

Red Meat Consumption and Breast Cancer Risk in Premenopausal Women: A Systematic Review and Meta-Analysis

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Abstract

Background: This comprehensive meta-analysis aimed to determine the impact of red meat consumption on breast cancer risk in premenopausal women.

Methods: We conducted a systematic search in major electronic databases (MEDLINE, Scopus, and ScienceDirect) until January 1st, 2016 for all the case-control and cohort studies that addressed the association between red meat consumption and breast cancer risk. The full-texts of the retrieved articles were reviewed by two independent authors. The quality of the studies was assessed using a score assigned to each item according to STROBE statement. We used the random effects model to obtain summary measures of odds ratio or relative risk with 95% confidence interval.

Results: Out of the 513 retrieved studies, 17 (9 case-control and 8 cohort) were entered into the meta-analysis. These studies analyzed 26675 cases of breast cancer and over 943557 control or comparison subjects. The results of the random effects meta-analysis indicated a significant association between red meat consumption and breast cancer risk (relative risk: 1.269; 95% confidence interval: 1.117, 1.441; *P*-value for heterogeneity=0.002). The pooled relative risk was 1.087 (95% confidence interval: 0.999, 1.183) for cohort studies and 1.548 (95% confidence interval: 1.255, 1.909) for case-control studies.

Conclusion: The results of this meta-analysis showed that the women who consumed red meat had an increased risk of breast cancer. Further studies are required to investigate this association.

Keywords: Diet, Breast neoplasms, Meta-analysis, Red meat

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Introduction

Breast cancer, as the most common cancer among women, is the fifth most common cause of cancer death worldwide.^{1,2} It has been estimated that breast cancer affected 1,671,149 women and caused 521,907 deaths in 2012.³ A recent study indicated a higher incidence rate of breast cancer in developed countries, with the highest proportion of breast cancer mortality in developing countries.³

Epidemiological studies have provided support for the association between breast cancer and a number of risk factors, such as genetics,⁴ lifestyle,⁵ family history,⁶ parity,⁷ age at first birth,⁸ age at menarche and menopause,⁸ and environmental⁹ and physiological factors.¹⁰ Diet is another potential modifiable risk factor, and the effect of

a variety of dietary patterns on the incidence of breast cancer has been investigated extensively.¹¹⁻¹⁶ Differences in dietary patterns worldwide are well-established, which may contribute to the differences in the incidence of breast cancer.¹⁷⁻²⁰

Red meat consumption is a dietary factor with conflicting impacts on the risk of breast cancer. Some epidemiological studies have demonstrated that red meat consumption reduced the risk of breast cancer,²¹ whereas other studies declared an increased²²⁻²⁵ or unchanged risk.²⁶⁻²⁹ Other studies reported this association only in premenopausal or postmenopausal women.³⁰⁻³² A few meta-analyses that assessed the association between red meat intake and breast cancer risk yielded inconsistent results.³³⁻³⁶ Most have been conducted

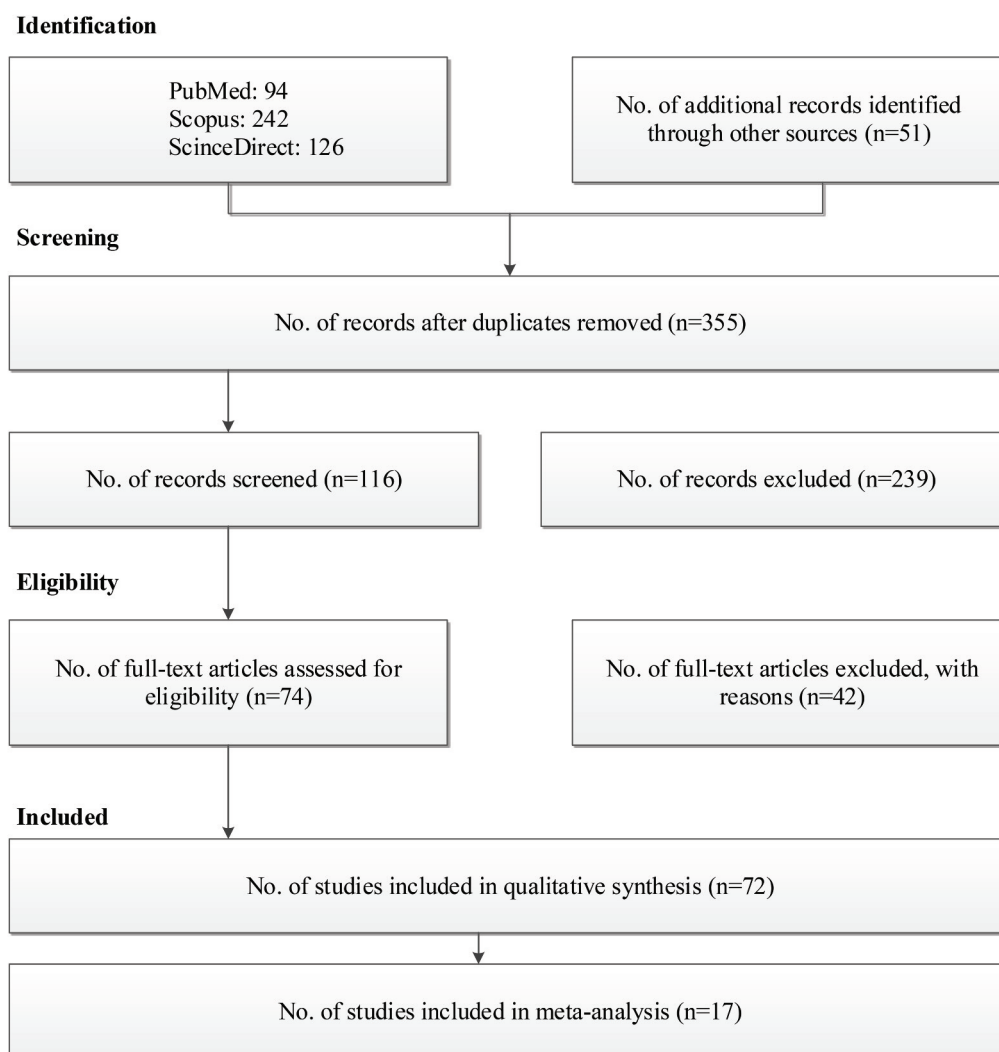


Figure 1. Flow diagram of the study selection process.

Table 1. Characteristics of the studies included in the meta-analysis.

Author	Year	Study design	Country	No. of cases	No. of controls	Type of control	No. of category	Relative risk (RR)	Lower limit	Upper limit
Lee et al. ⁴⁴	1991	Case-control	Singapore	200	420	Hospital	3	1.4	0.77	2.53
De Stefani et al. ⁴⁵	1997	Case-control	Uruguay	352	382	Hospital	4	2.26	1.24	4.12
Witte et al. ⁴⁶	1997	Case-control	U.S./Canada	140	222	Population	4	0.6	0.3	1.3
Ambrosone et al. ⁴⁷	1998	Case-control	U.S.	740	810	Population	4	0.92	0.25	3.32
Dai et al. ⁴⁸	2002	Case-control	China	1459	1556	Population	4	1.53	1.19	1.96
Hermann et al. ⁴⁹	2002	Case-control	Germany	122	199	Population	4	1.99	1.25	3.18
Zhang et al. ³²	2009	Case-control	China	438	438	Hospital-based	4	1.62	1	2.62
Fu et al. ³¹	2011	Case-control	U.S.	2386	1703	Nashville Breast Health Study	4	1.3	0.9	2
Ronco et al. ⁵⁰	2012	Case-control	Uruguay	253	497	Pereira Rossell Women's Hospital	2	2.2	1.35	2.6
Toniolo et al. ⁵¹	1994	Cohort	U.S.	180	829	Population	5	1.44	0.68	3.04
Missmer et al. ³⁶	2002	Cohort	U.S.	7379	343662	Meta-analysis		0.97	0.79	1.2
Holmes et al. ⁵²	2003	Cohort	U.S.	854	53104	Nurses in the U.S.	5	0.94	0.72	1.22
Cho et al. ⁵³	2006	Cohort	U.S.	1021	90659	Nurses' Health Study II	g/d	1.27	0.96	1.67
Taylor et al. ²²	2007	Cohort	U.K.	70	3334	Women aged 35-69		1.2	0.68	1.68
Pala et al. ²⁶	2009	Cohort	European countries	7119	312707	European Prospective Investigation into Cancer and Nutrition	5	1.05	0.94	1.18
Farvid et al. ²³	2014	Cohort	U.S.	2830	88803	Nurses' Health Study II	5	1.12	0.93	1.35
Farvid et al. ⁵⁴	2015	Cohort	U.S.	1132	44232	Nurses' Health Study II	5	1.43	1.05	1.94

on prospective studies.^{33,34,36} Menopausal status may be one of the possible reasons for the above mentioned issue. Therefore, the present, up-to-date and comprehensive meta-analysis aims to determine the effect of red meat consumption on breast cancer risk in premenopausal women based on the study design, ie. case-control and cohort studies.

Materials and Methods

Search strategies

In this meta-analysis, we conducted a systematic search for all the case-control and cohort studies that addressed the association between red meat consumption and risk of breast cancer. We searched MEDLINE, Scopus, and ScienceDirect electronic databases by entering Mesh terms “breast cancer” and “red meat” in titles, abstracts, or keywords until January 1st, 2016. The citations and references listed in retrieved articles were also manually searched to find the additional relevant articles not identified through the database searches (Figure 1).

Inclusion criteria and data extraction

The two authors (MG and SR) independently reviewed the retrieved studies to include eligible studies with the following criteria: (1) study design: cohort or case-control study; (2) year of the study; (3) geographical location of the study; (4) study population (all premenopausal or postmenopausal women); (5) dietary assessment methods; (6) definition of red meat intake; and (7) the number of cases and controls (in case-control studies), and exposed and non-exposed groups (in cohort studies) to calculate the odds ratio (OR) or relative risk (RR). If the related data were not available, the OR or RR estimates with 95% confidence interval (CI) were extracted.

In this study, red meat was defined as beef, pork, lamb, or their combination. Classification of red meat intake differed across the studies. For example, a number of studies divided red meat intake into 2, 3, 4, or 5 categories, whereas others divided it by intake unit. Hence, we compared the data from the highest red meat intake category to the lowest category²⁹ in this meta-analysis.

Quality assessment

The full-texts of the retrieved articles were reviewed by two independent authors (MG and SR). These authors determined the quality of the studies using a score assigned to each identified item according to the STROBE statement.³⁷ A third author (AK) was also considered as the arbiter to resolve any disagreements.

Statistical analysis

The summary measures of OR or RR with 95% CI were obtained using the random effects model. Cochran’s Q test was used to identify the heterogeneity of the results across the studies and quantified using the I² statistic. Q statistics with *P*<0.10 or I² statistic >50% were considered to have significant heterogeneity across the studies. We estimated the between-study variance using the tau-squared (t² or Tau²) statistic.³⁸ Egger’s linear regression test was employed to investigate publication bias with *P*<0.05 as the significance level. This meta-analysis was performed using comprehensive meta-analysis software, version 2.0. The PRISMA statement was also used as a guide in reporting this study.³⁹

Results

Description of the studies

We included 17 published studies that examined the role of red meat consumption in

premenopausal women in this study. Among these, 9 followed a case-control design and 8 were cohort researches. The studies contained 26675 cases of breast cancer and over 943557 control or comparison subjects.

Table 1 lists the characteristics of the studies included in this meta-analysis. Accordingly, 9 studies were carried out in the U.S., 2 in China, 2 in Uruguay, and 4 total studies in the U.K., Singapore, Germany, and European countries.

The results of the random-effects meta-analysis indicated a significant association between red meat intake and breast cancer risk (RR=1.269; 95% CI: 1.117, 1.441; *P*-value for heterogeneity=0.002; Figure 2).

The association between breast cancer risk and red meat consumption based on study design

Based on the results, the relationship between red meat consumption and breast cancer risk was different by type of the study. In other words, a statistically significant relationship existed in case-control studies (RR=1.548; 95% CI: 1.255, 1.909; *P*-value for heterogeneity=0.002), but not in cohort studies (RR=1.087; 95% CI: 0.999, 1.183; Figure 3).

Heterogeneity and publication bias

The Q-test results showed significant

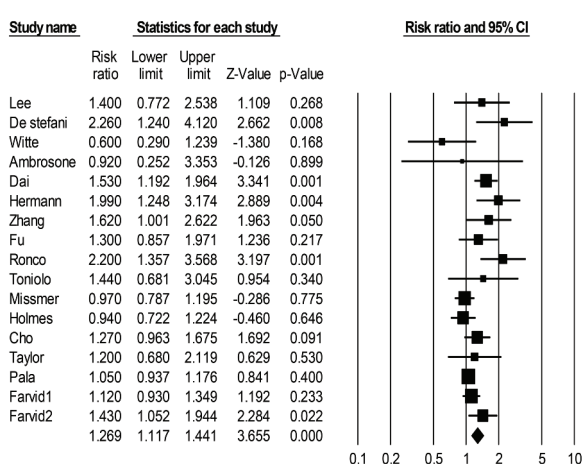


Figure 2. The forest plot of breast cancer risk associated with red meat consumption in premenopausal women.

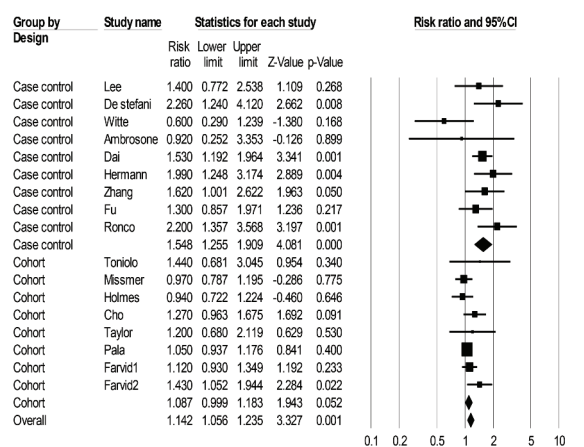


Figure 3. The forest plot of breast cancer risk associated with red meat consumption in premenopausal women according to study design.

heterogeneity among the studies ($P < 0.002$). The I^2 and tau squared statistics were 57.91% and 0.032, respectively. Out of the 17 studies that assessed the effect of red meat consumption on breast cancer risk, 4 reported non-significant negative associations and 13 reported positive associations, 5 of which were statistically significant. Although most studies revealed that consumption of red meat increased the risk of breast cancer, this relationship was statistically significant in a few studies. This finding has implied that the mechanism of publication bias based on statistical significance, in which significant studies are more frequently published, is not relevant in this case.

The funnel plot was almost asymmetric - the majority of small studies were gathered at the right side of the mean (Figure 4). However, the Egger's test results were not statistically significant and did not confirm this visual impression ($P < 0.053$). Rosenthal's Fail-safe N was 106, which meant that 106 studies with a mean risk ratio of 1.0 would be required for the cumulative effect to become statistically non-significant.

Discussion

The results of this meta-analysis revealed a significant positive relationship between red meat consumption and risk of breast cancer in premenopausal women. Accordingly, the women who consumed more red meat had a 1.27 greater risk of breast cancer compared to those who did not. The Q-test revealed a significant heterogeneity in the meta-analysis.

Although the results indicated a significant relationship between red meat consumption and increased risk of breast cancer, a conflicting result existed according to subgroup meta-analyses by study design (Figure 3). As reported in a similar meta-analysis,⁴⁰ the summary RR of the cohort studies was not similar to the case-control studies. Consequently, differences in the findings of the studies with different designs and those conducted in different geographical regions might be due to variations among countries in terms of dietary measurement instruments and dietary intake

factors. Furthermore, since red meat consumption takes several years to cause breast cancer and cohort studies are conducted over a short period of time, such studies fail to find this relationship. On the other hand, case-control studies that can measure the exposure without a time limit do not suffer from this limitation.

Generally, the studies that examined the relationship between red meat consumption and breast cancer risk did not reach a definitive conclusion. The results were affected by the method of measuring the variables and the small sample size. Despite these problems, this meta-analysis showed that red meat consumption could increase the risk of breast cancer in premenopausal women (Figure 2).

Obesity, as a risk factor for breast cancer, might be associated with menopause. This relationship might cause premenopausal women who consume red meat to be affected in a different way from postmenopausal women and increase the risk of breast cancer.⁴¹

Although the authors only found 17 studies on the relationship between red meat consumption and breast cancer risk in premenopausal women, Rosenthal's Fail-safe N was 106, which meant that 106 studies with a mean risk ratio of 1.0 would be required for the cumulative effect to become statistically non-significant. Missing 106 studies with the mean risk ratio of 1.0 is quite improbable. In other words, although the risk caused by red

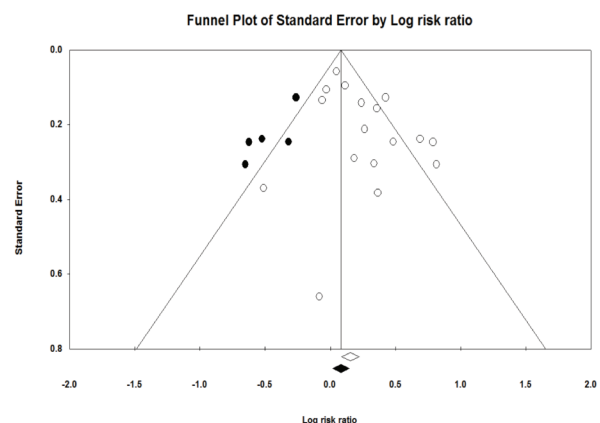


Figure 4. The funnel plot of red meat consumption and breast cancer risk.

meat consumption might have been overestimated, it was improbable for the actual risk of red meat consumption to be zero.

Overall, “the goal of a publication bias analysis should be to classify the results into one of three categories (a) where the impact of bias is trivial, (b) where the impact is not trivial but the major finding is still valid, and (c) where the major finding might be called into question”.⁴² Accordingly, this meta-analysis is placed in the second category.

Evidence has suggested that smaller studies have larger effects, which was also visible in our model. Nonetheless, there is no doubt concerning the relationship between the consumption of red meat and risk of breast cancer.

One of the limitations of the current study was that 10 studies included in the meta-analysis followed a case-control design, which could potentiate the recall bias. Additionally, using the food frequency questionnaire could result in bias due to measurement error and misclassification in exposure. This has been fully explained by Giovannucci et al.⁴³

Conclusion

The results of this meta-analysis have shown that women who consumed red meat had an increased risk of breast cancer. Future studies are needed to investigate this association. Guidelines have placed red meat consumption for breast cancer risk in category B; i.e. no clear harm or benefit. Thus, the results of this meta-analysis indicate the need to revise the guidelines.

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Authors' contributions

Study concept and design: Mohammad Ghorbani and Abbas Rezaianzadeh; Analysis and

interpretation of data: Mohammad Ghorbani, Abbas Rezaianzadeh, Shahab Rezaeian, and Aziz Kassani; Drafting of the manuscript: Mohammad Ghorbani; Critical revision of the manuscript for important intellectual content: Shahab Rezaeian, Abbas Rezaianzadeh, and Aziz Kassani; and Statistical analysis: Mohammad Ghorbani.

Conflicts of interest

No conflict of interest is declared.

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