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Protocol Study

Blood Lipidomic And Breast Cancer Risk: Protocol of A Systematic Review

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ABSTRACT

Background and objectives: Breast cancer is the most common type of cancer and the leading cause of death in women worldwide. Early detection of breast cancer by measuring metabolites that can be easily detected through blood tests will significantly help in time treatment, prevent cancer progression, and reduce the risk of death in breast cancer patients. One of the constant metabolic characteristics of cancer is lipidomic remodeling, which includes changes in fatty acid transport, lipogenesis, lipid storage, and beta-oxidation to supply energy. This review aims to compare lipid changes between women with and without breast cancer.

Materials and methods: The systematic review will search and summarize data on observational studies from Medline/PubMed, Scopus, Embase, and Web of Science databases and grey literature published between January 2000 and January 2025. Keywords related to 'breast cancer' and 'lipidomic' will be used to retrieve relevant documents. The PECOS model will be used to include eligible studies. The protocol of this systematic review follows the PRISMA-P statement.

Results and conclusion: This systematic review will help summarize the existing evidence about the use of blood lipids in breast cancer diagnosis and prognosis and recognize the current gaps in research to design further high-quality studies with the ultimate goal of easy and early detection of breast cancer.

Keywords: Blood lipids, Breast cancer, Lipidomic, Protocol, Systematic review

Highlights

- Early detection of breast cancer by measuring metabolites through blood tests will help in time treatment, prevent cancer progression
- This systematic review will search and summarize observational studies on blood lipids and breast cancer
- The PECOS model will be used to include eligible studies
- Keywords related to breast cancer and lipidomic will be used

Introduction

Breast cancer is a significant public health challenge worldwide, with an estimated 2.3 million new cases reported in 2020. While the majority of cases occur in developed nations, countries in transition also face a growing burden of breast cancer. Some Asian and African countries recorded incidence rates below 40 per 100,000 females, while Australia/New Zealand, Northern America, and parts of Europe had rates exceeding 80 per 100,000. Certain Asian and African countries recorded rates below 40 per 100,000 females, whereas Australia/New Zealand, Northern America, and parts of Europe exceeded 80 per 100,000. If current trends continue, the global burden of breast cancer is projected to escalate to over 3 million new cases and 1 million deaths annually by 2040, primarily driven by population growth and aging (1). Given the magnitude of breast cancer's impact on global health,

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understanding the factors contributing to its etiology and risk is crucial.

Metabolic reprogramming is now widely recognized as a hallmark of cancer (2). Tumors exhibit a typical phenotype characterized by uncontrolled cell proliferation, which requires efficient energy production and biosynthesis to support their rapid growth and spread. The sequential activation of oncogenes directly influences these metabolic alterations, the loss of tumor suppressors, and the challenges posed by the tumor microenvironment (TME), such as limited oxygen and nutrient availability (3). As a result, cancer cells develop a wide array of metabolic strategies that allow them to adapt and thrive in these hostile conditions. In recent years, the study of lipids in biological systems has gained attention as a potentially influential factor in breast cancer development and progression (4). In mammalian cells, fatty acids can be obtained through direct exogenous uptake from the surrounding microenvironment or de novo using nutrients like glucose or glutamine (5).

A well-established metabolic hallmark of cancer is lipidomic remodeling, which includes alterations in fatty acid (FA) transport, de novo lipogenesis, storage in the form of lipid droplets, and β-oxidation to generate adenosine triphosphate (ATP)(6). In addition, lipid metabolic reprogramming modifies the TME by influencing immune and stromal cells' recruitment, activation, and function. Tumor cells interact with cells in the TME, forming a reciprocal relationship that promotes cancer progression (7). Conversely, tumor cells actively modify the TME by secreting signaling molecules and metabolites that influence the function of cancer-associated fibroblasts (CAFs) and immune cells within the TME. These interactions contribute to a supportive environment for tumor growth and immune evasion (8). On the other hand, lipid metabolic reprogramming is characterized by increased lipid uptake, accumulation, or FA oxidation, which drives TME toward an immunosuppressive phenotype that supports tumor progression (8).

Although evidence suggests the potential of serum or plasma lipidomic profiling for screening, diagnosis, or prognosis of breast cancer (9), the results of systematic reviews remain controversial. For example, a systematic review by Ni et al. summarized the findings of 15 cohort studies retrieved from PubMed and EMBASE until April 2015. The review investigated the association between breast cancer and selected lipids, revealing mixed results. Ni et al. found that increased serum triglyceride (TG) levels were inversely associated with breast cancer risk. At the same time, subgroup analysis showed that elevated serum total cholesterol increased breast cancer risk by 16% in Asians. Conversely, higher high-density lipoprotein cholesterol (HDL-C) levels were associated with a 23% reduced risk in postmenopausal women. However, the review faced inconsistencies due to substantial heterogeneity, a limited number of databases, and the assessment of a small range of lipids (10). Another systematic review by Wu et al. included case-control studies on premenopausal women with and without breast cancer, drawing from documents published in PubMed, EMBASE, and Chinese databases up to December 2020. The meta-analysis revealed significant increases in serum TG and low-density lipoprotein cholesterol (LDL-C) in premenopausal women with breast cancer. However, no significant changes were observed in total cholesterol (TC) or HDL-C levels. Although the studies were of high quality, performed ethnicity subgroup analysis, and adjusted results for dietary factors such as fat, energy, vegetables, coffee, and alcohol intake, the review only examined a limited range of blood lipids, demonstrating high heterogeneity and some publication bias. Except for one study, all other studies were conducted in Asian and African countries (11). Nouri et al. systematically searched prospective cohort studies from PubMed, EMBASE, and Web of Science until January 2021. Their meta-analysis of 26 studies demonstrated a significant negative association between HDL-C levels and breast cancer risk (RR = 0.85). Despite the high quality of the included studies, the study only focused on a limited number of blood lipids, did not specify the assessment methods, and raised concerns about confounding bias, varying cut-off points, and a range of adjusted covariates (12). Similarly, a systematic review and meta-analysis by Touvier et al. retrieved prospective studies on the association between blood cholesterol and breast cancer risk from PubMed up to January 2014. Their findings revealed an inverse association between HDL-C and breast cancer risk in premenopausal women (HR = 0.82). However, the review had some limitations, including insufficient data sources, lack of exploration of specific cancer subtypes due to limited cases, and the exclusion of other blood lipids (13). Despite these concerns, the studies were rated as high quality, with no potential heterogeneity or publication bias.

In summary, lipidomic profiling would be a promising tool in breast cancer screening, diagnosis, or prognosis. At the same time, previous reviews highlighted several common limitations, including the inclusion of few selected blood lipids, insufficient data sources, language restrictions, potential publication bias, lack of a priori approach, and an unclear reviewing process (e.g., study selection, quality assessment, or data extraction). There was also noticeable heterogeneity and a failure to account for the strength of the evidence or potential confounders. Addressing these limitations, this review aims to contribute valuable insights into the complex relationship between lipid profiles and breast cancer, facilitating the

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development of targeted interventions and strategies for prevention and treatment by synthesizing the available evidence and assessing their clinical relevance. Our primary objective is to evaluate the association between changes in blood lipids and the risk of breast cancer, and the secondary objective of this systematic review is to determine the potential confounders affecting the abovementioned association.

Objectives

This systematic review protocol aims to assert a transparent literature review procedure on the association between lipidomic changes and the risk of breast cancer. The protocol includes the aims, details, and funding source of the systematic review, inclusion criteria, search strategy, risk of bias and quality assessment, and data synthesis procedures for combining data from eligible studies.

Materials and Methods

Protocol

The protocol of this systematic review was approved by the institutional review board (IRB) of the Nutrition and Metabolic Diseases Research Center (NRC)(code: NRC-0308) and the Ethical Committee of Ahvaz Jundishapur University of Medical Sciences (AJUMS)(ethical code: IR.AJUMS.REC.1403.549). The protocol of this review was written according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement (PRISMA-P, 2015) (14) and has been registered in the PROSPERO database (registration code: CRD42024598124).

Eligibility criteria

PECOS criteria will be used to conduct this study: P for 'participants', E for 'Exposure', C for 'Comparison', O for 'Outcome', and S for 'Study design'.

Participants

We will include studies on adult women aged 18 years and older who have been diagnosed with breast cancer. Early or locally advanced breast cancer will be defined by the TNM Classification of Malignant Tumors staging system, in which "T" stands for Tumor size and extent, "N" for Nearby lymph nodes involvement, and "M" for Metastasis presence or absence. We will consider participants who meet the criteria of any T, any N, and null M. This review covers both pre- and postmenopausal participants.

Exposure

The exposure will be any changes in serum, plasma, or blood lipids, such as different types of cholesterol, triglyceride, fatty acids, phospholipids, and lipoproteins, concerning breast cancer risk. The secondary outcome will be the relationship between blood lipidomic changes in different studied subgroups. Standard techniques to measure lipid profile include biochemical assays, Nuclear Magnetic Resonance (NMR) Spectroscopy, Mass Spectrometry, Thin-Layer Chromatography (TLC), High-Performance Liquid Chromatography (HPLC), Gas Chromatography.

Comparison

Individuals with breast cancer will be compared with those without breast cancer. The comparison group might be healthy or have complications except for breast cancer.

Outcomes

The primary outcome will be the diagnosis or prognosis of breast cancer. Secondarily, in case of sufficient data, subgroup analyses will be executed to explore the potential factors influencing lipid changes in patients with breast cancer.

Study design

This systematic review includes observational studies, namely cohort, case-cohort, nested case-control, case-control, or cross-sectional design.

Search strategy

Two independent reviewers will search Medline/PubMed, Scopus, Embase, and Web of Science electronic databases using "breast cancer" and "blood lipidomic" keywords and their synonyms to retrieve papers published between January 1, 2000, and January 1, 2025. Manual search will be implemented in PROSPERO, Preprints.org, and reference lists of the included articles and relevant reviews for finding the related documents. The free-text method, i.e., a combination of keywords from previous related reviews and MeSH terms from PubMed, will be used to ensure the most relevant results. The syntax will be developed by calculating the number needed to read (NNR). We will not limit our search to any specific language or region.

Only full-text of selected articles will be considered for inclusion as long as they provide the required data. The final report of this review will be written according to the guideline for PRISMA 2020 (15).

Data Collection

Study Selection

All obtained articles through a systematic search of electronic databases will be imported into a reference manager. After eliminating duplicate or multiple documents by their titles, two reviewers will screen the remaining references by titles and abstracts. Studies that do not meet the inclusion criteria will be excluded. The full text of potentially relevant papers will be downloaded and completely read to check their eligibility for inclusion in the systematic review. Any disagreement will be resolved through discussion. The process of this systematic review will follow the PRISMA 2020 guideline.

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Data Extraction And Management

The required data, including first author name, publication year, nation, language, study design, sample size, mean age, cancer stage, hormone receptors status, menstruation status, blood lipidomics and related cut-offs, comparison group, lipid measurement techniques, and adjusted confounders, will be extracted by two independent reviewers from the included studies. A pre-designed data extraction form in Microsoft Excel will be used for data extraction. The extraction sheet was formerly tested by the principal investigator (PI). In case of any disagreement, the discussion strategy, and if required, the third expert investigator will fix it. The extracted data will include study characteristics, such as the author's name. Data on funding sources and conflicts of interest will also be collected.

Risk Of Bias Assessment

Two independent colleagues will assess the risk of bias for all the included studies. The Newcastle-Ottawa Scale (NOS) will be applied, and it consists of three domains: selection, comparability, and exposure/outcome. The final quality will be concluded through star as follows: ≥5 points (cross-sectional) or 7-8 points (cohort and case-control studies) shows "very Good quality", 4 points (cross-sectional) or 5-6 points (cohort and case-control studies) shows "Good quality", 3 points (cross-sectional studies) or 4 (cohort and case-control studies) means "Satisfactory", 0-2 points (cross-sectional studies) or 0-3 points (cohort and case-control studies) shows "Unsatisfactory"(16). Any disagreement will be solved through discussion.

Data Analyses

Data will be analyzed using STATA software (version 14.2, STATA Corp., College Station, TX, USA). To assess the relationship between lipidomic changes and the risk of breast cancer, odds ratios (ORs) and risk ratios (RRs) will be reported in addition to relevant confidence intervals (95%CIs). Due to substantial heterogeneity in study designs, samples, and lipidomes, a random-effect model will be applied for data analysis. Differences in blood lipids will be compared to available minimum clinically important difference (MCID) values.

Heterogeneity

Due to the heterogeneity of the study methodology, Der Simonian Laired's random-effect model will be used to aggregate the data, and statistical heterogeneity will be tested using Cochran's and I-squared tests. A forest plot will illustrate the heterogeneity of the pooled data, and based on the I^2 value, the heterogeneity of the studies will be as follows: mild (0-40%), moderate (30-60%), severe (50-90%), or very severe heterogeneity (75-100%)(17).

Subgroup Analysis

If possible, the effects of potential subgroups on blood lipids will be explored. The subgroups could be: age, menstruation (menopause, non-menopause), other existing medical conditions (cardiovascular disease, hypertension, diabetes), sample type (blood, plasma, or serum), stage of cancer, measurement techniques (e.g., NMR spectroscopy, mass spectrometry), family history of breast cancer, body composition (waist circumference, body mass index, and fat percentage), regions or continents, heterogeneity of studies or risk of bias.

Publication Bias And Sensitivity Analysis

Publication bias will be assessed through funnel plot as a visual tool and through Begg's or Egger statistical tests. Sensitivity analysis will assess the consistency of the results of the primary outcomes by restricting studies to high methodological quality or low risk of bias. This analysis will broaden our insight into the robustness of the results and will diminish the potential effect of low-quality studies on the outcomes.

Conclusions

This systematic review will scrutinize the relevant documents on the association between blood lipidomics and breast cancer to identify blood lipid components that are relevant to breast cancer diagnosis. They could be cholesterol, triglyceride, fatty acids, phospholipids, lipoproteins, or related biomarkers. We will also identify the characteristics associated with breast cancer, like age and family history. This would help to identify target populations for screening, prevention, and treatment purposes of related lipidomes. Furthermore, this systematic review will result in the methodological assessment of the published documents. It will compare the findings based on the papers' qualities, and their limitations will be addressed in detail. Finally, the implications of this review and its findings, as well as the suggestions for future investigations, will also be emphasized.

List of abbreviations:

ATP adenosine triphosphate
TME tumor microenvironment
PRISMA-P Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
FA fatty acid
CAFs cancer-associated fibroblasts
TG triglyceride
HDL-C high-density lipoprotein cholesterol
LDL-C low-density lipoprotein cholesterol
TC total cholesterol

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The authors declare that they have no competing interests.

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