



Review

The association between fat mass and the risk of breast cancer: A systematic review and meta-analysis

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SUMMARY

Background & aims: Several cohort and case–control studies examined the association between fat mass (FM) and the risk of breast cancer; however, findings are conflicting. The purpose of the present study was to systematically review this association and conducted a meta-analysis, if possible.

Method: A systematic search of PubMed/Medline, Scopus, Web of Science and Embase databases was conducted for cohort and case–control studies, between January 2000 and 31 March 2018 with no language limitations. Multivariate adjusted relative risk (RR) estimates with 95% confidence intervals (CI) for each category of FM were pooled to examine the association.

Results: Finally, 12 papers were considered for quantitative synthesis. The pooled RR for the highest vs. the lowest FM (%) of cohort studies was 1.44 (95% CI: 1.33, 1.56; I^2 : 63.3%, $p = 0.008$). The overall effect size for adjusted case–control studies showed no significant association (1.49, 95% CI: 0.77, 2.90; I^2 : 93.2%; $p = 0.001$). After stratification by menopause, it was revealed that the association between FM and the risk of breast cancer in post-menopausal women (2.29, 95% CI: 1.12, 4.68; I^2 : 92%, $p = 0.0001$) was significant, while there was no significant association in pre-menopausal women (0.68, 95% CI: 0.18, 2.58; I^2 : 81.3%; $p = 0.02$).

Conclusion: Cohort studies showed that higher FM is positively associated with the risk for breast cancer. However, only case–control studies on post-menopausal women showed a positive link. Due to limited studies and high heterogeneity, findings should be interpreted with caution. More cohort studies are needed to clarify this association.

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1. Introduction

Obesity, an excess accumulation of adipose tissue, is linked with the risk of several types of cancer including colon, endometrial, kidney and breast [1]. Breast cancer is the most prevalent cancer among women, affecting more than 1.5 million women, annually. Based on the report by the World Health Organization in 2015, approximately 15% of all cancer mortality among women is dedicated to breast cancer [2]. In order to prevent breast cancer and increase its survivals, early detection and identification of risk factors is important [2,3].

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Although several risk factors are known for breast cancer, obesity is one of modifiable one that can be considered for the prevention of breast cancer [4]. Obesity is a multifactorial disease that is a consequence of interplay among environment, behavior, and genetic parameters. The effects of obesity genes and their associations with breast cancer are conflicting. However, some evidence showed the association of different obesity indices and breast cancer [5].

Body mass index (BMI) that is a common anthropometric index for obesity identification [1] cannot show the changes in adiposity with age [4]. In addition, BMI cannot distinguish fat mass (FM) from lean body mass. It is now recognized that BMI is not able to be a reliable index to distinguish FM from fat free mass (FFM). BMI is calculated based on only body weight and height and the differences in the proportions of FM and FFM are not taken into account. This point is of great important because they might have different prognostic significance [6].

In addition, age, gender, and race can impact upon FM, while BMI is not influenced by such characteristics [7]. Based on evidence, other anthropometric indices such as waist circumference (WC) and waist-to-hip ratio (WHR) are indirect indices for fat distribution that may fail to show true association between obesity and breast cancer due to their limitations. It seems another anthropometric index should be used for predicting the occurrence of breast cancer.

Adipose tissue is the main site for estrogen synthesis in postmenopausal women. As the risk of breast cancer is increasing after menopause, considering FM to predict breast cancer is likely to be more suitable compared to other anthropometric indices [4]. Several cohort and case–control studies examined the association between FM and the risk of breast cancer [1,4,8–13]. However, findings are inconsistent. Besides, the magnitude of association between FM and the risk of breast cancer has not been clear yet. Previous meta-analysis examined the association between other obesity indices and cancer. For instance, the meta-analysis by Renehan et al., showed that each 5 kg/m² increase in BMI was positively linked with the risk of breast cancer [14]. In other meta-analysis by Harvie et al., it was revealed that about 40% lower risk for breast cancer in women with smaller waist circumference [15]. Nevertheless, to the best of our knowledge, no systematic review and meta-analysis examined the association between FM and the risk of breast cancer, thus far. Accordingly, the purpose of the present study was to systematically review the association between FM and the risk of breast cancer in adult population and conducted a meta-analysis, if possible.

2. Material and methods

Search strategy:

This meta-analysis was planned, conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [16]. Four main databases including PubMed/Medline, Scopus, ISI Web of Science and Embase were searched to find studies examining the association between FM and breast cancer between January 2000 and 31 March 2018 with no language limitations. Search terms including free terms and Medical Subject Heading terms (MeSH) used were as follows: (“Breast cancer” OR “Breast Neoplasm” OR (Neoplasm and Breast) OR “Breast Tumor*” (Tumor and Breast) OR (Tumors and Breast) OR (Neoplasms and Breast) OR “Breast Carcinoma” OR “Breast Carcinomas” OR (Carcinoma and Breast) OR (Carcinomas and Breast) OR (“Mammary Neoplasms” and Human) OR “Human Mammary Neoplasm” OR “Human Mammary Neoplasms” OR (Neoplasm and “Human Mammary”) OR (Neoplasms and “Human

Mammary”) OR (“Mammary Neoplasm” and Human) OR “Breast Cancer” OR (Cancer and Breast) OR “Mammary Cancer” OR (Cancer and Mammary) OR (Cancers and Mammary) OR “Mammary Cancers” OR “Malignant Neoplasm of Breast” OR “Breast Malignant Neoplasm” OR “Breast Malignant Neoplasms” OR “Malignant Tumor of Breast” OR “Breast Malignant Tumor” OR “Breast Malignant Tumors” OR “Cancer of Breast” OR “Cancer of the Breast” OR “breast gland cancer” OR “breast gland neoplasm” OR “mamma cancer” OR “mammary gland cancer”) AND (“fat mass” OR “body composition” OR “body fat” OR adiposity) AND 2000/01/01:2018/03/31 [DP]. Additionally, the reference lists of retrieved publications were also reviewed to identify relevant papers that might be missed during electronic database search. The protocol of the study was registered in the international prospective register of systematic reviews (PROSPERO) database (<http://www.crd.york.ac.uk/PROSPERO>; registration number: CRD42018098839).

Study selection:

Studies that met the following criteria were included: (i) the study design was a prospective or case–control study; (ii) the exposure of interest was FM (both in the form of kilogram and percentage); (iii) the outcome of interest was the incidence of breast cancer; (iv) and (e) risk estimates with corresponding 95% confidence intervals (CIs). Human studies with other designs (cross-section, case series, case report, clinical trials, etc), animal and *In vitro* studies were all excluded. Studies on mortality from breast cancer or the recurrence of breast cancer or other types of cancer, grey literature (theses, books, abstracts in conferences, interviews, etc) were excluded as well. When one study on the same population were reported in more than one study, the publication containing larger sample size and more complete and sufficient information was selected.

Data extraction:

Two authors (N.N, P.I) independently evaluated study eligibility, extracted data (N.N, J.H) and conducted quality assessment (N.N, L.A). Using a unified form, variables including study name (first author's name and year of publication), location, study design, subject characteristics, sample size, number of cases and controls, ascertainment of cancer, cut point of fat mass, FM assessment tool, follow-up duration, person-year, adjusted variables, risk estimates and CI were extracted.

Risk estimates and 95% CI that were adjusted for the most variables were extracted. If any of necessary information for analysis was not available in the papers, corresponding authors were contacted by email in three reasonable time intervals. When we did not get any response from authors, they were excluded from analysis. In the next step, the two lists from the investigators were compared, and any disagreements were solved by the principal reviewer (B.L).

Quality assessment:

To examine methodological quality of the included studies, a 9-point scoring system based on the Newcastle–Ottawa Scale (NOS) for cohort and case–control studies was used [17]. In NOS checklist for cohort studies the following main items were considered for quality assessment: selection, comparability, and outcome. Main items assessed for the quality of case–control studies were as follows: selection, comparability, and exposure. The maximum score for NOS was 9; and a high-quality study in the present meta-analysis was defined as a study with minimum 5 points.

3. Statistical analysis

Pooled RR and 95% confidence intervals (CIs) for the highest vs. the lowest category of FM were computed using a random-effect model to identify the association between FM and the risk for breast cancer. The most fully adjusted RR of each paper was pooled with the DerSimonian and Laird method. Between-study heterogeneity was evaluated using the I^2 index. I^2 values more than 50% were considered substantial heterogeneity [18]. When there were at least two studies in each category, we performed subgroup analyses to find the main source of heterogeneity. Stratification was conducted using the following factors: country (American, non-American), menopause status (pre-menopause, post-menopause), follow up duration (less or more than 9 years), sample size (less or more than 12,000 subjects), and study quality (less or more than 5). To clarify the robustness of the pooled RR, sensitivity analysis was used. It identified the pooled RR after the removal of any included studies. To assess publication bias, Egger's regression asymmetry test was used. Statistical analyses were performed

using Stata, version 11.0 (Stata Corp, College Station, TX). P-value < 0.05 was considered statistically significant.

4. Result

Study characteristics and systematic review:

The procedures of study selection are depicted in Fig. 1. Of 5874 publications (2056 duplicates), 3761 were excluded after screening based on title and abstract. In the next step, the eligibility of 57 full-texts of papers was examined. Forty-five studies were excluded due to the following reasons: Irrelevant (n = 12), cross-sectional studies (n = 12), did not report FM (n = 7), studies did not report either HR or RR/OR (n = 3), other types of cancers (n = 5), studies on children (n = 1), studies did not report total FM (n = 3), studies on cancer survival (n = 2). Finally, 12 papers that fully met the inclusion criteria were included. As two case-control studies [10,18] did not report adjusted models, they could not be pooled with other case-control studies and they analyzed, separately.

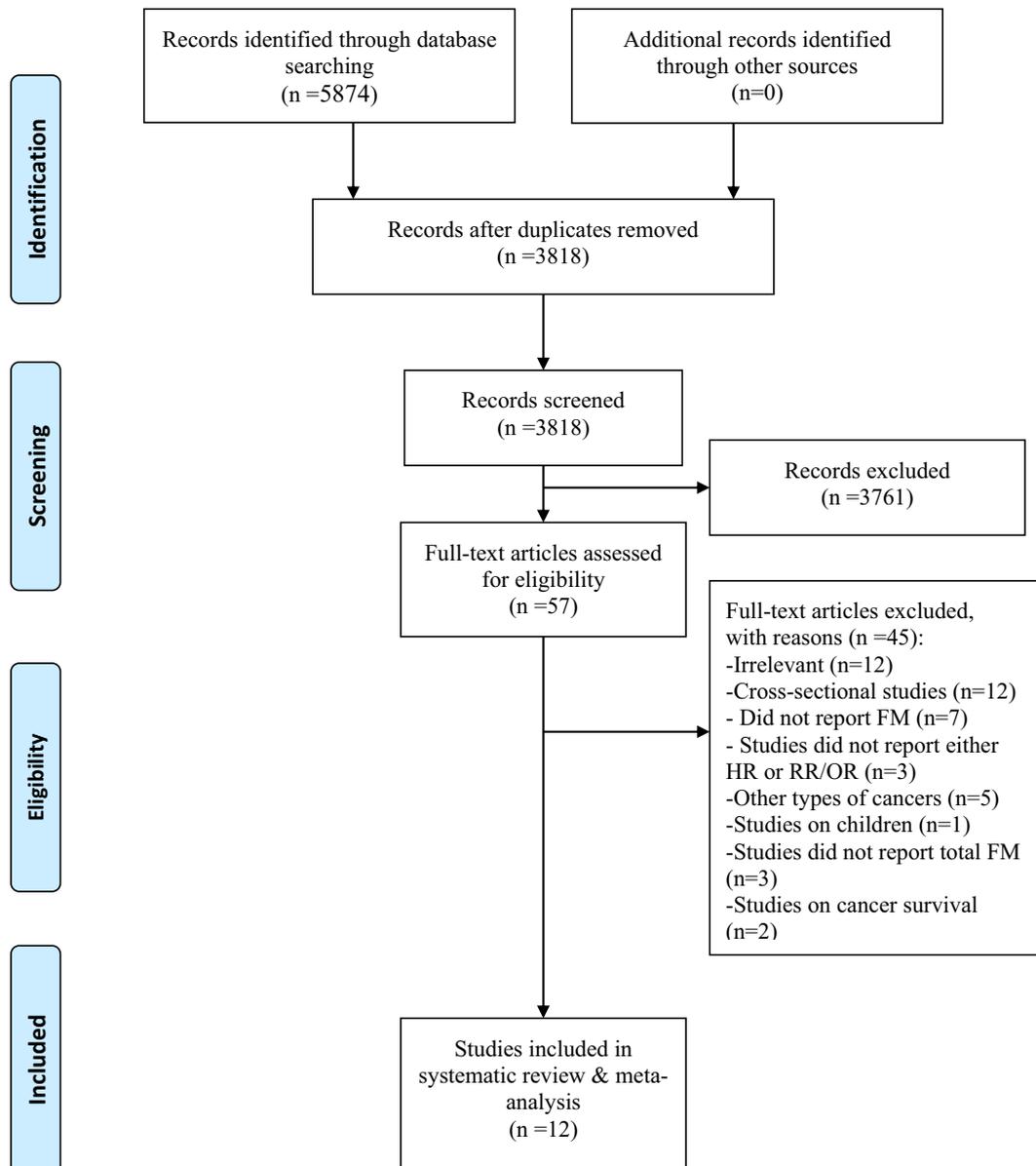


Fig. 1. Flow chart to select the eligible papers.

The characteristics of the included studies are summarized in Table 1. They were published between 2003 and 2018. Of 12 included studies, 7 had prospective cohort design [4,8,9,12,19–21] and 5 were case–control [10,11,13,18,22]. In cohort studies, a total of 5323 women with breast cancer diagnosed among 242,053 participants. Case-control studies contained 1496 cases and 2173 controls. Four studies were conducted in European countries [4,9,10,21], and the remaining were performed on American (n = 5) [8,10–12,22], Australian (n = 1) [20], and Asian (n = 2) [13,18] populations. All studies except five [10,11,13,18,23], included only postmenopausal women. In two case–control studies [11,13], findings were reported for pre- and postmenopausal women, separately. The duration of follow-up ranged from 5.7 to 12.9 years and the mean age of participants varied between 43 and 73.5 years old. Person-year was reported in only two cohort studies [9,12] and they were between 125,528 and 78,386. To measure FM, DXA (n = 1) [12] and different types of BIA (n = 11) [4,9,11,13,18–22]. The methodological quality of all cohort studies [4,8,9,12,19–21] and two case–control studies [11,13] was high (score > 5) (Table 1).

In only two cohort studies [4,12], the fat of trunk and its association with breast cancer was examined. Both studies reported that women with higher trunk fat were greater at risk for breast cancer compared to lower ones.

Most individual studies except two case-controls [10,18] were adjusted for different potential confounding factors, such as age, BMI, total energy intake, family history of breast cancer, and hormone replacement therapy use. As studies with crude models [10,18] cannot be pooled with adjusted ones, they pooled separately. In a case–control by Martins et al., it was revealed that women aged 41–60 years old with breast cancer had higher FM (>38%) [10]. According to another case–control study by Zunura et al., there was no association between higher FM and breast cancer among Malaysian women [18].

5. Meta-analysis

Cohort studies:

The combined multivariable-adjusted RR for the highest vs. the lowest FM (%) of 7 cohort studies [4,8,9,12,19–21] was 1.44 (95% CI: 1.33, 1.56) (Fig. 2), with high between-study heterogeneity (I^2 : 63.3%, $p = 0.008$). Only three studies reported FM in gram and the pooled effect size showed that the link between FM (g) and the risk of breast cancer was 1.43 (95% CI: 1.32, 1.54; I^2 : 92%, $p = 0.0001$). Stratification by location revealed that the association between FM and the risk of breast cancer in the U.S (1.59; 95% CI: 1.26, 2.00; I^2 : 0%) was stronger than other countries (1.42, 95% CI: 1.31, 1.55; I^2 : 72.6%; $p = 0.003$). Stratification by duration of follow-up and sample size did not attenuate the heterogeneity (Table 2). Only one study adjusted findings for total energy intake [12], after excluding this study no considerable change was observed in the overall effect size (1.42, 95% CI: 1.34, 1.50; I^2 : 80.2%; $p = 0.0001$). As the methodological quality of all the included cohort studies was high, we could not examine the effect of quality on findings.

Case-control studies:

The overall effect size extracted from 3 studies adjusted for covariates (5 effect sizes) [11,13,22] showed no significant association between FM and the risk of breast cancer in case–control studies (1.49, 95% CI: 0.77, 2.90; I^2 : 93.2%; $p = 0.001$) (Fig. 3). Pooling two studies with crude models [10,18] also showed no significant link (1.00, 95% CI: 0.96, 1.05; I^2 : 0%, $p = 0.57$). After stratification by menopause (in adjusted studies), it was revealed that the association between FM and the risk of breast cancer in

post menopausal women (2.29, 95% CI: 1.12, 4.68; I^2 : 92%, $p = 0.001$) was significant, while there was no significant association in pre-menopausal women (0.68, 95% CI: 0.18, 2.58; I^2 : 81.3%; $p = 0.02$). As breast cancer is affected by several covariates, we cannot make decision on the link based on crude models. Therefore, we analyzed adjusted and non-adjusted studies, separately and focused more on adjusted ones.

Publication bias:

Egger's linear regression test showed no publication bias neither for cohort ($p = 0.78$) nor case–control studies ($p = 0.58$).

Sensitivity analysis:

Sensitivity analysis confirmed the robustness of findings for cohort studies (range of pooled RR: 1.41 to 1.49). However, leaving out any case–control study changed the pooled effect size (range of pooled RR: 1.22 to 1.93).

6. Discussion

In the present meta-analysis on cohort studies, we found that women with higher FM (kg, percent) were at risk for breast cancer compared to those with lower one by 43% and 44%, respectively. However, the between-study heterogeneity was high. In addition, pooling case–control studies revealed that in women with higher FM (%) the risk for breast cancer was not significant compare to whom with lower one. Considerable association was existed in post-menopause women, while it was not significant in pre-menopause ones. However due to high heterogeneity and the lack of robustness, results should be interpreted by great caution.

To the best of our knowledge, the current study is the first systematic review and meta-analysis on the association between FM and the risk for breast cancer. Earlier, two meta-analyses examined the link between other anthropometric indices and the risk for breast cancer occurrence [15,24]. According to the study by Hidayat et al., on the link between BMI at a young age and breast cancer [24], it was found that every 5 kg/m² increase in BMI at young age (≤ 30 years old) was associated with a 14% and 13% greater risk for breast cancer in postmenopausal and all women, respectively [24]. Our meta-analysis was similar to Hidayat et al., from the view point of positive association between obesity and breast cancer. In another meta-analysis by Harvie et al., it was revealed that post-menopausal women with the smallest waist-to-hip ratio (WHR) and waist circumference (WC) had a 24% and 39% lower risk of breast cancer compared to those with the largest ones [15]. They also found that adjustment for BMI, attenuated the association in post-menopausal women. Regarding the association between obesity and breast cancer, our findings were in line with Harvie et al.'s study. Compared to Harvie et al., it seems that the link between FM and breast cancer is stronger than WC and WHR [15]. However, their findings were not heterogenic, while in our meta-analysis (both cohort and case–control studies), there was a considerable heterogeneity. In a meta-analysis by Nedooshan et al., it was found no association for FM and obesity associated (FTO) gene rs9939609 polymorphism with breast cancer. As many gene polymorphisms are involved in obesity and an increase in FM, is likely to be a link between breast cancer with other polymorphisms [5].

In the current meta-analysis, it was revealed that the association between FM and breast cancer in American population was stronger than non-Americans (RR: 59% vs. 42%, respectively). Although there was no heterogeneity in American studies, only two cohort studies were conducted in the U.S. Therefore, it seems making

Table 1
Characteristics of the included studies in the systematic review.

Cohort studies												
Author/Year	Location	Mean age (year)	Subjects	Total participants	Case	Control	Ascertainment of cancer	Cut point of fat mass	Assessment tool	Mean Follow-up (year)	adjustment	Quality score
Guo et al. (2018) [4]	UK	60	Post menopause	162,691	2913	–	ICD-10 C50	37.6 vs. 17.6 kg vs. 21.15 vs. 55.85%	BIA (Tanita BC-418MA)	5.7	1,2,3,4,5,6, 7,8,9,10,11,12	9
Rohan et al. (2013) [12]	US	62	Post menopause	11,393	537	–	Self-report	–	DXA	12.9	13, 14, 10, 1, 2, 3, 5, 4, 15, 16, 17, 9, 8, 7, 18, 19	9
Borgquist et al. (2009) [21]	Sweden	60	Post menopause with no hormone therapy	9685	305	–	Record linkage with Swedish Cancer Registry, Regional tumor registry for Southern Sweden Cancer registry	%	BIA (103, RLJ-systems, Detroit, MI)	10.3	13, 2, 5, 3, 20, 15, 4, 14, 21, 7, 8	8
Mellemkjaer et al. (2006) [9]	Danish	57	Post menopause	23,788	633	–	Record linkage with regional and national cancer registries in Sweden	≥39.3 vs. <30.1%	BIA 101-F	6.7	4, 3, 23, 14, 8	7
Krebs et al. (2006) [8]	U.S	73.5	Older postmenopause	7523	350	–	Review of medical records	Q4 (>43.4) vs. Q1 <35.4%	BIA Valhalla 1990B	11.3	13, 6, 25,23, 1, 9, 14, 26, 2, 5, 7	9
MacInnis et al. (2004) [20]	Australia	66.1	Post menopause	13,598	357	–	ICD 9th rubric 174.0–174.9, 10th revision rubric C50.0–C50.9	Q4 vs.Q1	BIA-101A RJL	9.1	2, 24, 14,9, 16	7
Lahmann et al. (2003) [19]	Sweden	60	Post menopause	13,375	228	–	Record linkage with regional and national cancer registries in Sweden	>36 vs. <27%	BIA-103 RJL	5.7	13, 11, 22, 4, 7,8, 3, 2, 6	7
Case-control studies												
Ameri et al. (2017) [13]	Iran	48	Pre-menopause post menopause	174	48	45	Examination by physicians	≥38.9 vs. ≤32%	BIA (Tanita)	–	1, 3, 14, 27	5
Zunura et al. (2016) [18]	Malaysia	45	Women aged 20–59 years old	112	56	56	Not reported	%- no category	BIA (Tanita)	–	Not adjusted	3
Bandera et al. (2013) [11]	US	43 58	Pre-menopause post menopause	1936	978	958	Self-report	>52.6 vs. ≤ 44.1 kg vs. >46.5 vs. ≤ 35.9% vs. >38%	BIA (Tanita® TBF-300A)	–	13, 10, 24, 14, 1, 23, 2, 5, 4, 28, 3, 16, 29	5
Martins et al. (2012) [10]	Goiania	48	Women	62	31	31	Not reported		BIA (model 1500 Bodystat)	–	Not adjusted	3
L.Ronco et al. (2009) [23]	Uruguay	Up to 70	Women up to 70 years old	1385	343	1042	Examination by physicians	IV vs.I	BIA	–	1, 2, 3, 5, 9, 15, 28, 30, 32, 33	4

BIA: bioimpedance analyzer; DXA: dual X-ray absorptiometry.

1: family history of breast cancer, 2: age at menarche, 3: age at first birth, 4: parity, 5: age at menopause, 6: previous HRT use, 7: smoking, 8: alcoholintake frequency, 9: physical activity, 10: ethnicity, 11: height, 12: body size at age 10, 13:age at enrollment, 14: education, 15: oral contraceptive use, 16:duration of hormone therapy, 17:previous breast biopsy, 18:intake of energy, 19: randomization status, 20:bilaxeral oophorectomy, 21: Occupation status, 22:Occupation, 23: Benign breast tumor, 24: Country of birth, 25: Hip bone mineral density, 26: live birth, 27: childbirth number; 28:education; 29: urban/rural status, 30:menopause status, 31:months of breastfeeding, 32: body mass index, bone weight.

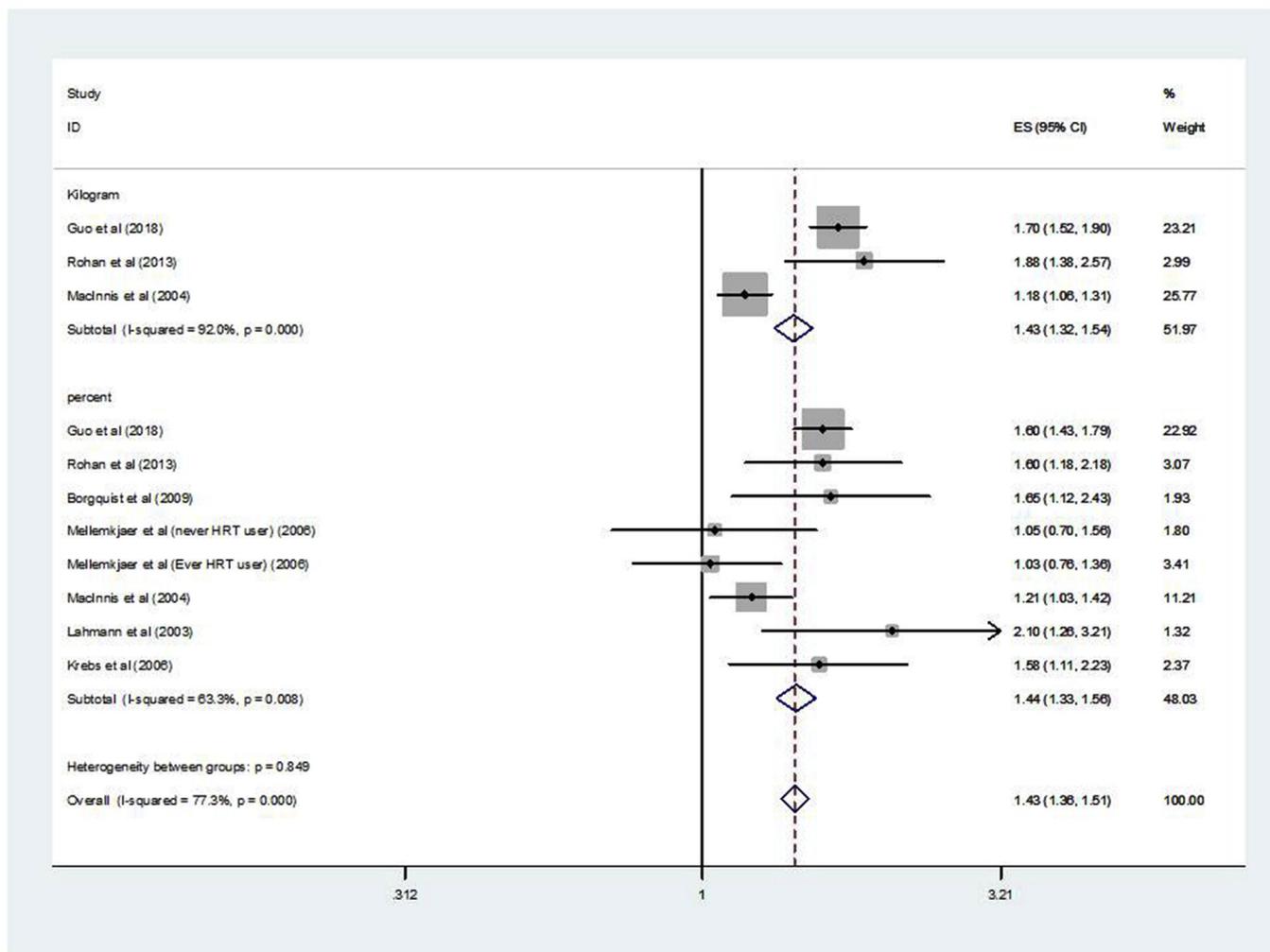


Fig. 2. Forest plot of the association between fat mass and the risk of breast cancer in cohort studies.

decision on the effects of geographical regions on this association needs more studies. It is notable that leaving out any cohort study did not change the pooled effect estimate considerably. In addition, methodological quality of the all cohort studies was high and we can be sure that findings were not influenced by study quality.

However, findings from case–control studies should be interpreted with great caution due to high heterogeneity and the lack of robustness. As there were only three case–control studies, we could not perform subgroup analysis to find the main source of

heterogeneity. As the study by L.Ronco et al. [22], had low quality among adjusted case–control studies, we excluded this study and examine the pooled effect size again. We found that the overall effect size fell to 1.36 (95% CI: 0.89, 2.09; p = 0.55) and the heterogeneity was removed.

The effects of central and general fat accumulation on hormone and growth factor metabolism that might be followed by the risk of breast cancer are likely to be different [15]. However, in our meta-analysis most studies reported only total fat mass not fat mass for

Table 2
Subgroup analysis for the association between fat mass and breast cancer.

	No. effect size	Pooled effect size (95% CI)	I ² (%)	P heterogeneity
Cohort				
Location				
U.S	2	1.59 (1.26, 2.00)	0	0.95
Other countries	6	1.42 (1.31, 1.55)	72.6	0.003
Follow up duration				
<9 years	4	1.28 (1.19, 1.39)	63.5	0.01
≥9 years	4	1.59 (1.47, 1.71)	74.1	0.004
Sample size				
<12,000	3	1.43 (1.35, 1.52)	87.7	0.0001
≥12,000	5	1.41 (1.25, 1.64)	56.5	0.04
Case-control (adjusted studies)				
Postmenopausal women	3	2.29 (1.12, 4.68)	92	0.0001
Premenopausal women	2	0.68 (0.18, 2.58)	81.3	0.02

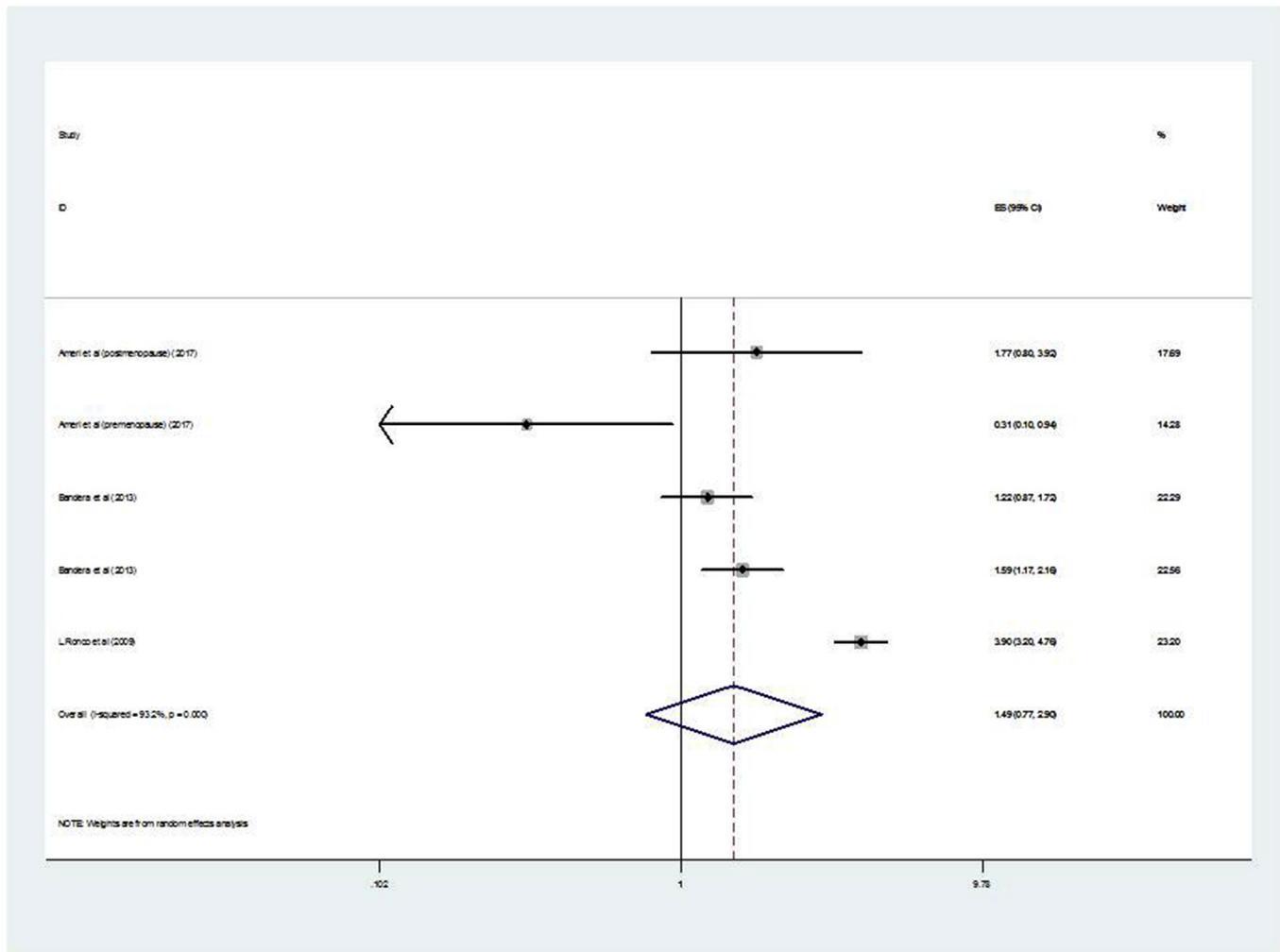


Fig. 3. Forest plot of the association between fat mass and the risk of breast cancer in adjusted case–control studies.

different parts of body (i.e. trunk), separately. Therefore, this matter remained unclear.

Mean age can also affect the association. Based on the study by Krebs et al. [8], on older postmenopausal women (mean age: 73.5 years), the link between adiposity and breast cancer was J-shaped. They also suggested that thinness in elderly subjects was a predictor for inflammation or sub-clinical disease that might elevate the risk for breast cancer [8]. However, in the present study the mean age of participants in all included studies except two [11,13] were similar and we could not stratified findings based on age. To examine the effect of Krebs et al. [8], study on the overall effect size, we excluded this study. Nevertheless, it was not changed considerably (RR: 1.40, 95%CI: 1.18, 1.66, I^2 :68.1; $p = 0.005$).

The association between FM and the risk for breast cancer can be partially explained by the following possible mechanisms: i) elevated serum levels of leptin and inflammatory markers including IL-6 and TNF-alpha following fat accumulation; ii) decreased levels of adiponectin levels that has anti-inflammatory effects; iii) increased insulin/insulin-like growth factors signaling; iv) dyslipidemia; v) elevated aromatase expression in adipose tissue; vi) a reduction in circulating sex-hormone-binding globulin and an increase in bioavailable estrogens levels [12].

Our systematic review and meta-analysis has several limitations. First, we cannot perform dose–response analysis due to the lack of sufficient information in most included cohort studies and limited case–control studies. Second, as all cohort studies reported the association in post-menopausal women we could not compare the link in both pre- and post-menopausal women. Third, due to limited studies that reported results for both HRT and non-HRT, separately we could not provide results based on this regard. Forth, different cut points were considered among studies that did not allow us to provide a certain cut point for FM that increase the risk for breast cancer.

Strengths of our meta-analysis were as follows: i) it was the first meta-analysis on the association between FM and risk for breast cancer; ii) study quality of the included studies was examined; and iii) subgroup analysis and sensitivity analysis were conducted to clarify the main factor of heterogeneity and the robustness of findings. Findings of the present study can be helpful for clinicians particularly nutritionists to prevent breast cancer occurrence in post-menopause using preventive and treatment strategies to reduce fat accumulation. Studying on other types of cancer and their associations with various anthropometric indices to find the best predictor for the risk of cancer is suggested.

7. Conclusion

The present meta-analysis on cohort studies provided evidence that higher FM is positively associated with the risk for breast cancer. However, only case–control studies on post-menopausal women showed a positive link. Heterogeneity in cohort studies remained considerably high. Due to limited studies and high heterogeneity, findings should be interpreted with caution. More cohort studies are needed to clarify this association and introduce a certain cut-off points for FM that is linked with breast cancer risk in various societies.

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Conflict of interest

The authors declared no conflict of interest.

References

- [1] Gupta A, Pandey A, Ayers C, Beg MS, Lakoski SG, Vega GL, et al. An analysis of individual body fat depots and risk of developing cancer: insights from the Dallas heart study. *Mayo Clin Proc* 2017;92(4):536–43.
- [2] World Health Organization. Breast cancer. 2018 Oct. Available at: <http://www.who.int/cancer/prevention/diagnosis-screening/breast-cancer/en/>.
- [3] Ghoncheh M, Pournamdar Z, Salehiniya H. Incidence and mortality and epidemiology of breast cancer in the world. *Asian Pac J Cancer Prev* 2016;17(S3):43–6.
- [4] Guo W, Key TJ, Reeves GK. Adiposity and breast cancer risk in postmenopausal women: results from the UK Biobank prospective cohort. *Int J Cancer* 2018;143(5):1037–46.
- [5] Nedooshan JJ, Kargar S, Neamatzadeh H, Haghghi F, Abadi RDM, Seddighi N. Lack of association of the fat mass and obesity associated (FTO) gene rs9939609 polymorphism with breast cancer risk: a systematic review and meta-analysis based on case-control studies. *Asian Pac J Cancer Prev* 2017;18(4):1031–7.
- [6] James F, Wootton S, Jackson A, Wiseman M, Copson E, Cutress R. Obesity in breast cancer—what is the risk factor? *Eur J Cancer* 2015;51(6):705–20.
- [7] Romero-Corral A, Somers VK, Sierra-Johnson J, Thomas RJ, Collazo-Clavell M, Korinek J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. *Int J Obes* 2008;32(6):959.
- [8] Krebs EE, Taylor BC, Cauley JA, Stone KL, Bowman PJ, Ensrud KE. Measures of adiposity and risk of breast cancer in older postmenopausal women. *J Am Geriatr Soc* 2006;54(1):63–9.
- [9] Mellemkjaer L, Bigaard J, Tjønnelund A, Christensen J, Thomsen B, Johansen C, et al. Body composition and breast cancer in postmenopausal women: a Danish prospective cohort study. *Obesity* 2006;14(10):1854–62.
- [10] Martins KA, Freitas-Junior R, Monego ET, Paulinelli RR. Anthropometry and lipid profile in women with breast cancer: a case-control study. *Rev Col Bras Cir* 2012;39(5):358–63.
- [11] Bandera EV, Chandran U, Zirpoli G, Gong Z, McCann SE, Hong C-C, et al. Body fatness and breast cancer risk in women of African ancestry. *BMC Cancer* 2013;13(1):475.
- [12] Rohan TE, Heo M, Choi L, Datta M, Freudenheim JL, Kamensky V, et al. Body fat and breast cancer risk in postmenopausal women: a longitudinal study. *J Cancer Epidemiol* 2013;2013:754815.
- [13] Ameri F, Akbari ME, Abdollahi M, Ajami M, Davoodi S. Body composition and anthropometric indices in pre-and postmenopausal women with breast cancer. *Koomesh* 2017;19(2).
- [14] Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;371(9612):569–78.
- [15] Harvie M, Hooper L, Howell A. Central obesity and breast cancer risk: a systematic review. *Obes Rev* 2003;4(3):157–73.
- [16] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151(4):264–9.
- [17] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25(9):603–5.
- [18] Zunura'in Z, Almardhiyah AA, Gan S, Arifin WN, Sirajudeen K, Bhavaraju V, et al. Anthropometric and reproductive factors among newly-diagnosed breast cancer patients and healthy women: a case-control study. *Asian Pac J Cancer Prev* 2016;17(9):4439–44.
- [19] Lahmann PH, Lissner L, Gullberg B, Olsson H, Berglund G. A prospective study of adiposity and postmenopausal breast cancer risk: the Malmo Diet and Cancer Study. *Int J Cancer* 2003;103(2):246–52.
- [20] MacInnis RJ, English DR, Gertig DM, Hopper JL, Giles GG. Body size and composition and risk of postmenopausal breast cancer. *Cancer Epidemiol Prev Biomark* 2004;13(12):2117–25.
- [21] Borgquist S, Jirstrom K, Anagnostaki L, Manjer J, Landberg G. Anthropometric factors in relation to different tumor biological subgroups of postmenopausal breast cancer. *Int J Cancer* 2009;124(2):402–11.
- [22] Ronco AL, Stefani ED, Deneo-Pellegrini H. Risk factors for premenopausal breast cancer: a case-control study in Uruguay. *Asian Pac J Cancer Prev* 2012;13(6):2879–86.
- [23] Ronco AL, Boeing H, De Stefani E, Schulz M, Schulze M, Pischoon T. A case-control study on fat-to-muscle ratio and risk of breast cancer. *Nutr Cancer* 2009;61(4):466–74.
- [24] Hidayat K, Yang CM, Shi BM. Body fatness at a young age, body fatness gain and risk of breast cancer: systematic review and meta-analysis of cohort studies. *Obes Rev* 2018;19(2):254–68.