RESEARCH ARTICLE

Vegetable Oil Intake and Breast Cancer Risk: a Meta-analysis

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Abstract

<u>Background</u>: Total fat intake may be associated with increased risk of breast cancer, and fish oil has been suggested as a protection factor to breast cancer. But the effect of vegetable oils is inconclusive. We aimed to investigate the association with high vegetable oils consumption and breast cancer risk, and evaluated their dose–response relationship. <u>Design</u>: We systematically searched the MEDLINE, EMBASE, Cochrane databases, and CNKI updated to December 2014, and identified all observational studies providing quantitative estimates between breast cancer risk and different vegetable oils consumption. Fixed or random effect models were used to estimate summary odds ratios for the highest vs. lowest intake, and dose-response relationship was assessed by restricted cubic spline model and generalized least-squares trend (GLST) model. <u>Results</u>: Five prospective cohort studies and 11 retrospective case-control studies, involving 11,161 breast cancer events from more than 150,000 females, met the inclusion criteria. Compared with the lowest vegetable oils consumption, higher intake didn't increased the risk of breast cancer with pooled OR of 0.88 (95% CIs:0.77-1.01), and the result from dose-response analyses didn't show a significant positive or negative trend on the breast cancer risk for each 10g vegetable oil/day increment (OR=0.98, 95% CIs: 0.95-1.01). In the subgroup analyses, the oils might impact on females with different strata of BMI. Higher olive oil intake showed a protective effect against breast cancer with OR of 0.74 (95% CIs: 0.60-0.92), which was not significant among the three cohort studies. <u>Conclusions</u>: This meta-analyses suggested that higher intake of vegetable oils is not associated with the higher risk of breast cancer. Olive oil might be a protective factor for the cancer occurrence among case-control studies and from the whole. Recall bias and imbalance in study location and vegetable oils subtypes shouldn't be ignored. More prospective cohort studies are required to confirm the interaction of the impact of vegetable oils on different population and various cancer characteristic, and further investigate the relationship between different subtype oils and breast cancer.

Keywords: Dietary fat-vegetable oils-breast cancer-cancer risk-meta-analyses

Introduction

Breast cancer is one of the most frequent cancer among women and ranks the second overall (Ferlay et al., 2010). In recent decades, the annual increases in female breast cancer incidence have been swelling in some parts of Asia (Youlden et al., 2014), such as China (Fan et al., 2014). In addition to effective breast cancer screening and reproductive factors changed, the environment, specifically the nutritional factors, maybe play a key role in the etiology, including Westernized dietary pattern with more calorie and fat (Fan et al., 2014).

The relationship between risk of cancer and dietary fat has been discussed in many studies (Schwingshackl and Hoffmann, 2014; Woo et al., 2014), and the effect of dietary fat on breast cancer was a longstanding and unresolved issue (Holmes et al., 1999). A recent publication about the dietary factors and breast cancer risk among Chinese females reported consumption of fat was significantly associated with increased risk of breast cancer (Liu et al., 2014), and the further studies indicated a high ratio of unsaturated to saturated lipids might be better (Couto et al., 2011). Some researches focused on the micronutrients, and Yang et al. (2014) analyzed 11 papers referred to 274 135 women and suggested an inverse associated between higher intake ratio of n-3/n-6 polyunsaturated fatty acids (PUFA) and risk of breast cancer.

Beside the researches on micronutrients, others reported the macronutrients as a component of the certain dietary patterns. Addition to meat and its products, butter, margarine, milk and diary products, oil is one of the most common dietary lipids, especially in Asian dietary. Fish oil, which is rich in ω-3 polyunsaturated fatty acid (n-3 PUFA), has been reported as one potential modifiable protective factor against cancers (Terry et al., 2003), whereas animal fat (except for fish) is considered a component of "*Western pattern*" or "*Unhealthy pattern*" in most studies (Buck et al., 2011; Castello et al., 2014;

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Karimi et al., 2014). However, due to the regional and expensive characters, the popularity of the fish oil is limited.

As one of the visible dietary lipids, vegetable oil, which contain various amount of both polyunsaturated and monounsaturated fat (Yu et al., 2004) have been gradually assuming greater importance, with North America showing the largest absolute increase in availability per capita over the past 30 years (Trichopoulou and Lagiou, 1997), and the total consumption in person is up to 50g/d in the developed region in East China (Zou et al., 2006). However, whether the vegetable oils increase the risk of breast cancer or not is lack of a systematic analysis and a confirmed conclusion.

In this study, we aimed to perform a comprehensive analysis and addressed the association with incidence of breast cancer and vegetable oil intake from two perspectives. First, we conducted highest verse lowest intake to analyze the impact of vegetable oil in categorical data. Then we assessed the consumption as a continuous variables and explore the trend of the each unit increment.

Materials and Methods

Data source and search

The search for articles on breast cancer incidence with vegetable oil intake was carried out by a computerized search of the MEDLINE, EMBASE, Cochrane database in English, and CNKI in Chinese, up dated to December 1st 2014, regardless of the publication status. We first performed the search about breast cancer, using the medical subject headings (MeSH) "*Breast cancer*". We also used the terms "*mammary*" and "*galactophore*" with combination of any of the following terms: "cancer", "*tumor*", "*carcinoma*", "*neoplasm*", and "*malignancy*". Then, we searched for the publications about vegetable oils, including olive oil, seeds oil, corn oil, soybean/ soya oil, sesame oil, palm oil and other compounds in diet discussed by other researchers (Martin-Moreno et al., 1994; Trichopoulou and Lagiou, 1997). In order to ensure that all studies referred to the vegetable oil were captured, the MeSH of "*dietary fat*", and the text words "*oil**" and "*lipid**" were performed, without selective keywords referring to the further restricted subtype of oil. Finally, we combined these two parts. In addition, we searched the reference lists of relevant articles, reviews, and meta-analysis papers manually, to confirm retrieval of all possible studies.

Study selection and quality assessment

Publications about the association between vegetable oils intake and breast cancer incidence were deemed eligible for this meta-analysis if they fulfilled all of the following inclusion criteria: 1) reported occurrence of breast cancer neither combined with other cancers nor related to the breast cancer recurrence; 2) evaluated exposure of vegetable oils intake rather than animal fat or margarine or micronutrient (e.g. monounsaturated fat or fatty acid), except for the clear clarification about the main source of the nutrient in original studies; 3) case-control or cohort studies; 4) sufficient information provided to estimate the relative risk (RR) or odds ratio (OR) and 95% confidence intervals (CI) for the highest and lowest exposure or different doses categories; 5) adjusted for corresponding confounding factors. Publications meeting these criteria were excluded if the subject population has been studied twice and the data has been updated in a subsequent report or with less information about our objective.

The Newcastle-Ottawa Scale (NOS) was used as a gauge to assess the quality of the inclusive publications in our study.

Data extraction

The following information was extracted from each report if available: article author, year of publication, study location, study design, number of cases and controls (or person-year in cohort studies), type and each category of vegetable oils intake, age and menopause status of population, OR/RR for the whole population and the subgroup (e.g. BMI, menopause status, hormone receptor status of breast cancer) as well as corresponding 95%CIs, and adjusted or matched variances. Considering that breast cancer is a rare disease (incidence rate <10%), the OR was assumed approximately the same as RR. The maximally adjusted OR/RR estimates were used for the meta-analysis as far as possible.

Two coworkers reviewed the articles and abstracts, assessed the quality and extracted the data independently. Any disagreement was adjudicated by a third reviewer.

Statistical analysis

Categorical and dose-response meta-analyses were conducted in the present review. The estimates comparing the highest category with the lowest one were used to conduct the categorical meta-analyses, while the data about vegetable oil intake from 3 or more categories were used to carry out the dose-response analyses, using the generalized least-squares trend (GLST) model (Greenland, 1995; Orsini et al., 2006) and restricted cubic splines with 4 knots at fixed percentiles 5%, 35%, 65%, and 95% of the distribution (Desquilbet and Mariotti, 2010; Zhou et al., 2012). The reference category in dose-response analyses was the lowest intake of each study. When the reference was not consistent with our purpose, estimates were recalculated using the method of Hamling et al. (2008). For each study, we assigned the midpoint of the upper and lower boundaries as the average of time exposure. If the upper boundary of the highest category was not provided, it had the same amplitude as the adjacent category. We estimated the risk increase of breast cancer occurrence for an increment of 10 g/day of vegetable oil intake.

All the pooled estimates were computed in fixed-effect model when heterogeneity was not an issue, otherwise the Der Simonian-Laird random-effect model was performed, which gives a more appropriate estimate of the prognosis effect when studies are statistically heterogeneous (DerSimonian and Laird, 1986). We used the Cochrane's Q test (significance level at $p<0.10$) and Higgins' I^2 index to describes the percentage of total cross-study variation that is due to heterogeneity rather than chance (cut points of 25% and 50% were used for low,

Table 1. The Characteristic of Eligible Studies

Author	Year	Region	Study design	Matched Variance	Recruitment Date	Dietary collection	Age	Follow-up	NOS	Total femals	Cases	Adjusted variance*
Richardson S^	1991	France	case-control	age	1983.2-1987.4	a dietary history questionnaire (55 food items)	28-66	-	6	924	409	a, c, g, k, l, m, n, p
Landa MC	1994	Spain	case-control	-	1987-1988	FFQ	(mean) 59.5	-	5	200	100	e, f
Martin-Moreno JM^	1994	Spain	case-control	age	1990.2-1991.7	a structured interview, a semi-quantitative FFQ (118 food items)	18-75	-	7	1750	762	a, b, d, e, i
La Vecchia C^	1995	Italy	case-control	-	1991.6-1994.2	a FFQ with 78 foods	23-74	-	6	5157	2569	a, b, c, e, f, g, k, m, n
Trichopoulou A^	1995	Greece	case-control	age/residence area	1989-1991	a validated (24 hrs recall standard), semiquantitative FFQ (115 food items)	not mentioned	-	6	2368	820	a, b, e, i, k, l, m, n
Mannisto S	1999	Finland	case-control	age/residence	1990.4-1995.12	a semiquantitative FFQ (110 food items)	25-75	-	6	764	310	a, b, g, h, i, j, l, m, o, p, q
Sieri S	2004	Italy	cohort	-	1987.6-1992.6	a self-given semiquantitative FFQ with 107 food items	34-70	9.5yrs	7	8984	207	a, c, e, h, k, l, n
Garcia SP	2006	Spain	case-control	-	1999.4-2001.6	a face to face interview with a semi-quantitative FFQ (88 items)	25-85	-	5	755	291	a, c, h, i, k, q
Bessaoud F^	2008	France	case-control	age/ community of residence/ rural or urban criterion	2002.6-2004.12	a validated FFQ	25-85	-	6	1359	437	c, e, i, j, m, n, p, r
Wang J	2008	US	case-control	age/race/ethnicity	1995-1999	a screening telephone interview and a structured questionnaire with at least 106 food items at a home visit	35-79	-	7	3748	1703	a, b, c, e, f, g, i, k, l, n, p, q, r
Wirfalt E	2011	Sweden	cohort		1991.3-1996.10	a 7-day menu book, a diet question-naire, and a 45-min diet history interview	45-79	10.3 yrs	8	15773	544	a, e
Zubiri O	2011	spain	cohort		not mentioned	a semi-quantitative FFQ (136-item)	not mentioned	6.1 yrs		7934	53	
Buckland G^	2012	Spain/ Italy/ Greece	cohort	postmenopausal	1992-2000	a personal interview, a self-administered semi-quantitative FFQ or diet history questionnaires or a food record	post-	9 yrs	7	62284	1256	a, b, c, e, g, h, i, j, k, l, m, o
Laake I	2012	Norway	cohort	-	1974-1988	a semiquantitative FFQ (80 food items)	17-49	24.8 yrs	7	38489	1397	a, c, e, h, i, j
Mobarakeh ZS	2014	Iran	case-control	-	2009.4-2009.5	a dietary habits questionnaire and interview	20-65	-	6	93	53	a, c, i
Mourouti N	2014	Greece	case-control	age/catchment area	2010.11-2012.7	a face to face interview, a semi-quantitative FFQ	not mentioned	-	7	500	250	b, c, h, i, j, k, p

*: The confounding factors involved in the articles: a.age, b.recodent (rural/urban), c. education, d. income, e. total energy intake, f.other fat, g.alcohol consumption, h.smoking, i.BMI/weight and hight/waist-to-hip ratio, j.activity, k.menopause status, l.age at menarche, m.age at first full-term pregnancy, n.parity, o.use of oral contraceptives/ estrogen replacement therapy, p.family history of breast cancer, q.history of benign breast disease, r.history of breast feeding; ^: Six studies included in dose-response meta-analyses; FFQ: food frequency questionnaire; PHVO-TFA: trans fatty acids intake from partially hydrogenated vegetable oils

moderate, and substantial level) (Higgins and Thompson, 2002; Higgins et al., 2003). Additional subgroup analysis were performed between studies, using predefined factors, such as published year, research location, study type, study size, BMI and menopause of population, and adjusted variance. And then we conducted meta-regression analyses to explore the heterogeneity. We did sensitive analysis to ensure that our results were stable and reliable enough. The probability of publication bias was assessed with the funnel plots and Egger's test (significant level at *p*<0.05). Statistical analyses were carried out using STATA 11.0 (STATA Corporation, Lakeway, Texas, USA), and the significant α level of 0.05 was used. All above was in accordance with Cochrane Handbook for Systematic Reviews of Interventions (5.1.0 vision, updated March 2011) (Green, 2011).

Results

Eligible studies

A total of 1524 publications were indentified.
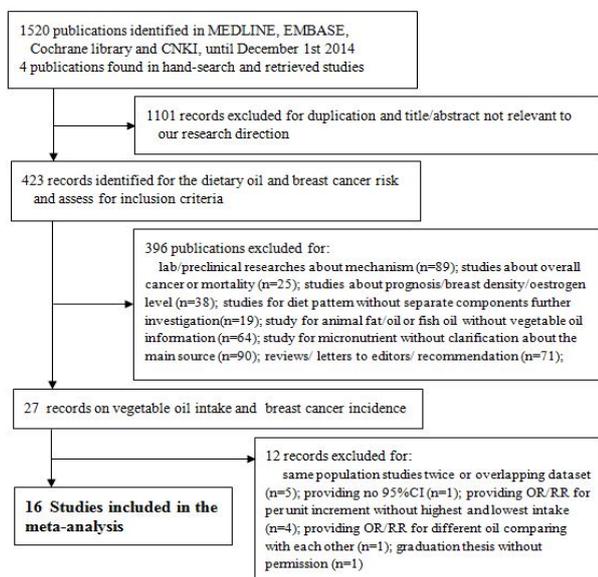

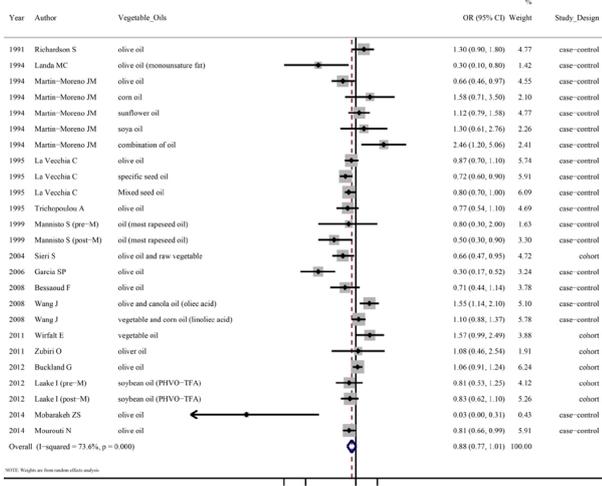**Figure 1. Flow Chart of Study Selection Process**

Figure 2. Forest Plot of OR and 95%CI in Random Effect Model for Highest *vs.* Lowest Category of Total Vegetable Oils Intake and Risk of Breast Cancer

Following the PRISMA chart (Figure 1), there were 27 publications investigating the association of the vegetable oil intake and breast cancer risk identified. After assessed by two reviewers independently, five publications were excluded for overlapping dataset with less information on our objective (Franceschi and Favero, 1999; Wirfalt et al., 2005; Sant et al., 2007; Bessaoud et al., 2012; Buckland et al., 2013), one for providing without 95%CIs (Toniolo et al., 1989), four studies (Katsouyanni et al., 1994; Kim et al., 2007; Trichopoulou et al., 2010; Demetriou et al., 2012) and one sub-study for seed oils (Trichopoulou et al., 1995) were omitted due to providing OR/RR for per unit increment without highest and lowest intake or different dosage categories. One publication was eliminated for providing OR/RR for different oil comparing with each other (Lubin et al., 1981). And one graduation thesis from Zhejiang University, China, was removed because it was under seal and we couldn't conduct the communication with its author. Hence, 16 publications (including one conference abstract) were deemed to eligible for the present meta-analysis (Richardson et al., 1991; Landa et al., 1994; Martin-Moreno et al., 1994; la Vecchia et al., 1995; Trichopoulou, 1995; Mannisto et al., 1999; Sieri et al., 2004; Garcia-Segovia et al., 2006; Bessaoud et al., 2008; Wang et al., 2008; Wirfalt et al., 2011; Zubiri Oteiza et al., 2011; Buckland et al., 2012; Laake et al., 2013; Mobarakeh et al., 2014; Mourouti et al., 2014) , including a total of 11 161 cases of breast cancer in over 150 000 women.

The characteristics of the eligible studies were shown in Table 1. In the 16 publications, nine were reported in recent 10 years. Most of the studies were based in the Europe, and in the rest, one from the US and other from Iran. There were five publications on the cohort studies, 11 on the population based or hospital based case-control studies. One studies based on the postmenopausal women,
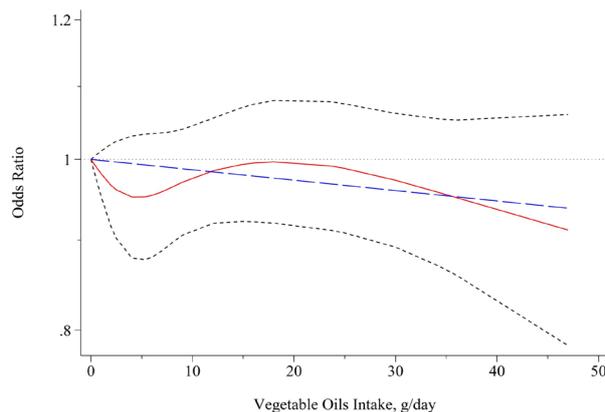

Figure 3. Linear and Nonlinear Dose-Response Relationship between Vegetable Oils Intake and Breast Cancer Risk. --6253 breast cancer cases in 73842 females of 6 studies in multivariate model, linear dose-response relationship was assessed by GLST model, and nonlinear dose-response relationship was assessed by restricted cubic spline model with four knots(5%, 35%, 65%, 95%). Solid red line denotes the nonlinear dose-response relationship of OR, with the black short-dash representing the corresponding 95% confidence intervals; blue longdash indicates the linear dose-response trend of OR; black dots line =1

Table 2. The Different Characteristic of Subgroup Studies

Author	Year	Region	Oils	Highest	Lowest	Subgoups
Richardson S^	1991	France	olive oil	>4.95 g/day	0	
Landa MC	1994	Spain	olive oil (monounsature fat)#	Highest	Lowest	
Martin-Moreno JM^	1994	Spain	olive oil	>2 tsp/day	0	
			corn oil	>7 tsp/week	0	
			sunflower	>7 tsp/week	0	
			soya oil	>7 tsp/week	0	
			combination of oil	>7 tsp/week	0	
La Vecchia C^	1995	Italy	olive oil	>40.7 g/day	≤10.7 g/day	premenopausal/ postmenopausal
			specific seed oil	>9.5 g/day	0	premenopausal/ postmenopausal
			Mixed seed oil	>3.0 g/day	<0.2 g/day	premenopausal/ postmenopausal
Trichopoulou A^	1995	Greece	olive oil	more than once/ day	less than once/ day	
Mannisto S	1999	Finland	oil (most rapeseed oil)	Highest	Lowest	premenopausal/ postmenopausal
Sieri S	2004	Italy	olive oil and raw vegetable	high score	low score	BMI<25/BMI≥25
Garcia SP	2006	Spain	olive oil	>27.3 g/day	≤3.1 g/day	
Bessaoud F^	2008	France	olive oil	>20.4 g/day	≤2 g/day	
Wang J	2008	US	olive and canola oil (oliec acid) #	Q4	Q1	premenopausal/ postmenopausal, ER+/ ER-
			vegetable and corn oil (linoliec acid) #	Q4	Q1	premenopausal/ postmenopausal, ER+/ ER-
Wirfalt E	2011	Sweden	vegetable oil	3.1 g/day (median)	0	ER+PR+/ER+PR-/ ER-PR-
Zubiri O	2011	spain	oliver oil	Q5	Q1	
Buckland G^	2012	Spain/ Italy/ Greece	olive oil	≥30.0 g/ day/2000kcal	<18.0 g/ day/2000kcal	premenopausal/ postmenopausal, BMI<25/ BMI≥25, ER&PR+/ ER&PR-
Laake I	2012	Norway	soybean oil (PHVO-TFA)#	Highest	Lowest	premenopausal/ postmenopausal
Mobarakeh ZS	2014	Iran	olive oil	Highest	Lowest	
Mourouti N	2014	Greece	olive oil and fish	Highest	Lowest	

#: The micronutrients with clear clarification about the main source of the micronutrient in original studies; PHVO-TFA: trans fatty acids intake from partially hydrogenated vegetable oils

and another 4 reported the vegetable oil impact on women with different menopause status, respectively. Only two studies provided the separate data on women whose BMI <25 and BMI ≥25, but almost half had been adjusted for it. All but one conference article were assessed by NOS and 7 of them had 7 or more stars.

Highest vs. Lowest meta-analyses

In 16 eligible studies, three of them analyzed different type of vegetable oil respectively, two of them reported pre- and postmenopausal cases and controls in separate studies. Thus, 25 sub-studies outcomes entered the final meta-analyses and result was shown in Figure 2. The summary OR for highest versus lowest intake was 0.88

(95%CIs: 0.77-1.01), with a substantial heterogeneity ($p<0.01$, $I^2=73.6\%$). There was no significant publication bias found by Egger's test ($p=0.12$) and funnel plots revealed little evidence of asymmetry.

Dose-response meta-analyses

Six studies (Richardson et al., 1991; Martin-Moreno et al., 1994; la Vecchia et al., 1995; Trichopoulou et al., 1995; Bessaoud et al., 2008; Buckland et al., 2012) consisted of more than 3 categories with numeric consumption, which could be unified into identical unit g/day, and two of them consisted of more than one type oils. Thus, a total of 12 sub-studies outcomes, referred to olive oil, safflower seed oil, peanut oil, soya oil, corn oil or mixed oil, about 6253
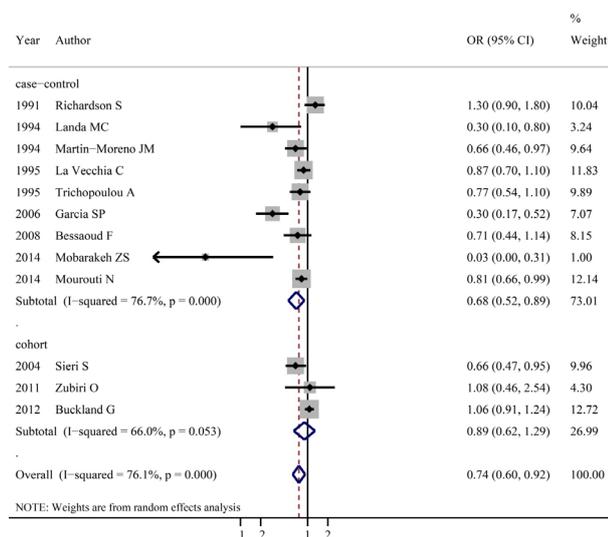
Figure 4. Forest Plot of OR and 95%CI in Random Effect Model for Highest *vs.* Lowest Category of Olive Oil Intake and Risk of Breast Cancer

cases in 73842 women, were included in dose-response analyses. The result didn't show an increase breast cancer risk for each 10g vegetable oil/day increment (OR=0.98, 95%CIs: 0.95-1.01, forest plots not shown). Further more, we found a slightly inverse, but not significant, association between vegetable oil intake and breast cancer risk from linear and non-linear dose-response curves (*p*>0.05, Figure 3). It was noted that all the estimates eligible for this part has been adjusted for total energy intake except for one (Richardson et al., 1991).

Subgroup analyses

We preformed the subgroup and sensitivity analyses with pre-designed confounding factors, and results were presented in Table 2. The odds ratio for breast cancer by vegetable oils intake remained the same when we stratified with the year of publication, size of studies, and the type of studies, as well as significant heterogeneity. Studies located in Europe showed that high intake of vegetable oils reduced breast cancer risk, with pooled OR of 0.85 (95%CIs: 0.75-0.98) and a slightly decline of heterogeneity (I²=67.0%). The higher dosage of vegetable oils consumption didn't appear a higher risk in either pre- or post-menopausal women. However, it impacted on the different hormone receptor status based on a much smaller population. Though the association was not altered greatly in two subgroups, both of them increased and were marginal with pooled OR of 1.04 (95%CIs: 0.99-1.10) and 1.13 (95%CIs: 0.91-1.40), respectively. In two cohort studies with a total of 392 732 person-year, which had been followed up for more than 9 years, there was a suggestion of an inverse, but not significant, association between vegetable oils intake and breast cancer risk in the population with BMI <25 (OR=0.63; 95%CIs: 0.27-1.49), whereas in BMI ≥25 females, the risk slightly increased with no heterogeneity, but still without significant (OR=1.10; 95%CIs: 0.93-1.29).

To improved accuracy, we did subgroup analyses for multiple adjusted variances as well. There was

not advanced effect of vegetable oils on breast cancer incidence, even though it was adjusted for total energy intake (OR=0.94; 95%CIs: 0.82-1.08; 10 studies), other fat (OR=0.94; 95%CIs: 0.77-1.14; 4 studies), BMI (OR= 0.80; 95%CIs: 0.63-1.01, 8 studies), activity (OR=0.89; 95%CIs: 0.76-1.04, 7 studies) or alcohol consumption (OR=0.95; 95%CIs: 0.80-1.14; 5 studies). And it showed a negative association with breast cancer incidence when the studies adjusted for smoking (OR=0.72; 95%CIs: 0.57-0.91, 6studies) or hormone-related factors (OR=0.84; 95%CIs: 0.72-0.98; 10 studies), including age at menarche, menopause status, oral contraceptives and hormonal replacement therapy use, age at first full term pregnancy and parity.

To investigate the impact of different types of vegetable oils on breast cancer risk, we separated them and analyzed respectively. Though it was not significant, high intake of corn oil showed a increased risk of breast cancer, whereas the soya/soy bean oil was similar with overall outcome. The heterogeneity of both two subgroups were reduced to 0. However, only olive oil has been reported individually in more than 2 studies. The statistically significant protection was obtained and shown in Figure 4. It is worthy of note that the significant inverse association was only observed in case-control studies, rather than cohort studies.

The heterogeneity remained substantial and we tried meta-regression analyses to further explore the heterogeneity in pre-designed factor present above, without significant result (data not shown). Summary risk estimates remained statistically significant when each study was omitted in turn, which indicated the result was stable and reliable.

Discussion

As we know, this is the first meta-analyses regarding the association between the breast cancer incidence and vegetable oils intake, including olive oil, corn oil, soya/soybean oil, etc.. We investigated from the perspective of macronutrients by two means, and explored the impact of vegetable oils directly. In the part of categorical analyses, we pooled the estimates for highest *vs.* lowest intake, and found there was no significant advance association between vegetable oils consumption and breast cancer risk. The finding was also supported by the linear dose-response meta-analyses for each 10g/day increment. Further more, the linear- and non-linear dose-response curves suggested a negative trend of the breast cancer risk on oils increasing intake, based on the correction with total energy intake.

This trend is coincidence with the previous studies. For the olive oil, Demetriou et al. (Demetriou et al., 2012) observed the breast cancer ratio fell by 5% (OR=0.95; 95%CIs: 0.92-0.99) for each once serve per week increase or 24% (OR=0.76; 95%CIs: 0.95-0.97) for each one spoon per day increase. And Trichopoulou et al. (Trichopoulou et al., 2010)reported no significant association with the risk of 0.93 (95%CIs: 0.80-1.08) for each 21g per day increment, based on a cohort study with more than 14 000 population. Likewise, Trichopoulou et al. (Trichopoulou et

Table 3. Subgroup Outcome of the Association Between Vegatable oils Intake and Risk of Breast Cancer

	No. of studies/strata	OR (95%CIs)	I-square	p[HG]	p[MR]
Overall	16	0.87 (0.77-0.99)	73.6	0.00	
Year of publication					
1.<2005	7	0.86 (0.73-1.02)	62.2	0.00	0.98
2.>2005	9	0.89 (0.75-1.06)	78.5	0.00	Ref.
Study design					
1.Cohort	5	0.94 (0.84-1.06)	39.1	0.15	0.85
2.Case-control	11	0.86 (0.72-1.02)	76.5	0.00	Ref.
Study size					
1.<2000	8	0.79 (0.58-1.06)	77.6	0.00	0.52
2.>2000	8	0.92 (0.82-1.03)	67.2	0.00	Ref.
Study location					
1.Europe	14	0.85 (0.75-0.95)	68.5	0.00	0.29
2.Other	2	0.93 (0.47-1.83)	87.2	0.00	Ref.
NOS score					
1.<7	8	0.69 (0.55-0.86)	72.7	0.00	0.04
2.≥7	7	0.99 (0.87-1.13)	64.8	0.00	Ref.
Oil					
olive oil	12	0.74 (0.60-0.92)	76.1	0.00	0.18
corn oil	2	1.13 (0.91-1.40)	0.0	0.39	Ref.
soy bean/soya oil	2	0.86 (0.68-1.08)	0.0	0.53	0.49
other vegetable oil	7	0.97 (0.79-1.19)	80.1	0.00	0.55
BMI					
<25	2	0.68 (0.25-1.87)	90.5	0.00	*
≥25	2	1.03 (0.86-1.24)	0.0	0.86	*
Menopause status					
pre-/peri-	4	0.94 (0.85-1.04)	56.7	0.03	*
post-	5	0.95 (0.88-1.03)	62.6	0.01	*
Hormone receptor status					
ER+ or PR+	3	1.05 (0.98-1.13)	0.0	0.98	*
ER- and PR-	3	1.06 (0.81-1.40)	60.5	0.06	*
Adjusted variance					
Age					
1.Yes	12	0.89 (0.79-1.02)	75.8	0.00	0.47
2.No	4	0.75 (0.57-1.00)	26.5	0.25	Ref.
Total energy intake					
1.Yes	10	0.92 (0.82-1.03)	68.0	0.00	0.18
2.No	6	0.63 (0.39-1.01)	81.5	0.00	Ref.
Other fat					
1.Yes	3	0.91 (0.71-1.15)	80.8	0.00	0.80
2.No	13	0.86 (0.74-0.99)	71.7	0.00	Ref.
Alcohol					
1.Yes	5	0.95 (0.80-1.14)	76.0	0.00	0.41
2.No	11	0.81 (0.68-0.98)	73.8	0.00	Ref.
Smoking					
1.Yes	6	0.72 (0.57-0.91)	74.1	0.00	0.15
2.No	10	0.95 (0.82-1.11)	73.1	0.00	Ref.

BMI					
1.Yes	10	0.88 (0.73-1.06)	75.7	0.00	0.81
2.No	6	0.85 (0.72-1.01)	71.7	0.00	Ref.
Activity					
1.Yes	5	0.83 (0.70-0.99)	46.8	0.08	0.58
2.No	11	0.90 (0.77-1.05)	78.4	0.00	Ref.
Menopausal status					
1.Yes	8	0.88 (0.74-1.03)	80.0	0.00	0.97
2.No	8	0.86 (0.70-1.07)	66.8	0.00	Ref.
age at menarche					
1.Yes	6	0.97 (0.78-1.20)	71.7	0.00	0.43
2.No	10	0.82 (0.71-0.96)	73.7	0.00	Ref.
Parity					
1.Yes	6	0.91 (0.76-1.08)	73.9	0.00	0.66
2.No	10	0.84 (0.70-1.00)	74.3	0.00	Ref.
age at FFTP					
1.Yes	6	0.85 (0.73-0.99)	61.3	0.01	0.73
2.No	10	0.89 (0.74-1.07)	77.4	0.00	Ref.
OC/HRT					
1.Yes	2	0.78 (0.46-1.35)	70.9	0.03	0.79
2.No	14	0.88 (0.77-1.00)	74.7	0.00	Ref.
Family history					
1.Yes	5	0.96 (0.74-1.25)	74.2	0.00	0.49
2.No	11	0.84 (0.73-0.96)	74.3	0.00	Ref.

*: meta-regression analysis is only conducted on the groups which include more than 10 sub-studies. p[HG]: p value of Q test of heterogenrity; p[MG]: p value of meta-regression analysis; NOS: Newcastle-Ottawa Scale; BMI: body mass index; ER: estrogen receptor; PR: prostrogen receptor; FFTP: first full-term pregnany; OC: oral contraceptives; HRT: hormone replace therapy

al., 1995) provided the evidence for seed oil that 4 times additional consumption per week resulted no rising risk (OR=1.00; 95%CIs: 0.96-1.05). On the whole, vegetable oils intake has no advanced effect on breast cancer occurrence.

We also found the different impact of vegetable oils on women with different strata of BMI. In the population with BMI <25, an apparent reduced risk was observed without significance (p=0.09), but it was less apparent in overweight and obesity women. The limited of studies might contributed the results, but we considered another possible explain that overweight or obesity women need a stricter energy-restricted dietary pattern. Numerous studies have investigated a possible relation between obesity and breast cancer (Alegre et al., 2013; Chan et al., 2014), regardless of race or ethnic groups. For this special group, it is necessary to lessen the fat and total calorie intake to the lowest category. In spite of this, some studies suggest the obesity population select vegetable oil, especially olive oil, during the diet periods (Flynn and Reinert, 2010).

In this study, a high intake of vegetable oil shows no significant advanced or protective effects towards pre- and postmenopausal breast cancer. No further research on the visible vegetable lipids. However, the studies in animal models and observation in humans found a high intake of n-6 polyunsaturated fat stimulated the development of breast cancer (Bartsch et al., 1999), and increased the risk for postmenopausal breast cancer (Thiebaut et al., 2007), whereas the most epidemiological studies did not find the epidemiological evidence on it. On the other hand, a recent study (Sulaiman et al., 2011) showed a lack of protective effects towards both pre- and postmenopausal breast cancer with higher intake of monounsaturated fat in Malaysia, which was different from some other researches. The author explained the variety outcome between different part of the world with difference in the monounsaturated fat sources.

The further research on the individual subtype of vegetable oils separately indicated a significant protection of olive oil on breast cancer risk. The soya/soybean oil remained negative association and the corn oil increased the risk without significance. The protection of olive oil on cancer, cardiovascular diseases and some metabolic chronic diseases has been discussed for along time. Psaltopoulou et al. summarized the inverse relationship between olive oil intake and the risk of eleven type of cancer (Psaltopoulou et al., 2011), and Pelucchi et al. calculated a summary estimate of 0.62 (95%CI, 0.44-0.88) for the highest level of olive oil consumption (Pelucchi et al., 2011), which is lower than ours. A possible explain to the difference could be that the more and updated articles in our review (9 case-control and 3 cohort studies

including 7000 breast cancer cases in the present study, while 6 case-control and 1 cohort studies including over 5300 cases in the previous analyses). Further more, it is worthwhile to note that the protection of olive oil disappeared in the summary OR of cohort studies, which declined the reliability of this conclusion. However, due to the limited data and smaller population, we failed to make a solid conclusion on other oils.

Vegetable oils are the important, if not essential, component in our daily dietary. They provide various amounts of mono- and polyunsaturated fatty acids as well as energy, which are potential antioxidants and chemopreventive factors that might affect the initiation, promotion and progression processes of carcinogenesis through several potential biologic mechanisms (Lopez-Miranda et al., 2010). A number of researches on the preventive or promotive effect of vegetable oils and their micronutrients had been carried out *in vitro* or *in vivo*. Olive oil has been well-researched in Europe. Escrich and his coworkers compared the extra-virgin olive oil (EVOO) dietary with high corn oil (HCO) and low fat dietary in the female Sprague-Dawley rats, and found the changes in tumor cell related to the structure and function of cell membranes, changes in cell-signaling transduction pathways (e.g. Ras/MAPK), modulation of gene expression, increased the apoptosis (Akt activity decreased and MAPK activity increased), reduced cellular oxidative stress and probably decreased DNA damage (Escrich et al., 2007; Costa et al., 2011; Escrich et al., 2014). Casaburi et al. concluded that the phenol fraction of olive oil has antitumor effects because of their capacity to inhibit proliferation and promote apoptosis in several breast cancer cell lines, MCF-7, SKBR3, MCF-7/Her2+, and JIMT-1 etc., by diverse mechanisms (Casaburi et al., 2013). For other vegetable oils nutrients, Yu et al. (2004) found the vegetable oils, independent of their unsaturated fatty acid content, acted as a role of antioxidant *in vitro*, were able to inhibit the formation of E2 peroxides and prevent E2-induced breast cancer carcinogenesis at initiation. Maillard et al. (2006) also reported an adequate content of α-linoleic acid (ALA) in the diet is required to allow a protective effect of β-carotene in mammary carcinogenesis, which indicated that the micronutrients in vegetable oils could cooperate with other food nutrients to protect from cancer and disease. On the other hand, Li et al. (2014) found that blending of soybean oil with selected vegetable oils could contribute as sources of important antioxidant related to the decreased PUFA, and increased MUFA content, which could resulted in the prevention of chronic diseases associated to oxidative stress, such as in cancer and coronary artery disease.

In spite of this, we should notice that it has been a popular belief that dietary high in ω-6 polyunsaturated fatty acid (n-6 PUFA), which is mainly from corn, sunflower or safflower oils, have a potential stimulating influence (Escrich et al., 2004; Escrich et al., 2014), and higher intake ratio of n-3/n-6 PUFA is associated with the lower risk of breast cancer among females (Yang et al., 2014), which suggests the importance of the dietary oil selection. However, any dietary lipids, especially vegetable oils, is composed of more than one single

micronutrient. And the fish oil consumption to the inland citizens, especially the residents living far from seaside and with low- or middle-income, is a health products more than the dietary fat.

Several limitations should be considered in the present review. First of all, there are short of individual patient data and original data in the process to do the further investigation. The further strata analyses for different hormone receptors status, menopause status and BMI should be taken into consideration to provide solid evidences. And the more information is required to explain the substantial heterogeneity. Secondly, since the eligible publication based on five prospective cohort studies and eleven retrospective case-control studies, the recall bias should not be ignored when we make conclusions, such as the protective effect of olive oil. And the most important in the present study was the imbalance in study location. In total 16 studies, only two of them were conducted out of Europe, and more than a half located in the Mediterranean countries, in where the olive oil is the most common, if not single, vegetable oil. It resulted in the subtype of oils and the ethnicity of research population were both single and short for representative.

However, we had to excluded three studies based on Asian countries according to the inclusion and exclusion criteria: Kim et al. (2007) from Korea provided the mean (±SD) consumption of sesame oil in both cases and controls, which suggested a significant inverse association with breast cancer risk (*p*<0.05), with neither different dose categories nor any confounding factors adjusted for (Kim et al., 2007). Wang (2006) has reported the vegetable oils intake was not associated with breast cancer risk significantly in the East China countryside in the graduation thesis which was under seal as a personal document. Another study from China reported a 54% ratio reduced (OR=0.46; 95%CIs: 0.31-0.67) in the more frequent vegetable oils intake females without correction with any confounding factors (Li et al., 2006). It'll have little possibility to change the result materially even though they are included (data not shown), which suggest our results stable and reliable.

More prospective cohort studies with large samples are required to confirm the interaction among the impact of vegetable oils, different population, and various cancer characteristic. Further investigation on the relationship between different subtype oils and breast cancer could be taken into considering. The lab research on micronutrients and the epidemiologic research on macronutrients should be combined as far as possible.

In conclusion, vegetable oils didn't act as a risk factor to breast cancer, and increasing the consumption, especially based on a certain total energy intake, would not increase the breast cancer risk, regardless of the correction with the pre-designed confounding factors or not. However, they might impact on females with different strata of BMI. An apparent negative association was observed in slimmer population, but it acted with a slightly risk increase without significant in overweight and obesity women. We didn't find the impact of oil on different menopause status and hormone receptor status. Moreover, subgroup analyses for different vegetable oils showed

that olive oil, which is one of the main components of Mediterranean diet and has been well researched for many years, could reduced the breast cancer risk. There were no significant association between other vegetable oils and the occurrence of breast cancer. Large cohort studies need to be conducted to clarify the relationship between Asian dietary pattern and the risk of breast cancer in different population. And further lab researches are required to better clarify the potentially protective mechanism on different micronutrients and macronutrients.

Acknowledgements

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