Olive oil and risk of breast cancer: a systematic review and dose–response meta-analysis of observational studies

Naria Sealy, Susan E. Hankinson and Serena C. Houghton*

Department of Biostatistics and Epidemiology, University of Massachusetts Amherst, Amherst, MA 01003, USA

Abstract

Olive oil consumption has been suggested to be inversely associated with breast cancer risk, probably due to its high MUFA and polyphenol content. The purpose of this meta-analysis was to assess the association between olive oil and breast cancer risk, including assessing the potential for a dose–response association. We performed a systematic search of PubMed, Web of Science, CINAHL and Cochrane Central Register of Controlled Trials through June 2020, identifying ten observational studies (two prospective studies and eight case–control studies) for meta-analysis. We estimated summary OR and 95 % CI for the highest $v.$ lowest olive oil intake category across studies using random effect models and assessed the dose–response relationship between olive oil and breast cancer risk using restricted cubic splines. The summary OR comparing women with the highest intake to those with the lowest category of olive oil intake was 0·48 (95 % CI 0·09, 2·70) in prospective studies and 0·76 (95 % CI 0·54, 1·06) in case–control studies, with evidence of substantial study heterogeneity (prospective $I^2 = 89$ %, case–control $I^2 = 82$ %). There was no significant dose–response relationship for olive oil and breast cancer risk; the OR for a 14 g/d increment was 0·93 (95 % CI 0·83, 1·04). There may be a potential inverse association between olive oil intake and breast cancer; however, since the estimates are non-significant and the certainty level is very low, additional prospective studies with better assessment of olive oil intake are needed.

Key words: **Olive oil: Mediterranean diet: Breast cancer: Meta-analyses**

Breast cancer is the most common cancer and the second leading cause of cancer deaths among females in the USA[1]. For decades, Mediterranean countries, such as Italy, Greece, and Spain, have had lower incidence of breast cancer than the USA[2]. The traditional diet of Mediterranean countries is characterised by high consumption of fruit, vegetables and olive oil, a low intake of red meat and dairy products and a moderate intake of red wine during meals[3,4]. Prior meta-analyses suggest that Mediterranean diets overall are associated with a decreased risk of breast cancer[5–7]. While the Mediterranean diet varies by country, olive oil is the main source of dietary fat[8,9] and has been of particular interest due to its potentially beneficial MUFA profile[10]. Additionally, extra virgin olive oil is high in polyphenols, which have been shown to have antioxidant and anti-inflammatory properties in *in vitro* studies[10]. Further, greater olive oil consumption has been associated with improvements in inflammatory biomarkers in meta-analyses of intervention and observational studies[4]. Oleocanthal, a specific polyphenol, is an agent reported to suppress cancer cells[11]. A few prior reviews and meta-analyses have suggested a potential reduction in breast cancer risk with increasing intake of olive oil[12–15]; however, they have often included studies that have examined monounsaturated fat intake, other vegetable/liquid oils and studies of dietary patterns with olive oil as a component, which may increase misclassification or be confounded by other foods. Additionally, if olive oil is found to decrease breast cancer risk, it is relatively easy to increase exposure levels in women as supplementation of extra virgin olive oil in a diet has been shown to have high adherence[16]. We therefore conducted a meta-analysis to summarise the association of olive oil intake specifically and breast cancer risk, as well as examine the potential of a dose–response relationship.

Methods

Search strategy

We performed a systematic search to identify relevant original research studies examining the association between olive oil and breast cancer risk in the following databases: PubMed, Web of Science, CINAHL and Cochrane Central Register of Controlled Trials through June 2020 with no initial search restrictions using the keywords 'olive oil' combined with 'breast neoplasms' or 'breast cancer'. Additionally, to identify studies not

captured by our search strategy, we examined the reference lists of relevant articles. This review was not registered in the International Prospective Register of Systematic Reviews.

Inclusion and exclusion criteria

We used commercially available software to remove duplicate records and to screen titles and abstracts for inclusion[17]. Studies were included in the present meta-analysis if they met the following inclusion criteria: (i) if they were an observational study (cohort, case–control, cross-sectional) or randomised control trial, (ii) conducted amongst human participants, (iii) had olive oil as a separate exposure of interest, (iv) had breast cancer risk as the outcome of interest and (v) reported risk estimates (relative risks, OR or hazard ratios) and 95 % CI or sufficient information for these to be estimated for three or more categories of olive oil intake. We additionally excluded: articles not in English, conference abstracts and studies of other exposures (e.g. liquid oils, monounsaturated fat), combination of oils (e.g. olive and canola oils) or dietary patterns that include olive oil as a component (e.g. olive oil and salad vegetable pattern). For studies with an overlapping study population, we used the study with the most complete information. Two authors, N. S. and S. C. H., independently identified articles meeting inclusion criteria from search results, and any disagreements were resolved by discussion or consultation with a third reviewer (S. E. H.).

Data extraction and risk of bias

One investigator (N. S.) abstracted the following information from selected studies, which was reviewed by a second investigator (S. C. H.): last name of the first author, year published, study location, study population characteristics (e.g. age, menopause status), study design, follow-up duration, number of cases, number of participants, exposure assessment, outcome assessment, exposure cut points for each category of intake and corresponding risk estimates and 95 % CI for the maximally adjusted model and covariates included. As breast cancer is a relatively rare event, OR and hazard ratio estimates were considered equivalent. For studies that presented risk estimates graphically only, we attempted to contact the study authors for precise risk estimates. Additionally, for articles that provided stratified results by menopause status, we abstracted risk estimates and 95 % CI for menopause strata. For each study, we additionally (S. C. H. and S. E. H.) assessed the risk of bias using the Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool assigning each bias domain as low, moderate, serious, critical or unclear[18].

Statistical analysis

Assuming study heterogeneity a priori, risk estimates for the highest v. lowest intake category were combined across studies to estimate an overall OR and 95 % CI using a random effects model[19,20]. In cases where the reference category reported was not the lowest intake category, we recalculated the OR using the method by Hamling et al.[21]. We additionally estimated a postmenopausal breast cancer specific summary OR and 95 % CI, for studies that reported stratified estimates by menopause status or if the study had been conducted among postmenopausal women only.

Heterogeneity among studies was assessed using Higgins I^2 statistic, where 25, 50 and 75 % were considered low, medium and high heterogeneity, respectively[22]. To examine potential sources of heterogeneity among case–control studies, we conducted subgroup analyses by study location (Italy, Spain, Greece v. other country), source of controls (hospital based v. population based), number of cases (<500 v. ≥500), exposure assessment (quantity consumed v. frequency consumed) and whether energy intake was controlled for. We did not assess heterogeneity among prospective studies since there were only two studies. Our analysis including the Prevención con Dieta Mediterránea (PREDIMED) trial by Toledo et al. was conducted using only the per protocol analysis, breaking the randomisation and allowing for its characterisation as a prospective study, not a randomised control trial[23]. This was done because the per protocol analysis examined the effect of olive oil specifically rather than the intention to treat analysis which examined the effect of the Mediterranean diet plus olive oil compared with a Mediterranean diet plus nuts or low fat diet (control arm). We assessed publication bias visually using a funnel plot. Analyses were repeated omitting one study at a time and estimating the overall OR, to evaluate the influence of a single study. Lastly, as a sensitivity analysis, we additionally estimated the OR using an inverse-variance fixed effects model.

Dose–response

The dose–response meta-analysis using random effects generalised least-squares regression described by Greenland & Longnecker[24] and Orsini et al.[25] were used to estimate the OR and 95 % CI for breast cancer associated with a 14 g/d (one tablespoon) increase in olive oil intake. For studies that reported frequency of consumption, a 14 g (one tablespoon) portion was assumed per instance. Second, to examine potential non-linear associations, we used restricted cubic spline models with three fixed knots at the 25th, 50th and 75th percentiles of the total reported intake distribution.

All statistical analyses were conducted using RevMan 5.3 (Nordic Cochrane Center) and SAS 9.3 (SAS Institute Inc.). All tests were two-sided, and P value <0·05 was considered statistically significant.

Grading the evidence and summary of findings

We assessed the overall quality and strength of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool[26]. S. C. H. independently assessed the quality of evidence which was then confirmed by a second investigator (S. E. H.).

Results

Search results

From our search strategy, we identified 757 records through June 2020 (Fig. 1). After removing 219 duplicate records and

757 records identified through June 2020
  PubMed (*n* 185)
  Web of Science (*n* 458)
  CINAHL (*n* 90)
  Cochrane (*n* 24)

219 duplicate records removed

484 non-relevant records excluded by screening of titles/abstracts

Two additional records identified from reference lists

Fifty-seven full-text articles reviewed for eligibility

Forty-seven full-text articles excluded
reviews, letters, editorials, conference abstracts (*n* 17)
non-English (*n* 4)
did not assess olive oil specifically (*n* 9)
reported olive oil only as part of a dietary pattern/ or combination of oils (*n* 10)
overlapping study population (*n* 2)
did not provide effect estimates and confidence intervals (*n* 2)
continuous estimates or less than three categories (*n* 3)
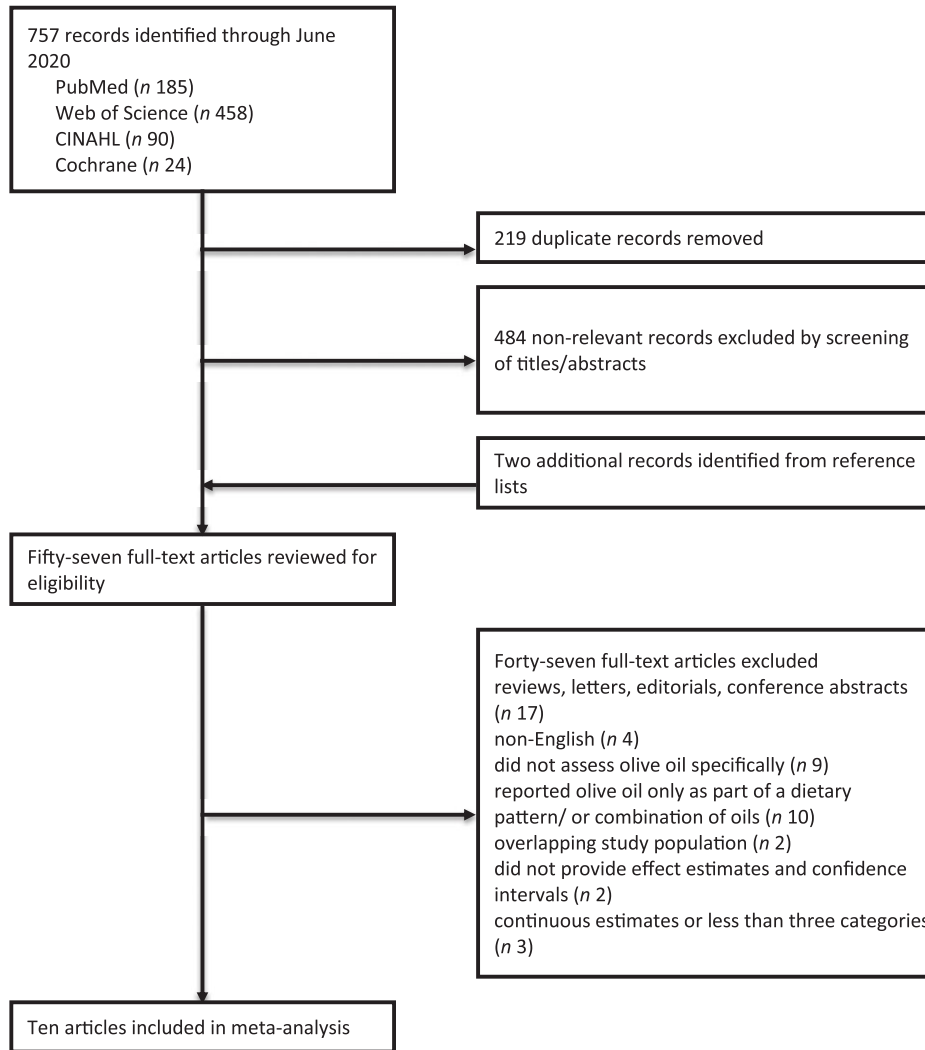
Ten articles included in meta-analysis

Fig. 1. Flow chart of study selection.

screening titles and abstracts of the remaining 538 records, we excluded 484 records that were not relevant. After reviewing reference lists of relevant articles, we identified an additional two articles not captured by our search strategy, leading to fifty-seven articles for full-text review. From these we excluded forty-seven articles that did not meet our criteria for inclusion; seventeen were reviews, editorials, or conference abstracts; four were not in English; nine did not assess olive oil specifically; ten reported olive oil only as part of a dietary pattern; two studies were excluded due to overlapping study populations; two did not provide both effect estimates and CI and three had continuous estimates or less than three categories. Therefore, ten articles were eligible for inclusion in the present meta-analysis[23,27–35].

Characteristics of studies

Characteristics of the ten included studies are presented in Table 1. The meta-analysis included a total of 7030 cases of breast cancer among 81 436 participants. Three of the ten studies[23,34,35] were conducted only among postmenopausal women, whereas the ages in the other studies ranged from 18 to 85. Except for two studies conducted in Kuwait[32] and Turkey[35], the majority of the studies were conducted in the European countries: Spain, Greece, Italy and France[23,27–31,33,34]. Eight of the studies were case–control studies[27–33,35] and two were prospective[23,34]. Two studies were considered to have low risk of bias[23,34], others ranged from moderate to critical[27–33,35] (online Supplementary Table S1).

Overall analyses

The random effects summary OR for breast cancer was 0·48 (95 % CI 0·09, 2·70) for prospective studies and 0·76 (95 % CI 0·54, 1·06) in case–control studies, comparing women with the highest intake to those with the lowest intake category of olive oil (Fig. 2). Heterogeneity between the studies was high (prospective $I^2 = 89\%$, case–control $I^2 = 82\%$). Visual inspection of the funnel plot suggested evidence of publication bias (Fig. 3). Influence analyses omitting one study at a time suggested moderate influence on the findings; the summary OR ranged from 0·69 (95 % CI 0·51, 0·94) when Richardson *et al.*[27] was omitted to 0·89 (95 % CI 0·71, 1·10) when García-Segovia *et al.*[31] was omitted

Table 1. Characteristics of selected studies

First author	Year published	Study location	Age range (years)	Study design	Cases (n)	Total subjects (n)	Dietary assessment	Highest v. lowest category	Exposure categories	Covariates
Richardson[27]	1991	France	28–66	Case–control, hospital-based controls	409	924	FFQ, fifty-five food items	>34·614 v. 0 g/week	g/week 0; ≤34·614; >34·614	Age, menopause status, alcohol, family history of breast cancer, BBD, menopause age, menarche age, parity, age at first pregnancy, education
Martin-Moreno[28]	1994	Spain	18–75	Case–control, population-based controls	762	1750	FFQ validated, 118 food items	>730 v. 0 Tsp/year	Tsp/year 0; 1–365; 366–730; >730	Age, SES, location, BMI, and total energy intake
Trichopoulou[29]	1995	Greece	Not given	Case–control, hospital-based controls	820	2368	FFQ validated, 115 food items	>1 time/d v. <1 time/d	Times/d < once per d; once per d; > once per d	Age, place of birth, age at first pregnancy, menarche age, menopause status, BMI, total energy intake, fruit and vegetable intake
La Vecchia[30]	1995	Italy	20–74	Case–control, hospital-based controls	2569	5157	FFQ validated, seventy-eight food items	>40·7 v. ≤10·7 g/d	g/d ≤10·7; 10·8–19·1; 19·2–28·1; 28·2–40·7; >40·7	Age, location, education, parity, age at first birth, menopause status, alcohol, total energy intake, other oils/fats intake
García-Segovia[31]	2006	Spain	25–85	Case–control, population-based controls	291	755	FFQ modified validated, eighty-eight food items	>27·4 v. ≤3·2 g/d	g/d ≤3·2; 3·3–8·7; 8·8–16·0; 16·1–27·4; >27·4	Age, smoking, education, BBD, menopause status, BMI, total energy intake (residual method)
Saleh[32]	2008	Kuwait	Mean, cases 47 (12) Mean, controls 50 (13)	Case–control, hospital-based controls	50	100	Structured questionnaire	4–7 times/week v. 1 time/week	Times/week Once per week; 2–3 per week; 4–7 times per week	Age (matched)
Bessaoud[33]	2008	France	25–85	Case–control, population-based controls	437	1359	FFQ validated, 162 food items	>20·03 v. ≤5·82 g/d	g/d 0–5·82; 5·83–11·04; 11·05–20·03; >20·03	Age (matched), location (matched), education, parity, breast-feeding, age at first pregnancy, duration of ovulatory activity, BMI, physical activity, family history of breast cancer, total energy intake
Buckland[34]	2012	Spain, Greece, and Italy	<45 to 65+	Cohort	1256	63 955	FFQ validated (Greece and Italy) or dietary history validated (Spain)	≥30·1 v. <18·1 g/d per 2000 kcal (8368 kJ)	g/d per 2000 kcal <18·1; ≥18·1 to <30·1; ≥30·1	Age, study centre, education, BMI, height, physical activity, smoking status, menarche age, age at first pregnancy, HRT use, oral contraception use, menopause age, alcohol, total energy intake excluding alcohol
Toledo[23]	2015	Spain	60–80	Randomised trial, but uses per-protocol estimates of association	35	4282	FFQ validated, 137 food items and MeDiet screener validated, fourteen food items	≥47·85 v. <0·38 g/d	g/d <0·38; ≥0·38 to <4·3554; ≥4·3554 to <24·94; ≥24·94 to <47·85; ≥47·85	Age, HRT, physical activity, BMI, alcohol, baseline adherence to Mediterranean diet, menopause age, total energy intake, smoking, diabetes, family history of cancer, statins
Pervaiz[35]	2017	Turkey	45–65+	Case–control, hospital-based controls	401	786	Structured questionnaire	Daily v. never	Times/d Never; sometimes; daily	Age, BMI, family history of breast cancer, menarche age, menopause age, parity, breast-feeding, smoking, physical activity, HRT

BBD, benign breast disease; Tsp, tablespoon; SES, socio-economic status; HRT, hormone replacement therapy.

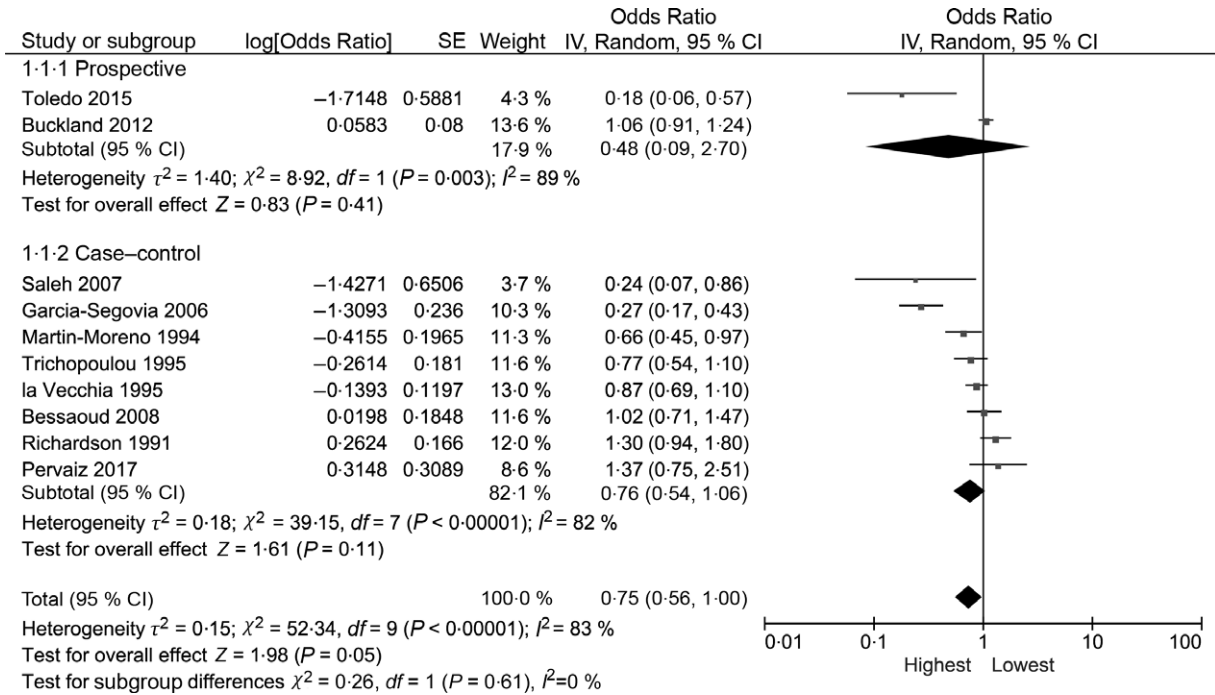Olive oil and breast cancer risk

1151

Fig. 2. Forest plot of studies examining the association between the highest *v.* lowest category of olive oil intake and breast cancer risk. IV, inverse variance.
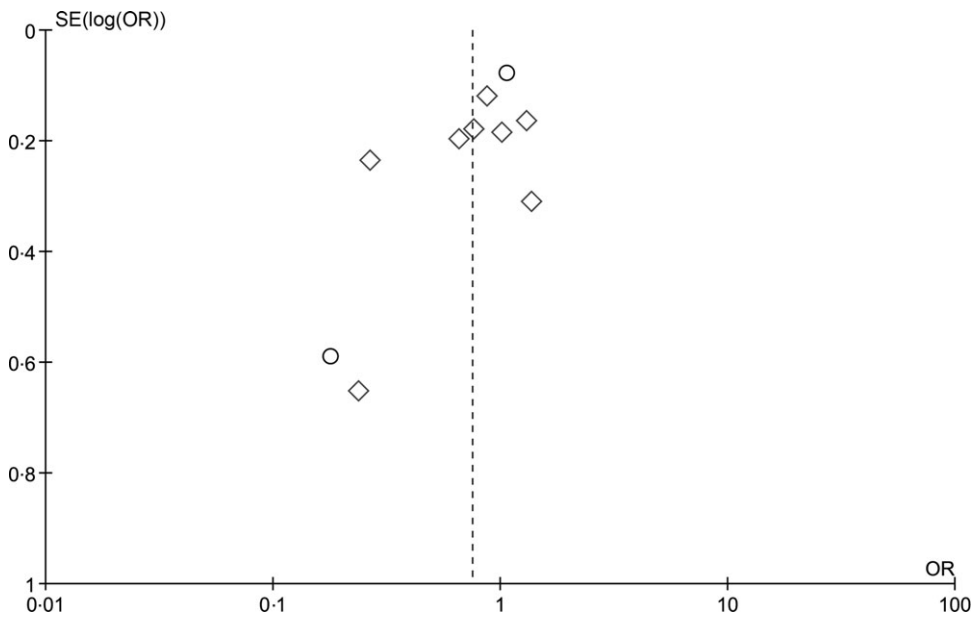

Fig. 3. Funnel plot for detection of publication bias for the highest *v.* lowest category of olive oil intake and breast cancer risk. ◯, Prospective; ◇, case–control.

(Table 2). The results were attenuated when we used a fixed effects method (OR 0·91, 95 % CI 0·82, 1·00). As a secondary analysis, we additionally repeated our case–control random effects model using the spline estimates in the study by Bessaoud *et al.* (OR 0·72, 95 % CI 0·51, 1·02)[33], rather than the quintile estimates we had abstracted, as both models were fully adjusted. For postmenopausal breast cancer, the random effects summary OR was 0·94 (95 % CI 0·71, 1·24; $I^2 = 74$ %; $P_{for\ heterogeneity} = 0·008$)

overall, 0·48 (95 % CI 0·09, 2·70; $I^2 = 89$ %; $P_{for\ heterogeneity} = 0·003$; *n* 2) for prospective studies and 1·00 (95 % CI 0·70, 1·42; $I^2 = 43$ %; $P_{for\ heterogeneity} = 0·19$; *n* 2) for case–control studies for highest *v.* lowest olive oil intake (Fig. 4).

Subgroup analyses

In subgroup analyses of case–control studies by study location, source of controls, exposure assessment, and adjustment for

Table 2. Influence of individual studies removed one at a time on the summary estimate
(Odds ratios and 95 % confidence intervals)

Study excluded	Random effects		Fixed effects	
	OR	95 % CI	OR	95 % CI
None – all studies	0·75	0·56, 1·00	0·91	0·82, 1·00
Richardson 1991[27]	0·69	0·51, 0·94	0·87	0·78, 0·97
Buckland 2012[34]	0·70	0·49, 0·98	0·81	0·71, 0·93
Pervaiz 2017[35]	0·71	0·52, 0·95	0·90	0·81, 0·99
Bessaoud 2008[33]	0·71	0·52, 0·98	0·90	0·81, 1·00
La Vecchia 1995[30]	0·72	0·51, 1·01	0·91	0·82, 1·02
Trichopoulou 1995[29]	0·74	0·54, 1·02	0·92	0·83, 1·02
Martin-Moreno 1994[28]	0·76	0·56, 1·03	0·93	0·84, 1·03
Saleh 2008[32]	0·79	0·59, 1·04	0·91	0·83, 1·01
Toledo 2015[23]	0·80	0·61, 1·06	0·92	0·83, 1·01
García-Segovia 2006[31]	0·89	0·71, 1·10	0·96	0·87, 1·07

total energy (Table 3), heterogeneity remained moderate to high for all subgroups. Among case–controls studies with 500 or more cases there was low heterogeneity; however, there were only three studies in this subgroup. Significant inverse associations were seen among studies that were conducted in traditional Mediterranean countries (i.e. Italy, Spain and Greece), for studies with 500 or more cases, and for studies that adjusted for total energy intake. Estimates were similar to the overall estimate for case–control studies for both studies that assessed the amount consumed and those that only assessed frequency of olive oil consumption.

Dose–response analyses

The OR for breast cancer in the dose–response meta-analysis with a 14 g/d increase in olive oil intake was 0·93 (95 % CI 0·83, 1·04). Since we made assumptions in the proportion of olive oil consumed (i.e. one time = 14 g) for studies that only reported frequency of consumption, when we restricted the analysis to exclude these studies the estimates were similar

(OR 0·93; 95 % CI 0·83, 1·04). There was no evidence of non-linear associations in the cubic spline analyses (Fig. 5), $P = 0.27$ and $P = 0.09$, respectively.

GRADE assessment

The overall quality and strength of the evidence were judged to be very low due to the limited number of studies and wide CI, some inconsistency and study heterogeneity, lack of dose–response association, high risk of bias in some of the included studies and possible publication bias.

Discussion

The present meta-analysis of ten studies, eight of which are case–control studies, including 81 436 individuals, examined the association between olive oil intake and breast cancer risk. Comparison of women in the highest category of olive oil intake compared with the lowest was suggestive of an inverse association with breast cancer, but not significant in either prospective or case–control analyses. There was no evidence of an association in dose–response analyses. Additionally, there was a limited number of studies and evidence of study heterogeneity and publication bias.

As there were only two prospective studies with substantial heterogeneity, the ability to draw conclusions from these is greatly limited. The prospective cohort that was larger but did not distinguish types of olive oil was null; whereas, the per protocol analysis of a smaller randomised trial that examined extra-virgin olive oil specifically multiple times during follow-up observed a significant strong inverse association.

When we use fixed effects models, the estimates were attenuated compared with the random effects models. One reason for this may be that the largest study included in the meta-analysis was null[34], which could then attenuate the results in fixed effect models due to the greater weight of large studies[36]. As we saw evidence of publication bias, a second
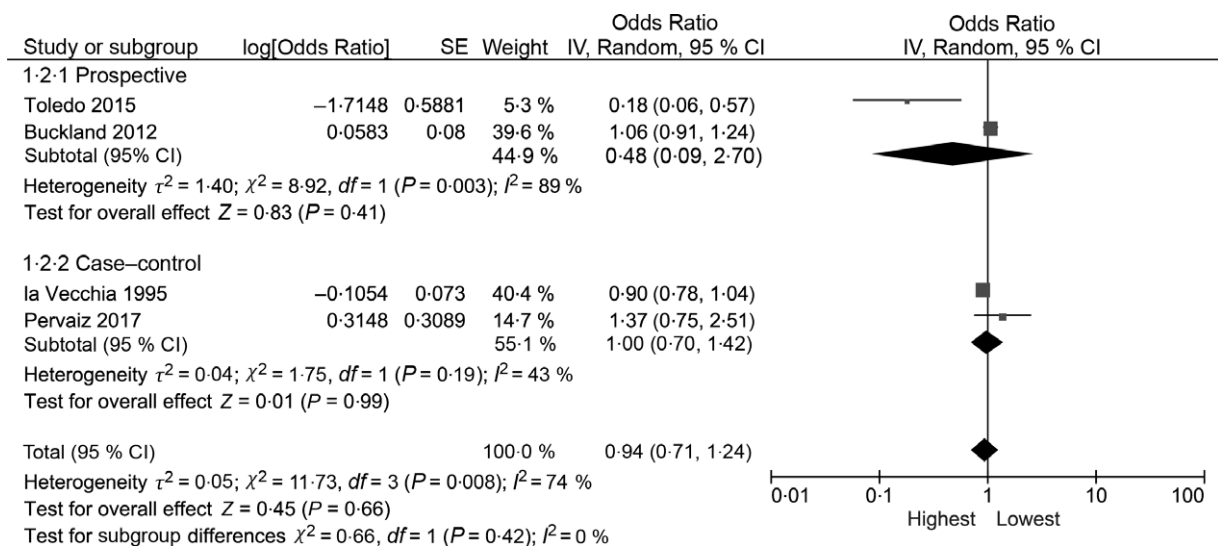

Fig. 4. Meta-analysis of the association between the highest v. lowest category of olive oil intake and breast cancer risk among postmenopausal women. IV, inverse variance.

Table 3. Subgroup analyses for case–control studies of olive oil and breast cancer

| Group	Number of studies	OR	95 % CI	I^2 (%)	$P_{for heterogeneity}$
Location					
Italy, Spain, Greece	4	0·60	0·39, 0·95	85	<0·001
Other countries	4	1·06	0·72, 1·57	58	0·07
Source of controls					
Hospital based	5	0·94	0·69, 1·28	65	0·02
Population based	3	0·57	0·28, 1·19	90	<0·001
Number of cases					
<500 cases	5	0·71	0·37, 1·39	89	<0·001
≥500 cases	3	0·80	0·67, 0·95	0	0·47
Exposure assessment					
Assessed amount consumed	5	0·75	0·48, 1·15	88	<0·001
Assessed frequency consumed	3	0·77	0·39, 1·51	69	0·04
Adjustment for total energy					
Adjusts for total energy	5	0·67	0·46, 0·98	83	<0·001
No adjustment for total energy	3	0·98	0·50, 1·91	69	0·04
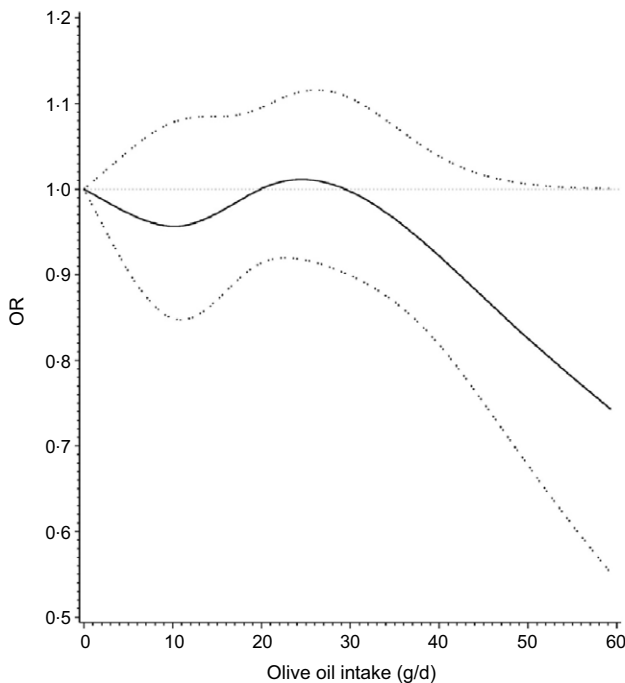
Fig. 5. Dose–response relationship between olive oil intake and breast cancer.

possibility is that the random effect model may be more sensitive to the lack of published non-significant smaller studies, as a greater weight is applied to smaller studies in random effects models than in fixed effects[36].

Our findings were similar to a meta-analysis by Psaltopoulou *et al.* (2011) that examined five olive oil and breast cancer studies conducted between 1990 and March 2011 and found that those with the highest category of olive oil consumption compared with the lowest was associated with lower odds of cancer (0·64; 95 % CI 0·46, 0·89)[14]. A more recent meta-analysis (through December 2014) that examined all vegetable oils, not limited to olive oil, and breast cancer risk comparing highest *v.* lowest consumption (*n* 16 studies) finding an OR of 0·88 (95 % CI 0·77, 1·01), and a dose–response meta-analysis among six studies found per

10 g of vegetable oil/d (OR 0·98, 95 % CI 0·95, 1·01)[15]. In a subgroup analysis of olive oil (*n* 12 studies), the authors reported an OR of 0·74 (95 % CI 0·60, 0·92), suggesting that olive oil may be driving the overall association[12]. Both previous meta-analyses included studies that included dietary patterns such as 'olive oil and salad vegetables' which may be one potential reason for the differences between our results. Additionally, due to differences in fatty acid profiles and phenolic compounds, the effects of olive oil on breast cancer risk may differ from other vegetable oils. As our results were non-significant, we cannot exclude the possibility that the significant inverse associations seen previously may be due to factors other than olive oil.

Olive oil did not appear to be associated with postmenopausal breast cancer in our analysis of studies that reported post-menopausal specific estimates. Of the two studies that stratified by menopause status[29,30], Trichopolou *et al.* found a stronger association among postmenopausal (estimates not given)[29], whereas La Vecchia *et al.* did not find that the association between olive oil and breast cancer varied by menopausal status[30].

One of the included studies in the meta-analysis was the PREDIMED study, a randomised trial conducted in Spain of the Mediterranean diet, comparing (1) Mediterranean diet plus extra-virgin olive oil and (2) Mediterranean diet plus nuts to a low-fat diet (control group)[23]. While limitations have been noted with the study's original randomisation[37], the estimates included in the meta-analysis were from a per protocol analysis *v.* the intention-to-treat analysis. The per protocol found similar directions of effects compared with the intention-to-treat analysis which found that the hazard was 0·38 (95 % CI 0·16, 0·87) for a Mediterranean diet plus extra virgin olive oil *v.* control, 0·62 (95 % CI 0·29, 1·36) for Mediterranean diet plus nuts *v.* control and 0·49 (95 % CI 0·25, 0·94) when both experimental arms (e.g. olive oil, nuts) were merged together *v.* control diet[23]. When the analysis was done using the olive oil intention-to-treat findings *v.* per protocol, similar summary estimates were observed. While randomised trials are the gold standard in epidemiological research as they can eliminate the potential for confounding if done correctly, we are unable to fully distinguish whether the observed association

is due to the Mediterranean diet or the olive oil. Given the Mediterranean olive oil arm had a significantly reduced risk and stronger magnitude than the nut arm, this suggests that olive oil is driving the association. The per protocol analysis, while better able to examined the effect of olive oil specifically, does not have the benefit of the randomisation. Though taken together, the results indicate that olive oil may reduce breast cancer risk.

The chemopreventive properties of olive oil have been hypothesised to be due to the antioxidant activity of its polyphenolic (e.g. hydroxytyrosol, tyrosol) and secoiridoid derivatives (e.g. oleuropein, oleocanthal)[10]. However, polyphenol concentrations in olive oil vary widely due to agricultural factors, processing and extraction methods, and storage[10]. Refined olive oil has a very low polyphenol concentration (approximately 0–5 mg/kg), followed by common olive oil (approximately 10–100 mg/kg), with extra virgin olive oil having the highest polyphenol content (approximately 15–400 mg/kg)[10]. Except for the PREDIMED study, which provided extra-virgin olive oil to trial participants and saw the largest reduction in risk[23], others studies do not distinguish between types of olive oil. If the chemopreventive action is greater for, or limited to extra-virgin olive oil, potential associations may be diluted by inclusion of refined olive oil intake in the exposure assessment.

One strength of the meta-analysis is that we examined the effect of olive oil alone, rather than including dietary patterns including olive oil, where it is unclear whether the association is due to olive oil or some other food in the dietary pattern. Additionally, we were able to examine the potential for a dose–response. However, as the studies included in the meta-analysis were observational studies (or used per-protocol analyses) and primarily case–control studies, misclassification of olive oil intake and residual confounding are probably present. Further, small numbers of published papers, potential publication bias and considerable heterogeneity among all studies probably due to variation in study designs and study population characteristics were present and thus the estimates should be treated with caution. Heterogeneity still persisted even in the subgroup analyses, though the subgroups were limited by small number of studies in each sub-group. Only one study examined tumour subtypes, limiting the ability to examine oestrogen receptor status. Further, the subgroup analyses indicated that the estimates may not be generalisable to non-Mediterranean countries. Lastly, the study was not registered in International Prospective Register of Systematic Reviews; however, we did not find a relevant protocol on the topic in International Prospective Register of Systematic Reviews.

In summary, olive oil may reduce breast cancer risk; however, as the certainty level is very low, additional prospective studies are needed before public health recommendations can be made. In addition to additional large prospective studies, more detailed exposure assessment information is needed, such as type of olive oil and cooking method, or biomarkers of olive oil intake.

Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114520003499

References

1. Centers for Disease Control and Prevention (2018) Breast Cancer Statistics. https://www.cdc.gov/cancer/breast/statistics/index.htm (accessed August 2018).
2. Schwingshackl L & Hoffmann G (2016) Does a Mediterranean-type diet reduce cancer risk? *Curr Nutr Rep* **5**, 9–17.
3. Bloomfield HE, Kane R, Koeller E, *et al.* (2015) *Benefits and Harms of the Mediterranean Diet Compared to Other Diets*. Washington, DC: Department of Veterans Affairs.
4. Schwingshackl L, Morze J & Hoffmann G (2020) Mediterranean diet and health status: active ingredients and pharmacological mechanisms. *Br J Pharmacol* **177**, 1241–1257.
5. Bloomfield HE, Koeller E, Greer N, *et al.* (2016) Effects on health outcomes of a Mediterranean diet with no restriction on fat intake: a systematic review and meta-analysis. *Ann Intern Med* **165**, 491–500.
6. van den Brandt PA & Schulpen M (2017) Mediterranean diet adherence and risk of postmenopausal breast cancer: results of a cohort study and meta-analysis. *Int J Cancer* **140**, 2220–2231.
7. Schwingshackl L, Schwedhelm C, Galbete C, *et al.* (2017) Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis. *Nutrients* **9**, 1063.
8. Linseisen J, Welch AA, Ocké M, *et al.* (2009) Dietary fat intake in the European Prospective Investigation into Cancer and Nutrition: results from the 24-h dietary recalls. *Eur J Clin Nutr* **4**, S61–S80.
9. Gaforio JJ, Visioli F, Alarcón-de-la-Lastra C, *et al.* (2019) Virgin olive oil and health: summary of the III International Conference on Virgin Olive Oil and Health Consensus Report, JAEN (Spain) 2018. *Nutrients* **11**, 2039.
10. Gorzynik-Debicka M, Przychodzen P, Cappello F, *et al.* (2018) Potential health benefits of olive oil and plant polyphenols. *Int J Mol Sci* **19**, 686.
11. Pang K-L & Chin K-Y (2018) The biological activities of oleocanthal from a molecular perspective. *Nutrients* **10**, 570.
12. Escrich E, Moral R & Solanas M (2011) Olive oil, an essential component of the Mediterranean diet, and breast cancer. *Public Health Nutr* **14**, 2323–2332.
13. Pelucchi C, Bosetti C, Negri E, *et al.* (2011) Olive oil and cancer risk: an update of epidemiological findings through 2010. *Curr Pharm Des* **17**, 805–812.
14. Psaltopoulou T, Kosti RI, Haidopoulos D, *et al.* (2011) Olive oil intake is inversely related to cancer prevalence: a systematic review and a meta-analysis of 13,800 patients and 23,340 controls in 19 observational studies. *Lipids Health Dis* **10**, 127.
15. Xin Y, Li X-Y, Sun S-R, *et al.* (2015) Vegetable oil intake and breast cancer risk: a meta-analysis. *Asian Pac J Cancer Prev* **16**, 5125–5135.
16. Vitolins M, Vitolins MZ, Blackwell CS, *et al.* (2017) The feasibility of walnut and extra virgin olive oil supplementation in older adults. *Int J Food Nutr Sci* **4**, 49–54.

17. Ouzzani M, Hammady H, Fedorowicz Z, et al. (2016) Rayyan–a web and mobile app for systematic reviews. Syst Rev 5, 210.

18. Sterne JA, Hernán MA, Reeves BC, et al. (2016) ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355, i4919.

19. DerSimonian R & Laird N (2015) Meta-analysis in clinical trials revisited. Contemp Clin Trials 45, 139–145.

20. DerSimonian R & Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7, 177–188.

21. Hamling J, Lee P, Weitkunat R, et al. (2008) Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med 27, 954–970.

22. Higgins JPT & Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21, 1539–1558.

23. Toledo E, Salas-Salvadó J, Donat-Vargas C, et al. (2015) Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial: a randomized clinical trial. JAMA Intern Med 175, 1752–1760.

24. Greenland S & Longnecker MP (1992) Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 135, 1301–1309.

25. Orsini N, Li R, Wolk A, et al. (2012) Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol 175, 66–73.

26. Atkins D, Best D, Briss PA, et al. (2004) Grading quality of evidence and strength of recommendations. BMJ 328, 1490.

27. Richardson S, Gerber M & Cenée S (1991) The role of fat, animal protein and some vitamin consumption in breast cancer: a case control study in Southern France. Int J Cancer 48, 1–9.

28. Martin-Moreno JM, Willett WC, Gorgojo L, et al. (1994) Dietary fat, olive oil intake and breast cancer risk. Int J Cancer 58, 774–780.

29. Trichopoulou A, Katsouyanni K, Stuver S, et al. (1995) Consumption of olive oil and specific food groups in relation to breast cancer risk in Greece. J Natl Cancer Inst 87, 110–116.

30. La Vecchia C, Negri E, Franceschi S, et al. (1995) Olive oil, other dietary fats, and the risk of breast cancer (Italy). Cancer Causes Control 6, 545–550.

31. García-Segovia P, Sánchez-Villegas A, Doreste J, et al. (2006) Olive oil consumption and risk of breast cancer in the Canary Islands: a population-based case–control study. Public Health Nutr 9, 163–167.

32. Saleh F, Reno W, Ibrahim G, et al. (2008) The first pilot study on characteristics and practice patterns of Kuwaiti breast cancer patients. J Environ Pathol Toxicol Oncol 27, 61–75.

33. Bessaoud F, Daurès J-P & Gerber M (2008) Dietary factors and breast cancer risk: a case control study among a population in Southern France. Nutr Cancer 60, 177–187.

34. Buckland G, Travier N, Agudo A, et al. (2012) Olive oil intake and breast cancer risk in the Mediterranean countries of the European Prospective Investigation into Cancer and Nutrition study. Int J Cancer 131, 2465–2469.

35. Pervaiz R, Tosun Ö, Besim H, et al. (2017) Dietary factors modify post-menopausal breast cancer risk: a case–control study from Turkish Cypriot population. Biomed Res Ther 4, 1171–1184.

36. Greenland S (1994) Invited commentary: a critical look at some popular meta-analytic methods. Am J Epidemiol 140, 290–296.

37. Estruch R, Ros E, Salas-Salvadó J, et al. (2018) Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med 378, e34.