (pOR=0.80, 95% CI 0.68–0.93) (Table 3). No publication bias was found for the total selected studies ($n = 7$) (Begg's funnel plot followed a symmetric shape; Egger's test had a p for bias of 0.609; Supplementary Fig. S5).

Seven studies investigated the favorable effects of specific dark green and yellow or orange vegetables on EC risk [18, 22, 27, 28, 31, 35, 37]. Four of the seven studies were of high quality, and all studies had a case-control design. A summary of these studies showed a 36% reduced risk of EC with consumption of dark green, yellow, or orange vegetables (pOR=0.64, 95% CI 0.42–0.97) (Table 3). No significant OR was observed in the subgroup of five Western countries (pOR/RR/HR = 0.77, 95% CI 0.50–1.17). No publication bias was found for the total selected studies ($n = 7$) (Begg's funnel plot followed a symmetric shape; Egger's test had a p for bias of 0.515; Supplementary Fig. S6).

Five studies explored the association between allium vegetables and EC risk and were all included in the pooled analyses [14, 16, 18, 28, 38]. The general results showed no significant protective effect of allium vegetables against EC risk. However, subgroup analyses of case-control studies ($n = 3$) and high-quality studies ($n = 3$) showed significant or marginally significant results (pOR = 0.63, 95% CI 0.42–0.94 and pOR/RR/HR = 0.69, 95% CI 0.45–1.06, respectively). No publication bias was found for the total selected studies ($n = 5$) (Begg's funnel plot followed a symmetric shape; Egger's test had a p for bias of 0.214; Supplementary Fig. S7).

DISCUSSION

In the meta-analysis of observational studies, we found that the consumption of vegetables in general, cruciferous vegetables, and dark green and yellow/orange vegetables, together with fruits, were significantly associated with a reduction in EC risk. The majority of the studies included in the current analyses were case-control studies (78%) and approximately 70% of them were judged to be of high quality. The pooled results of the cohort studies did not show significant results. Stratification of all studies by area showed that most of the studies conducted in Western countries identified a protective effect of vegetables, cruciferous vegetables, and fruits against EC risk, but no effect of dark green and yellow/orange vegetables was found. Subgroup analyses of studies from the US showed that vegetable intake was significantly associated with a reduced risk of EC, while those of Italy showed significant results for both vegetable and fruit intake. Overall, no worthy result of other specific citrus fruits or allium vegetables was found.

Vegetables and fruits are well-known to be healthy daily foods due to their high content of biologically active compounds such

Table 2. Methodological quality of studies based on the Newcastle-Ottawa scale.

Case-control study (*N* = 21)										
Study ID	**Selection**				**Comparability**	**Exposure**			**Score**	**Quality[a]**
	Adequate definition of cases	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases and controls**	**Ascertainment of exposure**	**Same method for cases and controls**	**Non-Response rate**		
Esposito et al, 2021 [13]	★	★	-	★	★★	★	★	★	8	high quality
Ricceri et al, 2017 [15]	★	-	-	★	★★	★	★	★	7	high quality
Plagens-Rotman et al, 2016 [16]	★	-	-	★	-	★	★	-	3	very high risk
Takayama et al, 2013 [19]	★	-	-	★	★★	-	★	-	5	high risk
Bosetti et al, 2012 [20]	★	★	-	★	★★	★	★	★	8	high quality
Chandran et al, 2010 [22]	★	-	★	★	★★	★	★	★	8	high quality
Foschi et al, 2010 [39]	★	★	-	★	★★	★	★	★	8	high quality
Bravi et al, 2009 [23]	★	★	-	★	★★	★	★	★	8	high quality
Yeh et al, 2009 [24]	★	-	-	★	★★	-	★	-	5	high risk
Galeone et al, 2009 [38]	★	★	-	★	★★	★	★	-	7	high quality
Dalvi et al, 2007 [26]	★	★	★	-	★★	★	★	★	8	high quality
Salazar-Martinez et al, 2005 [27]	★	-	-	-	★★	★	★	★	6	high risk
Tao et al, 2005 [28]	★	-	★	★	★★	★	★	★	8	high quality
Petridou et al, 2002 [29]	★	-	-	★	★★	★	★	★	7	high quality
Terry et al, 2002 [30]	★	★	★	★	★★	-	★	★	8	high quality
Littman et al, 2001 [31]	★	-	★	★	★★	★	★	★	8	high quality
McCann et al, 2000 [32]	★	-	★	★	★★	★	★	★	8	high quality
Goodman et al, 1997 [34]	★	-	★	★	★	★	★	★	7	high quality

Table 2. continued

Study ID	Selection				Comparability	Exposure			Score	Quality[a]
Case-control study (*N* = 21)										
	Adequate definition of cases	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases and controls**	**Ascertainment of exposure**	**Same method for cases and controls**	**Non-Response rate**		
Hirose et al, 1996 [35]	★	-	-	★	★	-	★	-	4	high risk
Tzonou et al, 1996 [36]	★	-	-	-	★★	★	★	★	6	high risk
La Vecchia et al, 1986 [37]	★	★	-	★	★★	★	★	★	8	high quality
Cohort study (*N* = 6)										
	Selection				***Comparability***	***Outcome***				
	Representativeness of exposed cohort	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Outcome of interest was not present at baseline**	**Comparability of cohorts**	**Assessment of outcome**	**Long follow-up enough for outcomes**	**Adequacy of follow up of cohorts**		
Dunneram et al, 2019 [14]	★	★	-	★	★★	★	★	-	7	high quality
Canchola et al, 2015 [17]	-	★	-	★	★★	★	★	-	6	high risk
Merritt et al, 2015 [18]	-	★	-	★	★	★	★	-	5	high risk
Kabat et al, 2010 [21]	★	★	-	★	★★	★	★	-	7	high quality
McCullough et al, 2007 [25]	★	★	-	★	★★	★	★	★	8	high quality
Terry et al, 1999 [33]	-	★	-	★	★★	★	★	★	7	high quality

[a]High quality (≥7), high risk (4–6), very high risk (≤3).
★ Denotes the presence of information, explanation, or evaluated elements according to the Newcastle-Ottawa scale within the study.

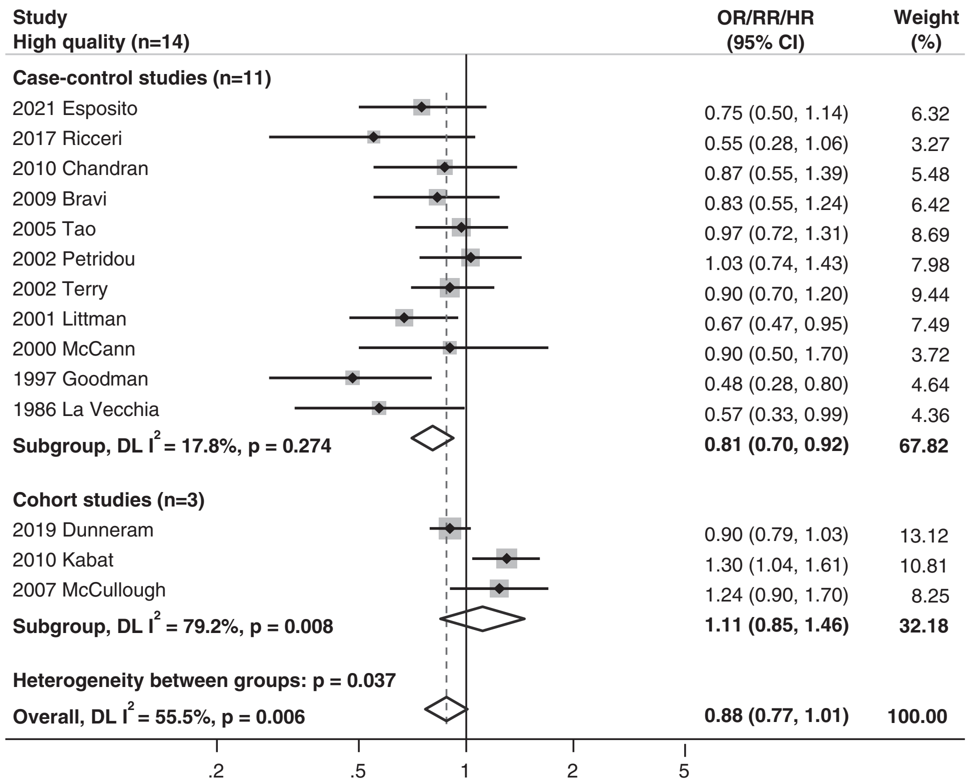

Fig. 2 Association between fruits intake and EC risk ($n = 14$, high quality studies). Weights are from random-effects model. ORsodds ratio, RR risk ratio, HR hazard ratio, CI confidence interval.

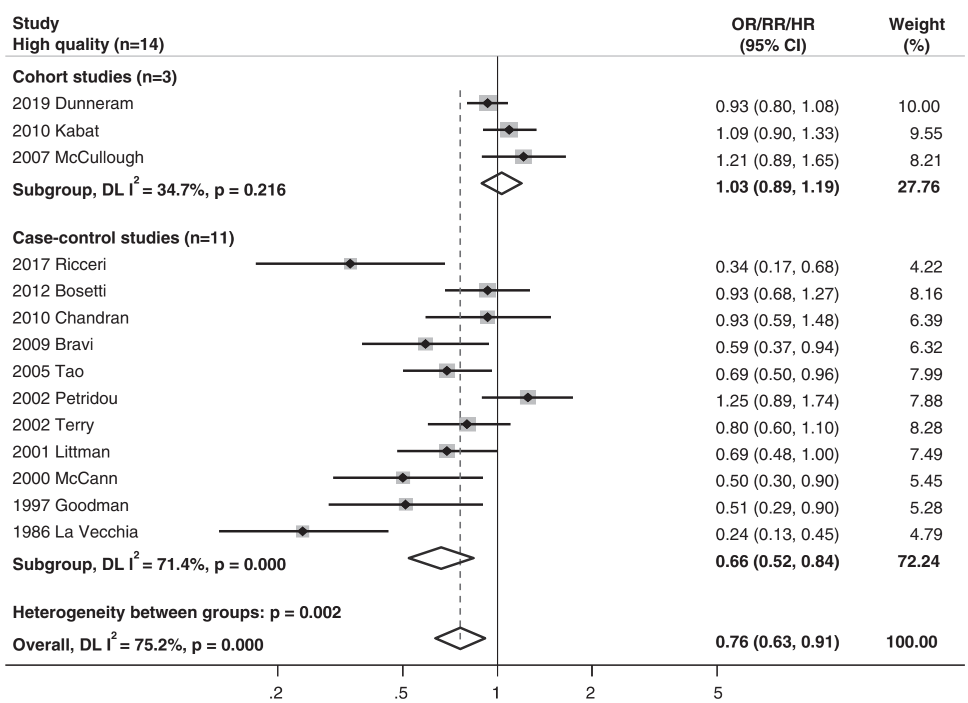

Fig. 3 Association between vegetables intake and EC risk ($n = 14$, high quality studies). Weights are from random-effects model. ORs odds ratio, RR risk ratio, HR hazard ratio, CI confidence interval.

as fibre, vitamins, minerals, and other phytochemicals (phytosterols, polyphenols, isoflavones, isothiocyanates, carotenoids, tocopherols, and indoles) [41, 42]. WCRF/AICR guidelines recommended eating a diet rich in vegetables and fruits for cancer prevention. However, limited evidence from previous studies is available [2]. Some kinds of vegetables and fruits have specific components that make them more exerted to others in protecting human health. For example, citrus fruits are enriched

Table 3. Subgroup analysis by specific fruits and vegetables.

Factor	No. of studies		Pooled OR/RR/HR	95%CI	I^2 (%)
	CC	CH			
Citrus Fruit (N = 6)					
High-quality	3	2	0.92	0.79–1.08	0.0
Western countries	3	3	0.98	0.88–1.10	0.0
Cruciferous vegetables (N = 7)					
High-quality	4	2	0.88	0.78–1.00	18.8
High-quality (CC)	4	-	**0.81**	**0.70–0.94**	0.0
Western countries	4	2	0.88	0.77-1.01	22.7
Western countries (CC)	4	-	**0.80**	**0.68–0.93**	0.0
Dark green/green and yellow/orange vegetable combined (N = 7)					
High-quality	4	0	**0.64**	**0.42–0.97**	79.0
Western countries	4	1	0.77	0.50–1.17	81.2
Western countries (CC)	4	-	0.68	0.39–1.19	81.2
Allium vegetable (N = 5)					
High-quality	2	1	0.69	0.45–1.06	61.6
Western countries	2	2	0.80	0.49–1.33	76.5

ORs odds ratio, *RR* risk ratio, *HR* hazard ratio, *CI* confidence interval, *CC* case-control study, *CH* cohort study. High quality judgment by Newcastle Ottawa Scale. Bold values denote the statistically significant effects.

with several bioactive compounds such as vitamin C and flavanones, that exhibit antioxidation, antimutation, and antiproliferation properties [43–45]. Dark green leafy and dark yellow vegetables are particularly low in calories and high in carotenoids, vitamin A, vitamin C, folate, fibre, potassium, magnesium, and calcium. Cruciferous vegetables have been shown to be rich in glucosinolates, which are then broken down into isothiocyanates (ITCs) and indoles in the body to have a bioactive effect [46, 47]. Furthermore, sulforaphane is a common isothiocyanate found in plant foods such as cruciferous vegetables that might play a role in their antimicrobial and anticarcinogenic effects [48]. In addition, allium vegetables such as garlic and onion, have high concentrations of organosulfur, amino acids, vitamins, and micronutrients, which give them potential anticarcinogenic action via antioxidant activity. Diallyl sulfide (DAS), an organosulfur substance, was shown to be partly responsible for the taste and odor of these vegetable. A study reported that DAS could effectively regulate P450 enzymes in the body and inhibit chemical toxicity and carcinogenesis [49]. Evidence has shown that a dietary pattern rich in vegetables might increase 2-α-hydroxylation [50], virtually devoid of peripheral oestrogenic activity via the 16-α-hydroxylation pathway [51], then help reduce the risk of EC. Additionally, fibre that is mainly provided by dietary intake of vegetables and fruits is said to interfere with oestrogen hormone metabolism by decreasing the concentration of intestinal β-glucuronidase and then increasing elimination of oestrogen by the faecal route, reducing reabsorption of oestrogen by the intestinal tract and leading to a reduction in hormone bioavailability [50, 52]. Hence, these vegetables and fruits are believed to have beneficial impacts on EC risk through their antioxidant and detoxification properties, regulation of the immune system, modulation of steroid hormone metabolism, and hormone concentrations [42, 53–56]. The abovementioned biological mechanisms somehow helped to explain the possible association between fruit and vegetable consumption and EC risk.

The findings of the current study are partly in line with the very first meta-analysis [6] published in 2007, which indicated a favorable effect of vegetable and cruciferous vegetable intake on EC, although no significant result was found for fruit intake. That study was based on one cohort and sixteen case-control studies, which is a possible limitation related to the quality of the included studies and subgroup analysis by geographical region. The study also collected information regarding other vegetable and fruit subgroups, such as allium, green/yellow vegetables, carrots, green leafy vegetables, and citrus fruits. However, no pooled analysis was performed. A possible strength of the 2007 meta-analysis compared to our study is that they conducted a dose-response meta-analysis, which was not performed in this study.

Our study has some strengths. First, this study summarized the largest number of available papers related to fruit and vegetable consumption and EC risk as a meta-analysis of observational studies after the first paper was published in 2007. Twenty-one case-control and six cohort studies helped scale up the information about vegetable and fruit types, making the results more specific. Second, almost all analyses were carried out based on studies of high quality, as assessed by the NOS, which was not addressed in the previous meta-analysis. Third, in the previous study, the authors admitted that the variety of populations might lead to a false estimation of pooled analyses, and we, therefore, tried to mitigate this concern by performing subgroup analysis of those studies by area and country, namely, Western areas, the US, and Italy. There are studies conducted in Asian countries such as China and Japan; however, the number of studies was inadequate for pooling these results together. In our study, publication bias seemed to be substantially avoided, except for the group of studies related to vegetable consumption and EC association. However, a sensitivity analysis was conducted by excluding three studies that were considered outliers, which helped clarify that the impact of publication bias did not change the direction of the findings, increasing the level of confidence in these pooled summaries.

This meta-analysis accounted for several limitations. First, some observational studies identified the effect of fruits and vegetables on EC risk in vulnerable populations (based on hormone replacement therapy (HRT), menopausal status, BMI), whose conditions were believed to be linked with the level of oestrogen exposure. However, the number of individual studies was limited, and a summary of those studies for an overall outlook could not be performed. Second, these studies mainly had a case-control design, while only 6 cohort studies were included despite the effort to add eligible studies to scale up the power of the review. For the main finding of the current study, almost all the results were obtained by summarizing case-control studies combined with cohort studies, or case-control studies alone. Subgroup analysis based on cohort studies did not show a significant association. Third, the number of studies was limited after division into subgroups of specific fruits and vegetables, which might result in a null association. However, a tendency towards marginally significant results for citrus fruit, allium vegetables, and localized areas was found. Fourth, it is important to note that the fruit and vegetable intake was measured by different units in the included papers, which might lead to heterogeneity among study evaluations. For example, some studies collected data by the amount of fruit and vegetable intake (g/day), while others were assessed by the frequency of intake (per day, per month, per week), level of intake (low, middle, high), or estimated portion/serving. However, we tried to limit the discrepancies by uniformly selecting the results comparing the highest level to the lowest level of consumption in these studies.

In conclusion, the summary of available data regarding the beneficial effect of fruits and vegetables showed promising evidence for future EC prevention. Improving adherence to healthy dietary habits, including consuming an adequate amount of vegetables in general, specific cruciferous vegetables, as well as fruits, the risk of EC seemed to be lower, that was strongly shown in Western area. Besides, dark green and yellow/orange vegetables were possibly considered to have beneficial effects. In the future, as the number of individual studies increases, a far-reaching meta-analysis based on observational studies should be encouraged to confirm the findings of this study.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article and its supplementary information file.

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AUTHOR CONTRIBUTIONS
YTL and JK designed, identified, and extracted relevant articles for analyses; YTL drafted the manuscript; JK and MG reviewed and edited the manuscript; All authors read and approved the final manuscript.

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The authors declare no competing interests.

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