Review

Cancer Epidemiology, Biomarkers & Prevention

Dietary Intake and Ovarian Cancer Risk: A Systematic Review

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Abstract

Ovarian cancer is a leading cause of gynecological cancer death. There is a need to identify modifiable dietary risk factors for this disease. To evaluate the role of diet in ovarian cancer risk, we performed a PRISMA-directed systematic review that included prospective cohort studies with >200 cases ($n = 24$). Higher risk for ovarian cancer was shown for total, animal, and dairy fat (five of nine studies), as well as total nitrate and possibly total vitamin C. No associations were demonstrated for red meat, fiber, vitamin A, vitamin E, β-carotene, or folate. Vegetables were associated with lower risk in one of three studies; fruit showed no association, although risk estimates were all greater than 1.0. Isoflavones and flavonoids were associated with modestly lower risk in two studies and tea intake was associated with lower risk in one of two studies. This review suggests that no specific dietary factors are consistently associated with ovarian cancer risk. Data by tumor subtypes are limited, but suggest that differential associations by tumor subtype may exist and should be evaluated. Studies of ample sample size, varied exposure, which can better control for dietary measurement error, are needed to fully define dietary recommendations for ovarian cancer prevention. *Cancer Epidemiol Biomarkers Prev; 23(2); 255–73. ©2013 AACR.*

Introduction

Ovarian cancer remains the leading cause of gynecological death in U.S. women with an estimated 22,280 new cases and 15,500 expected deaths in U.S. women in 2013 (1). A majority of new ovarian cancer cases are diagnosed at an advanced stage of disease, thus contributing to poor survival. Given the suboptimal prognosis for this disease, efforts to identify modifiable risk factors to reduce risk are warranted. Diet remains one of the key lifestyle factors thought to modify cancer risk, according to recent guidelines for cancer prevention published by the American Cancer Society Guidelines (1), although specific associations with ovarian cancer risk are less convincing (2).

The role of diet and specific dietary constituents in the development of ovarian cancer is not clearly understood (3) and the available evidence has been inconsistent in establishing associations. The only primary prevention intervention trial to evaluate the relationship between diet and ovarian cancer risk was a secondary analysis of the Women's Health Initiative (WHI) dietary modification trial. This trial of 48,835 postmenopausal women suggested that long-term (>4.1 years) adoption of a low-fat diet in postmenopausal women was associated with a significant 40% reduction in ovarian cancer risk (4) as compared with usual diet. Although the WHI is the only intervention trial to evaluate the role of diet in ovarian cancer prevention, evidence from ecological and descriptive data support further study of these associations. Briefly, Li and colleagues suggested that the increase in epithelial ovarian cancer seen in Japan over the past 60 years may be related to a concurrent transition toward a more Westernized eating pattern that is higher in fat and meat and lower in vegetables (5). Evidence as early as 1975 showed a possible association between dietary fat and high animal fat/protein intake and ovarian cancer (6–11), although not consistently (12, 13). Reductions in risk have been shown for total vegetable intake (14–17). In contrast, The Nurses' Health Study (NHS) did not show an association between vegetable intake and ovarian cancer (18) nor did the WHI analysis of carotenoid intake and ovarian cancer risk (19). Efforts to determine the relationship between micronutrients and ovarian cancer risk also are inconclusive (20–22). Studies evaluating the association between alcohol intake and ovarian cancer risk also provide mixed results (11, 21, 23, 24), although a recent pooled analysis of 5,342 cases suggested no association between alcohol intake and ovarian cancer risk overall or for specific tumor subtypes (25). A meta-analysis including 16,554 cases of epithelial ovarian cancer also showed no association, with the exception of endometrioid tumors where there was a modest reduction in risk (26).

A review of the evidence for dietary determinants of ovarian cancer risk was published in 2004. At that time,

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the evidence from 7 prospective cohort and 27 case–control studies suggested that vegetables, whole grains, and low-fat milk may be associated with lower risk, whereas meat intake may be associated with higher risk, but that limited studies and inconsistent results supported the need to continue to study these relationships (27). Issues such as recall bias common to case–control studies, insufficient sample size, and dietary measurement error are likely to contribute to the inconsistency in associations to date. In an effort to update and improve upon the current evidence, we conducted a systematic review of the literature on this topic limiting our focus to prospective cohort analysis of larger trials.

Materials and Methods

This systematic review followed the current recommendations of Preferred Reporting Items for Systematic Reviews and Meta-analysis Approach (PRISMA) in reporting the evidence in a specific topic area (28). Search engines used in this review included MEDLINE PubMed, CINAHL, and Cochrane Library, using the key words or medical subject headings "ovarian" and "cancer or carcinoma or neoplasm" combined with "diet" or "nutrition." Limits were set to include only human, English, adult, female, clinical trial, or randomized controlled trial (excluding reviews), and studies with publication dates between January 1, 2003 and March 15, 2013 in an effort to update an earlier comprehensive review (27) by Shultz and colleagues. In addition, the reference lists of all studies included as well as the reference lists of published systematic reviews and meta-analyses were searched for any additional publications. To focus the results on studies of greatest relevance in regard to ovarian cancer risk and dietary exposure, the following study criteria were applied as exclusionary criteria: nonfood containing exposures (i.e., acrylamide). To promote the inclusion of studies with less bias (recall of diet after diagnosis) and greater statistical power to evaluate associations, only prospective studies, as identified in the methods section of the manuscript, which included $\geq$200 ovarian cancer cases were included. On occasion, a second citation for the same study was included when the analysis reported on a different dietary exposure(s). Three additional publications that met inclusion criteria for this systematic review were identified by expert review and/or from citations within the selected manuscripts. Of note, studies addressing the relationship between diet and ovarian cancer survival, such as Zhang et al., were excluded (29).

Data abstractions for this systematic review were completed in duplicate by 2 of the study authors (T.E. Crane and B.R. Khulpateea); 95.6% of the studies were identified by both data extractions. Studies not identified by both extractions were reviewed by a third person (C.A. Thomson) and final decision regarding inclusion was made. Data extracted from each study included first author's last name, title, publication year, country/region where the study was conducted, study name, follow-up period, study design, sample size, type and stage of ovarian cancer, study outcomes, number of cases, dietary exposure, quantity of intake, relative risk (RR) and hazards ratio (HR), and 95% confidence intervals (CI). Seventy-four manuscripts were eligible for abstraction and in total 50 publications were excluded in this review (Fig. 1). Results are reported for the multivariate adjusted models for each study unless adjusted models were not reported in the publication.

Results

We identified 24 publications that met the qualifications for inclusion in our systematic review. These studies represented analysis of data from 10 cohorts including the Swedish Mammography cohort, the European Prospective Investigation of Cancer (EPIC) cohort, The California Teacher's cohort, The NHS and NHS II, The WHI, The Iowa Women's Health study, The National Institutes of Health-American Association of Retired Persons (NIH-AARP) cohort, the Canadian National Breast Screening study (NBSS) cohort, The Netherlands Cohort Study of Diet and Cancer, and the Hangzhou China cohort.

Dietary fat

Seven publications evaluated the relationship between dietary fat and foods high in dietary fat and ovarian cancer risk. Two specifically evaluated total fat and ovarian cancer risk. The NIH-AARP study of 695 cases collected over a 9-year period showed a 28% increase in ovarian cancer risk in women consuming greater amounts of fat (30), whereas the California's Teachers Study that included 289 cases showed no significant association (ref. 20; Table 1). The AARP study also showed that animal fat intake was associated with a 30% greater risk for ovarian cancer, an association not demonstrated in the California's Teachers Study analysis of saturated fat, fats also of animal origin. The EPIC and the Swedish Mammography Study specifically evaluated the relationship between red meat intake and ovarian cancer risk and found no significant association (12, 31). Alternately, 4 studies evaluated dairy intake (a source of animal fat) in relation to risk; 2 found no significant association (12, 20), whereas the study by Larsson and colleagues showed a 60% greater risk for invasive ovarian cancer in relation to dairy intake (33), an association that seemed to be largely attributed to milk and cheese, but not yogurt intake. The increased risk associated with dairy and specifically lactose intake was shown in the NHS cohort, but risk was limited to the subgroup of women diagnosed with a serous tumor subtype, accounting for a 2-fold higher risk (RR = 2.07; 95% CI, 1.27–3.40; ref. 34). Of note, the Netherlands Cohort Study found no association between milk or lactose and risk, although total dairy fat was modestly associated (RR = 1.53; 95% CI, 1.00–2.36; ref. 32).

Vegetable and fruit intake

Our systematic search identified only 3 prospective cohort analyses that met inclusion criteria in regard to fruit and vegetable intake and ovarian cancer risk (Table 2).

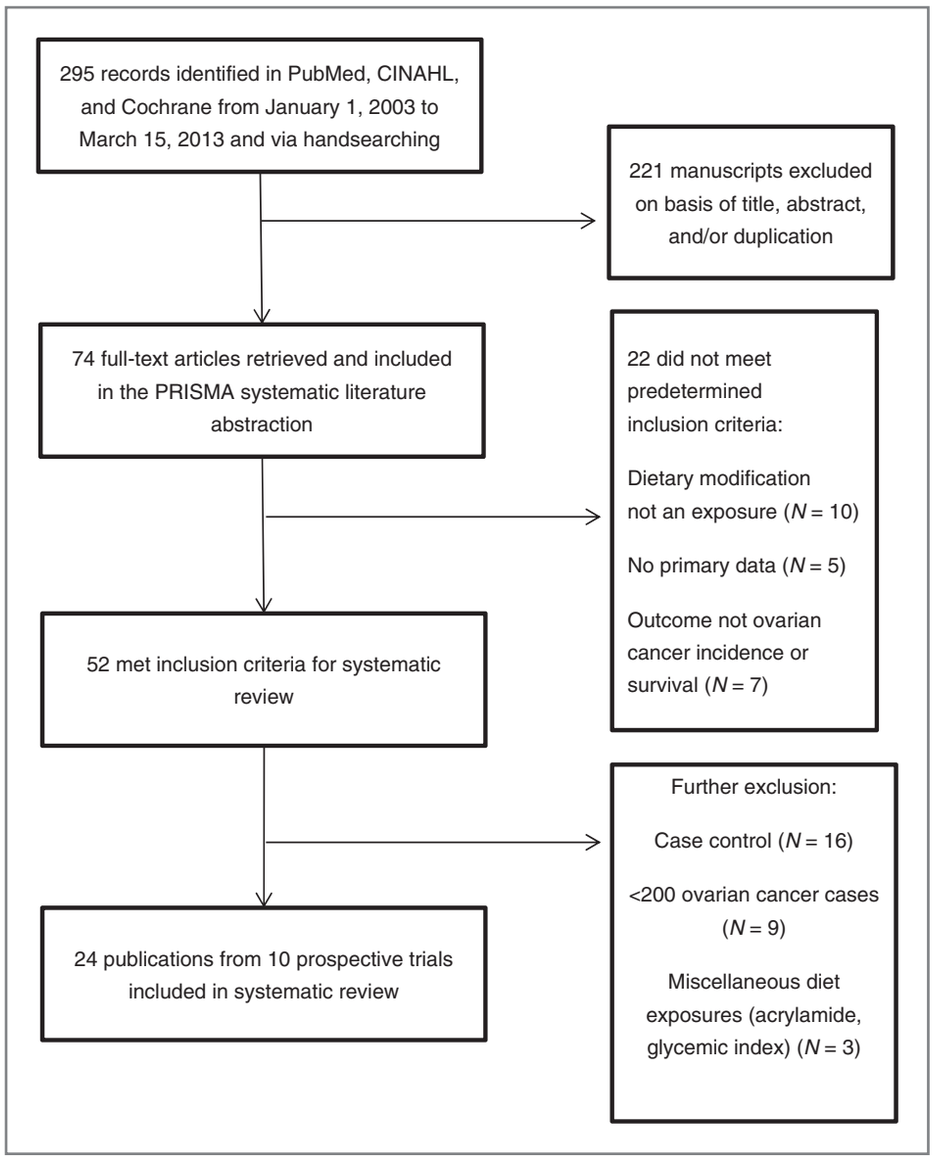

Figure 1. Systematic review process for studies evaluating the role of diet in the prevention of ovarian cancer since 2003, guided by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

In the Swedish Mammography Cohort, higher vegetable intake (≥3 servings per day) as compared with low vegetable intake (≤1.0 serving/day) was associated with a 39% lower risk for ovarian cancer (35), but no association was demonstrated in 2 other cohorts (36, 37). Intake of specific vegetable subtypes (cabbage, carrots, and beets, green leafy) demonstrated point estimates suggesting a lower risk estimate for ovarian cancer; however, none reached significance. There was a modest but nonsignificant lower risk for epithelial ovarian cancer in relation to intake of allium vegetables such as garlic/onion (RR = 0.79; 95% CI, 0.62–1.01) in the European cohort (36); yet no subclasses of vegetables were associated with risk in the Swedish Mammography cohort (35). Total fruit intake was associated with a nonsignificant 37% increase in risk in the Swedish Mammography cohort (RR = 1.37; 95% CI, 0.90–2.06; $P_{trend} = 0.07$) and risk estimates for total fruit were also nonsignificant, but greater than 1.0 in the EPIC and Netherlands cohorts. Findings from the California Teachers Study of 311 ovarian cancer cases suggested that a plant-based diet pattern that included 10 fruits and 8 vegetable servings/day was associated with greater risk for ovarian cancer (RR = 1.65; 95% CI, 1.06–2.54; ref. 38).

Micronutrient and plant-based bioactive intake

Eight publications were included that addressed the relationship between ovarian cancer risk and intake of select micronutrients including vitamins A, C, E, B6, folate, methyl donors (methionine, betaine), as well as bioactive compounds including carotenoids, flavonoids, and isoflavones (Table 2). In relation to vitamin A intake, data from the WHI that included 451 postmenopausal

Table 1. Prospective cohort studies of dietary fat, dairy, meat intake, and epithelial ovarian cancer risk, 2003 to 2013

Author, year, country/region	Study name, sample size, mean age	Dietary assessment/ instrument variable	Years f/u	Outcomes	Relative risk (95% CI)
Blank, 2012 (30) United States	AARP 695 cases in a sample of 151,522 61.7 years (mean age across quintiles)	Dietary fat as % of total energy intake separated into quintiles *Total fat intake (% of calories) median* Lowest quintile = 19.9% Highest quintile = 39.9% *% calories from animal fat (median intake)* Lowest quintile = 7.9% Highest quintile = 22% *% calories from plant fat (median intake)* Lowest quintile = 6.4% Highest quintile = 19.5% *% calories from saturated fat (median intake)* Lowest quintile = 5.7% Highest quintile = 13.2%	9 years	Incident ovarian cancer cases	Total $fat_{Q5:Q1}$ = 1.28 (1.01–1.63); P_{trend} = 0.04 Animal $fat_{Q5:Q1}$ = 1.30 (1.02–1.66); P_{trend} = 0.03 Plant $fat_{Q5:Q1}$ = 1.00 (0.79- 1.27); P_{trend} = 0.96 Saturated $fat_{Q5:Q1}$ = 1.03 (0.71–1.5); P_{trend} = 0.98 By tumor subtype[a] reported as % of calories from fat (10% kcals total fat and 5% for remaining): *Serous (n = 404)* Total fat = 1.14 (1.00–1.30) Animal fat = 1.10 (1.01–1.20) Plant fat = 1.02 (0.93–1.12) Saturated fat = 1.16 (0.89–1.52) *Mucinous (n = 36)* Total fat = 1.42 (0.93–2.17) Animal fat = 1.37 (1.06–1.77) Plant fat = 1.02 (0.74–1.39) Saturated fat = 1.39 (0.61–3.14)
Chang, 2007 (20) United States	California Teachers Study 289 cases (including borderline) in a sample of 97,275 50 years (median age at baseline)	Food Intake Questionnaire Macronutrients by quintiles of intake	8.1 years	Incident ovarian cancer cases	Total $fat_{q5:Q1}$ = 0.85 (0.58–1.24); P_{trend} = 0.26 Saturated $fat_{q5:Q1}$ = 0.72 (0.48–1.08); P_{trend} = 0.10 $Dairy_{high:low}$ = 0.84 (0.56–1.26); P_{trend} = 0.56
Fairfield, 2004 (34) United States	NHS 301 cases in a sample of 80,326 Women enrolled between the ages of 30 to 50 years of age	FFQ used to determine dairy product portions and frequency of consumption *Median lactose intake:* Lowest quintile = 3.2 g/day Highest quintile = 26 g/day	16 years (contacted every 4 years)	Incident ovarian cancer cases	$Lactose_{high:low}$ = 1.40 (0.98–2.01); P_{trend} = 0.10 By tumor subtype[b] *Serous (n = 174)* $Lactose_{high:low}$ = 2.07 (1.27–3.40); P_{trend} = 0.003 In addition, for each 11 g increase in lactose, a 20% increase in serous tumor was observed 1.20 (1.04–1.39)

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Table 1. Prospective cohort studies of dietary fat, dairy, meat intake, and epithelial ovarian cancer risk, 2003 to 2013 (Cont'd)

Author, year, country/region	Study name, sample size, mean age	Dietary assessment/ instrument variable	Years f/u	Outcomes	Relative risk (95% CI)
Larsson, 2004 (33) Sweden	Swedish Mammography Cohort 266 cases in a sample of 61,084 53.7 years (mean age across quartiles)	FFQ—High vs. low consumption of dairy products *Total dairy* Lowest intake = <2 servings/day Highest intake = ≥4 servings/day *Total milk* Lowest intake = ≤1 serving/day Highest intake = ≥2 servings/day *Total yogurt* Lowest intake = <1 serving/day Highest intake = ≥ serving/day *Total cheese* Lowest intake = < 1 serving/day Highest intake = ≥2 servings/day	13.5 years	Incident epithelial ovarian cancer cases	Total $dairy_{high:low}$ = 1.60 (1.10–2.50); P_{trend} = 0.02 Total $milk_{high:low}$ = 1.30 (0.90–1.90); P_{trend} = 0.27 Total $yogurt_{high:low}$ = 1.10 (0.80–1.50); P_{trend} = 0.42 Total $cheese_{high:low}$ = 1.20 (0.90–1.70); P_{trend} = 0.17 By tumor subtype[b] *Serous (n = 125)* Total $dairy_{high:low}$ = 2.00 (1.10–3.70); P_{trend} = 0.06 Total $milk_{high:low}$ = 2.00 (1.10–3.70); P_{trend} = 0.004 Total $yogurt_{high:low}$ = 1.40 (0.90–2.20); P_{trend} = 0.11 Total $cheese_{high:low}$ = 1.10 (0.70–1.90); P_{trend} = 0.69
Larsson, 2005 (31) Sweden	Swedish Mammography Cohort 288 cases in a sample of 66,651 Women enrolled between the ages of 40 and 76 years of age	FFQ—High vs. low consumption of Meat and eggs *Red meat* Lowest intake = <2 servings/week Highest intake = ≥4 servings/week *Fish* Lowest intake = <1 serving/week Highest intake = ≥3 servings/week *Egg* Lowest intake = <0.5 serving/week Highest intake = ≥3 servings/week	14.7 years	Incident epithelial ovarian cancer cases	Red $meat_{high:low}$ = 1.01 (0.70–1.46); P_{trend} = 0.27 $Fish_{high:low}$ = 1.08 (0.75–1.55); P_{trend} = 0.69 $Egg_{high:low}$ = 0.93 (0.55–1.57); P_{trend} = 0.95 No significant relationship with serous or nonserous epithelial ovarian cancer observed with consumption of red meat, fish, or eggs.
Mommers, 2006 (32) Netherlands	Netherlands Cohort Study on Diet and Cancer 252 cases in a sample of 62,573 (compared with a subcohort of 2,216)	FFQ—by quintiles of intake *Total milk* Lowest quintile = 0 g/day Highest quintile = ≥186 g/day	11.3 years	Incident epithelial ovarian cancer cases	Total $milk_{Q5:Q1}$ = 0.98 (0.65–1.48); P_{trend} = 0.97 Total dairy $fat_{Q5:Q1}$ = 1.53 (1.00–2.36); P_{trend} = 0.11 Total $lactose_{Q5:Q1}$ = 0.93 (0.60–1.45); P_{trend} = 0.32

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Table 1. Prospective cohort studies of dietary fat, dairy, meat intake, and epithelial ovarian cancer risk, 2003 to 2013 (Cont'd)

Author, year, country/region	Study name, sample size, mean age	Dietary assessment/ instrument variable	Years f/u	Outcomes	Relative risk (95% CI)
		Dairy fat Lowest quintile = <7.9 g/day Highest quintile = ≥31 g/day *Total lactose* Lowest quintile = <7.7 g/day Highest quintile = ≥21.1 g/day			By tumor subtype[c] *Serous (n = 126)* Total $milk_{Q5:Q1}$ = 0.79 (0.43–1.40); P_{trend} = 0.64 Total dairy $fat_{Q5:Q1}$ = 0.76 (0.42–1.39); P_{trend} = 0.63 Total $lactose_{Q5:Q1}$ = 0.72 (0.37–1.38); P_{trend} = 0.11
Schultz, 2007 (12) Europe	EPIC 581 cases in a sample of 325,731 51 years median age at enrollment	FFQ—intake of meat divided into quintiles *Total meat* Lowest quintile = <64 g/day Highest quintile = ≥109 g/day *Red meat* Lowest quintile = <25 g/day Highest quintile = ≥55 g/day *Egg* Lowest quintile = <9 g/day Highest quintile = ≥16 g/day *Total dairy* Lowest quintile = 131 g/day Highest quintile = ≥209 g/day *Cheese* Lowest quintile = <19 g/day Highest quintile = ≥44 g/day	8 years	Incident ovarian cancer cases	Total $meat_{Q5:Q1}$ = 0.78 (0.52–1.17)[d]; P_{trend} = 0.68 Red $meat_{Q5:Q1}$ = 1.04 (0.70–1.56)[d]; P_{trend} = 0.89 $Egg_{Q5:Q1}$ = 1.19 (0.85–1.67)[d]; P_{trend} = 0.31 Total $dairy_{Q5:Q1}$ = 0.58 (0.26–1.29)[d]; P_{trend} = 0.28 $Milk_{Q5:Q1}$ = 0.93 (0.70–1.25)[d]; P_{trend} = 0.88 By tumor subtype[b] *Serous (n = 228)* Total $meat_{Q5:Q1}$ = 1.27 (1.02–1.60)[d] Total $poutry_{Q5:Q1}$ = 1.31 (1.07–1.61)[d]

[a]Endometrioid tumor subtype nonsignificant for any category.
[b]Nonsignificant for endometrioid and mucinous tumor subtypes.
[c]Serous only subtype reported; multivariate model reported when available.
[d]Hazard ratio.

cases showed no significant association (19), similar to the null associations demonstrated in The NBSS (21). Vitamin C was examined in relationship to ovarian cancer risk in 3 studies. The California's Teachers Study showed a markedly higher risk for ovarian cancer in relation to vitamin C intake from food and supplements (RR = 1.96; 95% CI, 1.11–3.46; ref. 20), the other 2 studies also demonstrated an elevated point estimate, but neither was significant (19, 39). Similarly, higher risk estimates were shown in studies evaluating total vitamin E intake (dietary and supplement) and ovarian cancer risk, although none were statistically significant (19, 20, 39). Folate and

Table 2. Prospective studies of dietary intake of vegetable, fruit, and constitutive micronutrients and bioactives and epithelial ovarian cancer risk, 2003 to 2013

Author, year, country/region	Study name, sample size, mean age	Dietary assessment/ instrument variable	Years f/u	Outcomes	Relative risk (95% CI)
Larsson, 2004 (35) Sweden	Swedish Mammography Cohort 266 cases in sample of 61,084 53.9 years mean age at baseline	FFQ—high vs. low consumption of vegetables and fruit *High intake* ≥3 servings vegetables/day ≥3 servings fruit/day ≥5 servings fruit+vegetables/day ≥7 serving green leafy vegetable/week *Low intake* ≤1 serving vegetables/day ≤1 serving fruit/day ≤2 servings fruit+vegetables/day ≤1.5 servings green leafy vegetables/week	13.5 years	Incident epithelial ovarian cancer	$Vegetables_{high:low} = 0.61$ (0.38–0.97); $P_{trend} = 0.01$ $Fruit_{high:low} = 1.37$ (0.90–2.06); $P_{trend} = 0.07$ Fruit + $Veg_{high:low} = 0.78$ (0.51–1.20) Green leafy $veg_{high:low} = 0.83$ (0.55–1.25); $P_{trend} = 0.22$ No significant relationship with serous or nonserous epithelial ovarian cancer observed with consumption of vegetables or fruit
Schultz, 2005 (36) Europe	EPIC 581 cases in sample of 325,640 51 years median age at enrollment	FFQ—fruit and vegetable intake Fruits and vegetables analyzed in 80 g increments Leafy vegetables analyzed in 8 g increments Onion and garlic analyzed in 8 g increments	6.3 years	Incident epithelial ovarian cancer	Total fruits + $veg_{per\ 80\ g} = 1.02$ (0.95–1.10)[a] $Total\ fruits_{per\ 80\ g} = 1.08$ (0.99–1.18)[a] $Total\ vegetables_{per\ 80\ g} = 0.92$ (0.76–1.11)[a] $Leafy\ vegetables_{per\ 8\ g} = 0.98$ (0.90–1.07)[a] $Garlic/onion_{per\ 8\ g} = 0.79$ (0.62–1.01)[a] By tumor subtype[a] *Serous (n = 228)* Total fruits + $veg_{per\ 80\ g} = 1.07$ (0.95–1.18)[a] $Total\ fruits_{per\ 80\ g} = 1.14$ (0.99–1.31)[a] $Total\ vegetables_{per\ 80\ g} = 0.95$ (0.70–1.29)[a] $Leafy\ vegetables_{per\ 8\ g} = 1.01$ (0.88–1.17)[a] $Garlic/onion_{per\ 8\ g} = 0.73$ (0.50–1.08)[a] *Mucinous (n = 51)* Total fruits + $veg_{per\ 80\ g} = 1.10$ (0.88–1.37)[a] $Total\ fruits_{per\ 80\ g} = 1.26$ (0.98–1.62)[a] $Total\ vegetables_{per\ 80\ g} = 0.65$ (0.32–1.34)[a] $Leafy\ vegetables_{per\ 8\ g} = 0.87$ (0.61–1.24)[a] $Garlic/onion_{per\ 8\ g} = 1.36$ (0.76–2.41)[a] *Endometrioid (n = 56)* Total fruits + $veg_{per\ 80\ g} = 0.87$ (0.68–1.11)[a] $Total\ fruits_{per\ 80\ g} = 0.76$ (0.54–1.08)[a] $Total\ vegetables_{per\ 80\ g} = 1.00$ (0.56–1.79)[a] $Leafy\ vegetables_{per\ 8\ g} = 1.11$ (0.86–1.42)[a] $Garlic/onion_{per\ 8\ g} = 0.87$ (0.44–1.71)[a]

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Table 2. Prospective studies of dietary intake of vegetable, fruit, and constitutive micronutrients and bioactives and epithelial ovarian cancer risk, 2003 to 2013 (Cont'd)

Author, year, country/region	Study name, sample size, mean age	Dietary assessment/ instrument variable	Years f/u	Outcomes	Relative risk (95% CI)
Mommers, 2005 (37) Netherlands	Netherlands Cohort Study on Diet and Cancer 252 case in a sample of 62,573 (compared with a subcohort of 2,216) 55–69 years of age at enrollment	FFQ *Total vegetable and fruit—median intake* Lowest quintile = 207 g/day Highest quintile = 583 g/day *Total vegetable* Lowest quintile = 105 g/day Highest quintile = 291 g/day *Total fruit* Lowest quintile = 62 g/day Highest quintile = 343 g/day	11.3 years	Incident ovarian cancer cases	Total vegetable + $\text{fruit}_{Q5:Q1} = 1.13$ (0.70–1.82); $P_{trend} = 0.53$ Total $\text{vegetable}_{Q5:Q1} =$ 0.98 (0.61–1.58); $P_{trend} = 0.83$ Total $\text{fruit}_{Q5:Q1} =$ 1.11 (0.70–1.78); $P_{trend} = 0.46$
Micronutrient and bioactives in vegetables and fruit					
Chang, 2007 (20) United States	California Teachers Study 289 cases (including borderline) in a sample of 97,275 50 years median age at baseline	FFQ (block) *Total Vitamin C* Lowest quintile = ≤75 mg Highest quintile = >665 mg *Total folate* Lowest quintile = ≤272 μg Highest quintile = >711 μg *Total β-carotene* Lowest quintile = ≤1,409 μg Highest quintile = >4,601 μg *Total vitamin E* Lowest quintile = ≤7 mg Highest quintile = >207 mg *Isoflavones* Lowest tertile = <1 mg Highest tertile = >3 mg *Isothiocynantes* Lowest tertile = <5 μmol Highest tertile = >20 μmol	8.1 years	Incident ovarian cancer cases	Total vitamin $C_{Q5:Q1} = 1.96$ (1.11–3.46); $P_{trend} = 0.17$ Total $\text{folate}_{Q5:Q1} = 0.81$ (0.49–1.32); $P_{trend} = 0.34$ Total β-$\text{carotene}_{Q5:Q1} = 1.41$ (0.85–2.88); $P_{trend} = 0.08$ Total vitamin $E_{Q5:Q1} = 1.46$ (0.76–2.79); $P_{trend} = 0.28$ $\text{Isoflavones}_{Q3:Q1} = 0.56$ (0.33–0.96); $P_{trend} = 0.04$ $\text{Isothiocyanates}_{Q3:Q1} = 0.84$ (0.55–1.24); $P_{trend} = 0.35$

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Table 2. Prospective studies of dietary intake of vegetable, fruit, and constitutive micronutrients and bioactives and epithelial ovarian cancer risk, 2003 to 2013 (Cont'd)

Author, year, country/region	Study name, sample size, mean age	Dietary assessment/ instrument variable	Years f/u	Outcomes	Relative risk (95% CI)
Gates, 2007 (42) United States	NHS 347 cases in sample of 66,940 50.6 years mean age at baseline	FFQ with antioxidant and flavonoid content quantified by quintiles *Total Flavonoids—median intake* Lowest quintile = 8.5 mg/day Highest quintile = 42.6 mg/day *Myricetin—median intake* Lowest quintile = 0.1 mg/day Highest quintile = 2.4 mg/day *Kaempferol—median intake* Lowest quintile = 0.8 mg/day Highest quintile = 11.0 mg/day *Quercetin—median intake* Lowest quintile = 6.3 mg/day Highest quintile = 30.7 mg/day *Luteolin—median intake* Lowest quintile = 0.01 mg/day Highest quintile = 0.2 mg/day Highest quintile = 1.3 mg/day	8 years	Incident ovarian cancer cases	Total flavonoids$_{Q5:Q1}$ = 0.75 (0.51–1.09); P_{trend} = 0.02 Myricetin$_{Q5:Q1}$ = 0.72 (0.50–1.04); P_{trend} = 0.01 Kaempferol$_{Q5:Q1}$ = 0.60 (0.42–0.87); P_{trend} = 0.002 Quercetin$_{Q5:Q1}$ = 0.80 (0.55–1.16); P_{trend} = 0.04 Luteolin$_{Q5:Q1}$ = 0.66 (0.49–0.91); P_{trend} = 0.01 Apigenin$_{Q5:Q1}$ = 1.33 (0.96–1.83); P_{trend} = 0.03 By tumor subtype *Serous (n = 192)* Kaempferol$_{Q5:Q1}$ = 0.57 (0.36–0.90); P_{trend} = 0.004 Results for other variables and subtypes reported as not significant and not published.
Kotsopoulos, 2009 (40) United States	NHS 526 cases in sample of 159,957 from NHS and NHS II NHS: 60.3 years mean age at baseline NHSII: 40.2 years mean age at baseline	FFQ—betaine by quintiles of intake *Betaine—NHS* Lowest quintile = <70.5 mg/day Highest quintile = ≥127.3 mg/day *Betaine—NHS II* Lowest quintile = <80.6 mg/day Highest quintile = ≥138.9 mg/day	13.3 years	Incident epithelial ovarian cancer cases	Pooled results from NHS and NHS II Betaine$_{Q5:Q1}$ = 0.98 (0.74–1.31); P_{trend} = 0.51

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Table 2. Prospective studies of dietary intake of vegetable, fruit, and constitutive micronutrients and bioactives and epithelial ovarian cancer risk, 2003 to 2013 (Cont'd)

Author, year, country/region	Study name, sample size, mean age	Dietary assessment/ instrument variable	Years f/u	Outcomes	Relative risk (95% CI)
Larsson, 2004 (41) Sweden	Swedish Mammography Cohort 266 cases in a sample of 61,084 64 years mean age at diagnosis	FFQ—high vs. low intake Separated into quartiles of intake and then further analyzed based on weekly alcohol consumption *Folate* Lowest quartile = <155 μg/day Highest quartile = ≥204 μg/day *Alcohol* Low intake = ≤20 g/week High intake = >20 g/week	13.5 years	Incident epithelial ovarian cancer	Energy adjusted dietary folate$_{Q4:Q1}$ = 0.67 (0.43–1.04); P_{trend} = 0.08 Dietary folate w/low Etoh$_{Q4:Q1}$ = 0.80 (0.59–1.70); P_{trend} = 0.80 Dietary folate w/high Etoh$_{Q4:Q1}$ = 0.26 (0.11–0.60); P_{trend} = 0.001 By tumor subtype *Serous (n = 126)* Energy adjusted dietary folate$_{Q4:Q1}$ = 0.78 (0.41–1.48); P_{trend} = 0.34 Dietary folate w/low Etoh$_{Q4:Q1}$ = 1.15 (0.55–2.43); P_{trend} = 0.62 Dietary folate w/high Etoh$_{Q4:Q1}$ = 0.22 (0.06–0.85); P_{trend} = 0.01 *Endometrioid (n = 48)* Energy adjusted dietary folate$_{Q4:Q1}$ = 0.38 (0.14–1.04); P_{trend} = 0.06 *Mucinous (n = 21)* Energy adjusted dietary folate$_{Q4:Q1}$ = 0.28 (0.05–1.56); P_{trend} = 0.20 *Endometrioid ± clear cell ± mucinous (n = 74)* Dietary folate w/low Etoh$_{Q4:Q1}$ = 0.33 (0.11–0.99); P_{trend} = 0.08 Dietary folate w/high Etoh$_{Q4:Q1}$ = 0.38 (0.10–1.54); P_{trend} = 0.14
Navarro-Silvera, 2006 (21) Canada	NBSS 264 cases in sample of 48,766 59.4 years mean age at diagnosis	FFQ—folate and alcohol use *Folate* Lowest quartile = <248 μg/day Highest quartile = >357 μg/day *Alcohol* Low intake = <4 g/day High intake = ≥4 g/day	16.4 years	Incident ovarian cancer cases	Folate$_{Q4:Q1}$ = 0.75 (0.42–1.34)[a]; P_{trend} = 0.26 Folate (low alcohol)$_{Q4:Q1}$ = 0.97 (0.43–2.15)[a]; P_{trend} = 0.86 Folate (high alcohol)$_{Q4:Q1}$ = 0.59 (0.26–1.37)[a]; P_{trend} = 0.09

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Table 2. Prospective studies of dietary intake of vegetable, fruit, and constitutive micronutrients and bioactives and epithelial ovarian cancer risk, 2003 to 2013 (Cont'd)

Author, year, country/region	Study name, sample size, mean age	Dietary assessment/ instrument variable	Years f/u	Outcomes	Relative risk (95% CI)
Silvera, 2006 (39) Canada	NBSS 264 cases in sample of 48,776 59.3 years mean age at diagnosis	FFQ—high versus low intake by quartiles of intake *β-carotene* Lowest quartile = <3,274 μg/day Highest quartile = >7,000 μg/day *α-carotene* Lowest quartile = <5,839 μg/day Highest quartile = >15,500 μg/day *Total carotenoid* Lowest quartile = <26,272 μg/day Highest quartile = >51,000 μg/day *Total vitamin A* Lowest quartile = <6,589 IU/day Highest quartile = >11,534 IU/day *Total vitamin C* Lowest quartile = <122 mg/day Highest quartile = >247 mg/day *Total vitamin E* Lowest quartile = <17 mg/day Highest quartile = >28 mg/day	16.4 years	Ovarian cancer incidence	β-Carotene$_{Q5:Q1}$ = 0.97 (0.66–1.43)[a]; P_{trend} = 0.95 α-Carotene$_{Q5:Q1}$ = 0.94 (0.64–1.38)[a]; P_{trend} = 0.65 Total carotenoids$_{Q5:Q1}$ = 1.19 (0.81–1.74)[a]; P_{trend} = 0.40 Total vitamin A$_{Q5:Q1}$ = 0.79 (0.53–1.16)[a]; P_{trend} = 0.37 Total vitamin C$_{Q5:Q1}$ = 1.11 (0.75–1.66)[a]; P_{trend} = 0.59 Total vitamin E$_{Q5:Q1}$ = 1.24 (0.85–1.82)[a]; P_{trend} = 0.48
Thomson, 2008 (19) United States	WHI 451 cases in sample of 133,614 63.2 years mean age at baseline	FFQ—antioxidants/vitamins/selenium, carotenoids by quartile of intake *Total vitamin A* Lowest quartile = <640 mcg RAE/day Highest quartile = >2,326 mcg RAE/day *Total vitamin C* Lowest quartile = <90 mg/day Highest quartile = >130 mg/day *Total vitamin E* Lowest quartile = <7.4 mg ATE/day Highest quartile = >403.2 mg ATE/day	8.34 years	Incident ovarian cancer	Total vitamin A$_{Q4:Q1}$ = 1.14 (0.83–1.57)[a] Total vitamin C$_{Q4:Q1}$ = 1.22 (0.89–1.67)[a] Total vitamin E$_{Q4:Q1}$ = 1.22 (0.89–1.66)[a] Caroteniods$_{Q4:Q1}$ = 0.99 (0.72–1.38)[a] Total β-carotene$_{Q4:Q1}$ = 1.30 (0.94–1.8)[a] Total lycopene$_{Q4:Q1}$ = 1.02 (0.73–1.43)[a]

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Table 2. Prospective studies of dietary intake of vegetable, fruit, and constitutive micronutrients and bioactives and epithelial ovarian cancer risk, 2003 to 2013 (Cont'd)

Author, year, country/region	Study name, sample size, mean age	Dietary assessment/ instrument variable	Years f/u	Outcomes	Relative risk (95% CI)
		Total carotenoids Lowest quartile = <6,564 mcg/day Highest quartile = >13,642 mcg/day *Total β-carotene* Lowest quartile = <2,331 mcg/day Highest quartile = >7,605 mcg/day *Total lycopene* Lowest quartile = <2,736 mcg/day Highest quartile = >6,325 mcg/day			
Tworoger, 2006 (22) United States	NHS 481 cases in sample of 80,254 56.3 years mean age at baseline	FFQ—folate, methionine, B6 by quintiles of intake *Dietary folate* Lowest quintile = <178 μg/day Highest quintile = >323 μg/day	22 years	Epithelial ovarian cancer (includes borderline cancer)	Dietary folate$_{Q5:Q1}$ = 0.76 (0.52–1.12); P_{trend} = 0.30 Total folate$_{Q5:Q1}$ = 1.13 (0.83–1.53); P_{trend} = 0.08 Dietary methionine$_{Q5:Q1}$ = 0.92 (0.68–1.25); P_{trend} = 0.68 Dietary vitamin B6$_{Q5:Q1}$ = 1.27 (0.84–1.93); P_{trend} = 0.34 Total vitamin B6$_{Q5:Q1}$ = 1.17 (0.85–1.62); P_{trend} = 0.24 By tumor subtype *Serous/undifferentiated (n = 299)* Dietary folate$_{Q5:Q1}$ = 0.51 (0.31–0.84); P_{trend} = 0.01 Total folate$_{Q5:Q1}$ = 1.21 (0.82–1.77); P_{trend} = 0.08 Dietary methionine$_{Q5:Q1}$ = 0.81 (0.55–1.20); P_{trend} = 0.28 Dietary vitamin B6$_{Q5:Q1}$ = 1.62 (0.97–2.70); P_{trend} = 0.08 Total vitamin B6$_{Q5:Q1}$ = 1.27 (0.85–1.88); P_{trend} = 0.13 *Endometrioid (n = 71)* Dietary folate$_{Q5:Q1}$ = 1.82 (0.68–4.86); P_{trend} = 0.01 Total folate$_{Q5:Q1}$ = 1.21 (0.82–1.77); P_{trend} = 0.08 Dietary methionine$_{Q5:Q1}$ = 0.81 (0.55–1.20); P_{trend} = 0.28 Dietary vitamin B6$_{Q5:Q1}$ = 1.62 (0.97–2.70); P_{trend} = 0.08 Total vitamin B6$_{Q5:Q1}$ = 1.27 (0.85–1.88); P_{trend} = 0.13

NOTE: Multivariate model reported when available.

[a]Hazard ratio with 95% CI.

methyl donors associated with folate metabolism were not associated with ovarian cancer risk in the 5 studies testing these associations in this review (19–21, 40, 41). In one study, dietary folate was associated with lower risk in women reporting higher alcohol intake ($P_{trend} = 0.001$), largely driven by the more common serous tumor subtype (41). These associations were not shown to be significant in the Canadian cohort (21).

In relation to dietary carotenoid intake, The California Teachers' Study showed higher intake of β-carotene was associated with a 41% higher risk for ovarian cancer, but this was not significant in the fully adjusted model (20) as was true for WHI (19). In the Teachers' study, intake of isoflavones was associated with a lower risk for ovarian cancer with risk estimates of 0.56 ($P_{trend} = 0.04$). In the NHS with 347 cases of invasive disease, total flavonoid intake was associated with a 25% lower risk of ovarian cancer 0.75 ($P_{trend} = 0.02$) and lower point estimates of risk were specifically described for intake of the flavonoids luteolin and kaempferol. In relation to serous tumor subtype only kaempferol was associated with a decreased risk ($P_{trend} = 0.004$) for ovarian cancer (42).

Other dietary components

A number of additional dietary factors have been evaluated in relation to ovarian cancer risk, but on a limited basis (Table 3). In a study by Ascherbrook-Kilfoy and colleagues, total nitrates and animal-based nitrites largely consumed as processed meats were associated with a 31% and 34% higher risk for ovarian cancer, respectively. This study included 151,316 older adults and identified 709 ovarian cancer cases over an 11-year period of follow-up (43). Of note, nitrites from plant sources were not associated with risk. Fiber intake was evaluated as a possible protective dietary exposure in one study in Canada and while point estimates were below 1.0, neither total fiber nor specific types of fiber showed a significantly lower risk for ovarian cancer (44). Sugar intake including total sugar, total fructose, and total sucrose were associated with a lower risk of ovarian cancer in the AARP cohort (45), but higher point estimate in a study of 264 epithelial ovarian cancer cases in Canada (46). A few studies evaluated caffeine and/or coffee or tea intake and ovarian cancer risk. In the Iowa Women's Health Study, caffeine intake was not related to risk, nor was coffee intake (47). Similar nonsignificant associations were demonstrated in the EPIC cohort in relation to either coffee or tea intake (48). The NHS of 347 cases observed a protective association with tea intake and ovarian cancer risk (42).

Discussion

This systematic review of 24 large prospective studies, reflecting a much larger number of prospective studies than the earlier review by Schulz and colleagues (25), replicate some, but not all of the associations identified in the earlier review. Here we identified vegetables as protective in one study with point estimates <1.0 in the other 2 studies, consistent with earlier estimates. Specific constituents in vegetables such as isoflavones were also suggested to be associated with lower risk in this review, but were not specifically evaluated in the earlier report. We did not find a significant association with meat intake as reported in the earlier review, but did find evidence of greater risk in relation to nitrites in meat. Although the earlier review suggested risk may be lower in relation to whole grains and low fat milk, this review found no significant reduction in risk with these dietary exposures. Importantly, the large number of studies with nonsignificant and inconsistent findings suggests that either diet is not associated or only modestly associated with ovarian cancer risk or that studies may lack sufficient sample size or accuracy in dietary measurement to identify consistent associations.

Dietary fat and animal fat as well as animal-source nitrite intake are shown to be associated with a higher risk for ovarian cancer in this review, and are supported by mechanistic research. In fact, dietary fat, particularly of animal origin, has been linked to tumor promotion (49), inflammation (50), and elevated estrogen exposure (51), all of which would contribute to ovarian cancer risk. Furthermore, a secondary analysis of the WHI low-fat dietary intervention suggested low-fat diets followed for greater than 4.1 years may lower ovarian cancer risk in postmenopausal women (4). The lack of consistency in the epidemiological studies may reflect variance in the range of fat intake reported. In the AARP study (30), which showed an elevated risk related to total fat intake, high intake was characterized as > 39.9% total energy as fat, an amount slightly greater than the mean intake of 36% of total energy in the California's Teacher Study (20). Furthermore, the specific contribution of saturated versus monounsaturated fats was not evaluated in both cohorts and may vary for women residing in California versus older women residing throughout the United States. Similarly, the increased risk related to dairy shown in the Swedish Mammography cohort may also be a result of higher dairy fat intake reported by the Swedish women (33). Specifically, the upper quintile for the Swedish cohort was ≥4 servings/day, whereas in the European cohort highest intake is estimated at 209 g/day equivalent to approximately a single serving (1 cup) of milk. The AARP is the only cohort study to evaluate nitrates and nitrites in relation to ovarian cancer risk. The higher risk associated with animal-based nitrites could reflect correlated dietary exposures (dietary fat) or may suggest an alternate mechanism of carcinogenesis, such as the formation of nitrites from N-nitrosamine metabolism (52). Efforts to test these associations in other cohorts are needed.

In relation to other sources of dietary fat, 2 meta-analyses and a pooled analysis of prospective cohorts (similar to studies selected in this systematic review) have assessed the relationship between dairy, milk, or related diet exposures and ovarian cancer risk. The results, generally consistent with this systematic review, suggested lactose may be associated with higher risk (53, 54) whereas milk/dairy is not (54, 55). Of note, whole milk and butter,

Table 3. Prospective studies of nitrates, beverages, caffeine, fiber, and sugar intake and epithelial ovarian cancer risk, 2003 to 2013

Author, year, country/region	Study name, sample size, mean age	Dietary assessment/instrument variable	Years f/u	Outcomes	Relative risk (95% CI)
Ascherbrook-Kilfoy, 2012 (43) United States	AARP 709 cases in a sample of 151,316 61.9 years mean age at enrollment for entire AARP study population	Dietary nitrate and nitrites (total, plant and animal based) *Total nitrate median intake* Lowest quintile = 22 mg/1,000 kcals per day Highest quintile = 126.5 mg/1,000 kcals per day *Total nitrite median intake* Lowest quintile = 0.47 mg/1,000 kcals per day Highest quintile = 0.93 mg/1,000 kcals per day *Nitrite from animal source median intake* Lowest quintile = 0.09 mg/1,000 kcals per day Highest quintile = 0.33 mg/1,000 kcals per day *Nitrite from plant source median intake* Lowest intake = 0.27 mg/1,000 kcals per day Highest intake = 0.73 mg/1,000 kcals per day	1 year	Incident epithelial ovarian cancer	Total nitrate$_{Q5\text{-}Q1}$ = 1.31 (1.01–1.68); P_{trend} = 0.06 Total nitrite$_{Q5\text{-}Q1}$ = 1.18 (0.93–1.5); P_{trend} = 0.31 Nitrite from animal sources$_{Q5\text{-}Q1}$ = 1.34 (1.05–1.69); P_{trend} = 0.02 Nitrite from plant sources$_{Q5\text{-}Q1}$ = 1.03 (0.81–1.32); P_{trend} = 0.93 By tumor subtype *Serous (n = 374)* Total nitrate$_{Q5\text{-}Q1}$ = 1.27 (0.90–1.78); P_{trend} = 0.08 Total nitrite $_{Q5\text{-}Q1}$ = 1.22 (0.88–1.71); P_{trend} = 0.36 Nitrite from animal sources$_{Q5\text{-}Q1}$ = 1.05 (0.77–1.44); P_{trend} = 0.34 Nitrite from plant sources$_{Q5\text{-}Q1}$ = 1.00 (0.71–1.40); P_{trend} = 0.80 *Endometrioid (n = 66)* Total nitrate$_{Q5\text{-}Q1}$ = 1.88 (0.80–4.44); P_{trend} = 0.18 Total nitrite $_{Q5\text{-}Q1}$ = 1.15 (0.51–2.56); P_{trend} = 0.93 Nitrite from animal sources$_{Q5\text{-}Q1}$ = 1.33 (0.54–3.26); P_{trend} = 0.59 Nitrite from plant sources$_{Q5\text{-}Q1}$ = 1.02 (0.46–2.26); P_{trend} = 0.84 *Mucinous (n = 35)* Total nitrate$_{Q5\text{-}Q1}$ = 0.51 (0.18–1.46); P_{trend} = 0.17 Total nitrite$_{Q5\text{-}Q1}$ = 0.29 (0.08–1.09); P_{trend} = 0.10 Nitrite from animal sources$_{Q5\text{-}Q1}$ = 1.99 (0.60–6.58); P_{trend} = 0.37 Nitrite from plant sources$_{Q5\text{-}Q1}$ = 0.41 (0.12–1.36); P_{trend} = 0.15

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Table 3. Prospective studies of nitrates, beverages, caffeine, fiber, and sugar intake and epithelial ovarian cancer risk, 2003 to 2013 (Cont'd)

Author, year, country/region	Study name, sample size, mean age	Dietary assessment/instrument variable	Years f/u	Outcomes	Relative risk (95% CI)
Braem, 2012 (48) Europe	EPIC 1,244 cases in a sample of 330,849 50.6 years mean age	FFQ—coffee and tea consumption separated into quintiles *Coffee median intake reported* Lowest quintile = 125.6 mL/day Highest quintile = 562.9 mL/day *Tea median intake reported* Lowest quintile = 40.5 mL/day Highest quintile = 453.5 mL/day	11.7 years	Incident epithelial ovarian cancer	Total coffee$_{Q5:Q1}$ = 1.05 (0.75–1.46)[a]; P_{trend} = 0.43 Total tea$_{Q5:Q1}$ = 1.07 (0.78–1.46)[a]; P_{trend} = 0.83
Chang, 2008 (38) United States	California Teachers Study 311 cases (including borderline) in a sample of 97,292 Age not reported	5 dietary patterns quantified from FFQ Plant-based High-protein/high-fat High-carbohydrate Ethnic Salad and Wine	9 years	Incident ovarian cancer cases	Plant-based$_{Q5:Q1}$ = 1.65 (1.06–2.54); P_{trend} = 0.03 High protein/High fat$_{Q5:Q1}$ = 1.31 (0.82–2.10); P_{trend} = 0.18 High carbohydrate$_{Q5:Q1}$ = 1.69 (0.97–2.95); P_{trend} = 0.07 Ethnic$_{Q5:Q1}$ = 1.10 (0.75–1.59); P_{trend} = 0.56 Salad/wine$_{q5:Q1}$ = 1.00 (0.66–1.53); P_{trend} = 0.79
Gates, 2007 (42) United States	NHS 347 cases in a sample of 66,940 50.6 years mean age at enrollment	FFQ *Tea (nonherbal) intake by quartiles of intake* Lowest quartile = ≤1 serving/week Highest quartile = ≥2 servings/day	8 years	Ovarian cancer cases	Total tea$_{Q4:Q1}$ = 0.63 (0.40–0.99); P_{trend} = 0.03 No significant relationship with serous, endometrioid, or mucinous epithelial ovarian cancer observed with consumption of tea
Lueth, 2008 (47) United States	Iowa Women's Health Study 266 cases in a sample of 29,060 61.6 years mean age	FFQ—caffeine intake separated into quintiles *Total caffeine* Lowest quintile = ≤20 mg/day Highest quintile = ≥1,162 mg/day *Total coffee* Lowest quintile = 0 cups per day Highest quintile = >5 cups per day	18 years	Epithelial ovarian cancer	Total caffeine$_{Q5:Q1}$ = 1.16 (0.77–1.75)[a]; P_{trend} = 0.53 Total coffee$_{Q5:Q1}$ = 1.28 (0.76–2.16)[a]; P_{trend} = 0.51

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Table 3. Prospective studies of nitrates, beverages, caffeine, fiber, and sugar intake and epithelial ovarian cancer risk, 2003 to 2013 (Cont'd)

Author, year, country/region	Study name, sample size, mean age	Dietary assessment/instrument variable	Years f/u	Outcomes	Relative risk (95% CI)
Silvera, 2007 (44) Canada	NBSS Trial 264 cases in a sample of 48,776 59.4 years mean age at diagnosis	FFQ—fiber intake divided into quartiles *Total fiber* Lowest quartile = <15.6 g/day Highest quartile = >24 g/day *Soluble fiber* Lowest quartile = <4.4 g/day Highest quartile = >7.4 g/day *Insoluble fiber* Lowest quartile = <2.8 g/day Highest quartile = >5.1 g/day *Lignin* Lowest quartile = <1 g/day Highest quartile = >1/9 g/day *Cellulose* Lowest quartile = <3.4 g/day Highest quartile = >6.4 g/day	16.4 years	Incident ovarian cancer	Total fiber$_{Q4:Q1}$ = 0.77 (0.52–1.14)[a]; P_{trend} = 0.27 Soluble fiber$_{Q4:Q1}$ = 0.79 (0.51–1.23)[a]; P_{trend} = 0.29 Insoluble fiber$_{Q4:Q1}$ = 0.72 (0.47–1.10)[a]; P_{trend} = 0.09 Lignin$_{Q4:Q1}$ = 0.79 (0.52–1.19)[a]; P_{trend} = 0.13 Cellulose$_{Q4:Q1}$ = 0.73 (0.49–1.10)[a]; P_{trend} = 0.27
Silvera, 2007 (46) Canada	NBSS Trial 264 cases in a sample of 49,613 59.4 years mean age at diagnosis	FFQ—adjusted for total energy intake *Total sugar* Lowest quartile = <64 g/day Highest quartile = >95 g/day	16.4 years	Incident ovarian cancer	Total sugars$_{Q4:Q1}$ = 1.17 (0.76–1.79)[a]; P_{trend} = 0.21 Total sugars$_{Q3:Q1}$ = 1.68 (1.14–2.47)[a] Quartile 3: 80–95 g sugar/day
Tasevska, 2012 (45) United States	AARP 457 cases in a sample of 179,990 61.5 years mean age at enrollment	FFQ—sugar intake separated into quintiles *Total sugar median intake* Lowest quintile = 38.7 g/1,000 kcals per day Highest quintile = 91.5 g/1,000 kcals per day *Added sugars median intake* Lowest quintile = 2.4 tsp/1,000 kcals per day Highest quintile = 11.0 tsp/1,000 kcals per day *Total fructose median intake* Lowest quintile = 14.8 g/1,000 kcals per day Highest quintile = 40.6 g/1,000 kcals per day *Sucrose median intake* Lowest quintile = 13.6 g/1,000 kcals per day Highest quintile = 37.5 g/1,000 kcals per day	7.2 years	Incident ovarian cancer	Total sugars$_{Q5:Q1}$ = 0.7 (0.51–0.97)[a]; P_{trend} = 0.03 Added sugars$_{Q5:Q1}$ = 0.72 (0.51–1.00)[a]; P_{trend} = 0.02 Total fructose$_{Q5:Q1}$ = 0.68 (0.49–0.95)[a]; P_{trend} = 0.02 Sucrose$_{Q5:Q1}$ = 0.65 (0.47–0.89)[a]; P_{trend} = 0.004

NOTE: Multivariate model reported when available.
[a]Hazard ratio.

significant sources of dietary fat, were reported to be associated with higher risk for ovarian cancer in the meta-analysis by Qin (55), consistent with the association shown for total dairy intake in the Swedish Mammography cohort described here (33).

Large variance in vegetable exposure estimates (80 g for total vegetables vs. 8 g for selective vegetables such as leafy vegetables) may contribute to the inconsistency in the risk associations related to vegetable intake. Alternatively, select types of vegetables and the related target anticarcinogenic bioactivity of constitutive compounds within vegetables may offer differential risk reduction as is suggested by lower risk in relation to allium vegetable intake in the EPIC cohort (36) in comparison to null associations between isothiocyanate intake and risk in the California Teachers Study (20). Point estimates for risk in relation fruit intake here (35–37) and in the earlier review (27) suggest potential higher risk for ovarian cancer. Although not clearly understood, elevated risk may reflect a propensity for elevated insulin levels with higher glycemic index, particularly if women are older and/or overweight/obese. This hypothesis is supported by results from the NBSS wherein total sugars may be associated with greater ovarian cancer risk (46) and yet, conflict with results from the AARP cohort suggesting that total sugar intake as well as fructose intake (found in fruit and fruit juices) were associated with a lower risk of ovarian cancer (45). Of note, total sugar intake at the upper level in both cohorts was approximately 95 g/day, body mass indexes were similar across studies (approximately 26 kg/m^2) and the AARP cohort was only slightly older at 61.5 years versus 58.9 years in the NBSS. Certainly, measurement error variance across instruments is one possible explanation; efforts to assess measurement error using objective urinary measures in sugar intake are underway. Our findings suggesting a lack of consistent associations between total vegetable and fruit intake and risk are supported by a pooled analysis of 12 prospective studies that included 2,130 cases of invasive ovarian cancer (56).

Vitamin C intake and ovarian cancer risk suggested no significant association in 2 studies (19, 39), but one study showed a significantly higher risk (20); all 3 studies showed point estimates greater than 1.0 and the Chang study, while showing significant relative risk, also reported a nonsignificant P_{trend}. Differences in mean vitamin C intakes ranging within the upper quintiles from 130 mg/day (19) to >665 mg/day (20) were reported and may suggest that supplemental vitamin C versus dietary may be contributing to risk in the Chang study as intake above 200 mg/day would be difficult to achieve with dietary sources alone. The relationship between nutrient supplementation and a possible increase in cancer risk related to pro-oxidant properties has been demonstrated for other nutrients such as vitamin E (57) and β-carotene (58), and has also been suggested in relation to supplemental vitamin C (59).

Finally, our results suggest that tea intake may be associated with lower risk of ovarian cancer (42), although not consistently (48), whereas coffee and caffeine showed no association (47). A meta-analysis that included 1,244 cases of epithelial ovarian cancer did not support a lower risk with either coffee or tea intake (48).

Our systematic review has limitations. First, the lack of consistency in risk associations makes it difficult to define conclusively the role of specific dietary choices in modifying ovarian cancer risk. Furthermore, all the studies evaluated used food frequency questionnaires (FFQs) to evaluate self-reported diet. Measurement error is a well-known problem for FFQs and may have biased toward the null, a common finding here (60). None of the FFQs corrected for measurement error using objective measures. All studies used baseline diet to assess ovarian cancer risk over time; repeated measures or assessment of change in diet was not included in any of the studies. Use of repeat diet measures can be problematic in that cases occurring before (or even shortly after) diet assessments are collected would need to be excluded thus reducing sample size and statistical power to test these associations. However, repeatedly measuring diet over time may provide more accurate assessment of dietary exposures. In addition, for some dietary exposures there may be a threshold that must be reached to demonstrate a lower or a higher risk of disease. For select populations, these lower or upper thresholds for disease modulation may not be achieved. Furthermore, looking across populations internationally, the quantity as well as the nutrient or bioactive density of the food items may vary widely, further contributing to the inconsistent associations demonstrated. Finally, residual confounding cannot be ruled out. For example, higher intake of vegetables and fruit has been associated with higher self-reported physical activity and also lower rates of overweight/obesity. The selected studies controlled for confounding and mediating variables, but not consistently.

Few of the studies had adequate sample size to evaluate relationships for specific foods or specific types of fruits, vegetables, etc. In addition, data evolving for breast cancer systematic reviews and meta-analysis suggest that tumor subtype may be a pertinent factor to assess in relation to diet–disease associations. Here, 13 studies provided some data regarding specific associations for tumor subtypes; however, overall the confidence intervals were wide because of small subgroup sample size. The NHS evaluated risk by tumor subtype, in this case for lactose intake, and found a 2-fold higher risk in women in the highest quintile of lactose intake for serous tumors only (34) and kaempferol intake (42)—a bioactive primarily derived from intake of broccoli and tea was associated with a 43% reduction in risk for serous tumors. The EPIC cohort suggested that both total meat and poultry intake were associated with higher risk for serous tumor subtypes (12) whereas the Swedish Mammography cohort similarly found higher risk for serous subtype (33), but in this case related to total dairy and milk intake, associations not seen in the Netherlands cohort (32). Evidence from the AARP study cohort suggested that total fat was associated with a 14% higher risk for serous tumors; a nonsignificant

elevated risk for mucinous tumors was also demonstrated (RR = 1.42; 95% CI, 0.93–2.17; ref. 30).

Strengths of our systematic review include stringent inclusion criteria to evaluate only prospective studies and those with a larger number of ovarian cancer cases. The significant associations identified were relatively weak, but relevant in terms of modifying the risk of a cancer that carries with it a high mortality rate. We included studies that evaluated more common diet exposures as well as several less common exposures such as lactose, bioactive compounds, and beverage consumption.

In conclusion, there is a need for additional studies to evaluate the role of diet in ovarian cancer risk, including pooled studies of sufficient sample size to assess associations by tumor subtype as well as randomized, controlled trials of dietary exposures. The findings from this review suggest the potential for a higher risk of ovarian cancer in women consuming higher amounts of dietary fat, animal products (including dairy and nitrites), and possibly vitamin C or fruit; alternately in women who consume higher amounts of isoflavones, tea, and possibly vegetables, risk may be reduced, although the dietary exposures evaluated seem to be weak-moderate and not consistently demonstrated.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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