# Association between Non-alcoholic Fatty Liver Disease and Breast Cancer: A Systematic Review and Meta-analysis Study

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## Abstract

**Background:** Breast cancer (BC) is the most prevalent neoplasm in females globally, with an increasing incidence trend almost in all regions. Previous studies have indicated that non-alcoholic fatty liver disease (NAFLD) may be an emerging risk factor for extrahepatic cancers, including BC. This systematic review and meta-analysis study aimed to determine the association between NAFLD and the development of BC.

**Method:** Data were systematically collected without time limitation until 21 April 2022, from the following electronic databases: PubMed, Scopus, Embase, Web of Science, and Google Scholar. The association between NAFLD and BC with odds ratio (OR) was calculated with a 95% confidence interval (CI) and presented via forest plots. Hazard ratios along with incidence rate ratios in the cohort studies transformed into OR.

**Results:** According to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and the inclusion criteria herein, 11 eligible studies were obtained from various countries. The pooled OR of NAFLD as a risk of developing BC, using a random-effects model, was estimated at 1.61 (95% CI: 1.30-2.00) (Q-value: 51.35, I2 = 80.52%, $P < 0.0001$). Multivariate meta-regression analysis showed that the publication year-, country-, detection method-, study design-, and body mass index-adjusted status did not cause heterogeneity. The Egger's regression ($P = 0.32$) and the symmetry in the funnel plot showed no publication bias in the studies.

**Conclusion:** The present research revealed that NAFLD had a significant association with BC, independent of traditional risk factors.

***Keywords:*** Breast cancer, Non-alcoholic fatty liver disease, Systematic review, Association

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## Introduction

Breast cancer (BC) is known to be the most prevalent neoplasm in females globally, with an increasing trend of incidence almost in all regions.[1,2] BC is the leading cause of cancer death in females. The mortality rates of this fatal cancer also increased in most regions, specifically in developing countries.[3]

BC accounts for about a quarter of all malignant deaths in postmenopausal women and, on a global scale, is the second leading cause of cancer deaths, after lung cancer, in the female population.[4]

In 2018, a total of 18.1 million new cases of cancer was reported, and 9.6 million cancer-related deaths occurred.[5]

The increase in BC incidence is due to the improvement of BC screening tools and the significant rise in exposure to various risk factors in the female population.[3,4]

The American Cancer Society recommends that women with an average risk of BC (relative risk of 2%–4%, those who have first-degree relatives with BC, CHEK2 mutation, age of above 35 for the first birth, proliferative breast disease, mammographic breast density)[6] should have a regular screening mammogram from the age of 45 years.[7]

Furthermore, hormonal or reproductive factors, such as late age to menopause,[8] young age at menarche, null parity, delayed pregnancy, and family history, are the known risk factors for BC.[4,7]

A meta-analysis study on women showed that obesity, alcohol consumption, and birth control pills as modifiable risk factors were associated with BC.[8]

Non-alcoholic fatty liver disease (NAFLD) is one of the most commonly reported chronic liver diseases globally, with an overall prevalence of 25.2% worldwide and 29.62% in Asia.[9] Although NAFLD prognosis is generally good, it ranges from hepatic steatosis (HS) to non-alcoholic
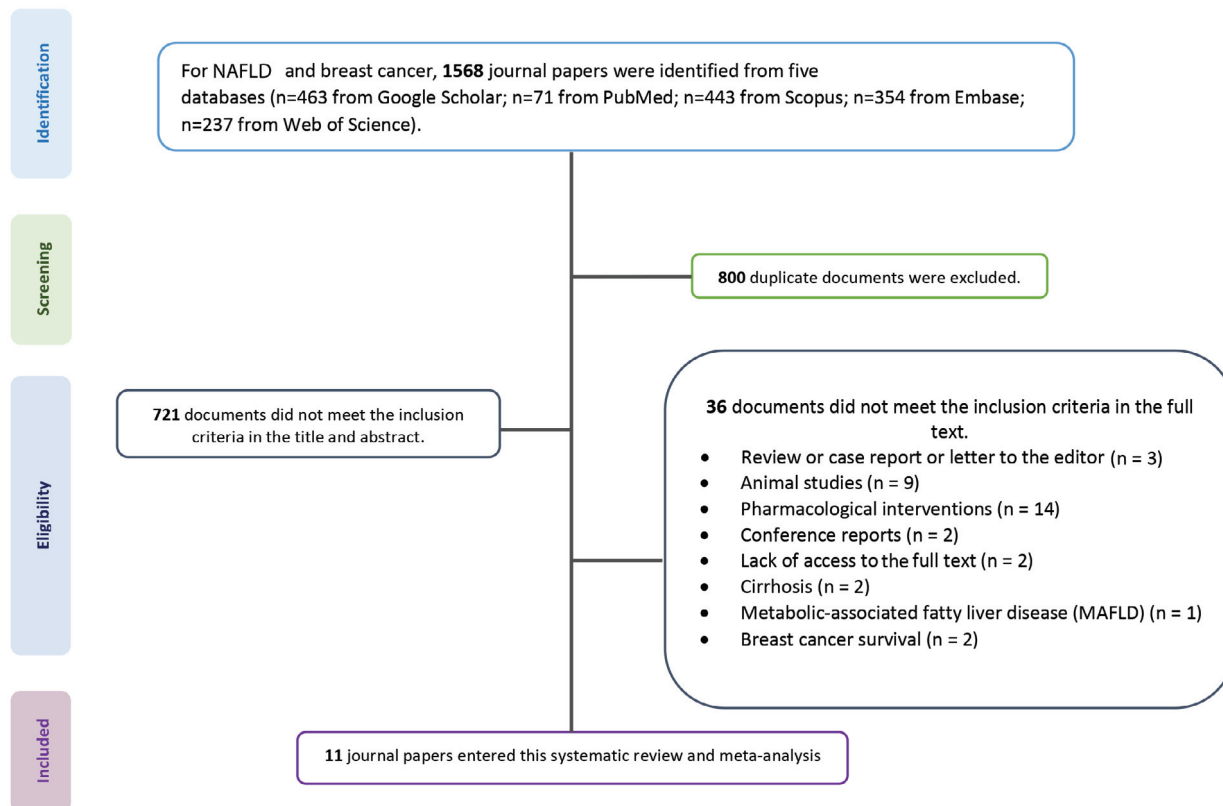


**Figure 1.** PRISMA flowchart presents the selection of the articles analyzed in this systematic review and meta-analysis.

n: Number; MAFLD: Metabolic-associated fatty liver disease; NAFLD: Non-alcoholic fatty liver disease

steatohepatitis (NASH) and cirrhosis.[7]

Some studies have suggested that NAFLD is a multisystem disease with extrahepatic complications,[10, 11] such as cardiovascular disease, chronic renal disease, decreased lung function, and extrahepatic malignancies.[7,12]

Malignancies are the second most common cause of death following cardiovascular disease in patients with NAFLD.[9, 13] Other studies have indicated that NAFLD may be an emerging risk factor for extrahepatic cancers, including BC.[7, 14]

To the best of our knowledge, no systematic review and meta-analysis independently have been published to estimate the linkage between NAFLD and BC. Therefore, this systematic review and meta-analysis paper aimed to determine the association between NAFLD and the development of BC.

## Materials and Methods

This study was designed via the preferred reporting items for systematic reviews and meta-analyses (PRISMA).[15]
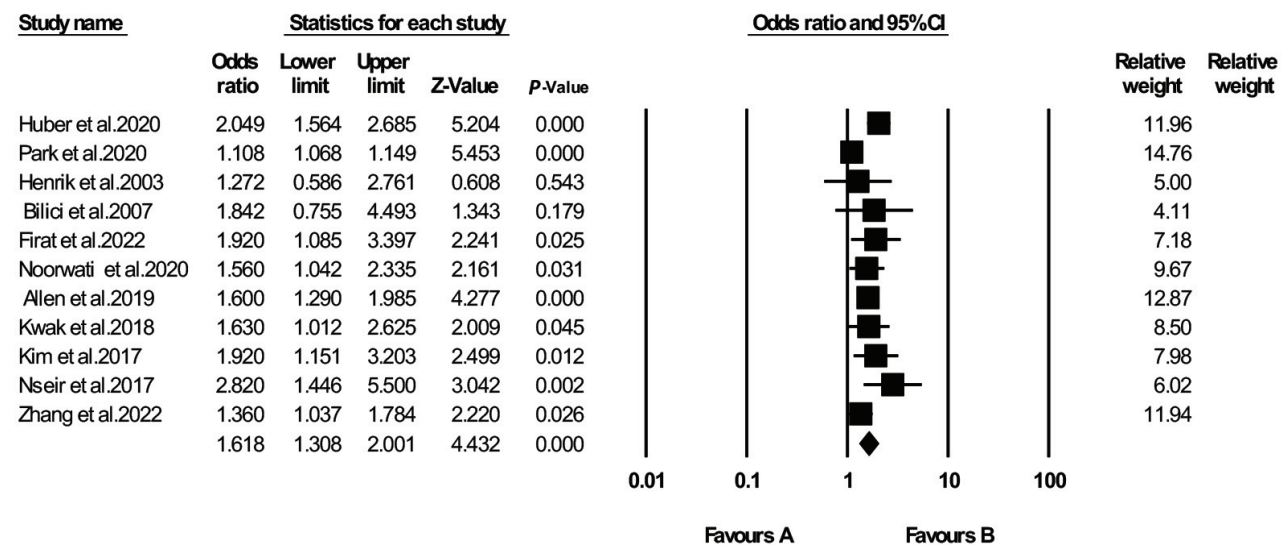
### Bibliographic search strategy

The related studies with English language were identified from five English sources, namely PubMed, Scopus, Embase, Web of Science, and Google Scholar, without time limitation until 21 April 2022. The search was performed using the Medical Subject Heading (MeSH) terms as follows: (Breast Neoplasm) OR (Breast Tumors)) OR (Breast Tumor)) OR (BC)) OR (Mammary Cancer)) OR (Breast Malignant Neoplasm)) OR (Breast Malignant Tumors)) OR (Breast Carcinoma)) AND (NAFLD) OR (NAFLD)) OR (NAFLD) OR (NAFLD)) OR (Non-alcoholic Fatty Liver)) OR (NASH)) OR (NASH). In addition, the list of bibliography of all the selected articles or their citations were manually searched in Google Scholar to find other relevant articles. Figure 1 illustrates the study selection process in PRISMA flowchart.

### Inclusion and exclusion criteria

After eliminating duplicates, the title and abstract of the related studies were screened. Subsequently, the full-text of the papers was reviewed by two authors independently to check the inclusion and exclusion criteria and assess the articles' quality. Contrasts of opinion between the reviewers were resolved by a third person alone and in consensus.

The inclusion criteria herein were as follows: 1) observational studies (case-control studies and cohort studies that investigated the association between NAFLD and BCs); 2) risk estimates, including odds ratio (OR), hazard ratio (HR), or incidence rate ratio (IRR), whose 95% confidence intervals (CI) were reported or could be calculated

| Study name | Statistics for each study | | | | | Odds ratio and 95%CI | Relative weight | Relative weight |
|---|---|---|---|---|---|---|---|---|
| | Odds ratio | Lower limit | Upper limit | Z-Value | P-Value | | | |
| Huber et al.2020 | 2.049 | 1.564 | 2.685 | 5.204 | 0.000 | | 11.96 | |
| Park et al.2020 | 1.108 | 1.068 | 1.149 | 5.453 | 0.000 | | 14.76 | |
| Henrik et al.2003 | 1.272 | 0.586 | 2.761 | 0.608 | 0.543 | | 5.00 | |
| Bilici et al.2007 | 1.842 | 0.755 | 4.493 | 1.343 | 0.179 | | 4.11 | |
| Firat et al.2022 | 1.920 | 1.085 | 3.397 | 2.241 | 0.025 | | 7.18 | |
| Noorwati et al.2020 | 1.560 | 1.042 | 2.335 | 2.161 | 0.031 | | 9.67 | |
| Allen et al.2019 | 1.600 | 1.290 | 1.985 | 4.277 | 0.000 | | 12.87 | |
| Kwak et al.2018 | 1.630 | 1.012 | 2.625 | 2.009 | 0.045 | | 8.50 | |
| Kim et al.2017 | 1.920 | 1.151 | 3.203 | 2.499 | 0.012 | | 7.98 | |
| Nseir et al.2017 | 2.820 | 1.446 | 5.500 | 3.042 | 0.002 | | 6.02 | |
| Zhang et al.2022 | 1.360 | 1.037 | 1.784 | 2.220 | 0.026 | | 11.94 | |
| | 1.618 | 1.308 | 2.001 | 4.432 | 0.000 | | | |

0.01   0.1   1   10   100

Favours A          Favours B

**Figure 2.** This figure shows the association between NAFLD and breast cancer.
NAFLD: Non-alcoholic fatty liver disease; CI: Confidence interval

**Table1.** Summary of the studies concerning the association between NAFLD and BC

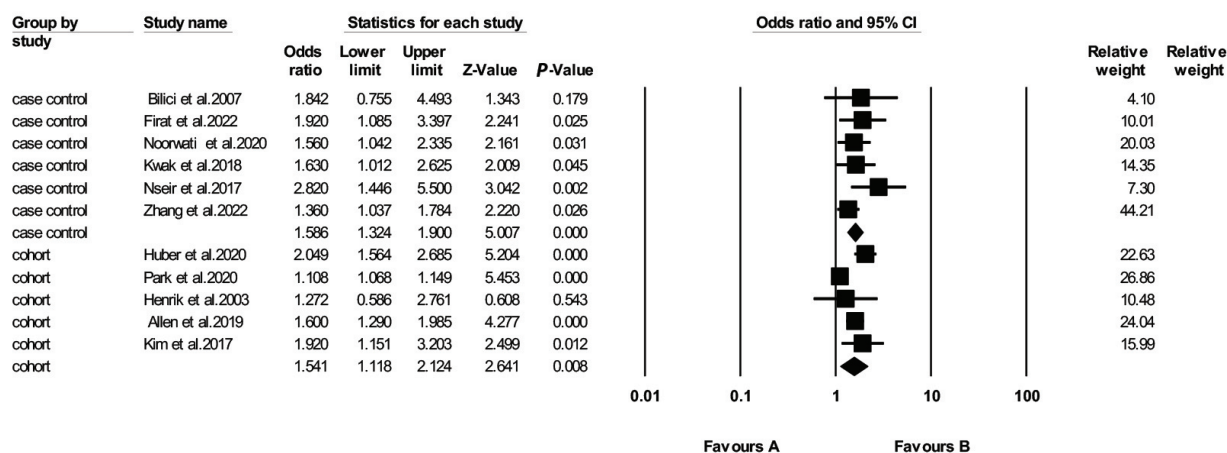| Study | Country | Sample size | Age (years) | OR (95% CI) | NAFLD diagnosis | BC diagnosis | Study design | Adjusted confounding factors | QS |
|---|---|---|---|---|---|---|---|---|---|
| Fýrat et al., 2022[19] | Turkey | 210 | Control:54.5 ± 11.6 Case:52.4 ± 10.1 | 1.92 (1.08-303) | Hepatic ultrasonography | Mammography | Case-control | Age, BMI, prevalence of HT, DM, HL | 4 |
| Noorwati et al., 2020[21] | Indonesia | 436 | 50 | 1.56 (1.04-2.33) | High-end ultrasound equipment. | Medical records | Case-control | - | 4 |
| Huber et al., 2020[20] | Germany | 30324 | 58 ± 14 | 2.04 (1.56-2.68) | Medical record | Medical record | Cohort | HT, DM, dyslipidemia, obesity, BMI, age, sex, physician, index year, and CCI | 5 |
| Park et al., 2020[11] | Korea | 7046153 | 49.08 ± 14.49 | 1.10 (1.01-1.14) | FLI | Medical record | Cohort | Age, smoking status, drinking, regular exercise, DM, and BMI | 8 |
| Allen et al., 2019[23] | USA | 10204 | 54 | 1.60 (1.30-2.0) | Medical record. | Medical record | Cohort | Age and sex | 8 |
| Kwak et al., 2018[7] | Korea | 444 | Control:51.6 ± 9.3 Case: 51.7 ± 9.3 | 1.63 (1.01-2.62) | Hepatic ultrasonography | Mammography | Case-control | Menstrual and reproductive factors, age, and BMI | 7 |
| Kim et al., 2017[9] | Korea | 11981 | 53.2±9.5 | 1.92 (1.15-3.20) | Hepatic ultrasonography | Pathological | Cohort | Age and sex | 8 |
| Nseir et al., 2017[24] | Occupied Palestinian Territory | 146 | Case: 54.8 ± 12 Control: 57.5 ± 9.6 | 2.82 (1.44-5.50) | Abdominal CT examination | Mammographic | Case-control | Age and BMI | 9 |
| Bilici et al., 2007[17] | Turkey | 80 | Case:47.5 ± 11.9 Control:43.4 ± 6.0 | 1.84 (0.75-4.49) | Hepatic ultrasonography | Medical record | Case-control | Age | 5 |
| Henrik et al., 2003[22] | Denmark | 840 | 56 | 1.27 (0.58-2.76) | Medical record | Pathological | Cohort | - | 5 |
| Hong et al., 2022[5] | China | 1976 | Case: 50.0 ± 10.9 Control:50.6 ± 10.9 | 1.36 (1.04-1.79) | Hepatic ultrasonography | Ultrasonography | Case-control | - | 6 |

QS: Quality study; NAFLD: Non-alcoholic fatty liver disease; BC: Breast cancer; CCI: Charlson comorbidity index; BMI: Body mass index; CT: Computerized tomography; OR: Odds ratio; FLI: Fatty liver index; CI: Confidence interval; DM: Diabetes mellitus; HT: Hypertension; HL: Hyperlipiemia;"-": not applicable

using the data reported in the articles; 3) studies with full-text access published in English.

On the other hand, inconsistency in data, the use of inappropriate statistical methods, uncertainty of sampling method, duplicate articles, review articles and meta-analysis, letter to editor, short reports, case reports, case series, cross-sectional studies, conference reports, animal studies, and papers that did not have enough data to calculate the OR were the excluded from the current research.

It should be mentioned that in this study, NAFLD was defined by histopathologic tests, imaging, or ICD-10 codes, demonstrating HS, or medical record. BC was defined based on pathology tests, mammography, and medical records.



**Figure 3.** Subgroup meta-analysis of the association between NAFLD and breast cancer based on the study design.
NAFLD: Non-alcoholic fatty liver disease; CI: Confidence interval

## Data collection

An Excel data extraction form was used for collecting the following data from eligible studies: the first author, year of publication, country of study, sample size, NAFLD diagnosis, BC diagnosis, study design, and adjusted confounding factors (Table 1).

## Quality assessment (risk of bias)

The quality of the included studies was evaluated based on the Newcastle–Ottawa Scale (NOS). According to the NOS assessment score, the quality of a study was considered good (6<), moderate (3-5), and low (<3). Therefore, the studies with acceptable (moderate and good) quality were eligible for meta-analysis.[16]

## Statistical analysis

The association between NAFLD and BC with OR was calculated with a 95% CI and presented via forest plots. In this plot, OR greater than one indicates a risk factor, and OR less than one shows a protective effect. HRs and IRRs in the cohort studies transformed into OR. The expected heterogeneity among the studies was evaluated with statistical methods, Cochran's Q test, and the $I^2$ index. Egger's regression was utilized for publication bias assessment.

A fixed-effect model was used when there was no literature heterogeneity. Otherwise, we employed the random effect model. Through the use of the multivariable meta-regression model and subgroups analysis, the effects of probable factors in heterogeneity were investigated. The meta-analysis was conducted with the trial version of Comprehensive Meta-Analysis software vs. 3.

## Results

### Search results and eligibility of the studies

In this systematic review, 1568 articles were found by searching the entire databases and considering the inclusion criteria. Afterwards, we removed 800 articles due to duplication, as well as 721 papers due to non-compliance with the inclusion criteria in the title and abstract.

However, 36 articles were excluded according to the exclusion criteria after reading the full-text of articles, including: review or case report or letter to the editor (n = 3), animal studies (n = 9), pharmacological interventions (n = 14), conference reports (n = 2), lack of access to full-text (n = 2), cirrhosis studies (n = 2), metabolic-associated fatty liver disease (MAFLD) (n = 1), BC survival (n = 2), and risk factors for NAFLD (n = 1).

Finally, 11 studies met the evaluation criteria, which entered this study (Figure 1).

### Characteristics of the eligible studies

The total eligible studies contained 11 journal papers with 7,102,785 as the sample size. The smallest sample size belonged to a case-control study in Turkey[17] with 80 subjects and the largest sample size to a cohort study in Korea[18] with a sample size of 7,046,153.
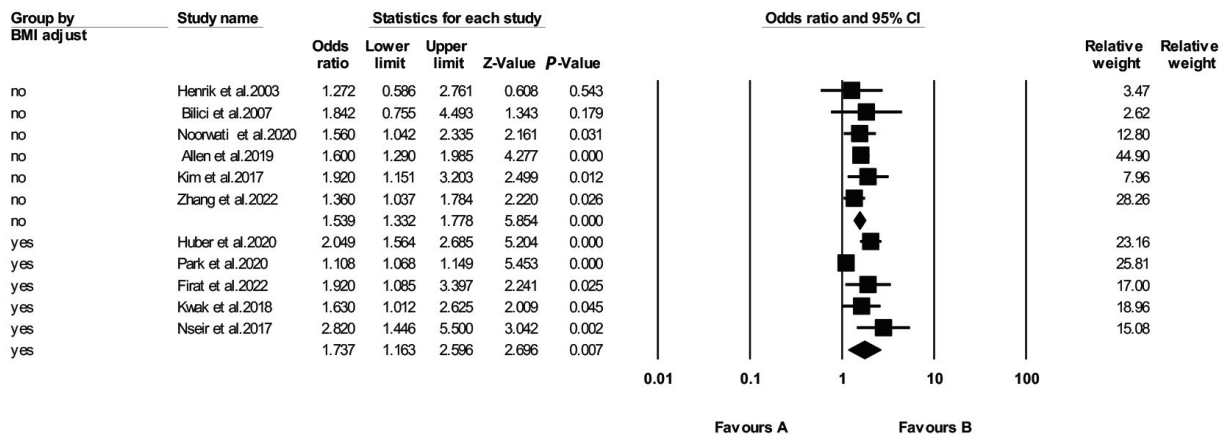


**Figure 4.** Subgroup meta-analysis of the association between NAFLD and breast cancer adjusted based on BMI variable.
NAFLD: Non-alcoholic fatty liver disease; BMI: Body mass index; CI: Confidence interval

**Table 2.** Result of multivariate meta-regression model for detecting probable sources of heterogeneity

| The probable source of heterogeneity | Multivariable | |
|---|---|---|
| | Coefficient (95%CI) | *P*-value |
| Year | 0.003(-0.054-0.060) | 0.91 |
| Country | -0.08 (-1.05-0.87) | 0.69 |
| Design of the study | -0.18(-0.69-0.32) | 0.47 |
| Detection method of breast cancer | -0.38 (-1.59-0.82) | 0.78 |
| Status of adjusted BMI | -0.01 (-0.54-0.57) | 0.96 |

BMI: Body mass index; CI: Confidence interval

Based on geographical regions, three studies were performed in Korea,[7,9,18] two in Turkey,[17,19] one in Germany,[20] and one in Indonesia,[21] Denmark,[22] the USA,[23] Occupied Palestinian Territory,[24] and China[5] (Table 1).

In addition, there were five cohort and six case-control studies. The method of BC diagnosis was mammography (n = 3), pathology (n = 2), ultrasonography (USG) (n = 1), and the use of medical records (n = 5) (Table 1).

According to the NOS quality assessment, no studies scored as low quality, five had medium quality, and the other six was revealed to have good quality (Table 1).

*Association between NAFLD and BC*

A total of 7,102,785 women, including 62,886 women with BC, were studied. The pooled OR of BC was analyzed based on 11 studies in order to examine the association between NAFLD and BC risk. Utilizing a random-effects meta-analysis,

the overall OR of NAFLD, as a risk of developing BC, was estimated at 1.61 (95% CI: 1.30-2.00) (Q-value: 51.35, I2 = 80.52%, $P < 0.0001$) (Figure 2).

Multivariable meta-regression analysis showed that the publication year-, country-, BC detection method-, study design-, and body mass index (BMI)-adjusted status did not represent heterogeneity (Table 2).

The results of subgroup analysis displayed that the pooled OR of BC in the case-control studies was 1.58 (95% CI: 1.32-1.90), which was 1.54 (95% CI: 1.11-2.12) in the cohort studies (Figure 3).

Additionally, the pooled OR of BC in the studies was revealed, where the BMI variable was adjusted at 1.73 (95% CI: 1.16-2.59) and not adjusted study at 1.53 (95% CI: 1.33-1.77) (Figure 4).

*Publication bias*

The funnel plot and Egger's test were used for



**Funnel plot of standard error by Log odds ratio**
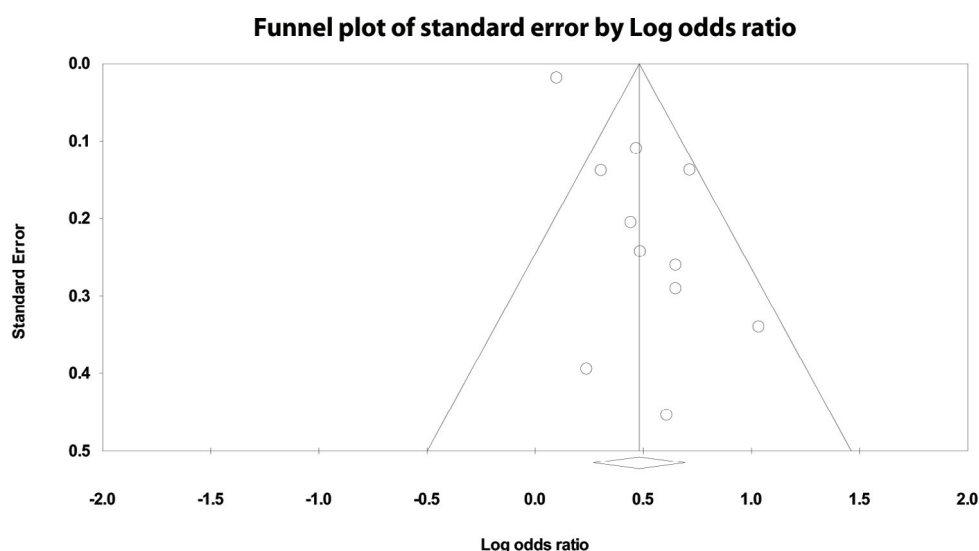
**Figure 5.** This figure shows the funnel plot with pseudo 95% confidence limits for detection of publication bias among the included studies.
Log: Logarithm

assessing the presence of publication bias. The result of Egger's regression ($P = 0.32$) and the symmetry in funnel plot interpretation indicated no publication bias in studies, as displayed in figure 5.

## Discussion

This systematic review was designed in order to evaluate the link between NAFLD and BC. In this study, we analyzed a total of 7,102,785 subjects, including 62,886 women with BC. The pooled OR was analyzed based on 11 studies to examine the association between NAFLD and BC risk. The overall OR of NAFLD, as a risk of developing BC, was estimated at 1.61 (95% CI: 1.30-2.00).

Early diagnosis and accurate therapy are critical for BC. A number of predictive BC risk models have been developed, but none of the research considered NAFLD.[25, 26] Over the past years, the association between NAFLD and BC has attracted a great deal of scientific attention.

Certain papers have indicated that BC is a common extrahepatic complication of NAFLD.[14, 27] It is known that NAFLD causes liver, heart, and kidney diseases.[12] Furthermore, numerous studies on the risk of extrahepatic malignancies have shown a link between NAFLD and certain types of cancer.[11, 14, 19]

The present study shed light on the significant association between NAFLD and BC, so that confirmed NAFLD as an independent risk factor for women with BC. These results are consistent with those reported in previous studies, demonstrating an association between NAFLD and BC.[7, 14, 21, 24] Accordingly, NAFLD is linked to BC, regardless of the known risk factors.

A case-control study showed an association between NAFLD and BC in Occupied Palestinian Territory;[24] however, the sample size was small, at just 73 cases. Furthermore, BC incidence and the outcomes vary according to ethnic background.[7, 28]

Kwak et al. found a statistically significant difference in NAFLD patients with non-obese BC and a control group.[7] Lee et al. also demonstrated that NAFLD is a predictor for BC

and a prognostic factor for its recurrence.[29] In a Korean study that included patients with non-cirrhotic NAFLD, a 1.9-fold greater incidence of BC was observed in women.[30] Other cohort studies also revealed a relationship between NAFLD and BC incidence.[9, 27]

Some possible mechanisms can explain the relationship between BC and NAFLD.[7, 31] Primarily, NAFLD is closely associated with increased pro-inflammatory cytokine levels, such as tumor necrosis factor alpha and interleukin-6, and decreased adiponectin levels,[7, 27] promoting cancer through tumor cell proliferation, anti-apoptotic effects, and angiogenesis.[7, 32] Secondly, NAFLD plays a significant role in developing systemic insulin resistance;[32] insulin can bind to insulin-type I growth factor receptor (IGF-1) expressed on breast cells, and downstream signaling pathways stimulate the proliferation of BC cells.[33] In addition, hyperinsulinemia can increase hepatic synthesis of IGF-I, while decreasing liver expression of IGF-1 binding proteins, resulting in elevated levels of free IGF-I.[34] These changes in NAFLD may lead to BC development.[17, 35]

The diagnosis of NAFLD can be generally confirmed through imaging studies, and the disease can be staged through liver biopsy.[9] In practice, it is difficult to perform a liver biopsy for routine screening due to the invasive and non-economic nature of the procedure.[21, 36] The essential imaging examinations for the diagnosis of liver steatosis include ultrasound computerized tomography and magnetic resonance imaging.[24] Ultrasound is used extensively in clinical practice and health screening to detect liver fat infiltration.[21, 37] However, ultrasound is not sufficiently sensitive for slight steatosis detection and cannot quantify the severity of steatosis in hepatocytes.[24] USG at 60%-70% sensitivity is commonly used in clinical practice.[38, 39] USG sensitivity can arise once two radiologists are present.[17]

Our research also revealed the pooled OR of BC in studies where the BMI variable was adjusted at 1.73 and not adjusted as a confounder variable was 1.53. That mentioned, when the

effect of BMI as a confounding factor is not controlled, the association between non-alcoholic fatty liver and BC is weaker. Still, when its effect is controlled as a confounding factor, the association between fatty liver and BC becomes stronger.

Noorwati Sutandyo et al. demonstrated that HS plays a more critical role as a risk factor in BC occurrence compared with anthropometric BMI.[21] Even though fatty liver is associated with increased BMI, the risk of BC may not be linked to general obesity. The logical explanation for this conclusion is thought to be another factor(s) in the pathogenesis of fatty liver disease, which is also responsible for developing BC.

We herein demonstrated that NAFLD could be a significant intermediate biomarker of BC risk. These results could be put in use as a source of hypotheses for future studies on the biological mechanisms underlying this relationship, considering NAFLD as the main predictor or as a mediator variable in the causal pathway of BC development.

The strengths of this study include the comprehensive search strategy in five international databases, the large total sample size, the stringent methodology, and meta-analysis subgroups, including study design- and BMI-adjusted status.

This study had certain limitations that should be considered. To begin with, we did not assess the known risk factors herein, such as family history of BC, diabetes, breastfeeding, tobacco use, hormone replacement treatment, and a history of benign breast disease (such as atypical hyperplasia). Furthermore, in all the studies in our systematic review NAFLD diagnosis was made using USG, a non-invasive imaging method, rather than biopsy. It could be suggested that future research use magnetic resonance imaging, a non-invasive and susceptible test.

## Conclusion

In conclusion, the current study revealed a significant association between NAFLD and BC, independent of traditional risk factors. Further research is needed to determine which BC subtype is most associated with NAFLD and determine BC screening recommendations for women with NAFLD. Moreover, these results warrant further research to assess the mechanism of BC in women in association with NAFLD. Our findings provide a platform for other mechanistic studies of NAFLD as a hidden vector or interim biomarker of cancer risk in obesity.

## Availability of Data and Materials

The research data used to support the findings of this study are available from the corresponding author of this work upon request.

## Ethics Approval

The authors of this study followed the ethical principles of systematic reviews, including guidance on authorship, avoiding redundant (duplicate) publication, avoiding plagiarism, transparency, and ensuring accuracy with no potential complications. This review was not registered.

## Conflict of Interest

None declared.

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