INPLASY PROTOCOL

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Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
The authors declare no conflict of interest.

Incidence of Breast cancer among Non-alcoholic fatty liver disease patients: a systematic review and meta-analysis protocol

Zhang, J[1]; Wang, Y[2]; Xia, X[3]; Feng, Q[4].

Review question / Objective: **The goal of this work is to assess the observational associations between NAFLD and BC incidence and try to discuss and analyze its complications.**
Condition being studied: **NAFLD is also a process in which chronic inflammation develops and gradually worsens, and the high-risk factors of the two also have some similarities. There is evidence about the relationship between NAFLD and BC survival, and complications during BC treatment. The presence of ET-associated NAFLD could compromise the survival potentially. Tamoxifen will increase risk of newly developed fatty liver, exacerbates the condition for patients with existed-NAFLD and is harmful to recovery, as a cheap and effective estrogen-receptor antagonist used for breast cancer treatment. However, there are few clinical reports on the relationship between NAFLD and BC. Whether the two are related since the onset need more research support. Hence, we try to assess the observational associations between NAFLD and BC incidence and try to discuss and analyze its complications.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 October 2020 and was last updated on 13 October 2020 (registration number INPLASY2020100046).

INTRODUCTION

Review question / Objective: **The goal of this work is to assess the observational associations between NAFLD and BC incidence and try to discuss and analyze its complications.**

Rationale: **Non-alcoholic fatty liver disease (NAFLD) is gradually increasing the burden of human health as the most common chronic liver disease. As a metabolic disease, more and more studies have shown NAFLD as a multisystem disease**

increases risk of extra-hepatic organs disease. the second most common cause of death caused by NAFLD is malignant tumors. Causal discussion is rare and controversial between NAFLD and breast cancer.

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METHODS

Search strategy: A systematic electronic search will be conducted in the following databases:the Cochrane Library, Pubmed, Embase (via Ovid) and Web of Science, SinoMed, Chinese National Knowledge Infrastructure(CNKI), Chinese Science and Technology Periodicals Database, and Wanfang Database for papers published from inception to September 2020. The search strategy will be developed by the research team in collaboration with an experienced librarian and checked by a referee according to the Peer Review of Electronic Search Strategy guidelines16. And it will involve two kinds of terms, "Breast Cancer" and "NAFLD" that will be combined with the Cochrane Highly Sensitive Search Strategy for the identification of cohort studies in Pubmed by Boolean operations. Chinese and English will be included. And two reviewers will manually screened eligible studies to unduplicate references.

Participant or population: We will include BC patients with pre-existed NAFLD over 18 years old, and excluded BC patients with other patients with merged malignancies or liver disease, cardiovascular diseases and diabetes, which may become our confounding factors with a higher risk

Intervention: People with pre-existed NAFLD among breast cancer patients.

Comparator: People without pre-existed NAFLD among breast cancer patients.

Study designs to be included: We will include all case-control studies, prospective and retrospective cohort study.

Eligibility criteria: A temporal analysis between NAFLD and subsequent risk of breast cancer was performed, and risk estimates (either relative risks [RRs] or odds ratios [ORs]) with corresponding 95% confidence intervals (CIs) were provided. Following the rare disease assumption (low number of cancer events), we assumed rate ratio, hazard ratio, and odds ratio to approximate the relative risk (RR).

Information sources: The Cochrane Library, Pubmed, Embase (via Ovid) and Web of Science, SinoMed, Chinese National Knowledge Infrastructure(CNKI), Chinese Science and Technology Periodicals Database, and Wanfang Database.

Main outcome(s): The main outcomes are incidence and mortality for the longitudinal association of NAFLD and BC which reported the estimates (with 95% CIs, SEs, or P values).

Additional outcome(s): The secondary outcomes is the average age, sex at diagnosis of BC in NAFLD patients and the severity of NAFLD.

Data management: All selected studies were reviewed and evaluated by two independent investigators (J. Zhang, X. Y.

Liu), applying blinding to reduce bias. The study assessed the longitudinal association between NAFLD and the incidence of BC will be considered eligible (with 95% CIs, or p values). The title, abstract and bibliographies of all relevant meta-analysis of each article will be screened and assessed against predefined inclusion criteria, meanwhile all repetitions and studies does not meet the inclusion criteria will be excluded.

Quality assessment / Risk of bias analysis: Meta-analyses and bias analyses will be stratified by sex and age, where possible. Those observational studies will be evaluated the methodological quality according to the Newcastle-Ottawa Scale (NOS), which is a validated scale for non-randomized studies in meta-analyses. the NOS scale uses a star system to assess the quality of a study in three domains: selection, comparability, and outcome/ exposure. The NOS assigns a maximum of five stars for selection (or four stars in the case of longitudinal studies), two stars for comparability, and three stars for outcome/ exposure. the final score is from 0-9, scored ≥7 was considered high quality.

Strategy of data synthesis: If a meta-analysis is possible, statistical analysis will be conducted using Revman 5.3. We will investigate heterogeneity using Cochrane's Q test and I2, If there is great heterogeneity within the studies (p value of Q test25%), We will use the random effects model. The publication bias will be assessed with the funnel plot and Egger's test.

Subgroup analysis: We will consider the following variables: age, sex, the aetiology of the disease, type of breast cancer, and it's severity evaluated by the steatosis level and inflammation level, and the duration of NAFLD. Finally, evaluation of the methodological heterogeneity will take into account the study design and the risk of bias of the studies included.

Sensibility analysis: We will perform a sensitivity analysis as follows: (a) random allocation, (b) concealed allocation, (c) methodological quality, (d) subjects blinding, (e) therapists blinding, (f) outcomes assessor blinding, (g) intention to treat analysis, and (h) drop outs.

Language: Chinese and English will be included.

Country(ies) involved: China.

Keywords: NAFLD, Nonalcoholic fatty liver disease, BC, breast cancer, protocol, meta-analysis, systematic review.

Contributions of each author:
Author 1 - Jing Zhang - The author is the idea proposer and data collector of the paper and drafted the manuscript.
Author 2 - Yiting Wang - The author assisted in data collection and statistical analysis.
Author 3 - Xinyi Xia - Management literature and supervision.
Author 4 - Quansheng Feng - The author read, provided feedback and approved the final manuscript.