howIs Metabolic Syndrome a Risk Factor for Breast Cancer in Premenopausal Women? A Meta-Analysis

Heather O'Donnell, Dr. Amy Abruzzi, Dr. Jane Miller

May 7, 2022

Bloustein Honors Research Program

Edward J. Bloustein School of Planning and Public Policy, Rutgers University

Abstract

Background: Breast cancer has become increasingly common in premenopausal women. Metabolic syndrome is diagnosed when an individual has three of the following five components: low HDL cholesterol, high triglycerides, high blood sugar, high blood pressure, and high BMI. It affects about 20% to 25% of the global population. This study explores whether metabolic syndrome is a risk factor for breast cancer in premenopausal women, who experience unique health effects, yet are understudied.

Methods: The CINAHL, OVID Medline, PubMed, Scopus, and Web of Science databases were searched in October 2022. Inclusion criteria were English language and point estimates and confidence intervals of the association between metabolic syndrome and breast cancer risk in premenopausal women. The search and screening process yielded 10 eligible articles, which were synthesized and analyzed in this meta-analysis.

Results: The meta-analysis for the case-control studies produced a pooled odds ratio of 1.5, which indicates that premenopausal women who have metabolic syndrome have about 46% higher odds of developing breast cancer than those who do not have it. The meta-analysis for the cohort studies produced a pooled risk ratio of 0.9, which indicates that premenopausal women who have metabolic syndrome are about 9% less likely to develop breast cancer than those who do not have metabolic syndrome.

Conclusions: Healthcare providers, public health professionals, and health educators could use these findings to implement evidence-based breast cancer prevention, management, and screening programs. Future research should explore how confounding factors and the number and type of metabolic syndrome components affect breast cancer risk.

Keywords: Metabolic syndrome, breast cancer, premenopausal women, meta-analysis

Introduction

Breast cancer, the leading cause of cancer incidence and the second leading cause of cancer mortality among females (Alkabban and Ferguson, 2023), accounted for 2.26 million incident cases and 685,000 deaths in females worldwide in 2020 (Sung et al., 2021). According to the National Breast Cancer Coalition (2023), a woman dies from breast cancer every 13 minutes, and about four million people in the United States were living with a history of breast cancer as of 2019. Breast cancer has led to more disability-adjusted life years (DALYs) in women worldwide than any other kind of cancer (WHO, 2023). Although it is more commonly diagnosed in postmenopausal women (aged 50+ years), it has become increasingly common in premenopausal women (aged 18-50 years) in the past two decades in both the United States and around the globe. It accounts for 42.4% of all cancers occurring in women aged 15 to 49 years (Haynes, 2017). About 9% of all new breast cancer cases are found in women younger than 45 years (CDC, 2023). Breast cancer incidence in the United States increased 0.7% from 2010 to 2018 among women aged 20 to 39 years and 0.4% from 2002 to 2018 among women aged 40 to 49 years (Ellington et al., 2022). Similarly, from 1998 to 2012, the age-standardized premenopausal breast cancer incidence rates increased in twenty high-income countries (Heer et al., 2020; Silva-Igua et al., 2020). In 2018, there were 645,000 new breast cancer diagnoses and 130,000 deaths globally among premenopausal women (Heer et al., 2020). This proportion will continue to increase based on current trends.

Compared to postmenopausal women, premenopausal women experience more aggressive forms of breast cancer and are more likely to be diagnosed at later stages of the disease (Chollet-Hinton et al., 2016). Premenopausal women also face higher breast cancer recurrence and mortality rates compared with postmenopausal women (Anders et al., 2008;

Chollet-Hinton et al., 2016; Laudisio et al., 2019). Premenopausal breast cancer is more likely than postmenopausal breast cancer to be hormone receptor-negative, which does not have as many treatment options as hormone receptor-positive breast cancers (Vaz-Luis et al., 2022). While advanced breast cancer incidence rates in the United States have decreased among women aged 60 years and older in recent decades, they have increased among premenopausal women (Nichols et al., 2017).

Breast cancer diagnosis and treatment cause premenopausal women to experience many adverse physical, psychosocial, and financial issues that postmenopausal women do not experience. With regards to physical issues, they experience severe pain, weight gain, hair loss, decreased fertility, and premature menopause (Avis et al., 2016). With regards to psychosocial issues, they experience body image dissatisfaction, anxiety, depression, loneliness, and social isolation (Al-Azri et al., 2014; Giacomo et al., 2016; Rosenberg et al., 2013). They also worry about whether they will be able to work and care for young children, maintain optimal reproductive health, and prevent recurrence when they are in remission (Avis et al., 2016; Haynes, 2017). With regards to financial issues, they experience unemployment due to insurance costs and an inability to find jobs that accommodate their medical needs (Avis et al., 2016). The detrimental health effects and the growing burden of premenopausal breast cancer make it a priority to investigate causal pathways and risk factors that might suggest prevention strategies (Laudisio et al, 2019).

Although the specific etiology of breast cancer is unknown, there are traditional risk factors that have been recognized, including female gender, family history of cancer, age, genetic mutations, dense breasts and reproductive and menstrual history (CDC, 2022; Oh et al., 2017; Srinivisan et al., 2022). However, there are also lifestyle and behavioral risk factors grit running

that individuals can change, including overweight, alcohol consumption, cigarette smoking, an unhealthy diet, and physical inactivity (CDC, 2022; Ellington et al., 2022; Silva-Igua et al., 2020; Surakasula et al., 2014). Several of these risk factors are related to metabolic syndrome (Grundy et al., 2004; Moore et al., 2017).

Metabolic syndrome, also known as Syndrome X or insulin resistance syndrome, increases the risk of developing cardiovascular disease twofold and type II diabetes mellitus fivefold over the next five to ten years (Alberti et al., 2009; Ekinci et al., 2020; Hauner and Hauner, 2014). It is a cluster of disorders comprising dyslipidemia, high blood pressure, insulin resistance, and central obesity (Bhandari et al., 2014; Swarup et al., 2022, Xue and Michels, 2007). Throughout the twentieth century, its meaning has evolved from a cluster of metabolic risk factors into a multifactorial health condition with five interrelated components. Kylin's definition of metabolic syndrome in the 1920s (Alberti et al., 2006) was followed by definitions from Reaven (Alberti et al., 2006), Kaplan (Kaplan, 1989), the World Health Organization (Alberti et al., 2009), the National Cholesterol Education Program Adult Treatment Panel III (Alberti et al., 2009), the American Heart Association and National Heart, Lung, and Blood Institute (Alberti et al., 2009), and the International Diabetes Federation (Alberti et al., 2009). The NCEP ATP III guidelines are the most frequently used diagnostic criteria, which require the presence of three or more of the following five components: a triglyceride level above 150 mg/dl, a waistline of 35 inches or more, a blood pressure of 130/85 mm Hg or higher, a fasting blood glucose level greater than 100 mg/dl, and a high-density blood lipoprotein level cholesterol under 50 mg/dl (Buono et al., 2020; Dibada et al., 2018; Eskandari et al., 2020; Grundy et al., 2004).

The metabolic syndrome prevalence rate generally increases with advancing age. About 40% to 45% of people aged 50 years and older have metabolic syndrome (Hauner and Hauner, 2014). It currently affects about 33% of adults in the United States ("What is Metabolic Syndrome?", 2022) and about 20% to 25% of adults in the world (Belete et al., 2021; Grundy, 2008). The metabolic syndrome prevalence rate is increasing in conjunction with the obesity prevalence rate, which has almost doubled since the 1980s (Dong et al., 2021; Perez-Martinez et al., 2017). Metabolic syndrome and type II diabetes have become more prevalent in industrialized countries (Procopiou and Philippe, 2005). In 2018, more than two-thirds of adults in the United States were overweight or obese (Flegal et al., 2012). About one-third of the global population has obesity, and scientists estimate that 57.8% of the global population will have obesity by 2030 (Dong et al., 2021). Compared to developing countries, developed countries experience higher rates of obesity and metabolic syndrome due to physical inactivity and excessive consumption of saturated fats and refined carbohydrates. However, developing countries are increasingly adopting many of the lifestyle characteristics of wealthy and industrialized countries (Xue and Michels, 2007).

The metabolic syndrome prevalence rate is increasing among not just the general population, but also among younger and premenopausal women. From 2011 to 2016, the metabolic syndrome prevalence rate increased in women and those aged 20 to 39 years by 5% (Hirode and Wong, 2020). About 20% of people younger than 40 years in the United States now have metabolic syndrome, and patterns suggest this proportion will continue to increase over time (Hirode and Wong, 2020). While the obesity, diabetes, and metabolic syndrome rates are increasing, the age of onset for those conditions is steadily decreasing (Kang et al., 2018). This makes it important to focus on premenopausal women.

Literature Review

Previous meta-analyses and systematic reviews have consistently found that metabolic syndrome is associated with a significantly or a moderately increased breast cancer risk in postmenopausal women (Bhandari et al., 2014; Esposito et al., 2012; Esposito et al., 2013; Guo et al., 2019; Pan et al., 2020; Rosato et al., 2011; Pierobon and Frankenfeld, 2013; Srinivasan et al., 2022; Xue and Michels, 2007; Zhao et al., 2020). However, the findings in the literature for premenopausal women remain contradictory and unclear. In general, published meta-analyses on this topic have tended to group women of any age together or provide only limited stratified data on premenopausal women. Only six out of sixteen previous meta-analyses and systematic reviews have investigated the association between metabolic syndrome and breast cancer risk in premenopausal women (Guo et al., 2019; Hernandez et al., 2014; Munsell et al., 2014; Pierobon and Frankenfeld, 2013; Xue and Michels, 2007; Zhao et al., 2020). Three meta-analyses and systematic reviews have found no difference in risk (Hernandez et al., 2014; Xue and Michels, 2007; Zhao et al., 2020), two have found a decreased risk (Guo et al., 2019; Munsell et al., 2014), and one has found an increased risk (Pierobon and Frankenfeld, 2013). These contradictory results point to a gap in the literature. Additionally, the six meta-analyses and systematic reviews were published in 2020 or earlier, and they relied upon studies published in 2018 or earlier. This indicates that they do not include and synthesize the findings from multiple studies that have been conducted and published after 2020. As such, this study aims to investigate whether metabolic syndrome is a risk factor for breast cancer in premenopausal women through a meta-analysis of the existing literature that identifies and synthesizes relevant

articles in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Data and Methods

Identification and Search Strategy

In order to identify published articles that explored whether metabolic syndrome is a risk factor for breast cancer in premenopausal women, a systematic search was conducted in October 2022. The PRISMA flow diagram was used to guide the identification, screening, and inclusion process for this review (Page et al., 2021) (Fig. 1).

Database Searches

After meeting with a research librarian, it was decided that we would conduct this search in the academic library databases Cumulative Index to Nursing and Allied Health Literature (CINAHL), Ovid MEDLINE, PubMed, Scopus, and Web of Sciences. These databases spanned multiple topics that related to my project, including health sciences, life and biomedical sciences, medicine, allied health, and public health. Standardized keywords were then searched across all databases. Boolean search modes were used with term combinations aimed to capture the independent and dependent variables, as well as the population. For the independent variable of metabolic syndrome, the terms “metabolic syndrome” OR “insulin resistance syndrome” OR “syndrome X” were used. For the dependent variable, the terms “breast” AND (“cancer” OR “malignancy” OR “neoplasm” OR “tumor” OR “growth” OR “lump”)) were used.

For the population, the terms “premenopausal women” OR “pre-menopausal women” OR “young women” OR “younger women” OR “menstruating women” were used. All of the above keywords were searched in the aforementioned databases using AND Boolean operators. The

full keyword string can be found at the top of the PRISMA flow diagram (Fig 1). In addition to the key terms mentioned, a filter for the English language was used to narrow the search results to align with the inclusion criteria. No date or geographic setting restrictions were imposed to ensure a review of all relevant studies. Fig. 1 shows the number of articles produced by each database, as well as the duplicates that were removed.

Other Identification Strategies

In order to obtain a comprehensive list of studies, citation searching or snowballing methods were used to identify studies that may not have been captured by traditional database searching. Citations of previously mentioned meta-analyses on the relationship between metabolic syndrome and breast cancer risk in premenopausal women (Guo et al., 2019; Hernandez et al., 2014; Munsell et al., 2014; Pierobon and Frankenfeld, 2013; Xue and Michels, 2007; Zhao et al., 2020) were screened to identify individual studies that align with the inclusion criteria for this review. Articles identified from snowballing were included with articles identified from database searching in the screening process to ensure that they underwent the same process.

Screening and Inclusion

After completing database and snowball searches, there were a combined 460 articles to screen for inclusion and exclusion criteria. These studies were imported into RefWorks to eliminate duplicates and to facilitate the literature screening process of all non-duplicated articles containing titles and abstracts (327 total). In order to be included in this meta-analysis, the study must be in the English language, include metabolic syndrome as the independent variable, include breast cancer incidence as the dependent variable, include premenopausal women as the population, and contain point estimates and 95% confidence intervals. 17 meta-analyses and

systematic reviews and 8 review articles were excluded from this analysis. Additionally, six articles were excluded because they did not contain sufficient data on premenopausal women for a meta-analysis, nine articles because they only contained data on breast cancer mortality instead of incidence, and 57 because they contained data on only one metabolic syndrome component and not metabolic syndrome. The number of articles excluded for each criterion are shown in Figure 1.

After review of titles and abstracts, articles were included only if they aligned with the aforementioned inclusion and exclusion criteria. Following this screening of all search results, ten articles were determined to align with the necessary criteria for this meta-analysis. Of these articles, 4 were case-control studies, and 6 were cohort studies. The included articles utilize data ranging from 1993 to 2014, and they cover 9 countries and geographic regions. The descriptive characteristics of the included articles can be found in Table 1.

Independent and Dependent Variables

The independent variable for this analysis was metabolic syndrome.

JANE MILLER
Separate paragraphs for each major variable, with citations. Discuss whether the included studies all used a consistent definition of MS, and if so, what that definition was. You can refer back to (avoid repeating the details of) definitions given in the intro.

The dependent variable was breast cancer incidence, which measures how commonly or frequently breast cancer occurs in a certain population over a given period by calculating the number of newly diagnosed cases. It is also a measure of risk because it determines the

likelihood of an individual developing breast cancer over a certain time period (Schneider and Lilienfeld, 2015).

Analytical Plan

In order to investigate the association between metabolic syndrome and breast cancer risk in premenopausal women, I will conduct a meta-analysis in Stata of the point estimates and 95% confidence intervals from previously published individual studies on this topic, stratified by two different study designs: case-control and cohort. (Advanced Research Computing Statistical Methods and Data Analytics, 2021).

The generation of meta-analysis estimates in Stata automatically assigned weights based on the precision of the results, pooled odds and risk ratios, confidence intervals, and heterogeneity ratings (Advanced Research Computing Statistical Methods and Data Analytics, 2021). With regards to weighting of studies, studies with larger sample sizes and narrower confidence intervals had more precise results and were thus assigned higher weights. Compared to studies with smaller sample sizes and wider confidence intervals, these studies had a greater contribution to the overall calculation of pooled odds and risk ratios (Cooper, 2016; Petitti, 1999). Pooled odds and risk ratios and confidence intervals were calculated based on the weights of each individual study and can be interpreted as the overall effect size for each of the two study designs.

The heterogeneity rating is a measure used to represent the overall level of variation or diversity between individual studies combined in the meta-analysis (Petitti, 1999). Higher levels of heterogeneity make it difficult to compare results between studies because there may be problematic differences or inconsistencies that are due to something besides chance (Israel and Richter, 2011; Petitti, 1999). The heterogeneity figure used in this analysis was the inconsistency

index I^2, which describes the percentage of variation between studies that is due to heterogeneity. An I^2 value of 75% or higher indicates a substantial level of heterogeneity that can point to potentially problematic inconsistencies between studies. This means that the summary estimate must be interpreted with caution (Cooper, 2016; Haidich, 2010).

encie between studies

JANE MILLER
specify inconsistences IN WHAT? could be study design, sample size, location/year, or things other than variation in odds ratios (or relative risks) which I believe is the aspect of heterogeneity summarized.

Results

Descriptions of Included Studies

After the identification and screening process was completed, ten scholarly articles on the association between metabolic syndrome and breast cancer incidence in premenopausal women were chosen for inclusion in the study. This review includes data that was collected from 1974 to 2014. Studies were conducted in various countries, including China, India, Italy, and Korea. Sample sizes ranged from 50 to 7.8 million premenopausal women or women aged less than 50 years. Descriptive characteristics of the individual studies can be found in Table 1.

The study designs included four case-control studies and six cohort studies.

Meta-Analyses of the Association between Metabolic Syndrome and Breast Cancer Incidence in Premenopausal Women

Case-Control Studies

Two separate meta-analyses were run: one for case-control studies and one for cohort studies. As shown in Figure 2, the first meta-analysis looked at odds ratios of case-control studies. Four case-control studies were included. The resulting meta-analysis produced a pooled odds ratio of 1.5 (the dashed vertical line) and a 95% confidence interval of 1.0 to 2.1. This indicates that premenopausal women who have metabolic syndrome have about 46% higher odds of developing breast cancer than premenopausal women who do not have metabolic syndrome. This result is statistically significant at the 95% confidence level because the pooled confidence interval does not include the null value of 1 (the solid black vertical line), which would indicate that there is no association between metabolic syndrome and breast cancer.

In regard to odds ratios across individual studies, all four case-control studies featured an odds ratio of above one, which indicates an increased breast cancer risk in premenopausal women who have metabolic syndrome, but none were statistically significant (Noh et al., 2013; Ronco et al., 2012; Wani et al., 2017; Xiang et al., 2020). An I^2 test for heterogeneity was conducted, resulting in an I^2 value of 9.1% and p-value of 0.3, which indicates a very small amount of variance or heterogeneity between studies that is not statistically significant (Cooper, 2016).

Cohort Studies

The same procedure was used for the cohort studies. As shown in Figure 3, the second meta-analysis looked at risk ratios of the six cohort studies. The resulting meta-analysis produced a pooled risk ratio of 0.9 and a 95% confidence interval of 0.9 to 0.9. This indicates that premenopausal women who have metabolic syndrome are about 9% less likely to develop breast cancer than premenopausal women who do not have metabolic syndrome, and this result is statistically significant.

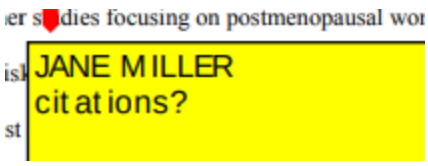
All six cohort studies featured a risk ratio below one, which indicates a decreased breast cancer risk in premenopausal women who have metabolic syndrome. In regard to statistical significance across individual studies, four out of the six studies featured statistically significant odds ratios and confidence intervals (Bjorge et al., 2010; Hwang et al., 2020; Hwang; Hwang). The remaining two studies featured odds ratios and confidence intervals that were not statistically significant (Agnoli et al., 2015; Dibaba et al., 2019). An I^2 test for heterogeneity was conducted, resulting in an I^2 value of 83.9% and p-value of 0.000, which indicates a considerable amount of variance or heterogeneity between studies that is statistically significant (Cooper, 2016).

Discussion

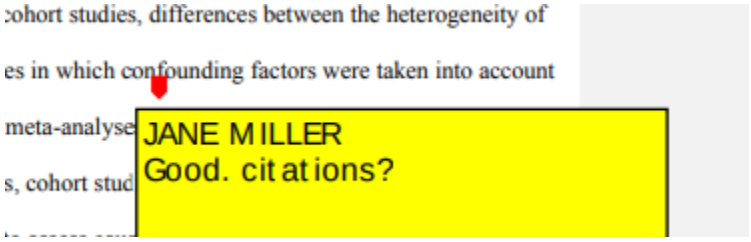
Main Findings

The purpose of this meta-analysis was to examine whether metabolic syndrome is a risk factor for breast cancer in premenopausal women by synthesizing and analyzing the data from multiple published studies, stratified by study design. The two study designs demonstrated conflicting results, with case-control studies supporting the hypothesis that metabolic syndrome was a risk factor for breast cancer in premenopausal women, but cohort studies finding the opposite of the predicted effect. These findings can be generalized to the 9 countries and geographic regions where the studies took place.

The meta-analysis findings for the four case-control studies are consistent with prior meta-analyses of other studies focusing on postmenopausal women because they indicate an increased breast cancer risk.



However, the cohort studies conflict with the literature because they indicate a decreased breast cancer risk. This discrepancy has most likely occurred due to differences between the design of case-control and cohort studies, differences between the heterogeneity of results in the study designs, or differences in which confounding factors were taken into account in the individual studies included in the meta-analyses.



Compared to case-control studies, cohort studies have higher internal validity, which is the extent to which a study can be used to assess causality (Schneider and Lilienfeld, 2015). Cohort studies also provide more accurate results about the causal relationship between metabolic syndrome and breast cancer because they follow individuals from the exposure of metabolic syndrome to the development of breast cancer. Since cohort studies ensure that metabolic syndrome precedes breast cancer development, they are less prone to recall bias and are thus more reliable than case-control studies (Lizama et al., 2017). Recall bias occurs when subjects do not accurately recall or acknowledge previous exposures (Althubaiti, 2016; Schneider and Lilienfeld, 2015). Cohort studies are prospective (concurrent) studies, meaning that they identify exposure status in the present and follow the subjects into their future to determine their health outcomes (Schneider and Lilienfeld, 2015). However, case-control studies are retrospective (case-referent), meaning that they enroll subjects based on their disease status

(cases have disease, controls do not) and then determine if the subjects had the exposure to estimate the association between the exposure and the health outcome (Schneider and Lilienfeld, 2015).

However, the pooled risk ratio for the cohort studies contained a high level of heterogeneity and lower agreement, while the pooled odds ratio for the case-control studies contained a low level of heterogeneity and higher agreement. Based on the heterogeneity results, we can be more confident in the case-control study design.

The differences in results between study designs and the differences in levels of heterogeneity could both be attributable to the differences in the types of confounding factors studies controlled for, and how. Confounding factors are unmeasured additional variables that influence the association between an exposure and an outcome, leading to an inaccurate comparison (Cooper, 2016; Schneider and Lilienfeld, 2015). Different studies took into account different sets of confounding factors, which might explain some of the heterogeneity.

Both case-control and cohort studies use statistical methods to control for potential confounding factors. Case-control studies factor out the effects of potential confounders by matching cases to controls based on shared characteristics. Overall, the case-control studies adjusted more for pregnancy-related cofactors, while the cohort studies adjusted more for lifestyle or behavioral cofactors. Not only were there differences between studies of different designs, but there were also differences within studies of the same design. All of the case-control studies examined the following confounding factors: age at menarche, family history of breast cancer, number of pregnancies, and age (Noh et al., 2013; Ronco et al., 2012; Wani et al., 2017; Xiang et al., 2020). Three of the four case-control studies also examined breastfeeding as a confounding factor (Ronco et al., 2012; Wani et al., 2017; Xiang et al., 2020). All of the cohort

studies examined the following confounding factors: smoking and age at measurement (Agnoli et al., 2015; Bjorge et al., 2010; Dibaba et al., 2018; Hwang et al., 2020; Hwang et al., 2020; Hwang et al., 2020). Five of the six cohort studies also examined physical activity as a confounding factor (Agnoli et al., 2015; Dibaba et al., 2018; Hwang et al., 2020; Hwang et al., 2020; Hwang et al., 2020). Four of the six cohort studies also examined alcohol intake as a confounding factor (Agnoli et al., 2015; Hwang et al., 2020; Hwang et al., 2020; Hwang et al., 2020). Descriptive characteristics of the confounding factors can be found in Table 2.

Strengths

The main strength is the meta-analysis method, which is more advantageous than an individual study because it quantifies the difference between smaller individual studies to show a pooled effect size. It synthesizes and explores trends and patterns among many individual studies that vary based on sampling methods, dates, geographic locations, and study designs (Cooper, 2016; Petitti, 1999). It increases the statistical power, generalizability if the studies represent a range of populations, and accuracy of results by producing a smaller standard error and a narrower confidence interval (Petitti, 1999). It produces a more precise estimate of the effect of a risk factor for a disease than any individual study that contributes to the pooled analysis (Haidich, 2010; Lee, 2019). It can settle controversies that result from studies with conflicting results (Lee, 2019). A meta-analysis is also more advantageous than a qualitative literature review because it is more objective and less likely to be influenced by the author's opinion (Lee, 2019). It uses a systematic and explicit approach outlined in the PRISMA guidelines to identify eligible articles (Petitti, 1999).The systemic nature of this approach decreases bias and merit, and the explicit nature of this approach improves replicability and transparency (Cooper, 2016; Petitti, 1999). This approach also incorporates the use of precise inclusion and exclusion criteria

and the use of various databases that were relevant to my research question, such as CINAHL, OVID Medline, PubMed, Scopus, and Web of Science (Haidich, 2010). Meta-analyses are at the top of the hierarchy of evidence, which ranks the strength of results obtained from medical research (Haidich, 2010; University of Canberra Library, 2022).

Secondly, the results in this study were stratified by study design, which allowed for comparison between different study designs because different study designs will yield different types of point estimates and different results. A meta-analysis that combines different types of studies would produce a summary effect size that ignores important differences between studies (Lee, 2019). To the best of our knowledge, this is the first meta-analysis that explores how the association between metabolic syndrome and breast cancer in premenopausal women varies by study design. Thirdly, this study fills in a gap from previous research by studying premenopausal women, who have been understudied.

Limitations

This meta-analysis includes several limitations, which are attributable to time constraints, data limitations, and study design limitations. First, a sensitivity analysis could not be performed to analyze the role of heterogeneity in the cohort studies due to the time constraints for this project. A sensitivity analysis is a repeat of the primary meta-analysis, substituting alternative ranges of values for unclear decisions. It is an important component of a meta-analysis because it assesses the stability of the conclusions by exploring the effect of including or excluding studies based on methodological quality, variance, and sample size (Petitti, 1999). It investigates the effect of certain studies that are highly influential in the analysis (Haidich, 2010). Secondly, the meta-analysis was based on data only from observational studies, not experimental studies, which decreased the quality of the evidence (Guyatt et al., 2008; Hernandez et al., 2014).

However, due to the nature of the topic, there will likely not be experimental studies because researchers cannot "give" women the exposure of metabolic syndrome. That is not ethical nor feasible, since metabolic syndrome is a condition and combination of risk factors people develop over time. Additionally, there was a small sample size in several of the studies as well as the meta-analysis overall, which increased the chances of obtaining inconclusive results that were influenced by confounding factors.

One confounding factor in the cohort studies was age at measurement. Four of the six cohort studies categorized premenopausal women as women aged fifty years and younger (Bjorge et al., 2010; Hwang et al., 2020; Hwang et al., 2020; Hwang et al., 2020). However, it is possible that the age marker for what constitutes menopause is not accurate since all women undergo menopause at different ages. The interchangeable use of the terms ‘menopausal status’ and ‘age’ may lead to misclassification bias, which occurs when study participants are categorized into an incorrect category. This could change the observed association between metabolic syndrome and breast cancer (Centre for Evidence-Based Medicine, 2023). The studies should track women only by their actual menopausal status instead of by their age because stratifying by age might lead to inaccurate results. Furthermore, three of the six cohort studies examined the following breast cancer subtypes: invasive and in situ breast cancer, instead of breast cancer in general (Hwang et al., Hwang et al., 2020; Hwang et al., 2020). One of the four case-control studies also examined the following breast cancer subtypes: estrogen receptor-positive (ER+)/ progesterone receptor-positive (PR+), ER+/PR-, and ER-/PR- breast cancer (Xiang et al., 2018).

Implications for Future Research, Policy, and Practice

Overall, this study does not clearly indicate whether metabolic syndrome is a risk factor or a protective factor for breast cancer in premenopausal women due to the differing results between study designs. However, it builds upon existing knowledge of how modifiable risk factors influence breast cancer incidence, which can inform the implementation of metabolic syndrome and breast cancer prevention and management strategies, as well as health education programs. A better understanding of the relationship between metabolic syndrome and breast cancer in premenopausal women can play an integral role in breast cancer primary prevention and secondary prevention.

Primary prevention focuses on reducing breast cancer incidence rates in the population records by intervening on the shared behavioral and lifestyle risk factors for metabolic syndrome and breast cancer. Some of those risk factors include physical inactivity, alcohol consumption, obesity, hypertension, insulin resistance, and an unhealthy diet that is high in red meat and total fat and low in fruits and vegetables (Akinyemiju et al., 2022; Alberti et al., 2009; Eskandari et al., 2020; Uzunlulu et al., 2016). Healthcare providers should encourage a healthy lifestyle in preventative settings (Gianturco et al., 2020). Some lifestyle changes individuals should make to reduce their risk for breast cancer include achieving and maintaining a healthy weight, engaging in at least 150 minutes of moderate-intensity physical activity each week, managing stress, limiting alcohol intake, and quitting or avoiding tobacco use (American Heart Association, 2023; Gezgen et al., 2012; Gianturco et al., 2020; Jevtic et al., 2010; NHLBI, 2022; Perez-Martinez et al., 2017). Individuals should also follow a healthy and balanced diet, such as the DASH (Dietary Approaches to Stop Hypertension) eating plan, which includes fruits, vegetables, and whole grains and limits saturated fats, sodium (salt), added sugars, and alcohol (NHLBI, 2022; Perez-Martinez et al., 2017). Individuals who already have metabolic syndrome should manage

their condition by taking medications that target the following five components: high blood pressure, high blood sugar, high blood triglyceride levels, low HDL levels, and obesity (NHLBI, 2022). A combination of medications and lifestyle changes will reduce breast cancer risk.

Secondary prevention focuses on preventing the development of breast cancer symptoms through the appropriate use of screening and early diagnostic tools. Healthcare providers must identify individual patients with metabolic syndrome and work with patients to reduce lifestyle risk factors and improve health outcomes (Alberti et al., 2009). Screening guidelines include checking for blood pressure, blood sugar, cholesterol, triglyceride, and BMI/obesity (NHLBI, 2022). From an intervention point of view, it is important to identify premenopausal women with metabolic syndrome as a high-risk group for breast cancer because breast cancer risk increases across the lifespan (Surakasula et al., 2014). The younger women are, the more time they have to make specific lifestyle changes that will combat metabolic syndrome and reduce their breast cancer risk, such as maintaining a healthy weight, engaging in more physical activity, eating a plant-based diet, and seeking treatment for dyslipidemia, hypertension, and diabetes (Akinyemiju et al., 2022; Dibaba et al., 2018; Yuan et al., 2021). These are interventions that have proven to be effective in reducing postmenopausal breast cancer risk, and evidence suggests that they will also be effective in reducing premenopausal breast cancer risk (Akinyemiju et al., 2022; Dibaba et al., 2018; Perez-Martinez et al., 2017). Routine breast cancer screening can detect breast cancer at an early stage for postmenopausal female patients with metabolic syndrome, who are a high-risk population (Zhao et al., 2020). Lifestyle modifications can improve prognosis and reduce the risk of adverse outcomes and mortality for individuals who have already been diagnosed with breast cancer (Hamer and Warner, 2017).

This study also highlights potential priorities for future research on whether metabolic syndrome is a risk factor for breast cancer in premenopausal women. First, future studies should employ a sensitivity analysis to explore the high level of heterogeneity in the results of the cohort studies and to detect biases that are inherent in cohort studies. Through the analysis of alternating combinations of studies, a sensitivity analysis can investigate the effect of excluding studies that focus on breast cancer subtypes, as well as studies that measure metabolic syndrome differently, on the overall pooled effect estimate. An understanding of the sources of the heterogeneity that exists in a group of studies can lead to the effective development of prevention and treatment strategies and the identification of new research topics (Haidich, 2010).

Secondly, future studies should examine the role of confounding and mediating factors, such as race, ethnicity, breastfeeding, parity, income residence, physical inactivity, alcohol intake, tobacco smoking, unhealthy dietary habits, and use of hormone replacement therapy, in the association between metabolic syndrome and breast cancer risk. Depending on the data, this may be through stratification or adjustment in our models. Metabolic syndrome and breast cancer share several risk factors, including physical inactivity, alcohol intake, tobacco smoking, and unhealthy dietary habits (American Heart Association, 2023; CDC, 2022; Giovannucci et al., 2010; Porto et al., 2011; Xue and Michels, 2007). Thus, the observed association between metabolic syndrome and breast cancer risk may be partly attributed to the clustering of the two conditions as a result of shared risk factors (Michels et al., 2003; Weiderpass et al., 1997; Wideroff et al., 1997). Thirdly, future studies should explore the association between individual components of metabolic syndrome and breast cancer risk to determine the extent to which each component influences breast cancer risk as a distinct entity (Rose et al., 2007). This would lead to targeted prevention programs and policies focusing on certain components that are shown to

be key contributors to breast cancer risk and pathways. Nine meta-analyses found associations between the individual metabolic syndrome components and an increased breast cancer risk in postmenopausal women (Boyle et al., 2012; Esposito et al., 2013; Fadhila et al., 2021; Guo et al., 2019; Han et al., 2017; Munsell et al., 2014; Rosato et al., 2011; Pierobon and Frankenfeld, 2013; Renehan et al., 2008; Srinivisan et al., 2022; Xue and Michels, 2007; Zhao et al., 2020,) and one meta-analysis did not observe an association between elevated triglycerides and breast cancer risk (Wu et al., 2021). One did not find an association between high blood pressure and breast cancer risk (Seretis et al., 2019). One did not find an association for diabetes (Sellers et al., 1994). Among postmenopausal women, obesity and diabetes appear to be the top two components contributing to breast cancer risk. It is unclear from the existing meta-analyses if these same components are associated with increased breast cancer risk in premenopausal women.

In addition to individual components, studies should examine whether the number of components affects breast cancer risk. This would require measuring metabolic syndrome as an ordinal variable instead of a nominal variable. Earlier studies have studied the number of metabolic syndrome components, but they have lumped together postmenopausal women and premenopausal women. Five out of ten meta-analyses have demonstrated that metabolic syndrome has a greater effect on breast cancer risk in postmenopausal women as the number of metabolic syndrome components increases (Bhandari et al., 2014; Esposito et al., 2013; Guo et al., 2019; Rosato et al., 2011; Zhao et al., 2020). With regards to premenopausal women, there is controversy over whether the effects of metabolic syndrome components are additive, meaning that the combination of the metabolic syndrome components contributes to the same breast cancer risk as the sum of each individual component alone, or synergistic, meaning that the

combination of the metabolic syndrome components contributes to a higher breast cancer risk than the sum of each individual component (Uzunlulu et al., 2016). Several studies have suggested that the risk associated with multiple metabolic syndrome components is synergistic, and that the biological mechanisms linking metabolic syndrome components and breast cancer risk are interconnected (Chen et al., 2012; Lamar et al., 2015; Osaki et al., 2012; Rosato et al., 2011; Zeller et al., 2015). The nature of the meta-analysis may make it easier to determine if there is a synergistic association between the metabolic syndrome components in breast cancer risk.

Another avenue for future research is to examine the role of menopause in the changing direction of the association. Although previous literature has indicated that metabolic syndrome is a risk factor for breast cancer in postmenopausal women (Bhandari et al., 2014; Esposito et al., 2012; Esposito et al., 2013; Guo et al., 2019; Pan et al., 2020; Pierobon and Frankenfeld, 2013; Rosato et al., 2011; Srinivasan et al., 2022; Xue and Michels, 2007; Zhao et al., 2020), the cohort studies in this meta-analysis indicate that metabolic syndrome is a protective factor for breast cancer in premenopausal women (Agnoli et al, 2015; Bjorge et al., 2010; Dibaba et al., 2019; Hwang et al., 2020; Hwang; Hwang). Additional case-control and cohort studies from different databases than those I found, some aspects of which could use meta-analysis or systematic review to examine larger patterns in breast cancer risk, should aim to understand the biological mechanisms that cause the risk of breast cancer in women with metabolic syndrome to change direction after menopause. It would also be useful to study perimenopausal women, whose bodies are making the natural transition to menopause (Mayo Clinic, 2023). Since the amount of estrogen circulating in the body is a risk factor for ER+ breast cancer (Dall and Britt, 2017; Srinivasan et al., 2022; Susan G. Komen for the Cure, 2017), future studies should explore the

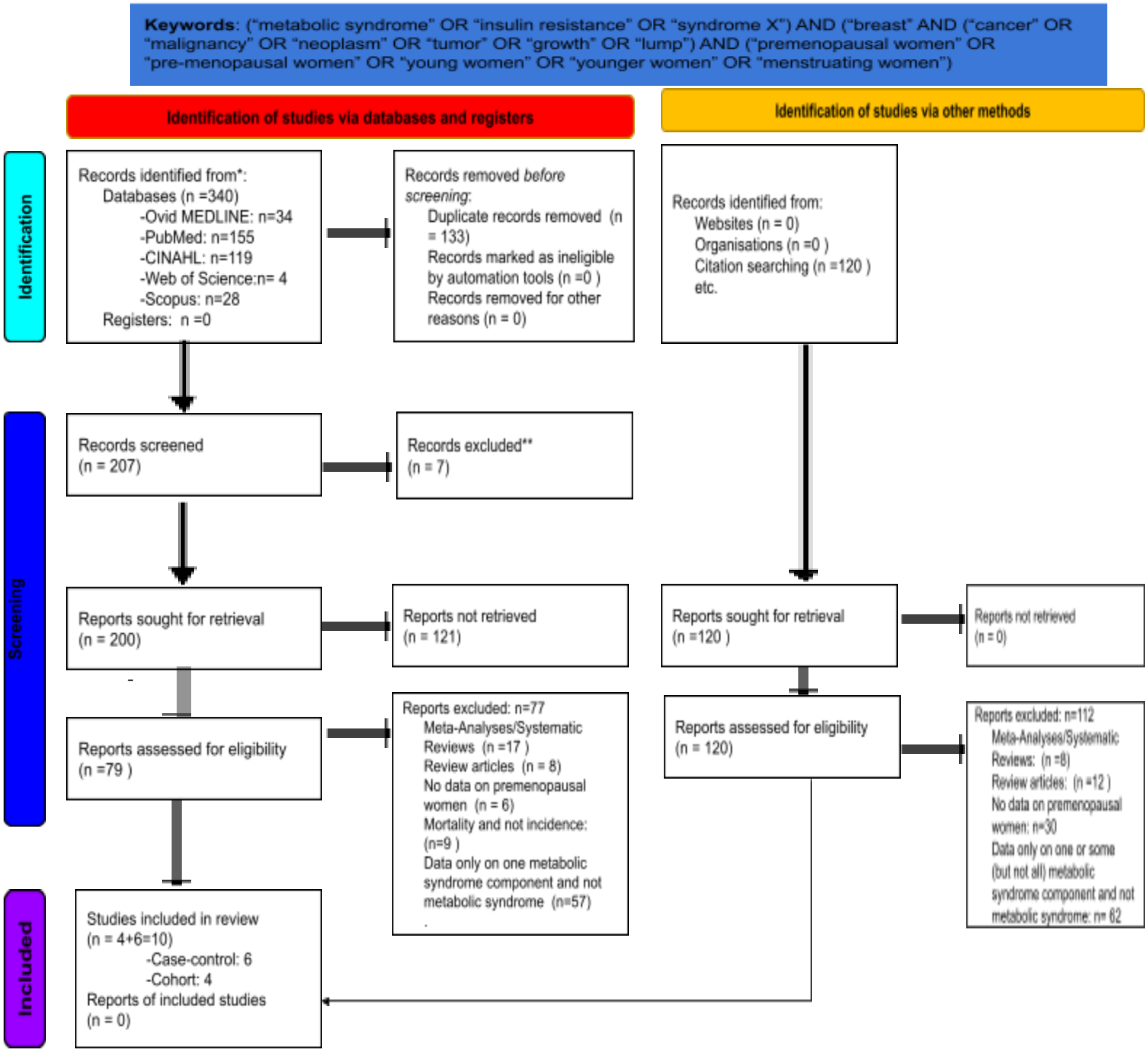
role of menopause in ER+ breast cancer risk for women with metabolic syndrome. A better understanding of the biological mechanisms and pathways underlying the relationships between menopause, metabolic syndrome, and breast cancer risk will ultimately pave the path for evidence-based public health prevention programs.

Conclusion

In concordance with previous literature on postmenopausal women, the case-control studies in this meta-analysis indicate increasing odds of developing breast cancer in premenopausal women with metabolic syndrome. However, in contrast with previous literature, the cohort studies in this meta-analysis indicate a decreased risk of developing breast cancer in premenopausal women with metabolic syndrome. This meta-analysis highlights the importance of evidence-based breast cancer prevention programs that target modifiable risk factors through lifestyle and clinical interventions to reduce breast cancer incidence rates in both premenopausal and postmenopausal women.

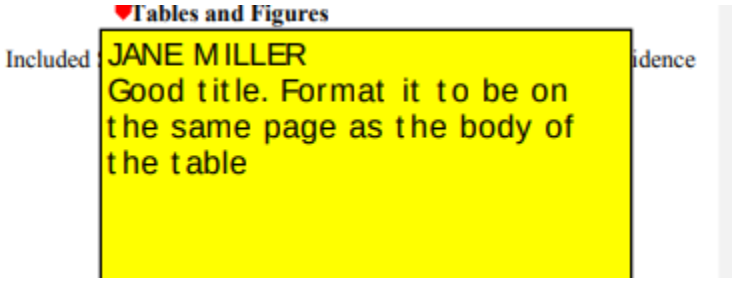
Future studies on this topic stratified by individual components of metabolic syndrome, confounding factors, age, menopausal status, and breast cancer subtypes, could clarify the biological mechanisms underlying the role of menopause in the altering direction of breast cancer risk for women with metabolic syndrome.

Figure 1: PRISMA Flow Diagram



Tables and Figures

Table 1: Descriptions of Included Studies on the Association between Metabolic Syndrome and Breast Cancer Incidence in Premenopausal Women



Date		
Publication Date	**Date of Data Collection**	**Country**
Case-Control Studies		
	2012-2013	China
	2012-2014	India
	1995-2011	Korea
	2004-2010	Uruguay
Cohort Studies		
	1974-2005	Austria, Norway
	1993-2008	Italy
	2009-2014	Korea
	2009-2014	Korea
	2009-2014	Korea
	2009-2014	United States

Table 2: Breast Cancer Incidence in Case-Control and Cohort Studies Included in a 2023 Meta-Analysis

Author	**Publication Date**	**Breast Cancer Incidence**
Xiang	2020	595 cases per 1127 people
Wani	2017	50 cases per 100 people
Noh	2013	270 cases per 810 people
Ronco	2012	367 cases
Bjorge	2010	4,862 cases per 2,892,465 people
Agnoli	2015	593 cases per 22,494 people
Hwang	2020	87,747 cases per 13,377,349 people (invasive and in situ breast cancer)
Hwang	2020	79,447 cases per 13,456,796 people (invasive breast cancer)
Hwang	2020	8,300 cases per 13,377,349 people (in situ breast cancer)

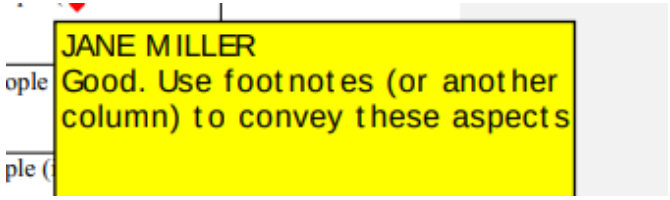
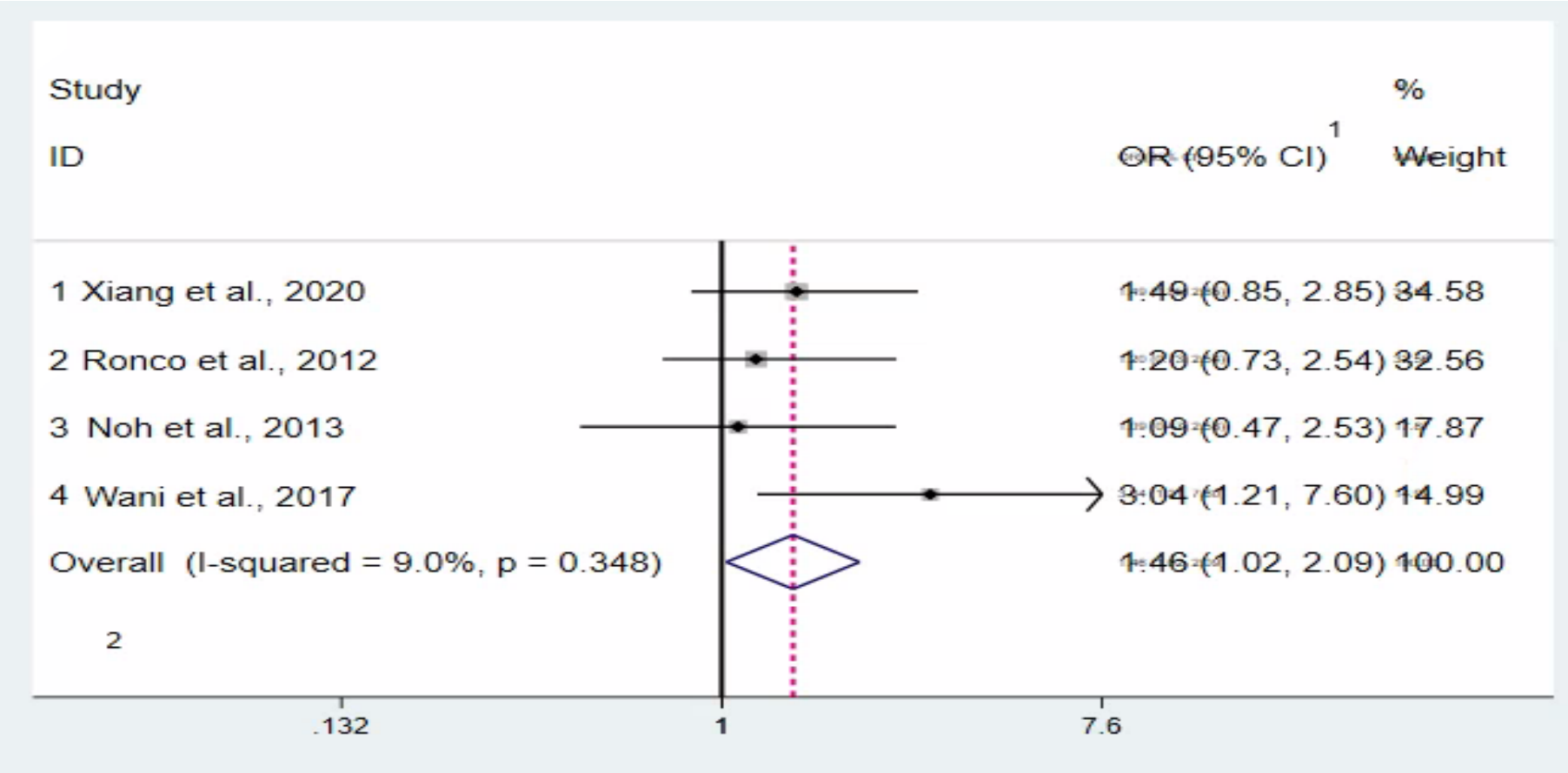


Table 2: Confounding Factors Controlled For

Case-control (4)		
	Confounding Factor	**# of Studies**
	Age at menarche	4
	Family history of breast cancer	4
	# pregnancies	4
	Age	4
	Breastfeeding	3
Cohort (6)		
	Smoking	6
	Age at measurement	6
	Physical Activity	5
	Alcohol intake	4

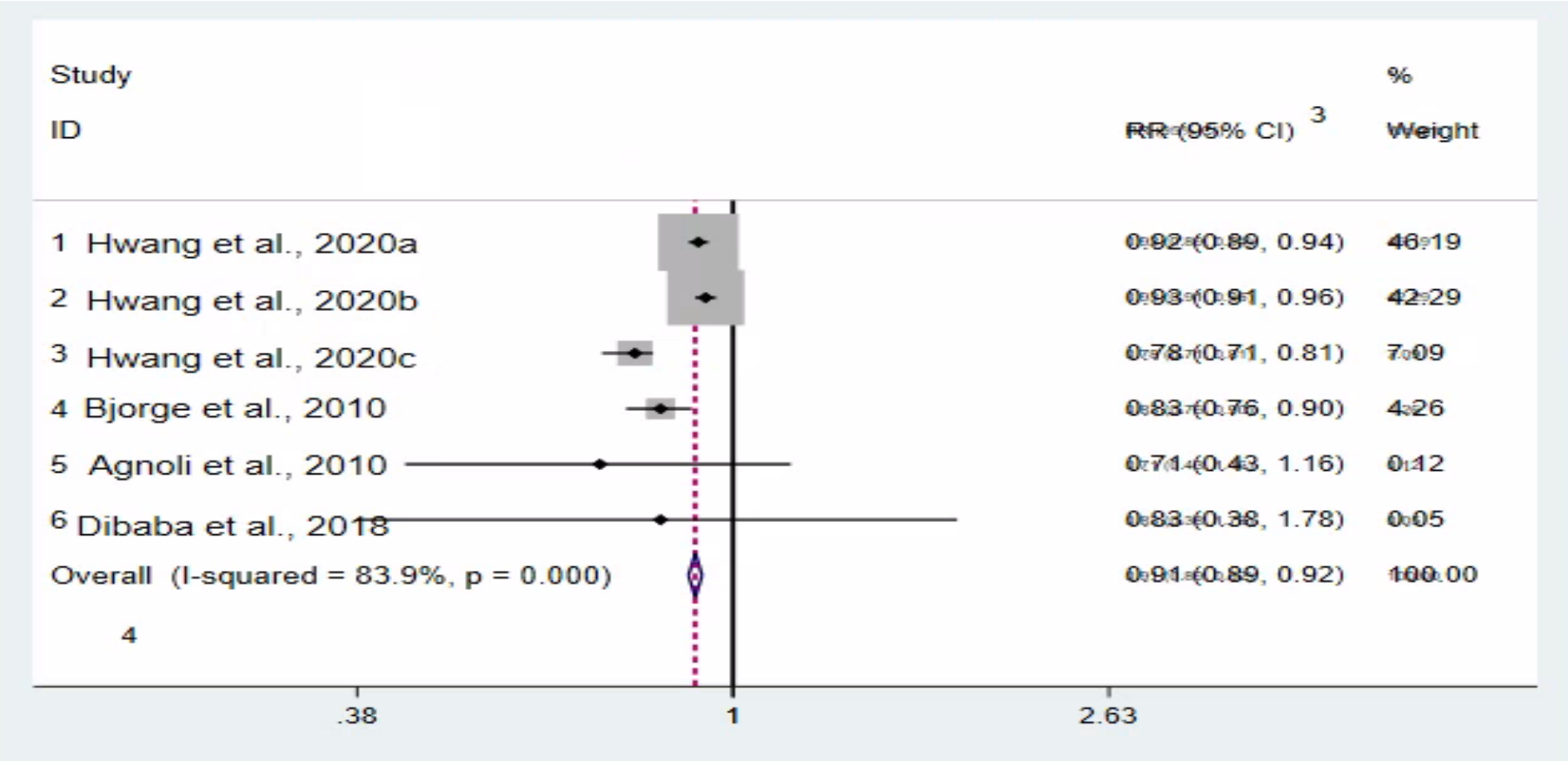
Figure 2: Meta-analysis of the Association between Metabolic Syndrome and Breast Cancer Incidence in Premenopausal Women: Case-Control Studies



[1] OR (95% CI) = Odds Ratio (95% Confidence Interval)

[2] I^2 = 9.0%, p=0.348

Figure 3: Meta-analysis of the Association between Metabolic Syndrome and Breast Cancer Incidence in Premenopausal Women: Cohort Studies



[3] RR (95% CI) = Risk Ratio (95% Confidence Interval)

[4] I^2 = 83.9%, p=0.000

References

Agnoli, C., Grioni, S., Sieri, S., Sacerdote, C., Ricceri, F., Tumino, R., Frasca, G., Pala, V., Mattiello, A., Chiodini, P., Iacoviello, L., De Curtis, A., Panico, S., & Krogh, V. (2015). Metabolic syndrome and breast cancer risk: A case-cohort study nested in a multicentre Italian cohort. *PLoS ONE, 10*(6), e0128891. https://doi-org.proxy.libraries.rutgers.edu/10.1371/journal.pone.0128891

Akinyemiju, T., Oyekunle, T., Salako, O., Gupta, A., Alatise, O., Ogun, G., Adeniyi, A., Deveaux, A., Hall, A., Ayandipo, O., Olajide, T., Olasehinde, O., Arowolo, O., Adisa, A., Afuwape, O., Olusanya, A., Adegoke, A., Tollefsbol, T. O., Arnett, D., . . . Daramola, A. (2022). Metabolic Syndrome and Risk of Breast Cancer by Molecular Subtype: Analysis of the MEND Study. Clinical Breast Cancer, 22(4), e463-e472. 10.1016/j.clbc.2021.11.004

Al-Azri, M. A., Awisi, H. A., Rasbi, S. A., Shafie, K. E., Hinai, M. A., Habsi, H. A., & Moundhri, M. A. (2014). Psychosocial Impact of Breast Cancer Diagnosis among Omani Women. *Oman Medical Journal, 29*(6), 437-444. 10.5001/omj.2014.115

Alberti, K. G. M. M., Zimmet, P., & Shaw, J. (May 2006). Metabolic syndrome-a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Paper presented at the, *23*(5) 469-480. 10.1111/j.1464-5491.2006.01858.x https://api.istex.fr/ark:/67375/WNG-5XKNJ0KD-F/fulltext.pdf

Alberti, K. G. M. M., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., Fruchart, J., James, W. P. T., Loria, C. M., & Smith, S. C., Jr. (2009). Harmonizing the Metabolic Syndrome: A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute;

American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation, 120*(16), 1640-1645. 10.1161/CIRCULATIONAHA.109.192644

Alkabban, F. M., & Ferguson, T. (2023). *Breast Cancer.* StatPearls Publishing LLC. https://www-ncbi-nlm-nih-gov.proxy.libraries.rutgers.edu/books/NBK482286/

Althubaiti, A. (2016). Information bias in health research: definition, pitfalls, and adjustment methods. *Journal of Multidisciplinary Healthcare, 9*(1), 211-217. 10.2147/JMDH.S104807

Anders, C. K., Hsu, D. S., Broadwater, G., Acharya, C. R., Foekens, J., Zhang, Y., Wang, Y. X., Marcom, P. K., Marks, J. R., Febbo, P. G., Nevins, J. R., Potti, A., & Blackwell, K. L. (2008). Young Age at Diagnosis Correlates With Worse Prognosis and Defines a Subset of Breast Cancers With Shared Patterns of Gene Expression. *Journal of Clinical Oncology, 26*(20), 3324-3330. 10.1200/JCO.2007.14.2471

Avis, N. E., Crawford, S., & Manuel, J. (2005). Quality of Life Among Younger Women With Breast Cancer. Journal of Clinical Oncology, 23(15), 3322-3330. 10.1200/JCO.2005.05.130

Belete, R., Ataro, Z., Abdu, A., & Sheleme, M. (2021). Global prevalence of metabolic syndrome among patients with type I diabetes mellitus: a systematic review and meta-analysis. *Diabetology and Metabolic Syndrome, 13*(1), 25. 10.1186/s13098-021-00641-8

Bhandari, R., Kelley, G. A., Hartley, T. A., & Rockett, I. R. H. (2014). Metabolic Syndrome Is Associated with Increased Breast Cancer Risk: A Systematic Review with

Meta-Analysis. *International Journal of Breast Cancer, 2014*(2014), 189384-13. 10.1155/2014/189384

Bjorge, T., Lukanova, A., Concin, H., Hallmans, G., Haggstrom, C., Stattin, P., Engeland, A., Jonsson, H., Tretli, S., Ulmer, H., Manjer, J., Stocks, T., Selmer, R., Nagel, G., & Almquist, M. (2010). Metabolic syndrome and breast cancer in the me-can (metabolic syndrome and cancer) project. *Cancer Epidemiology, Biomarkers & Prevention, 19*(7), 1737-1745. https://doi-org.proxy.libraries.rutgers.edu/10.1158/1055-9965.EPI-10-0230

Boyle, P., Boniol, M., Pasterik M., Smans, M., Curado, M. P., Mullie, P., Gandini, S., Bota, M., Bolli, G. B., Rosenstock, J., Autier, P., Koechlin, A., Robertson, C., Valentini, F., Coppens, K., Fairley, L. -., Zheng, T., & Zhang, Y. (2012). Diabetes and breast cancer risk: a meta-analysis. *Breast Cancer Research and Treatment, 107*(9), 1608-1617. 10.1038/bjc.2012.414

Breast Cancer. (2023). World Health Organization. https://www.who.int/news-room/fact-sheets/detail/breast-cancer

Breast Cancer Facts & Figures . (2023). National Breast Cancer Coalition. https://www.stopbreastcancer.org/information-center/facts-figures/

Breast Cancer In Young Women. (2023). Centers for Disease Control and Prevention. https://www.cdc.gov/cancer/breast/young_women/bringyourbrave/breast_cancer_young_women/index.htm#:~:text=Although%20breast%20cancer%20mostly%20occurs,than%2045%20years%20of%20age.

Buono, G., Crispo, A., Giuliano, M., De Angelis, C., Schettini, F., Forestieri, V., Lauria, R., De Laurentiis, M., De Placido, P., Rea, C. G., Pacilio, C., Esposito, E., Grimaldi, M., Nocerino, F., Porciello, G., Giudice, A., Amore, A., Minopoli, A., Botti, G., . . . Arpino,

G. (2020). Metabolic syndrome and early stage breast cancer outcome: results from a prospective observational study. *Breast Cancer Research and Treatment, 182*(2), 401-409. 10.1007/s10549-020-05701-7

Carreira, H., Williams, R., Funston, G., Stanway, S., & Bhaskaran, K. (2021). Associations between breast cancer survivorship and adverse mental health outcomes: A matched population-based cohort study in the United Kingdom. *PLoS Medicine, 18*(1), e1003504. 10.1371/journal.pmed.1003504

Catalogue of bias: Misclassification bias. (2023). Centre for Evidence-Based Medicine. https://catalogofbias.org/biases/misclassification-bias/#:~:text=Occurs%20when%20a%20study%20participant,or%20research%20outcome%20of%20interest.

Chen, W., Lu, F., Liu, S., DU, J., Wang, J., Qian, Y., Shen, C., Jin, G., Hu, Z., & Shen, H. (2012). Cancer risk and key components of metabolic syndrome: a population-based prospective cohort study in Chinese. *Chinese Medical Journal, 125*(3), 481-485. 10.3760/cma.j.issn.0366-6999.2012.03.015

Chollet-Hinton, L., Anders, C. K., Tse, C., Bell, M. B., Yang, Y. C., Carey, L. A., Olshan, A. F., & Troester, M. A. (2016). Breast cancer biologic and etiologic heterogeneity by young age and menopausal status in the Carolina Breast Cancer Study: a case-control study. Breast Cancer Research: BCR, 18(1), 79. 10.1186/s13058-016-0736-y

Cooper, H. (2016). *Research Synthesis and Meta-Analysis* (Fifth Edition ed.). SAGE Publications, Incorporated. 10.4135/9781071878644

Dall, G. V., & Britt, K. L. (2017). Estrogen Effects on the Mammary Gland in Early and Late Life and Breast Cancer Risk. *Frontiers in Oncology, 7*, 110. 10.3389/fonc.2017.00110

Dibaba, D. T., Ogunsina, K., Braithwaite, D., & Akinyemiju, T. (2018). Metabolic syndrome and risk of breast cancer mortality by menopause, obesity, and subtype. Breast Cancer Research and Treatment, 174(1), 209-218. 10.1007/s10549-018-5056-8

Dong, S., Wang, Z., Shen, K., & Chen, X. (2021). Metabolic Syndrome and Breast Cancer: Prevalence, Treatment Response, and Prognosis. *Frontiers in Oncology, 11*, 629666. 10.3389/fonc.2021.629666

Dutheil, F., Aubert, C., Pereira, B., Dambrun, M., Moustafa, F., Mermillod, M., Baker, J. S., Trousselard, M., Lesage, F., & Navel, V. (2019). Suicide among physicians and health-care workers: A systematic review and meta-analysis. *PLoS ONE, 14*(12), e0226361. 10.1371/journal.pone.0226361

Ekinci, O., Eren, T., Kurtoglu Yakici, M., Gapbarov, A., Aydemir, M. A., Saglam, Z. A., & Alimoglu, O. (2020). Relationship Between Metabolic Syndrome and Postmenopausal Breast Cancer/Relacion del sindrome metabolico con el cancer de mama posmenopausico. Cirugia Española, 98(9), 540. 10.1016/j.cireng.2020.06.009

Ellington, T. D., Miller, J. W., Henley, S. J., Wilson, R. J., Wu, M., & Richardson, L. C. (2022). Trends in Breast Cancer Incidence, by Race, Ethnicity, and Age Among Women Aged ≥20 Years — United States, 1999–2018. *MMWR. Morbidity and Mortality Weekly Report, 71*(2), 43-47. 10.15585/mmwr.mm7102a2

Eskandari, D., Khodabandehloo, N., Gholami, A., Samadanifard, H., & Hejrati, A. (2020). Investigation of the association between metabolic syndrome and breast cancer patients. *European Journal of Translational Myology, 30*(1), 187-193. 10.4081/ejtm.2019.8776

Esposito, K., Chiodini, P., Colao, A., Lenzi, A., & Giugliano, D. (2012). Metabolic Syndrome and Risk of Cancer: A systematic review and meta-analysis. *Diabetes Care, 35*(11), 2402-2411. 10.2337/dc12-0336

Esposito, K., Chiodini, P., Colao, A., Lenzi, A., & Giugliano, D. (2013). Metabolic Syndrome and Risk of Cancer: A systematic review and meta-analysis. *Diabetes Care, 35*(11), 2402-2411. 10.2337/dc12-0336

Fadhila, S. N., Murti, B., & Widyaningsih, V. (2021). Overweight and Obesity as Risk Factors of Breast Cancer in Premenopausal and Postmenopausal Women: Meta-Analysis. *Journal of Maternal and Child Health (Surakarta), 6*(6), 678-689. 10.26911/thejmch.2021.06.06.06

Flegal, K. M., Carroll, M. D., Kit, B. K., & Ogden, C. L. (2012). Prevalence of Obesity and Trends in the Distribution of Body Mass Index Among US Adults, 1999-2010. *American Journal of Health Promotion, 307*(5), 491-497. 10.1001/jama.2012.39

Gezgen, G., Roach, E. C., Kizilarslanoglu, M. C., Petekkaya, I., & Altundag, K. (2012). Metabolic syndrome and breast cancer: an overview. *Journal of B.U. ON., 17*(2), 223-229. https://www-ncbi-nlm-nih-gov.proxy.libraries.rutgers.edu/pubmed/22740197

Giacomo, D. D., Cannita, K., Ranieri, J., Cocciolone, V., Passafiume, D., & Ficorella, C. (2016). Breast cancer and psychological resilience among young women. *Journal of Psychopathology, 22*, 191-195. https://jpsychopathol.it/wp-content/uploads/2016/12/05_DiGiacomo-1.pdf

Gianturco, V., Gianturco, L., Regnoli, R., Bodini, B. D., Turiel, M., Trapani, M., Bini, F., & De Angelis, G. (2020). Healthy Promotion for Fighting Metabolic Syndrome: Insights from Multi-Center HeRO-FiT Cohort. *International Journal of Environmental Research and Public Health, 17*(15), 5424. 10.3390/ijerph17155424

Giovannucci, E., Harlan, D. M., Archer, M. C., Bergenstal, R. M., Gapstur, S. M., Habel, L. A., Pollak, M., Regensteiner, J. G., & Yee, D. (2010). Diabetes and Cancer: A consensus report. *Diabetes Care, 33*(7), 1674-1685. 10.2337/dc10-0666

Grundy, S. M. (2008). Metabolic Syndrome Pandemic. *Arteriosclerosis, Thrombosis, and Vascular Biology, 28*(4), 629-636. 10.1161/ATVBAHA.107.151092

Grundy, S. M., Brewer, H. B., Jr, Cleeman, J. I., Smith, S. C., Jr, Lenfant, C., & Conference Participants. (2004). Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Arteriosclerosis, Thrombosis, and Vascular Biology, 24*(2), e13-e18. 10.1161/01.ATV.0000111245.75752.C6

Guo, M., Liu, T., Li, P., Wang, T., Zeng, C., Yang, M., Li, G., Han, J., Wu, W., & Zhang, R. (2019). Association Between Metabolic Syndrome and Breast Cancer Risk: An Updated Meta-Analysis of Follow-Up Studies. *Frontiers in Oncology, 9*, 1290. 10.3389/fonc.2019.01290

Guyatt, G. H., Oxman, A. D., Kunz, R., Vist, G. E., Falck-Ytter, Y., & Schünemann, H. J. (2008). What is "quality of evidence" and why is it important to clinicians? Bmj, 336(7651), 995-998. 10.1136/bmj.39490.551019.BE

Haidich, A. B. (2010). Meta-analysis in medical research. *Hippokratia, 14*(Suppl 1), 29-37. https://www-ncbi-nlm-nih-gov.proxy.libraries.rutgers.edu/pubmed/21487488

Hamer, J., & Warner, E. (2017). Lifestyle modifications for patients with breast cancer to improve prognosis and optimize overall health. Canadian Medical Association Journal (CMAJ), 189(7), E268-E274. 10.1503/cmaj.160464

Hauner, D., & Hauner, H. (2014). Metabolic syndrome and breast cancer: is there a link? *Breast Care, 9*(4), 277-281. 10.1158/1055-9965.EPI-20-0300.

Haynes, T. (2022). Premenopausal breast cancer – the challenge of research to help young women. The Institue of Cancer Research. https://www.icr.ac.uk/blogs/science-talk/pagedetails/premenopausal-breast-cancer-how-the-icr-is-helping-get-to-grips-with-the-data

Heer, E., Harper, A., Escandor, N., Sung, H., McCormack, V., & Fidler-Benaoudia, M. M. (2020). Global burden and trends in premenopausal and postmenopausal breast cancer: a 6 population-based study. The Lancet Global Health, 8(8), e1027-e1037. 10.1016/S2214-109X(20)30215-1

Hernandez, A. V., Guarnizo, M., Miranda, Y., Pasupuleti, V., Deshpande, A., Paico, S., Lenti, H., Ganoza, S., Montalvo, L., Thota, P., & Lazaro, H. (2014). Association between Insulin Resistance and Breast Carcinoma: A Systematic Review and Meta-Analysis. *PLoS ONE, 9*(6), e99317. 10.1371/journal.pone.0099317

Hierarchy of Evidence-Based Practice in Health. (2022). University of Canberra Library. https://canberra.libguides.com/c.php?g=599346&p=4149721

Hirode, G., & Wong, R. J. (2020). Trends in the Prevalence of Metabolic Syndrome in the United States, 2011-2016. *JAMA: The Journal of the American Medical Association, 323*(24), 2526-2528. 10.1001/jama.2020.4501

Hwang, K., Han, K., Oh, S., Koo, B. K., Lee, S. K., Kim, J., Seo, H. J., Jung, J., Kim, B. H., & Hur, H. (2020). Influence of metabolic syndrome on risk of breast cancer: A study analyzing nationwide data from korean national health insurance service. *Cancer*

Epidemiology, Biomarkers & Prevention, 29(10), 2038-2047. https://doi-org.proxy.libraries.rutgers.edu/10.1158/1055-9965.EPI-20-0300

Introduction to Meta-Analysis in Stata. (2021). Advancing Research Computing Statistical Methods and Data Analytics. https://stats-oarc-ucla-edu.proxy.libraries.rutgers.edu/stata/seminars/introduction-to-meta-analysis-in-stata/

Israel, H., & Richter, R. R. (2011). A Guide to Understanding Meta-analysis. *The Journal of Orthopaedic and Sports Physical Therapy, 41*(7), 496-504. 10.2519/jospt.2011.3333

Jevtic, M., Velicki, R., Popovic, M., Cemerlic-Adjic, N., Babovic, S. S., & Velicki, L. (2010). Dietary influence on breast cancer. *Journal of B.U. ON., 15*(3), 455-461. https://www-ncbi-nlm-nih-gov.proxy.libraries.rutgers.edu/pubmed/20941810

Kang, C., LeRoith, D., & Gallagher, E. J. (2018). Diabetes, Obesity, and Breast Cancer. *Endocrinology (Philadelphia), 159*(11), 3801-3812. 10.1210/en.2018-00574

Kaplan, N. M. (1989). The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Archives of Internal Medicine (1960), 149*(7), 1514-1520. 10.1001/archinte.149.7.1514

Lamar, M., Rubin, L. H., Ajilore, O., Charlton, R., Zhang, A., Yang, S., Cohen, J., & Kumar, A. (2015a). What Metabolic Syndrome Contributes to Brain Outcomes in African American & Caucasian Cohorts. *Current Alzheimer Research, 12*(7), 640-647. 10.2174/1567205012666150701102325

Laudisio, D., Barrea, L., Muscogiuri, G., Annunziata, G., Colao, A., & Savastano, S. (2020). Breast cancer prevention in premenopausal women: role of the Mediterranean diet and its components. Nutrition Research Reviews, 33(1), 19-32. 10.1017/S0954422419000167

Lee, Y. H. (2019). Strengths and Limitations of Meta-Analysis. *The Korean Journal of Medicine, 94*(5), 391-395. 10.3904/kjm.2019.94.5.391

Li, P., Wang, T., Zeng, C., Yang, M., Li, G., Han, J., & Wu, W. (2020). Association between metabolic syndrome and prognosis of breast cancer: a meta-analysis of follow-up studies. Diabetology & Metabolic Syndrome, 12(1), 10. 10.1186/s13098-019-0514-y

Lizama, N., Heyworth, J., Thomson, A., Slevin, T., & Fritschi, L. (2017). Self-reported shift work, recall bias, and belief about disease causation in a case-control study of breast cancer. *Cancer Epidemiology, 50*(Pt A), 9-15. 10.1016/j.canep.2017.07.007

Metabolic Syndrome Diagnosis. (2022). National Heart, Lung, and Blood Initiative. https://www.nhlbi.nih.gov/health/metabolic-syndrome/diagnosis

Metabolic Syndrome Treatment. (2022). National Heart, Lung, and Blood Initiative. https://www.nhlbi.nih.gov/health/metabolic-syndrome/treatment

Michels, K. B., Solomon, C. G., Hu, F. B., Rosner, B. A., Hankinson, S. E., Colditz, G. A., & Manson, J. E. (2003). Type 2 Diabetes and Subsequent Incidence of Breast Cancer in the Nurses' Health Study. *Diabetes Care, 26*(6), 1752-1758. 10.2337/diacare.26.6.1752

Moore, J. X., Chaudhary, N., & Akinyemiju, T. (2017). Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988–2012. *Preventing Chronic Disease, 14*, E24. 10.5888/pcd14.160287

Munsell, M. F., Sprague, B. L., Berry, D. A., Chisholm, G., & Trentham-Dietz, A. (2014). Body Mass Index and Breast Cancer Risk According to Postmenopausal Estrogen-Progestin Use and Hormone Receptor Status. *Epidemiologic Reviews, 36*(1), 114-136. 10.1093/epirev/mxt010

Nichols, H. B., Schoemaker, M. J., Wright, L. B., McGowan, C., Brook, M. N., Mcclain, K. M., Jones, M. E., Adami, H., Agnoli, C., Baglietto, L., Bernstein, L., Bertrand, K. A., Blot, W. J., Boutron-Ruault, M. C., Butler, L. M., Chen, K., Doody, M. M., Dossus, L., Eliassen, A. H., . . . Swerdlow, A. J. (2017). The premenopausal breast cancer collaboration : A pooling project of studies participating in the national cancer institute cohort consortium. *Cancer Epidemiology, Biomarkers & Prevention, 26*(9), 1360-1369. 10.1158/1055-9965.EPI-17-0246

Noh, H., Song, Y., Park, J., Kim, B., & Choi, Y. (2013). Metabolic factors and breast cancer risk in Korean women. *Cancer Causes & Control, 24*(6), 1061-1068. https://doi-org.proxy.libraries.rutgers.edu/10.1007/s10552-013-0183-3

Oh, H., Eliassen, A. H., Beck, A. H., Rosner, B., Schnitt, S. J., Collins, L. C., Connolly, J. L., Montaser-Kouhsari, L., Willett, W. C., & Tamimi, R. M. (2017). Breast cancer risk factors in relation to estrogen receptor, progesterone receptor, insulin-like growth factor-1 receptor, and Ki67 expression in normal breast tissue. *NPJ Breast Cancer, 3*(1), 39-8. 10.1038/s41523-017-0041-7

Osaki, Y., Taniguchi, S., Tahara, A., Okamoto, M., & Kishimoto, T. (2012). Metabolic syndrome and incidence of liver and breast cancers in Japan. *Cancer Epidemiology, 36*(2), 141-147. 10.1016/j.canep.2011.03.007

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., . . . Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Online), 372*, n71. 10.1136/bmj.n71

Pan, K., Chlebowski, R. T., Mortimer, J. E., Gunther, M. J., Rohan, T., Vitolins, M. Z., Adams‐Campbell, L. L., Ho, G. Y. F., Cheng, T. D., & Nelson, R. A. (2020). Insulin resistance and breast cancer incidence and mortality in postmenopausal women in the Women's Health Initiative. *Cancer, 126*(16), 3638-3647. 10.1002/cncr.33002

Pérez-Martínez, P., Mikhailidis, D. P., Athyros, V. G., Bullo, M., Couture, P., Covas, M. I., de Koning, L., Delgado-Lista, J., Díaz-López, A., Drevon, C. A., Estruch, R., Esposito, K., Fitó, M., Garaulet, M., Giugliano, D., García-Ríos, A., Katsiki, N., Kolovou, G., Lamarche, B., . . . López-Miranda, J. (2017). Lifestyle recommendations for the prevention and management of metabolic syndrome: an international panel recommendation. *Nutrition Reviews, 75*(5), 307-326. 10.1093/nutrit/nux014

Perimenopause. (2023). Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/perimenopause/symptoms-causes/syc-20354666

Petitti, Diana B., *Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis*, 2nd edn (New York, 1999; online edn, Oxford Academic, 1 Sept. 2009), https://doi.org/10.1093/acprof:oso/9780195133646.001.0001.

Pierobon, M., & Frankenfeld, C. L. (2013). Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. *Breast Cancer Research and Treatment, 137*(1), 307-314. 10.1007/s10549-012-2339-3

Porto, L. Â M., Lora, K. J. B., Soares, J. C. M., & Costa, L. O. B. F. (2011). Metabolic syndrome is an independent risk factor for breast cancer. *Archives of Gynecology and Obstetrics, 284*(5), 1271-1276. 10.1007/s00404-011-1837-6

Prevention and Treatment of Metabolic Syndrome. (2023). American Heart Association. https://www.heart.org/en/health-topics/metabolic-syndrome/prevention-and-treatment-of-metabolic-syndrome

Renehan, A. G., Dr, Tyson, M., PhD, Egger, M., MD, Heller, R. F., MD, & Zwahlen, M., PhD. (2008). Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *The Lancet (British Edition), 371*(9612), 569-578. 10.1016/S0140-6736(08)60269-X

Ronco, A. L., De Stefani, E., Deneo-Pellegrini, H., & Quarneti, A. (2012). Diabetes, overweight and risk of postmenopausal breast cancer: A case-control study in uruguay. *Asian Pacific Journal of Cancer Prevention : APJCP, 13*(1), 139-146. https://doi-org.proxy.libraries.rutgers.edu/10.7314/APJCP.2012.13.1.139

Rosato, V., Bosetti, C., Talamini, R., Levi, F., Montella, M., Giacosa, A., Negri, E., & La Vecchia, C. (2011). Metabolic syndrome and the risk of breast cancer in postmenopausal women. *Annals of Oncology, 22*(12), 2687-2692. 10.1093/annonc/mdr025

Rose, D. P., Haffner, S. M., & Baillargeon, J. (2007). Adiposity, the Metabolic Syndrome, and Breast Cancer in African-American and White American Women. *Endocrine Reviews, 28*(7), 763-777. 10.1210/er.2006-0019

Rosenberg, S. M., & Partridge, A. H. (2013). Premature menopause in young breast cancer: Effects on quality of life and treatment interventions. *Journal of Thoracic Disease, 5 Suppl 1*(Suppl 1), S55-S61. 10.3978/j.issn.2072-1439.2013.06.20

Schneider, D., & Lilienfeld, D. E. (2015). *Lilienfeld's Foundations of Epidemiology*. Oxford University Press, Incorporated.

Sellers, T. A., Sprafka, J. M., Gapstur, S. M., Rich, S. S., Potter, J. D., Ross, J. A., McGovern, P. G., Nelson, C. L., & Folsom, A. R. (1994). Does Body Fat Distribution Promote Familial Aggregation of Adult Onset Diabetes Mellitus and Postmenopausal Breast Cancer? *Epidemiology (Cambridge, Mass.), 5*(1), 102-108. 10.1097/00001648-199401000-00015

Seretis, A., Cividini, S., Markozannes, G., Tseretopoulou, X., Lopez, D. S., Ntzani, E. E., & Tsilidis, K. K. (2019). Association between blood pressure and risk of cancer development: a systematic review and meta-analysis of observational studies. *Scientific Reports, 9*(1), 8565. 10.1038/s41598-019-45014-4

Silva-Igua, L., De La Peña, J., Rubiano, W., & Ruiz-Sternberg, A. M. (2020). Premenopausal breast cancer is a health challenge: nutritional habits show potential to prevent this disease. *Breast Cancer: Basic and Clinical Research, 14*, 1178223420974665. 10.1177/1178223420974665

Srinivasan, M., Arzoun, H., Gk, L. B., & Thangaraj, S. R. (2022). A Systematic Review: Does Insulin Resistance Affect the Risk and Survival Outcome of Breast Cancer in Women? *Curēus (Palo Alto, CA), 14*(1), e21712. 10.7759/cureus.21712

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians, 71*(3), 209-249. 10.3322/caac.21660

Surakasula, A., Nagarjunapu, G. C., & Raghavaiah, K.V. (2014). A comparative study of pre- and post-menopausal breast cancer: Risk factors, presentation, characteristics and management. *Journal of Research in Pharmacy Practice, 3*(1), 12-18. 10.4103/2279-042X.132704

Swarup, S., Goyal, A., Grigorova, Y. & Zeltser, R. (2022). *Metabolic Syndrome.* StatPearls Publishing LLC. https://www-ncbi-nlm-nih-gov.proxy.libraries.rutgers.edu/books/NBK459248/

The Who, What, Where, When and Sometimes, Why. (2022). Susan G. Komen for the Cure. https://www.komen.org/breast-cancer/facts-statistics/research-studies/topics/blood-estrogen-levels-and-the-risk-of-breast-cancer/

Uzunlulu, M., Telci Caklili, O., & Oguz, A. (2016). Association between Metabolic Syndrome and Cancer. *Annals of Nutrition and Metabolism, 68*(3), 173-179. 10.1159/000443743

Vaz-Luis, I., Francis, P. A., Di Meglio, A., & Stearns, V. (2021). Challenges in Adjuvant Therapy for Premenopausal Women Diagnosed With Luminal Breast Cancers. *American Society of Clinical Oncology Educational Book, 41*(41), 1-e61. 10.1200/EDBK_320595

Wani, B., Aziz, S. A., Ganaie, M. A., & Mir, M. H. (2017). Metabolic syndrome and breast cancer risk. *Indian Journal of Medical and Paediatric Oncology: Official Journal of Indian Society of Medical & Paediatric Oncology, 38*(4), 434-439. https://doi-org.proxy.libraries.rutgers.edu/10.4103/ijmpo.ijmpo_168_16

Weiderpass, E., Gridley, G., Persson, I., Nyrén, O., Ekbom, A., & Adami, H. (1997). Risk of endometrial and breast cancer in patients with diabetes mellitus. *International Journal of Cancer, 71*(3), 360-363. 10.1002/(SICI)1097-0215(19970502)71:3<360::AID-IJC9>3.0.CO;2-W

What Are the Risk Factors for Breast Cancer?. (2022). Centers for Disease Control and Prevention. https://www.cdc.gov/cancer/breast/basic_info/risk_factors.htm

What Is Metabolic Syndrome? (2022). National Institute of Health Heart, Lung, and Blood Institute.

https://www.nhlbi.nih.gov/health/metabolic-syndrome#:~:text=Metabolic%20syndrome%20is%20common%20in,health%20problems%20it%20can%20cause.

Wideroff, L., Gridley, G., Mellemkjaer, L., Chow, W. -., Linet, M., Keehn, S., Borch-Johnsen, K., & Olsen, J. H. (1997). Cancer Incidence in a Population-Based Cohort of Patients Hospitalized With Diabetes Mellitus in Denmark. *JNCI : Journal of the National Cancer Institute, 89*(18), 1360-1365. 10.1093/jnci/89.18.1360

Wu, J., Lei, X., Pan, X., Zeng, X., & Li, W. (2021). Association between serum lipids and breast cancer risk in premenopausal women: systematic review and meta-analysis. *Journal of International Medical Research, 49*(11), 30006052110610-3000605211061033. 10.1177/03000605211061033

Xiang, Y., Zhou, W., Duan, X., Fan, Z., Wang, S., Liu, S., Liu, L., Wang, F., Yu, L., Zhou, F., Huang, S., Li, L., Zhang, Q., Fu, Q., Ma, Z., Gao, D., Cui, S., Geng, C., Cao, X., . . . Yu, Z. (2020). Metabolic syndrome, and particularly the hypertriglyceridemic-waist phenotype, increases breast cancer risk, and adiponectin is a potential mechanism: A Case–Control study in Chinese women. *Frontiers in Endocrinology, 10*, 905. https://doi-org.proxy.libraries.rutgers.edu/10.3389/fendo.2019.00905

Xue, F., & Michels, K. B. (2007). Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. *American Journal of Clinical Nutrition, 86*(3), 823. 10.1093/ajcn/86.3.823S.

Yuan, Y., Pan, K., Mortimer, J., Chlebowski, R. T., Luo, J., Yan, J. E., Yost, S. E., Kroenke, C. H., Adams‐Campbell, L., Nassir, R., Sun, Y., Shadyab, A. H., Vitolins, M. Z., Saquib, N., Wild, R. A., Manson, J. E., & Nelson, R. A. (2021). Metabolic syndrome risk components and mortality after triple‐negative breast cancer diagnosis in

postmenopausal women in the Women's Health Initiative. Cancer, 127(10), 1658-1667. 10.1002/cncr.33407

Zhao, P., Xia, N., Zhang, H., & Deng, T. (2020). The Metabolic Syndrome Is a Risk Factor for Breast Cancer: A Systematic Review and Meta-Analysis. Obesity Facts, 13(4), 384-396. 10.1159/000507554