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The Impact of Soy Isoflavone Intake on Mammographic Density: A Systematic Review and Meta-analysis

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ABSTRACT

Background: It is suggested that the comparatively elevated consumption of soy in Asian countries may contribute to the decreased incidence of breast cancer observed in these regions when compared to the Western world. The objective of this meta-analysis study was to investigate the impact of daily soy supplementation on mammographic density, which is recognized as one of the most influential risk factors for breast cancer.

Methods: PubMed, Scopus, and Web of Science were queried until May 2024. We extracted publications that met our specific eligibility criteria to obtain data on fractional anisotropy and brain connectivity. The digital data was extracted using the WebPlotDigitizer. We utilized the most recent iteration of Stata (version 18) to perform a meta-analysis on the data. The quality evaluation of the studies was conducted utilizing a critical appraisal instrument.

Results: The results of the analysis revealed that the soy-receiving group had 80% lower percentage of mammographic densities compared to those receiving the placebo, which was statistically significant. The two groups had statistically different body mass index (BMI) values as the soy-receiving group had 19% higher BMI values than the control group.

Conclusion: The findings indicate that soy consumption has a modest impact on mammographic density percentage, which may hold clinical significance.

INTRODUCTION

Breast cancer is one of the most commonly diagnosed types of cancer at present, and it is the fifth leading cause of cancer-related deaths. A non-modifiable risk factor of breast cancer is the density of breast tissue. Breast density is categorized into several groups in clinical practice, including low-density, high-density, and fatty breasts. Higher breast tissue density is commonly observed in younger women, those with a lower body mass index (BMI), during pregnancy or breastfeeding periods, and in women undergoing hormonal replacement therapy. Higher breast density is associated with greater risks of breast cancer, a trend that is seen in both premenopausal and postmenopausal women.[1] Indeed, women with extremely dense breasts have an

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estimated 4 to 6 times higher risk of developing breast cancer compared to women with minimal breast density.[2]

Since mammographic density has been suggested to be an indicator of cell growth and division and is frequently used as a biological marker to indicate a person's risk of developing breast cancer since the 1970s and a high level of mammographic density is associated with greater risk of breast cancer compared to low mammographic density, it is plausible that the effects of soy intake would be observable on mammograms.[3,4] Researchers have utilized both qualitative and quantitative measurements of breast density and quantitative assessments are a stronger detection choice. Most studies have defined breast density as the percentage of the breast occupied by dense tissue.[5]

Research on regions where breast cancer incidence is lower shows that dietary interventions, such as increased soy intake, may be an important strategy to reduce breast cancer risk. Asian populations, who traditionally consume soy-rich diets up to 10 times more than Caucasian women, have historically lower breast cancer rates.[6] In Asian countries, where traditional soy-based foods like tofu and soy milk are commonly consumed, soy, soy-derived foods, and red clover are the richest dietary sources of isoflavones. Isoflavones include genistein, daidzein, and glycitein.[7] Because of the structural similarity between plant-derived isoflavones and the human hormone 17β estradiol, it could have an effect on women's health.[8,9] Indeed, isoflavones act as selective estrogen receptor modulators. It is suggested that isoflavones compete with the body's own estrogen to bind to estrogen receptor sites. However, isoflavones have a weaker effect compared to the body's natural estrogen, and therefore, they are believed to reduce overall estrogen exposure. Studies have demonstrated that soy isoflavones may be as effective as hormone replacement therapy in managing conditions associated with menopause, such as osteoporosis and menopausal symptoms.[6]

The present study aimed to synthesize the current evidence from the published literature by conducting a systematic review and meta-analysis. The objective was to outline the collective findings of studies that have examined the association between soy isoflavone intake and the mammographic density.

METHODS

Search strategy

This study is a systematic review and meta-analysis aimed at evaluating the impact of soy isoflavone intake on mammographic density. The review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor and transparency in the study selection and data extraction process. In accordance with the PRISMA guidelines[10], two independent researchers, conducted comprehensive searches across multiple electronic databases, including PubMed,

Scopus, and Web of Science. Additionally, Google Scholar, was used to identify studies published in English. Non-English language studies were excluded due to language limitations. The searches were performed to identify articles published up to the end of 2023. The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and text words, including the following keywords: ("Isoflavone" OR "Phytoestrogen" OR "Daidzein" OR "Genistein" OR "Soy" OR "Soybean" OR "Soyfood" OR "Tofu" OR "Miso" OR "Red Clover") AND ("Breast Densities" OR "Mammographic Breast Density" OR "Breast Densities" OR "Mammographic Breast Density" OR "Mammographic Breast Densities" OR "Mammographic Density" OR "Mammographic Densities"). In addition to the database searches, the researchers also manually checked the reference lists of the included articles, as well as relevant review articles and meta-analyses, to identify any additional potentially relevant publications.

Inclusion criteria and study selection

To be considered for inclusion in the systematic review and meta-analysis, the studies were required to meet the following prespecified eligibility criteria:

Study Design

The studies must have employed a cohort study, nested case-control, or case-control study design.

Exposure measurement: the exposure of interest must have been defined as the intake of soy isoflavones, including genistein and daidzein, or the consumption of soy protein, soy foods/products (such as tofu, soybeans, lentils, miso), or the assessment of isoflavone levels in urine or plasma.

Outcome Definition

In this study, mammographic density was defined as the primary outcome of interest. To ensure methodological rigor, only studies employing robust epidemiological designs were included. Specifically, we limited our analysis to studies that utilized a cohort, nested case-control, case-control, or randomized controlled trial design. This criterion guarantees that the assessment of mammographic density is based on well-established research methods, thereby strengthening the validity and reliability of our findings.

Study Selection

Two independent reviewers conducted the initial screening of titles and abstracts to assess potential relevance. In cases where there was a disagreement between the two reviewers during this stage, the issue was resolved through discussion. If a consensus could not be reached, a third reviewer was consulted to make the final decision regarding inclusion.

Data extraction

Two researchers independently reviewed each potential article and extracted the relevant information. A data extraction form was developed for the review. In cases where there was a disagreement between the two researchers regarding the inclusion of a study or the extraction of data, the issue was resolved through discussion. If the disagreement could not be resolved, a third reviewer was consulted to make the final decision.

A customized data extraction form was created for the review, capturing a range of details. These included bibliographic information, participant demographics (such as menopausal status, average age, sex, baseline cancer risk, and country), intervention specifics (source of intervention, isoflavone dosage, placebo type, and adherence), intervention duration, the number of participants randomized and completing each study group, and the method used to measure breast density. Additionally, data on percentage mammographic density and reported side effects were collected. Baseline cancer risk was defined as the likelihood of developing cancer prior to any intervention, influenced by factors like age, sex, family history, lifestyle, and other pertinent characteristics. The form also recorded the number of participants, mean changes in breast density (either absolute change or annual change), and the variability of these changes (or final breast density and its variability if the changed data were unavailable) for each study group at the most recent available time point.

Risk of bias assessment

The methodological quality of the included articles was evaluated using the Newcastle-Ottawa Scale.[11] Two independent reviewers conducted the quality assessment for all of the studies included in the review. Any discrepancies that arose between the two reviewers' assessments were discussed between them in an attempt to reach a consensus. In situations where the two reviewers could not resolve the disagreement, a third reviewer was consulted to help determine the final quality rating for the study in question.

Statistical analysis

A meta-analysis was conducted to evaluate the percentage of mammographic density, reported as mean ± standard deviation or standard error of the mean, between the isoflavone-rich intervention group and the control group. The pooled mean difference and 95% confidence intervals were calculated using a random effects model. The study-specific standardized mean difference (SMD) was also combined using a random effects model to determine the pooled estimate of the difference in percentage mammographic density between the isoflavone intervention and control groups.

$$\mathrm{SDpooled} = \mathrm{sqrt}\left(\frac{\left((\mathrm{n1}-1)*\mathrm{SD1}^2+(\mathrm{n2}-1)*\mathrm{SD2}^2\right)}{\mathrm{n1}+\mathrm{n2}-2}\right)$$

$$\frac{\mathrm{M1}-\mathrm{M2}}{\mathrm{SDpooled}}$$

Data points from graphical representations in the included studies were extracted using the WebPlotDigitizer software (Automeris LLC, Frisco, Texas) (12). All statistical analyses were two-tailed, with statistical significance set at a P-value <0.05.

Publication bias assessment

Given that fewer than 10 studies were included in this meta-analysis, formal tests for publication bias, such as Egger's regression test and funnel plots, were not conducted. This limitation should be considered when interpreting the results.[13,14]

RESULTS

A comprehensive literature search was conducted across multiple databases to identify studies addressing the association between soy isoflavone intake and mammographic density. The search strategies were tailored to each database, and the total number of records retrieved is summarized in Table 1.

Study selection

The systematic search strategies resulted in a total of 2070 studies from the selected databases (Figure 1). After eliminating 199 duplicate studies, of the 1871 articles screened by title and abstract, 1847 were excluded because they did not address mammographic density as an outcome, or did not investigate soy isoflavones (or related exposure). The remaining 24 articles were evaluated based on their titles and abstracts. Finally, after excluding articles that did not meet the eligibility criteria, 7 studies were included in our study's synthesis.

In our analysis, we included 1120 participants receiving soy and 298 receiving placebo.

Table 1. Search strategies and results of the searching procedure

Data base	Search strategy	results
PubMed	(((((mammographic[Title/Abstract]) OR ("mammographic density"[Title/Abstract])) OR (mamo*[Title/Abstract])) OR (mammography[Title/Abstract])) OR (breast[Title/Abstract])) AND ((("Soy Isoflavone"[Title/Abstract]) OR (soy[Title/Abstract])) OR (soybean[Title/Abstract]))	1809
WOS	(((TS=("mammographic")) OR TS=(mammography)) OR TS=("mammographic density")) OR TS=(Mammo*) AND ((TS=(soy)) OR TS=(soybean)) OR TS=("Soy Isoflavone")	130
Scopus	(TITLE-ABS-KEY(soy) OR TITLE-ABS-KEY("Soy Isoflavone") OR TITLE-ABS-KEY(soybean)) AND (TITLE-ABS-KEY(Mammo*) OR TITLE-ABS-KEY("mammographic density") OR TITLE-ABS-KEY("mammographic") OR TITLE-ABS-KEY(mammography))	107
Google scholar	intitle:"mammographic density" OR intitle:"mammography" AND (intitle:"soy isoflavone" OR intitle:"soy" OR intitle:"soybean")	24

Four studies were conducted on American participants, 2 on English and 1 in Malaysian populations. Soy-receiving groups had a mean age of 52.96±8.73 years and placebo-receiving group had a mean age of 52.24±10.16 years. Table 2 summarizes the included studies.

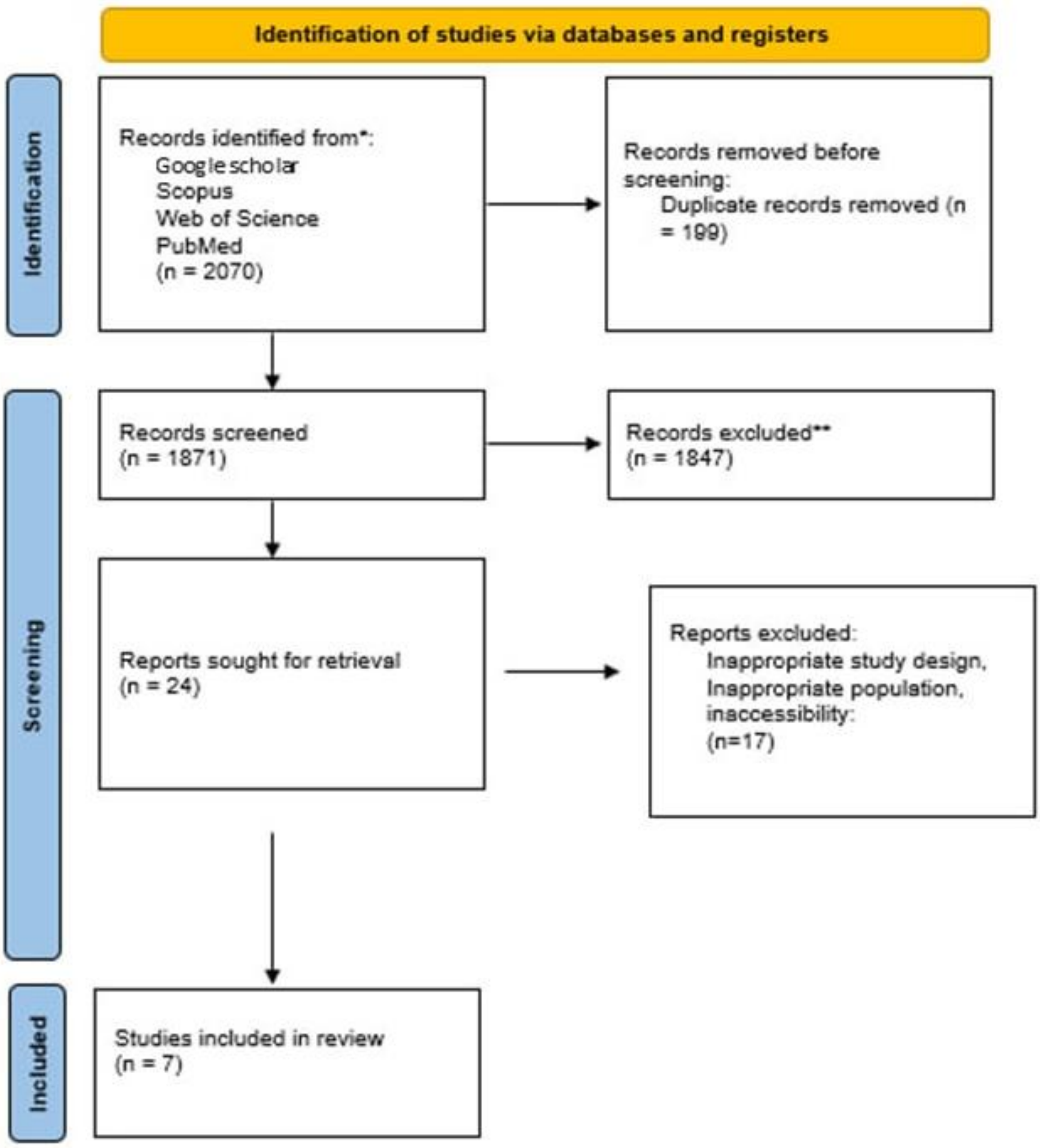

Figure 1. Flow diagram of study selection procedure.

Table 2. Summary of included studies

Author	Year	Country	Case	Control	Soy dose (mg)	Follow-up	Age (cases)	Age (controls)	BMI (cases)	BMI (controls)	Mean mammographic density (cases)	Mean mammographic density (controls)
G Maskarinec	2003	USA	15	15	100	12m	43.3	41.1	23	23.6	37.1	49.9
Charlotte Atkinson	2003	England	86	91	N/A	12m	55.1	55.2	25.3	25.3	58	61.8
Gertraud Maskarinec	2000	USA	514	N/A	N/A	N/A	53.9	N/A	N/A	N/A	N/A	31.6
Martijn Verheus	2008	England	70	56	N/A	N/A	66.3	65.3	25.7	26.3	7.9	10.7
Nadia Rajaram	2023	Malaysia	57	33	N/A	N/A	56	56.8	21.3	12.3	22.4	12.7
Gertraud Maskarinec	2004	USA	98	103	50	24m	43.2	42.8	26.2	25.9	40.5	43.2

N/A; Not Available

Risk of Bias

The methodological quality of the included studies was evaluated using the Newcastle-Ottawa Scale, which assesses 3 main domains—selection, comparability, and outcome/exposure assessment. Overall, most studies demonstrated moderate to high quality, particularly in the selection domain, where sample recruitment and data sources were adequately described. However, in several studies, details regarding the method used to measure mammographic density lacked clarity, potentially introducing measurement bias. Despite these limitations, the Newcastle-Ottawa Scale results suggest that the majority of the included studies provide reliable data and contribute substantially to the overall evidence base of this review.

Meta-analysis

The results of our analyses revealed that the soy-receiving groups had 8% lower mammographic densities compared to the placebo-receiving group, which was statistically significant (Figure 2).

In this study, BMI was analyzed as a secondary outcome to explore its association with the primary outcome (mammographic density). While the primary focus was on the intervention's effect on mammographic density, BMI was included to understand its role as a potential modifier or confounder. The 2 groups had statistically different BMI values as the soy receiving group had 19% higher BMI values than the control group (Figure 3).

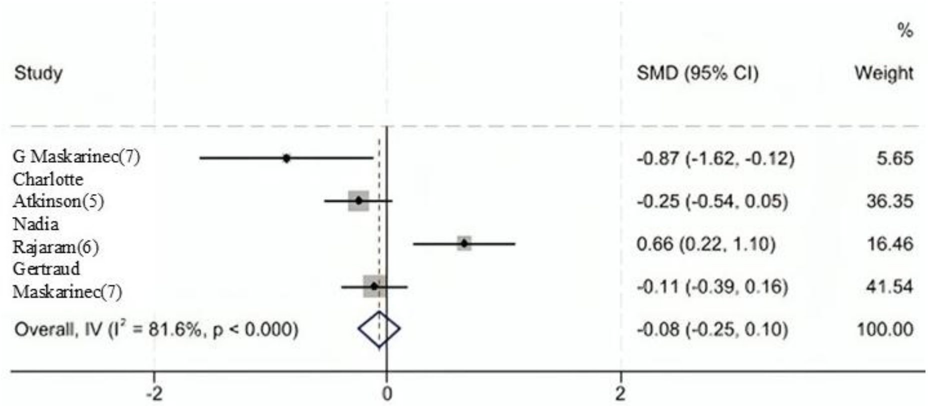

Figure 2. Forest plot of mammographic differences

DISCUSSION

The correlation between soy consumption and the risk of developing breast cancer has shown varying results in observational epidemiological studies. Following the initial findings by Lee *et al.* in a case-control study conducted in Singapore, which demonstrated a significant protective effect in premenopausal women[16], similar strong effects were observed in subsequent case-control studies among premenopausal women in Japan[17] and in Asian-born women residing in the United States. A recent cohort study conducted in Japan similarly demonstrated a decreased risk of breast cancer when individuals consumed high levels of isoflavones.[18] A study conducted in China[19] and among Asian-Americans in Los Angeles County[20] indicated that consuming a large amount of food during adolescence has a protective effect. Nevertheless, additional Chinese studies and a prospective study investigating the impact of consuming tofu and miso soup in Asian women did not yield statistically significant results. In addition, several studies conducted on non-Asian women, who consumed significantly lower amounts of soy, had mostly yielded unclear results. A recent analysis[21] concluded that the overall data showed no negative relationship between soy consumption and the incidence of breast cancer, except for a potential impact of consuming soy at a young age and consuming high amounts in specific Asian groups.[22] The findings align with the conclusions of the recent analysis, suggesting that consuming high amounts of soy may have a preventive impact against breast cancer. This effect may be due to the effect of soy intake on mammographic density.

This study examined the relationship between self-reported soy food intake and breast size in healthy pre- and postmenopausal women who had mammography screening. The results showed that there was a negative correlation between soy food intake and breast size, namely in the non-dense area, as evaluated in mammographic pictures. In contrast to our initial hypothesis, they observed a positive correlation between the consumption of soy and the proportion of breast tissue, as well as higher levels of breast tissue proportion among Chinese and Japanese women who had a lower likelihood of developing breast cancer. These findings suggest that soy may contribute to an increased risk of breast cancer due to its estrogenic properties. An alternative argument, however, may be that the size of the non-dense patches, which is inversely related to soy, is significant in determining breast cancer risk. The presence of a tumor in the mammary gland has been suggested as a potential risk factor for breast cancer. This is due to the increased development of ductal stem cells, which is influenced by factors during pregnancy and high energy consumption in early life. While these researchers did not gather data on soy consumption during childhood, they suggested that soy foods, whether consumed alone or as part of an Asian diet that is low in fat, high in cereal, and low in dairy and red meat, may play a role in the variations in mammographic characteristics among different ethnic groups. Dietary patterns can be determined from nutritional data using factor analysis, as demonstrated in various papers.[25]

Our hypothesis suggests that soy consumption throughout the developing years may influence mammographic characteristics by reducing the fat component of the breast. This effect is believed to be due to soy's impact on the growth of the female breast during that specific period. Comparative growth studies[26] provide evidence for the significance of childhood nutrition in determining adult anthropometric parameters. A dietary effect on breast development before puberty accords with the results from migrant studies revealing that it takes two or more generations to raise breast cancer risk.[18] The temporal lag suggests that only the offspring of migrants who were born and raised in the host nation will have a similar risk as the local population. This shows that potential environmental and behavioral factors have an impact early in life or during pregnancy.[27] Furthermore, there is data indicating that exposures during the neonatal period and adolescence play a significant role in determining the risk of developing breast cancer later in life, in addition to the indications provided by migration studies. The incidence of high-risk mammographic patterns, for example, was related to the weight of the placenta, the primary estrogen-producing organ during pregnancy.[28]

A Western diet, as opposed to an Asian one, may lead to increased body fat mass[18] during preadolescence, mediated through more accessible sex steroids. The high soy component of Asian diets may possibly limit the release of sex hormones and their effects on body fat through the antiestrogenic actions of isoflavones.[29]

The greater percentages of mammographic density seen among Asian women do not necessarily contradict the hypothesis of mammographic density. It appears from a recent case–control study that the connection between percentages of densities and breast cancer is of equal strength in women of different ethnicities despite the fact that density levels vary by ethnicity. While the connection between soy consumption and mammographic densities has not been explored before, earlier dietary research[30] has indicated limited correlations between micro- and macronutrients and mammographic densities. In a case-control study, there was a positive correlation between energy-adjusted saturated fat intake and mammographic densities, while fiber and carotenoids showed an inverse correlation.

The intervention group experienced a 6.1% decrease in areas of density, while the control group only had a 2.1% decrease, during a reduced fat intervention.[31] A reduction in cholesterol and saturated fat consumption, specifically, was found to be associated with a decrease in mammographic density. Increased consumption of fats and elevated levels of high-density lipoprotein cholesterol[23,33,34] were shown to be associated with denser mammographic patterns, indicating a potential link between blood lipid levels and the risk of breast cancer. A recent study[32] on a large group of Caucasian women found that there were slight variations in mammographic densities based on levels of vitamins B12, C, and E, as well as polyunsaturated fat intake.

Possible disparities in video quality between clinics and subjects could have resulted in measurement inaccuracies. In order to reduce the subjective element of the assessment process, they dedicated significant efforts to educating the readers and regularly compared the findings among them. The strong correlation coefficient suggests a significant degree of standardization in mammographic evaluation. Due to the inaccuracies in measuring dietary and mammographic density, the complex nature of determining mammographic densities, and the inherent bias in recalling dietary information, it is challenging to detect a minor impact. Given that the main objective of this study was to investigate the relationship between soy food consumption, we did not explore beneficial outcomes across various food items.

The absence of a comprehensive record of soy consumption throughout one's life and the use of a cross-sectional research methodology restrict the capacity of our investigation to demonstrate causal relationships. The dietary assessment inquired solely about consumption over the previous year. Consequently, it is unclear if the consumption of soy at the period when breast development took place was comparable to the current level of intake. It is possible that the influence of soy on the appearance of mammography in Caucasian women was not observed because those who reported soy intake likely began consuming these foods later in life, rather than during childhood. However, the consumption of soy may serve as an indication of Chinese and Japanese ethnicity, as well as a sign of childhood dietary habits that encompass various nutritional factors, including but not limited to soy-based foods. These eating habits may account for some physical measurements observed in adult women.

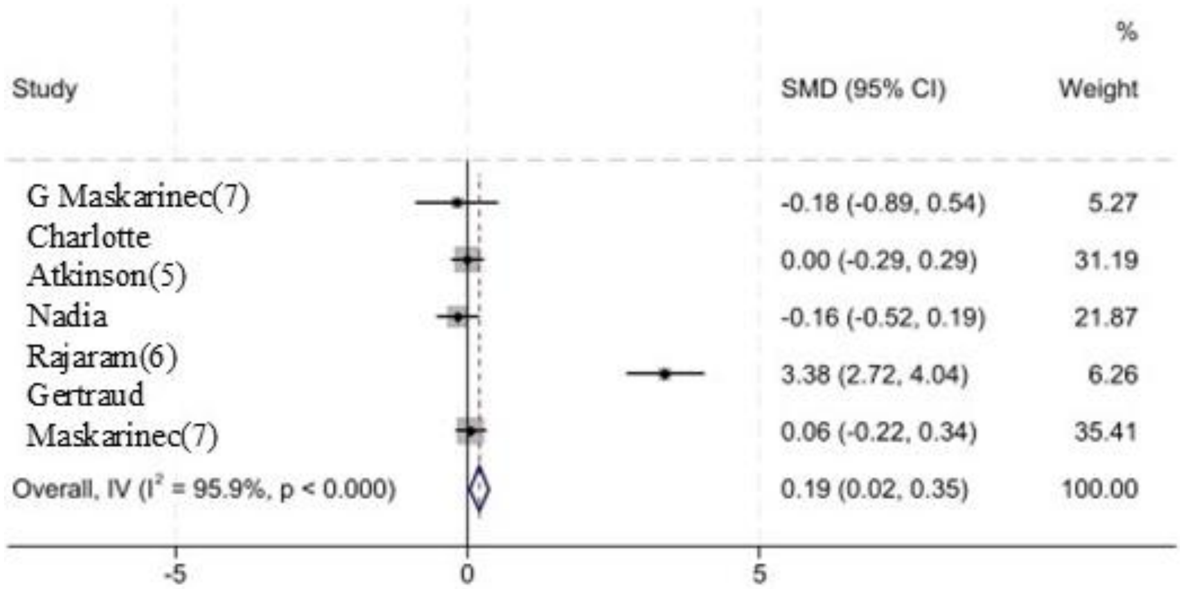

Figure 3. Forest plot of BMI differences

CONCLUSION

To conclude, this meta-analysis revealed that the Soy receiving group had 80% lower mammographic densities compared to the placebo-receiving group which was statistically significant. Therefore, soy could be considered as an effective supplementary therapy. However further large scaled observational studies are still required to support these findings.

ETHICAL CONSIDERATIONS

As this study is a review of published literature, no ethical approval or consent was required.

DATA AVAILABILITY

The data are not public but are available upon request from the corresponding author.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

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