Breast Cancer Research

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Association between metabolic dysfunction-associated steatotic liver disease and breast cancer risk in Korean women: a nationwide population-based cohort study

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Abstract

Purpose Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common chronic liver disorder linked to systemic metabolic imbalance. Although MASLD has been associated with extrahepatic cancers, including breast cancer, evidence is limited, especially among Asian populations. Given the younger peak incidence of breast cancer in Korea, this study examined the association between MASLD and breast cancer risk in middle-aged Korean women.

Methods We conducted a nationwide, population-based cohort study of 483,279 randomly selected Korean women aged 40–60 years who underwent health checkups from 2012 to 2015. MASLD was defined using the International Classification of Disease-10 (ICD-10) codes or a fatty liver index (FLI ≥ 60) with metabolic criteria. Breast cancer cases were identified using ICD-10 codes (C50, D05) and followed through 2021. Adjusted hazard ratios (HRs) were estimated with Cox proportional hazards models, including subgroup analyses by body mass index (BMI) and menopausal status.

Results MASLD was not significantly linked to overall breast cancer risk (adjusted HR = 1.089, 95% CI 0.984–1.205, $p = 0.099$). However, women with BMI 25–30 kg/m^2 showed a significantly higher risk (adjusted HR = 1.077, $p = 0.011$). Although postmenopausal women had a lower overall risk, MASLD was significantly associated with increased risk in postmenopausal women with BMI 25–30 kg/m^2 (adjusted HR = 1.203, 95% CI 1.029–1.407, $p = 0.021$).

Conclusion In this large Korean cohort, MASLD was not independently linked to overall breast cancer risk, but moderate obesity and menopause may influence this relationship. These findings highlight the need to consider metabolic and hormonal factors in risk assessment.

Keywords MASLD, Breast cancer, Body mass index, Menopausal status

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Introduction

Metabolic dysfunction—including obesity, insulin resistance, and hepatic steatosis—is increasingly recognized as a risk factor for cancer development [1]. Nonalcoholic fatty liver disease (NAFLD), recently renamed metabolic dysfunction-associated steatotic liver disease (MASLD), reflects the liver-specific expression of systemic metabolic imbalance [2]. Under updated consensus guidelines, MASLD is diagnosed when hepatic steatosis is accompanied by at least one cardiometabolic risk factor, such as obesity, type 2 diabetes, or dyslipidemia [2]. This updated definition highlights the metabolic origins of MASLD and its potential link to cancer. Previous studies have shown association between MASLD and increased risk of extrahepatic cancers, including breast cancer [3–5].

In women, the transition to menopause is accompanied by estrogen decline, leading to metabolic changes such as increased visceral fat, insulin resistance, and dyslipidemia [6–8]. These shifts are closely linked to the pathophysiology of MASLD and may also contribute to the development of hormone-sensitive cancers like breast cancer. Proposed mechanisms include hyperinsulinemia, chronic inflammation, and altered estrogen metabolism, which may interact with hepatic steatosis to influence cancer risk [9, 10].

Although prior studies have examined the links between metabolic syndrome or NAFLD and breast cancer risk [5, 11], few have specifically explored how hepatic steatosis interacts with menopausal status. Moreover, many previous studies used cross-sectional designs and did not stratify by menopausal status. These limitations make it difficult to clarify their combined influence on breast cancer development.

Accordingly, we aimed to assess the association between MASLD and breast cancer risk in a large, population-based cohort of middle-aged Korean women. We also examined whether this association varied by menopausal status to better understand how hormonal and metabolic factors together may affect breast cancer risk.

Methods

We established a nationwide retrospective cohort using combined data from four national databases in Korea: the Korean National Health Insurance Service (NHIS), the Health Insurance Review and Assessment Service, the Korea Central Cancer Registry, and Statistics Korea. These databases cover nearly the entire Korean population and include longitudinal data on demographics, health screening results, medical diagnoses, prescriptions, cancer cases, and confirmed causes of death. All personal identifiers were anonymized before analysis. Because of the retrospective nature of the study, the requirement for written informed consent was waived. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of the Catholic University of Korea (local IRB number, KC23ZISI0410) and was conducted in compliance with relevant data protection laws and ethical standards in the Republic of Korea.

Study design and patient enrollment

The study population consisted of women aged 40–60 years who had undergone at least one general health screening between January 1, 2012 and December 31, 2015. In Korea, the NHIS health examination program provides biennial health screening for all individuals aged 40 and above. The date of the first screening within this period was defined as the index date. Because the NHIS database only records the year, not the specific date, the year prior to enrollment was designated as a washout period to ensure that participants hand no pre-existing cancer diagnoses and to establish a clean baseline before follow-up.

Due to the extensive size of the NHIS database, we limited the study cohort to a random sample of one million women, selected by residential region to ensure a balanced representation of both urban and rural areas. Follow-up for incident breast cancer (International Classification of Disease [ICD]-10 codes C50 and D05) began on January 1 of the year following enrollment and continued until December 31, 2021. Women were excluded if they had any cancer diagnosis (ICD-10, any C codes) within 1 year before or after the index date, as these were considered synchronous malignancies. Additional exclusions were prior cancer history before 2012, heavy alcohol intake (≥ 20 g/day), liver cirrhosis, viral hepatitis, chronic kidney disease, organ transplantation, or missing key covariate data. The full list of exclusion diagnostic codes is provided in Supplementary Table 1.

Variable definitions

Baseline demographic, clinical, socioeconomic, and lifestyle data were obtained from NHIS records. Menopausal status was determined based on health screening information: women who self-reported menopause or were aged 50 years or older at baseline were classified as postmenopausal; all others were categorized as premenopausal. This age threshold reflects the average natural menopausal age of Korean women (49–51years) [12, 13].

Physical activity level was measured using responses from the health screening questionnaire, which recorded the number of days per week spent walking, doing moderate-intensity exercise, and performing vigorous-intensity exercise. Total weekly physical activity was estimated in metabolic equivalents (METs) using the formula:

(2 METs x days of walking) + (4 METs x days of moderate-intensity activity) + (6 METs x days of vigorous-intensity activity).

The resulting scores were divided into quartiles and used to define physical activity categories for this analysis.

Comorbidities such as hypertension, diabetes mellitus, dyslipidemia, and cardiovascular disease were identified through ICD-10 codes from inpatient and outpatient claims (see Supplementary Table 1). To assess the overall comorbidity burden, we used the Charlson Comorbidity Index (CCI), a validated tool for measuring chronic disease severity. Each condition was assigned a weighted score, and total CCI scores were included as covariates in the multivariable models (Supplementary Table 2) [14–16].

Definition of MASLD

MASLD was defined based on updated international criteria that include hepatic steatosis, metabolic dysfunction, and alcohol intake. Women were considered to have MASLD if they had a documented diagnosis of hepatic steatosis (ICD-10 code K76.0). For those without a clinical diagnosis, MASLD was defined by meeting all three of the following conditions [17]:

1. Evidence of steatosis indicated by either a fatty liver index (FLI) ≥ 60 or a hepatic steatosis index (HSI) ≥ 36.
2. At least one marker of metabolic dysfunction, including:
   - Body mass index (BMI) ≥ 23 kg/m² or waist circumference ≥ 85 cm.
   - Fasting plasma glucose ≥ 100 mg/dL, antidiabetic medication use, or a diagnosis of type 2 diabetes (ICD-10 code: E11).
   - Systolic blood pressure ≥ 130mmHg, diastolic blood pressure ≥ 85mmHg, or antihypertensive medication use.
   - Triglyceride levels ≥ 150 mg/dL or lipid-lowering therapy use.
   - HDL cholesterol < 50 mg/dL or lipid-lowering therapy use;
3. Alcohol consumption less than 20 g/day.

The FLI is a widely validated prediction model that incorporated triglyceride levels, BMI, gamma-glutamyl transferase (GGT), and waist circumference (WC) [18]. The FLI score ranges from 0 to 100 and is calculated as follows:

$$FLI = \frac{e^{0.953 \cdot ln(TG) + 0.139 \cdot BMI + 0.718 \cdot ln(GGT) + 0.053 \cdot WC - 15.745}}{1 + e^{0.953 \cdot ln(TG) + 0.139 \cdot BMI + 0.718 \cdot ln(GGT) + 0.053 \cdot WC - 15.745}} \times 100$$

As noted in international guidelines from the European Association for the Study of the Liver [17], noninvasive biomarkers like the FLI are recommended for defining MASLD in large population-based studies, since liver biopsy or imaging is not practical in asymptomatic general populations.

In Korean validation studies [19, 20], an FLI cutoff of ≥ 30 showed good diagnostic performance for detecting fatty liver confirmed by ultrasonography, with an area under the receiver operating characteristic curve of 0.82 (95% CI, 0.81–0.84). In this study, we used a stricter cutoff of FLI ≥ 60 to define hepatic steatosis, since individuals with viral hepatitis, alcoholic liver disease, or other chronic liver conditions were excluded. Women who did not meet either the diagnostic code criteria or the FLI threshold were categorized as the non-MASLD group.

The HSI, which includes the alanine aminotransferase to aspartate aminotransferase ratio, BMI, sex, and diabetes status, has also been validated as a noninvasive indicator for hepatic steatosis [21]. Although HSI was calculated in this study, the primary classification of exposure relied only on the FLI, as it is the most widely used and internationally validated noninvasive marker, ensuring consistency throughout the cohort.

Study outcomes

The primary outcome of this study was the risk of breast cancer and ductal carcinoma in situ (DCIS) (ICD-10 codes C50 and D05) in relation to MASLD. The secondary outcome examined whether the association between MASLD and breast cancer risk differed by menopausal status and BMI. BMI was divided into three categories: ≤25, > 25 to < 30, and ≥ 30 kg/m².

Statistical analysis

Descriptive statistics were used to compare baseline demographic and clinical characteristics between groups, applying Student's *t*-tests for continuous variables and chi-squared tests for categorical variables. The cumulative incidence of breast cancer was estimated using Kaplan–Meier curves and compared with log-rank tests. To determine factors associated with breast cancer risk, univariable and multivariable Cox proportional hazards regression models were created, adjusting for relevant covariates. Effect modification by menopausal status and BMI was formally evaluated by including interaction terms with MASLD in the Cox models. The multivariable model was adjusted for the following prespecified covariates: BMI, waist circumference, income level, smoking status, alcohol consumption, physical activity level, diabetes mellitus, hypertension, dyslipidemia, history of cardiac disease, age at menarche, contraceptive pill use, and CCI score. Statistical significance was defined as a two-sided p-value below 0.05. All analyses were performed

using SAS software (version 9.3, SAS Institute Inc., Cary, NC, USA).

Results

Patient flow diagram of the cohort

A total of 703,607 women underwent national health screening in Korea between 2013 and 2016 (Fig. 1). After excluding those outside the 40–60 age range ($n = 132,917$), 570,690 women remained. Among these, 87,411 were further excluded due to heavy alcohol sue, chronic liver or kidney disease, prior cancer, organ transplantation, or missing key data. The final cohort comprised 483,279 women, of whom 35,049 (7.3%) were classified as having MASLD, and 448,230 (92.7%) as non-MASLD.

Baseline characteristics according to MASLD status

Baseline characteristics by MASLD status are summarized in Table 1. Of the 483,279 women included, 7.3% ($n = 35,049$) were classified as having MASLD, while 92.7% ($n = 448,320$) were in the non-MASLD group. Women with MASLD had higher BMI and waist circumference, and more frequent metabolic comorbidities compared with those without MASLD (all $p < 0.001$). They were more likely to be current smokers, less physically active, and in lower income quartiles. Differences

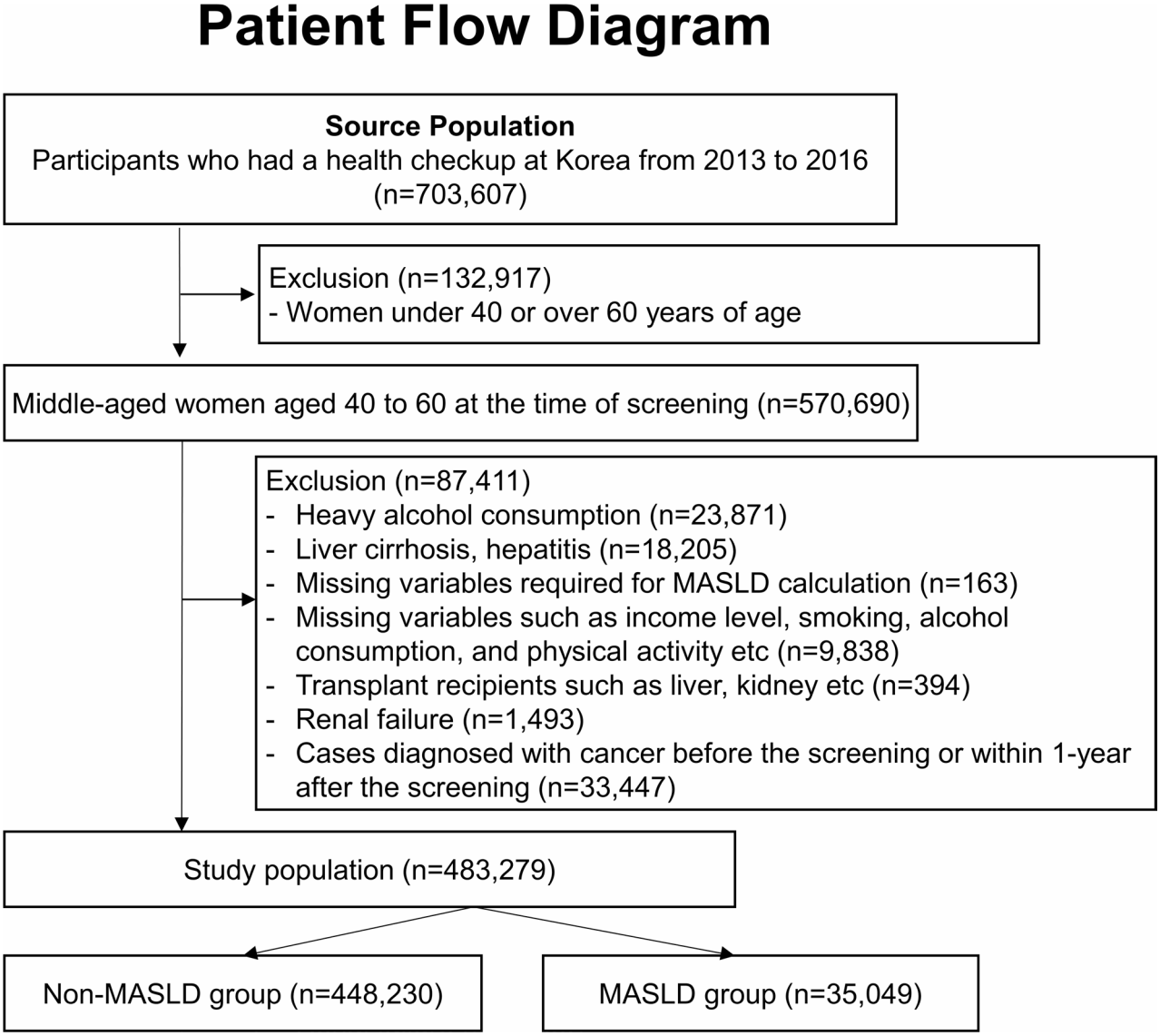

Fig. 1 Flowchart of participants selection in the retrospective cohort study. Participants were women who underwent a national health checkup in Korea between 2013 and 2016 (n = 703,607). After excluding women aged < 40 or > 60 years (n = 132,917), 570,690 middle-aged women were eligible. Further exclusions based on specific clinical and data-related criteria resulted in a final cohort of 483,279 women, who were classified into the Non-MASLD group (n = 448,230) and MASLD group (n = 35,049)

Table 1 Baseline characteristics of the study subjects

	Total, *n* = 483,279 (%)	**Non-MASLD, *n* = 448,230 (%)**	**MASLD, *n* = 35,049 (%)**
Breast cancer			
No	474,188 (98.1)	439,819 (98.1)	34,369 (98.1)
Yes	9091 (1.9)	8411 (1.9)	680 (1.9)
BMI			
≤25	344,108 (71.2)	341,544 (76.2)	2564 (7.3)
>25 and < 30	106,604 (22.1)	93,929 (21.0)	12,675 (36.2)
≥30	32,567 (6.7)	12,757 (2.8)	19,810 (56.5)
Age			
≤40 and < 45	77,346 (16.0)	72,563 (16.2)	4783 (13.7)
≤45 and < 50	93,690 (19.4)	87,681 (19.5)	6009 (17.1)
≤50 and < 55	169,586 (35.1)	157,169 (35.1)	12,417 (35.4)
≤55 and < 60	142,657 (29.5)	130,817 (29.2)	11,840 (33.8)
Waist circumference			
85<	384,334 (79.5)	379,732 (84.7)	4602 (13.1)
≤85 and < 100	91,145 (18.9)	67,709 (15.1)	23,436 (66.9)
≤100	7800 (1.6)	789 (0.2)	7011 (20.0)
Income level			
1st quartile	9841 (2.0)	8406 (1.9)	1435 (4.1)
2nd quartile	143,717 (29.7)	133,632 (29.8)	10,085 (28.8)
3rd quartile	165,601 (34.3)	152,488 (34.0)	13,113 (37.4)
4th quartile	164,120 (34.0)	153,704 (34.3)	10,416 (29.7)
Smoking			
Non-smoker	463,982 (96.0)	431,286 (96.2)	32,696 (93.3)
Former smoker	6351 (1.3)	5660 (1.3)	691 (2.0)
Current smoker	12,946 (2.7)	11,284 (2.5)	1662 (4.7)
Weekly alcoholic consumption frequency			
None	369,233 (76.4)	342,392 (76.4)	26,841 (76.6)
1–2	102,896 (21.3)	95,574 (21.3)	7322 (20.9)
3–4	9993 (2.1)	9203 (2.1)	790 (2.2)
5–7	1157 (0.2)	1062 (0.2)	96 (0.3)
Physical activity level			
1st quartile	116,819 (24.2)	106,027 (23.7)	10,792 (30.8)
2nd quartile	115,943 (24.0)	107,313 (23.9)	8630 (24.6)
3rd quartile	136,252 (28.2)	126,789 (28.3)	9463 (27.0)
4th quartile	114,265 (23.6)	108,101 (24.1)	6164 (17.6)
DM			
No	432,929 (89.6)	406,489 (90.7)	26,440 (75.4)
Yes	50,350 (10.4)	41,741 (9.3)	8609 (24.6)
HTN			
No	375,088 (77.6)	356,026 (79.4)	19,062 (54.4)
Yes	108,191 (22.4)	92,204 (20.6)	15,987 (45.6)
Dyslipidemia			
No	359,535 (74.4)	338,348 (75.5)	21,187 (60.5)
Yes	123,744 (25.6)	109,882 (24.5)	13,862 (39.5)
Cardiac disease			
No	433,367 (89.7)	403,891 (90.1)	29,476 (84.1)
Yes	49,912 (10.3)	44,339 (9.9)	5573 (15.9)
Age at menarche			
5–14	137,898 (28.5)	127,592 (28.5)	10,306 (29.4)
≥15	281,979 (58.4)	261,135 (58.3)	20,844 (59.5)
Unknown	63,402 (13.1)	59,503 (13.2)	3899 (11.1)
Contraceptive pill usage			

Table 1 (continued)

	Total, *n* = 483,279 (%)	Non-MASLD, *n* = 448,230 (%)	MASLD, *n* = 35,049 (%)
Non-use	353,569 (73.2)	328,022 (73.2)	25,547 (72.9)
Less than 1-year	36,322 (7.5)	33,429 (7.5)	2893 (8.2)
More than 1-year	16,086 (3.3)	14,627 (3.3)	1459 (4.2)
Unknown	77,302 (16.0)	72,152 (16.0)	5150 (14.7)
CCI (mean ± SD)	2.82 ± 1.17	2.78 ± 1.13	3.32 ± 1.49
Menopausal status			
Premenopausal	162,771 (33.7)	152,642 (34.1)	10,129 (28.9)
Postmenopausal	320,508 (66.3)	295,588 (65.9)	24,920 (71.1)

BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; CCI, Charlson comorbidity index; SD, standard deviation

in menopausal status, reproductive factors, and alcohol intake were also noted (Table 1).

Risk of breast cancer according to MASLD status

Table 2 shows the results of the Cox proportional hazards models evaluating the relationship between MASLD and breast cancer risk. In the univariate analysis, MASLD was not significantly linked to breast cancer (hazard ratio (HR) = 1.056, 95% confidence interval (CI) 0.977–1.142, $p = 0.173$). After adjusting for potential confounding factors—including age, BMI, menopausal status, income, lifestyle factors, and comorbidities—MASLD still showed no significant association with breast cancer (adjusted HR = 1.089, 95% CI 0.984–1.205, $p = 0.099$).

In the multivariable model, several variables were independently associated with breast cancer risk. Compared to women with BMI ≤ 25 kg/m², those with a BMI between 25 and 30 kg/m² had a significantly higher risk (adjusted HR = 1.077, 95% CI 1.017–1.141, $p = 0.011$), whereas BMI ≥ 30 kg/m² was not significantly associated. Women aged 50–55 had a higher risk compared to those aged 40–45 (adjusted HR = 1.249, 95% CI 1.029–1.515, $p = 0.025$). In contrast, being postmenopausal was linked to a significantly lower breast cancer risk (adjusted HR = 0.631, 95% CI 0.524–0.759, $p < 0.001$).

Figure 2 shows the Kaplan–Meier curves for cumulative breast cancer incidence by MASLD status. Over a median follow-up of 7.51 ± 0.92 years, the curves began to diverge slightly after about 3 years; however, the difference was not statistically significant (Fig. 2, non-MASLD group, $n = 448{,}230$; MASLD group, $n = 35{,}049$; log-rank $p = 0.183$).

Menopausal status: baseline characteristics and breast cancer risk associated with MASLD

Table 3 summarizes the baseline characteristics by menopausal status and MASLD presence. Of the total cohort, 162,771 women (33.7%) were premenopausal and 320,508 (66.3%) were postmenopausal. In both groups, women with MASLD had significantly higher BMI and waist circumference than those without MASLD ($p < 0.001$ for all comparisons). Notably, the proportion of women with BMI ≥ 30 kg/m² was markedly higher in the MASLD group, both among premenopausal (62.5% vs. 3.1%) and postmenopausal women (53.0% vs. 2.7%). The prevalence of metabolic comorbidities such as diabetes, hypertension, and dyslipidemia was significantly greater in the MASLD group within both menopausal categories ($p < 0.001$ for all). The mean CCI score was also higher for MASLD participants, both among premenopausal (3.07 vs. 2.58) and postmenopausal women (3.42 vs. 2.89) ($p < 0.001$). In terms of lifestyle factors, women with MASLD were more likely to be current smokers and reported lower levels of physical activity, regardless of menopausal status ($p < 0.001$ for all).

Breast cancer incidence also differed by MASLD status. Among premenopausal women, the MASLD group had a slightly lower incidence of breast cancer compared to the non-MASLD group (1.9% vs. 2.3%, $p = 0.008$). Conversely, among postmenopausal women, incidence was slightly higher in the MASLD group (2.0% vs. 1.7, $p < 0.001$).

Table 4 shows the Cox proportional hazards model results for the association between MASLD and breast cancer, stratified by menopausal status. For premenopausal women, MASLD was linked to a lower breast cancer risk in the univariate analysis (HR = 0.842; 95% CI 0.728–0.973; $p = 0.020$), but this relationship was no longer significant after multivariable adjustment (adjusted HR = 0.977; 95% CI 0.808–1.182, $p = 0.812$). In the postmenopausal group, univariate analysis showed a higher breast cancer risk in women with MASLD (HR = 1.206; 95% CI 1.099–1.324, $p < 0.001$). However, this association weakened and was not statistically significant in the multivariable model (adjusted HR = 1.124; 95% CI 0.997–1.267, $p = 0.057$).

Subgroup analysis by BMI and menopausal status

As an additional analysis, we explored the relationship between MASLD and breast cancer risk within BMI categories. Supplementary Table 3 summarizes baseline characteristics across three BMI groups (≤ 25, > 25 to < 30, and ≥ 30 kg/m²) by MASLD status. In all groups, women

Table 2 Risk of breast cancer from analyses using Cox proportional hazard models in middle-aged women

	Univariate analysis		Multivariable analysis	
	HR (95% CIs)	***P* value**	**HR (95% CIs)**	***P* value**
MASLD		0.173		0.099
No	Reference		Reference	
Yes	1.056 (0.977–1.142)		1.089 (0.984–1.205)	
BMI				
≤25	Reference		Reference	
>25 and < 30	1.038 (0.988–1.091)	0.141	1.077 (1.017–1.141)	0.011
≥30	1.052 (0.969–1.142)	0.224	1.065 (0.951–1.194)	0.276
Age				
≥40 and < 45	Reference		Reference	
≥45 and < 50	0.936 (0.878–0.997)	0.041	0.989 (0.927–1.055)	0.735
≥50 and < 55	0.758 (0.715–0.803)	< 0.001	1.249 (1.029–1.515)	0.025
≥55 and < 60	0.681 (0.640–0.724)	< 0.001	1.137 (0.935–1.383)	0.200
Waist circumference				
<85	Reference		Reference	
≥85 and < 100	0.980 (0.930–1.034)	0.467	0.955 (0.892–1.023)	0.188
≥ 100	0.989 (0.838–1.168)	0.899	0.897 (0.736–1.094)	0.285
Income level				
1st quartile	Reference		Reference	
2nd quartile	0.997 (0.856–1.161)	0.969	0.996 (0.854–1.162)	0.962
3rd quartile	1.007 (0.865–1.172)	0.928	1.016 (0.872–1.183)	0.843
4th quartile	1.117 (0.960–1.300)	0.151	1.116 (0.958–1.301)	0.158
Smoking				
Non-smoker	Reference		Reference	
Former smoker	1.048 (0.876–1.071)	0.484	1.005 (0.839–1.203)	0.958
Current smoker	0.964 (0.845–1.099)	0.584	0.963 (0.843–1.100)	0.578
Weekly alcoholic consumption frequency				
None	Reference		Reference	
1–2	1.018 (0.968–1.071)	0.484	0.969 (0.921–1.020)	0.232
3–4	1.281 (1.125–1.459)	< 0.001	1.239 (1.087–1.412)	0.001
5–7	1.037 (0.682–1.576)	0.865	1.043 (0.686–1.586)	0.842
Physical activity level				
1st quartile	Reference		Reference	
2nd quartile	1.100 (1.037–1.166)	0.002	1.070 (1.008–1.135)	0.026
3rd quartile	1.043 (0.958–1.105)	0.150	1.020 (0.963–1.081)	0.497
4th quartile	1.001 (0.943–1.064)	0.964	0.986 (0.928–1.048)	0.657
DM				
No	Reference		Reference	
Yes	0.893 (0.832–0.958)	0.002	0.974 (0.891–1.066)	0.570
HTN				
No	Reference		Reference	
Yes	0.930 (0.884–0.977)	0.004	1.017 (0.962–1.075)	0.559
Dyslipidemia				
No	Reference		Reference	
Yes	0.908 (0.866–0.953)	< 0.001	0.986 (0.936–1.039)	0.606
Cardiac disease				
No	Reference		Reference	
Yes	0.901 (0.839–0.966)	0.004	0.969 (0.900–1.043)	0.398
Age at menarche				
5–14	Reference		Reference	
≥15	0.797 (0.761–0.834)	< 0.001	0.855 (0.816–0.897)	< 0.001
Unknown	0.871 (0.815–0.930)	< 0.001	0.912 (0.800–1.039)	0.167
Contraceptive pill usage				

Table 2 (continued)

	Univariate analysis		Multivariable analysis	
	HR (95% CIs)	***P* value**	**HR (95% CIs)**	***P* value**
Non-use	Reference		Reference	
Less than 1-year	0.892 (0.821–0.969)	0.007	0.882 (0.812–0.958)	0.003
More than 1-year	0.992 (0.884–1.113)	0.896	1.028 (0.916–1.154)	0.639
Unknown	0.984 (0.930–1.041)	0.573	0.944 (0.840–1.062)	0.341
CCI (mean ± SD)	0.963 (0.946–0.981)	< 0.001	0.985 (0.963–1.009)	0.218
Menopausal status				
Premenopausal	Reference		Reference	
Postmenopausal	0.733 (0.703–0.764)	< 0.001	0.631 (0.524–0.759)	< 0.001

BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; CCI, Charlson comorbidity index; SD, standard deviation

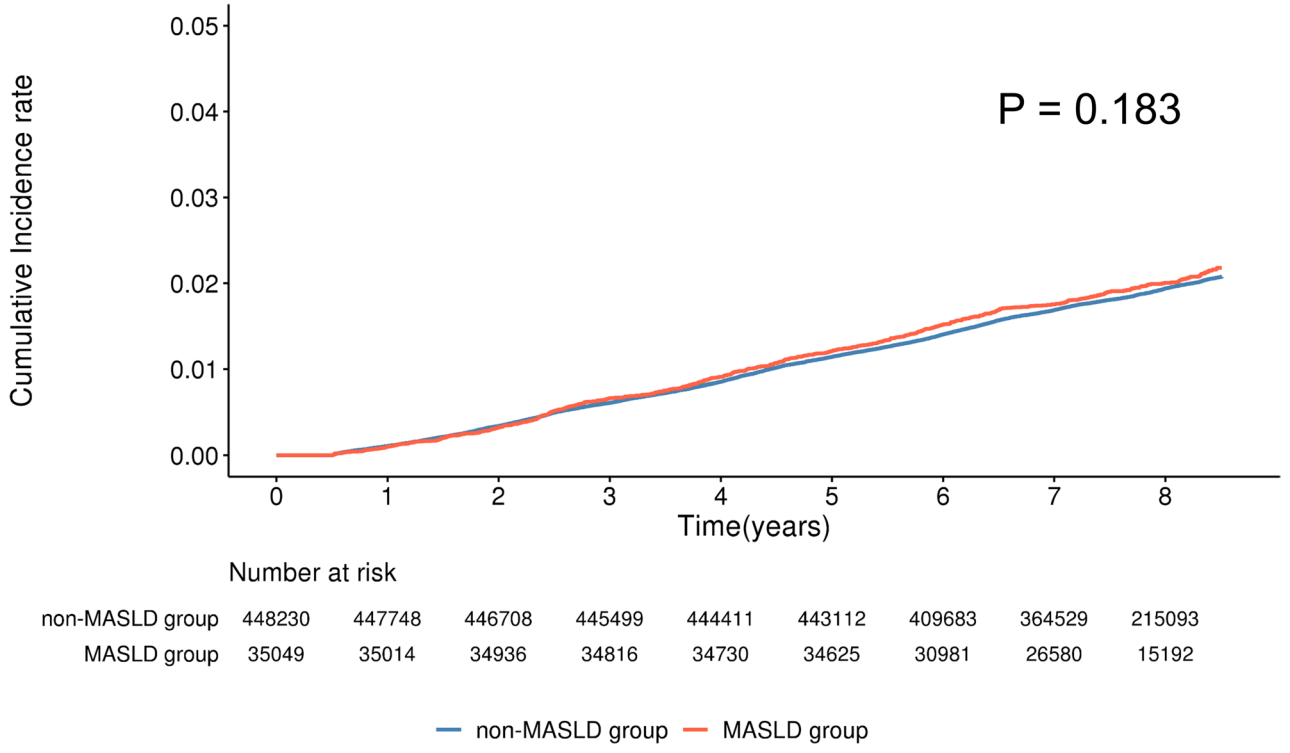

Fig. 2 Kaplan–Meier analysis of the incidence of breast cancer according to MASLD. Participants were categorized into the MASLD group (n = 35,049) and the non-MASLD group (n = 448,230). The log-rank test revealed no statistically difference in breast cancer incidence between the two groups (p = 0.183, median follow up 7.51 ± 0.92 years)

with MASLD were older, had greater waist circumference, and more metabolic comorbidities than those without MASLD ($p < 0.001$ for all comparisons). However, breast cancer incidence did not differ significantly by MASLD status within any BMI category ($p = 0.152$, 0.211, and 0.869, respectively). Supplementary Table 4 provides the related risk estimates. Among women with BMI 25–30 kg/m^2, MASLD was associated with higher risk breast cancer (adjusted HR = 1.149; 95% CI 1.003–1.316, $p = 0.046$). No significant associations were found in other BMI categories.

Figure 3 shows the multivariable associations stratified by both BMI and menopausal status, indicating that the significant increase in risk was observed specifically in postmenopausal women with BMI 25–30 kg/m^2.

To explore this interaction further, we conducted subgroup analyses (Supplementary Table 5) among women with BMI 25–30 kg/m^2, stratified by menopausal status. MASLD was consistently associated with higher waist circumference, comorbidities, smoking and lower physical activity. However, breast cancer incidence was not significantly different by MASLD status in either premenopausal or postmenopausal women ($p = 0.691$ and $p = 0.058$, respectively). In the corresponding Cox regression analysis (Supplementary Table 6), MASLD was not associated with breast cancer risk among premenopausal women (adjusted HR = 1.010; 95% CI 0.767–1.330,

Table 3 Baseline characteristics of middle-aged women by menopause status

	Premenopausal women		Postmenopausal women	
	Non-MASLD, *n* = 152,642 (%)	**MASLD, *n* = 10,129 (%)**	**Non-MASLD, *n* = 295,588 (%)**	**MASLD, *n* = 24,920 (%)**
Breast cancer				
No	149,116 (97.7)	9936 (98.1)	290,703 (98.4)	24,433 (98.1)
Yes	3526 (2.3)	193 (1.9)	4885 (1.7)	487 (2.0)
BMI				
≤25	119,850 (78.5)	543 (5.4)	221,694 (75.0)	2021 (8.1)
>25 and < 30	28,008 (18.4)	2977 (29.4)	65,921 (22.3)	9698 (38.9)
≥30	4784 (3.1)	6609 (65.2)	7973 (2.7)	13,201 (53.0)
Waist circumference				
< 85	134,735 (88.3)	1298 (12.8)	244,997 (82.9)	3304 (13.3)
≥85 and < 100	17,678 (11.6)	6544 (64.6)	50,031 (16.9)	16,892 (67.8)
≥100	229 (0.1)	2287 (22.6)	560 (0.2)	4724 (18.9)
Income level				
1st quartile	3183 (2.1)	500 (4.9)	5223 (1.8)	935 (3.8)
2nd quartile	48,399 (31.7)	3178 (31.4)	85,233 (28.8)	6907 (27.7)
3rd quartile	49,889 (32.7)	3533 (34.9)	102,599 (34.7)	9580 (38.4)
4th quartile	51,171 (33.5)	2918 (28.8)	102,533 (34.7)	7498 (30.1)
Smoking				
Non-smoker	145,821 (95.5)	9325 (92.1)	285,465 (96.6)	23,371 (93.8)
Former smoker	2562 (1.7)	270 (2.7)	3098 (1.0)	421 (1.7)
Current smoker	4259 (2.8)	534 (5.2)	7025 (2.4)	1128 (4.5)
Weekly alcoholic consumption frequency				
None	104,536 (68.5)	6960 (68.7)	237,856 (80.5)	19,881 (79.8)
1–2	43,815 (28.7)	2874 (28.4)	51,759 (17.5)	4448 (17.8)
3–4	3958 (2.6)	271 (2.7)	5245 (1.8)	519 (2.1)
5–7	333 (0.2)	24 (0.2)	728 (0.2)	72 (0.3)
Physical activity level				
1st quartile	40,164 (26.3)	3116 (30.8)	72,993 (24.7)	8134 (32.6)
2nd quartile	32,512 (21.3)	2223 (21.9)	67,671 (22.9)	5949 (23.9)
3rd quartile	38,289 (25.1)	2604 (25.7)	82,221 (27.8)	6463 (25.9)
4th quartile	41,677 (27.3)	2186 (21.6)	72,703 (24.6)	4374 (17.6)
DM				
No	145,060 (95.0)	8196 (80.9)	261,429 (88.4)	18,244 (73.2)
Yes	15,081 (5.0)	1933 (19.1)	34,159 (11.6)	6676 (26.8)
HTN				
No	137,561 (90.1)	6956 (68.7)	218,465 (73.9)	12,106 (48.6)
Yes	15,081 (9.9)	3173 (31.3)	77,123 (26.1)	12,814 (51.4)
Dyslipidemia				
No	133,752 (87.6)	7273 (71.8)	204,596 (69.2)	13,914 (55.8)
Yes	18,890 (12.4)	2856 (28.2)	90,992 (30.8)	11,006 (44.2)
Cardiac disease				
No	145,019 (95.0)	9185 (90.7)	258,872 (87.6)	20,291 (81.4)
Yes	7623 (5.0)	944 (9.3)	367,162 (12.4)	4629 (18.6)
Age at menarche				
5–14	58,936 (38.6)	4259 (42.1)	68,656 (23.2)	6047 (24.3)
≥15	61,519 (40.3)	3963 (39.1)	199,616 (67.5)	16,881 (67.7)
Unknown	32,187 (21.1)	1907 (18.8)	27,316 (9.3)	1992 (8.0)
Contraceptive pill usage				
Non-use	102,620 (67.2)	6649 (65.6)	225,402 (76.3)	18,898 (75.8)
Less than 1-year	11,085 (7.3)	938 (9.3)	22,344 (7.5)	1955 (7.9)
More than 1-year	3613 (2.4)	337 (3.3)	11,014 (3.6)	1122 (4.5)

Table 3 (continued)

	Premenopausal women		Postmenopausal women	
	Non-MASLD, *n* = 152,642 (%)	MASLD, *n* = 10,129 (%)	Non-MASLD, *n* = 295,588 (%)	MASLD, *n* = 24,920 (%)
Unknown	35,324 (23.1)	2205 (21.8)	36,828 (12.4)	2945 (11.8)
CCI (mean ± SD)	2.58 ± 0.95	3.07 ± 1.37	2.89 ± 1.20	3.42 ± 1.53

BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; CCI, Charlson comorbidity index; SD, standard deviation

$p = 0.941$). In contrast, among postmenopausal women, MASLD was independently linked to a significantly higher risk of breast cancer (adjusted HR = 1.203; 95% CI 1.029–1.407, $p = 0.021$).

These results are shown in Supplementary Fig. 1, which displays Kaplan–Meier curves for cumulative breast cancer incidence by MASLD and menopausal status in women with BMI between 25 and 30 kg/m^2. Over a median follow-up of 9.32 ± 2.99 years, no significant difference was found between MASLD and non-MASLD groups in the overall cohort (a, $p = 0.147$) or among premenopausal women (b, $p = 0.781$; median follow-up, 8.51 ± 0.94 years). In contrast, a significant difference was observed among postmenopausal women (c, $p = 0.040$; median follow-up, 7.51 ± 0.93 years).

Discussion

In this large, population-based cohort study of middle-aged Korean women, MASLD was not associated with breast cancer risk in the overall population. However, subgroup analyses showed a significant association in postmenopausal women with moderate obesity (BMI 25–30 kg/m^2), suggesting that menopausal status and BMI-defined adiposity may modify this relationship.

Previous studies have suggested a link between MASLD and breast cancer. For instance, a Korean cohort study by Kim et al. [5] found a significantly higher breast cancer incidence among MASLD patients (HR 1.92). Likewise, Huber et al. [22] and Liu et al. [4] reported modest associations in European cohorts (HR 1.20 and 1.19, respectively). However, these studies often relied on imaging or claims-based diagnoses, lacked consistent metabolic definitions, and were conducted in diverse populations, limiting their generalizability.

Compared to Park et al. [23], who also analyzed Korean NHIS data, our study differed in key methodological aspects. Park et al. defined hepatic steatosis solely by FLI, and found a modest association with breast cancer risk in postmenopausal women with high FLI (≥ 60). In contrast, we applied the updated MASLD definition, requiring both hepatic steatosis and at least one cardiometabolic risk factor, while excluding other chronic liver diseases. We also incorporated ICD-10 code (K76.0) to improve diagnostic accuracy. These stricter criteria likely captured a more metabolically uniform population, better aligned with the current MASLD consensus. Additionally, while Park et al. used FLI as a continuous scale, we applied a clinically meaningful cutoff to identify individuals with both hepatic steatosis and metabolic dysfunction. Such differences in disease definition, cohort composition, and analysis may explain the divergent findings, despite similar data sources. Our result highlights the importance of consistent diagnostic criteria when evaluating the link between fatty liver disease and breast cancer risk.

Although our study did not find a statistically significant link between MASLD and breast cancer in the overall population, several mechanisms support the biological plausibility of this relationship. MASLD reflects systemic metabolic dysfunction, which may promote cancer development through insulin resistance, chronic inflammation, and altered estrogen metabolism-particularly in postmenopausal women [24–27]. Elevated insulin and IGF-1 levels, common in MASLD, have proliferative effects on breast tissue, while hepatic steatosis may influence estrogen clearance, potentially increasing peripheral estrogen levels, a known risk factor for hormone receptor-positive breast cancer [26, 28].

Despite these plausible pathways, the lack of a significant association in our overall analysis suggests that MASLD alone may not be a strong independent risk factor for breast cancer, particularly after adjusting for key confounders like BMI, menopausal status, and other comorbidities. It's also possible that its impact is confined to certain subgroups or interacts with unmeasured metabolic factors. Moreover, the current MASLD diagnostic criteria require both hepatic steatosis and metabolic dysfunction, individuals with hepatic steatosis alone may have been excluded. Therefore, MASLD, as defined by these stricter criteria, may not be a strong standalone predictor of breast cancer risk [23].

Our stratified findings demonstrated clear effect modification by menopausal status and BMI. Notably, women with a BMI between 25 and 30 kg/m^2 had a significantly higher risk of breast cancer (adjusted HR = 1.077, 95% CI 1.017–1.141, $p = 0.011$), while no such association was seen in women with BMI ≥ 30 kg/m^2. This may be explained by the relatively low rate of severe obesity among Korean women [29] and the possibility that even moderate adiposity can meaningfully affect hormonal and metabolic profiles in this group. Previous studies have indicated that greater adiposity may increase peripheral conversion of androgens to estrogen in fat

Table 4 Risk of breast cancer in analyses using Cox proportional hazard models according to menopausal status in middle-aged women

	Premenopausal women				**Postmenopausal women**			
	Univariate analysis		**Multivariable analysis**		**Univariate analysis**		**Multivariable analysis**	
HR (95% CIs)	***P* value**	**HR (95% CIs)**	***P* value**	**HR (95% CIs)**	***P* value**	**HR (95% CIs)**	***P* value**	
MASLD		0.020		0.812		< 0.001		0.057
No	Reference		Reference		Reference		Reference	
Yes	0.842 (0.728–0.973)		0.977 (0.808–1.182)		1.206 (1.099–1.324)		1.124 (0.997–1.267)	
BMI								
≤25	Reference		Reference		Reference		Reference	
>25 and < 30	0.915 (0.841–0.995)	0.039	0.956 (0.869–1.051)	0.352	1.153 (1.084–1.227)	< 0.001	1.167 (1.086–1.254)	< 0.001
≥30	0.820 (0.714–0.941)	0.005	0.909 (0.748–1.104)	0.335	1.237 (1.117–1.370)	< 0.001	1.231 (1.069–1.417)	0.004
Waist circumference								
< 85	Reference		Reference		Reference		Reference	
≥ 85 and < 100	0.863 (0.784–0.949)	0.003	0.925 (0.818–1.046)	0.214	1.092 (1.023–1.164)	0.008	0.958 (0.882–1.041)	0.310
≥ 100	0.819 (0.614–1.092)	0.174	0.954 (0.674–1.352)	0.793	1.125 (0.918–1.378)	0.258	0.861 (0.676–1.097)	0.226
Income level								
1st quartile	Reference		Reference		Reference		Reference	
2nd quartile	1.117 (0.876–1.424)	0.374	1.071 (0.838–1.369)	0.584	0.927 (0.762–1.128)	0.449	0.947 (0.778–1.154)	0.592
3rd quartile	1.185 (0.929–1.510)	0.171	1.137 (0.891–1.451)	0.301	0.922 (0.759–1.120)	0.413	0.938 (0.771–1.141)	0.523
4th quartile	1.344 (1.055–1.711)	0.017	1.272 (0.997–1.622)	0.053	1.004 (0.827–1.220)	0.965	1.021 (0.839–1.242)	0.836
Smoking								
Non-smoker	Reference		Reference		Reference		Reference	
Former smoker	0.879 (0.674–1.148)	0.344	0.876 (0.670–1.144)	0.330	1.152 (0.904–1.469)	0.253	1.143 (0.895–1.458)	
Current smoker	0.812 (0.656–1.004)	0.055	0.826 (0.666–1.024)	0.081	1.063 (0.900–1.256)	0.472	1.069 (0.903–1.266)	
Weekly alcoholic consumption frequency								
None	Reference		Reference		Reference		Reference	
1–2	0.990 (0.921–1.063)	0.774	1.000 (0.930–1.075)	0.995	0.948 (0.882–1.019)	0.147	0.945 (0.879–1.016)	0.125
3–4	1.175 (0.972–1.421)	0.096	1.201 (0.992–1.453)	0.061	1.290 (1.079–1.544)	0.005	1.288 (1.076–1.542)	0.006
5–7	1.011 (0.505–2.023)	0.976	1.023 (0.511–2.048)	0.949	1.051 (0.622–1.776)	0.853	1.056 (0.625–1.785)	0.839
Physical activity level								
1st quartile	Reference		Reference		Reference		Reference	
2nd quartile	1.081 (0.986–1.186)	0.096	1.068 (0.973–1.171)	0.165	1.071 (0.992–1.157)	0.081	1.070 (0.991–1.156)	0.085
3rd quartile	0.992 (0.907–1.086)	0.869	0.980 (0.895–1.073)	0.660	1.050 (0.976–1.131)	0.193	1.052 (0.977–1.133)	0.180
4th quartile	0.975 (0.892–1.065)	0.576	0.957 (0.876–1.047)	0.340	0.998 (0.923–1.078)	0.950	1.003 (0.928–1.084)	0.946
DM								
No	Reference		Reference		Reference		Reference	
Yes	0.856 (0.739–0.992)	0.039	0.907 (0.760–1.083)	0.280	0.972 (0.896–1.054)	0.490	0.990 (0.892–1.099)	0.853
HTN								
No	Reference		Reference		Reference		Reference	
Yes	0.888 (0.798–0.988)	0.029	0.942 (0.840–1.055)	0.301	1.038 (0.978–1.018)	0.216	1.030 (0.967–1.098)	0.360
Dyslipidemia								
No	Reference		Reference		Reference		Reference	
Yes	1.014 (0.923–1.114)	0.769	1.084 (0.980–1.199)	0.115	0.961 (0.907–1.018)	0.179	0.952 (0.896–1.012)	0.115
Cardiac disease								
No	Reference		Reference		Reference		Reference	
Yes	0.850 (0.728–0.992)	0.039	0.882 (0.753–1.033)	0.120	0.991 (0.914–1.073)	0.816	0.988 (0.909–1.074)	0.778
Age at menarche								
5–14	Reference		Reference		Reference		Reference	
≥15	0.891 (0.828–0.958)	0.002	0.899 (0.835–0.966)	0.004	0.817 (0.769–0.869)	< 0.001	0.816 (0.767–0.868)	< 0.001
Unknown	0.906 (0.831–0.987)	0.025	0.939 (0.757–1.165)	0.569	0.783 (0.706–0.870)	< 0.001	0.851 (0.717–1.009)	0.064
Contraceptive pill usage								
Non-use	Reference		Reference		Reference		Reference	
Less than 1-year	0.903 (0.793–1.029)	0.126	0.909 (0.798–1.036)	0.151	0.874 (0.785–0.973)	0.014	0.867 (0.779–0.966)	0.009

Table 4 (continued)

	Premenopausal women				Postmenopausal women			
	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
HR (95% CIs)	*P* value	HR (95% CIs)	*P* value	HR (95% CIs)	*P* value	HR (95% CIs)	*P* value	
More than 1-year	0.922 (0.742–1.146)	0.464	0.957 (0.769–1.190)	0.691	1.054 (0.920–1.208)	0.446	1.053 (0.918–1.206)	0.461
Unknown	0.949 (0.878–1.025)	0.184	0.989 (0.807–1.213)	0.918	0.904 (0.831–0.983)	0.018	0.922 (0.799–1.066)	0.273
CCI (mean ± SD)	0.971 (0.939–1.004)	0.087	0.991 (0.952–1.032)	0.675	0.984 (0.963–1.006)	0.151	0.982 (0.954–1.010)	0.270

BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; CCI, Charlson Comorbidity index; SD, standard deviation

tissue, especially in postmenopausal women [9, 30, 31], providing important biologic context for our findings. The menopausal-status-specific associations may also be explained by differing endocrine-metabolic dynamics: in premenopausal women, higher BMI is linked to anovulation and reduced ovarian estrogen production [32], whereas in postmenopausal women adipose aromatase activity and chronic inflammation become more influential drivers of estrogenic and pro-tumorigenic signaling [33]. MASLD, a condition characterized by insulin resistance and chronic low-grade inflammation, overlaps with these adiposity-related mechanisms, which may clarify why MASLD was associated with breast cancer only in postmenopausal women with moderate obesity. Recent longitudinal data from Korean women further support this interpretation. In a large prospective cohort, Cho et al. [34] showed that mammographic density and reproductive hormone changes during the menopausal transition differ substantially by BMI category, highlighting the dynamic interplay between adiposity and endocrine-metabolic fluctuations. These findings provide additional biological context for the menopausal-status-specific associations observed in our study.

Interestingly, postmenopausal women in our cohort showed a lower risk of breast cancer compared to premenopausal women (adjusted HR = 0.631, $p < 0.001$). This result may partly reflect the age-related pattern of breast cancer incidence in Korea, where the highest rates occur in the early 50s [35]—a period that often includes both early postmenopausal and late premenopausal women. Moreover, younger women who develop breast cancer earlier may have different tumor characteristics or genetic predispositions. These findings suggest that menopausal status should not be viewed as a simple binary variable. The interplay of MASLD with hormonal changes and moderate adiposity during this transitional period may elevated breast cancer risk in middle-aged Korean women.

This study has several notable strengths. First, we analyzed a large, nationwide, population-based cohort with long-term follow-up, which improves the generalizability and statistical power of our results. Second, we used an updated diagnostic definition of MASLD that requires evidence of both hepatic steatosis and metabolic dysfunction, likely minimizing population heterogeneity and better representing clinically significant disease. Third, our stratified analyses by menopausal status and BMI revealed subgroup-specific associations that might have been missed in the overall analysis.

Nevertheless, several limitations should be noted. First, MASLD was identified using either diagnostic codes or a combination of the FLI and metabolic criteria. While imaging methods like ultrasound may have supported diagnosis in practice, our dataset did not include direct imaging or histologic confirmation, which could have introduced some misclassification. Second, we lacked data on breast cancer subtypes, such as hormone receptor status or human epidermal growth factor receptor (HER2) expression, which limited our ability to analyze subtype-specific associations. Third, although we adjusted for numerous covariates, residual confounding from unmeasured factors—such as genetic background or detailed reproductive history—cannot be entirely ruled out. In addition, because BMI is incorporated into both the metabolic criteria and the FLI used to define MASLD, fully disentangling the independent effects of BMI and MASLD is inherently difficult; this structural interdependence may have contributed to the attenuation of association in the fully adjusted model. Furthermore, menopausal status was determined self-report or an age-based proxy. Although the age ≥ 50 definition aligns with population-level evidence indicating that Korea women typically experience natural menopause between 49 and 51 years of age, some degree of nondifferential misclassification is possible, which may have biased the associations toward the null. Lastly, because our cohort was linked to Korean women, the results may not be fully applicable to populations with different genetic profiles or lifestyle patterns.

Our findings have implications for clinical risk assessment and public health. While MASLD was not independently associated with breast cancer overall, middle-aged women with moderate obesity or undergoing menopausal transition may warrant closer monitoring. Given the increasing prevalence of MASLD in East Asia [36] and its metabolic implications, its potential contribution

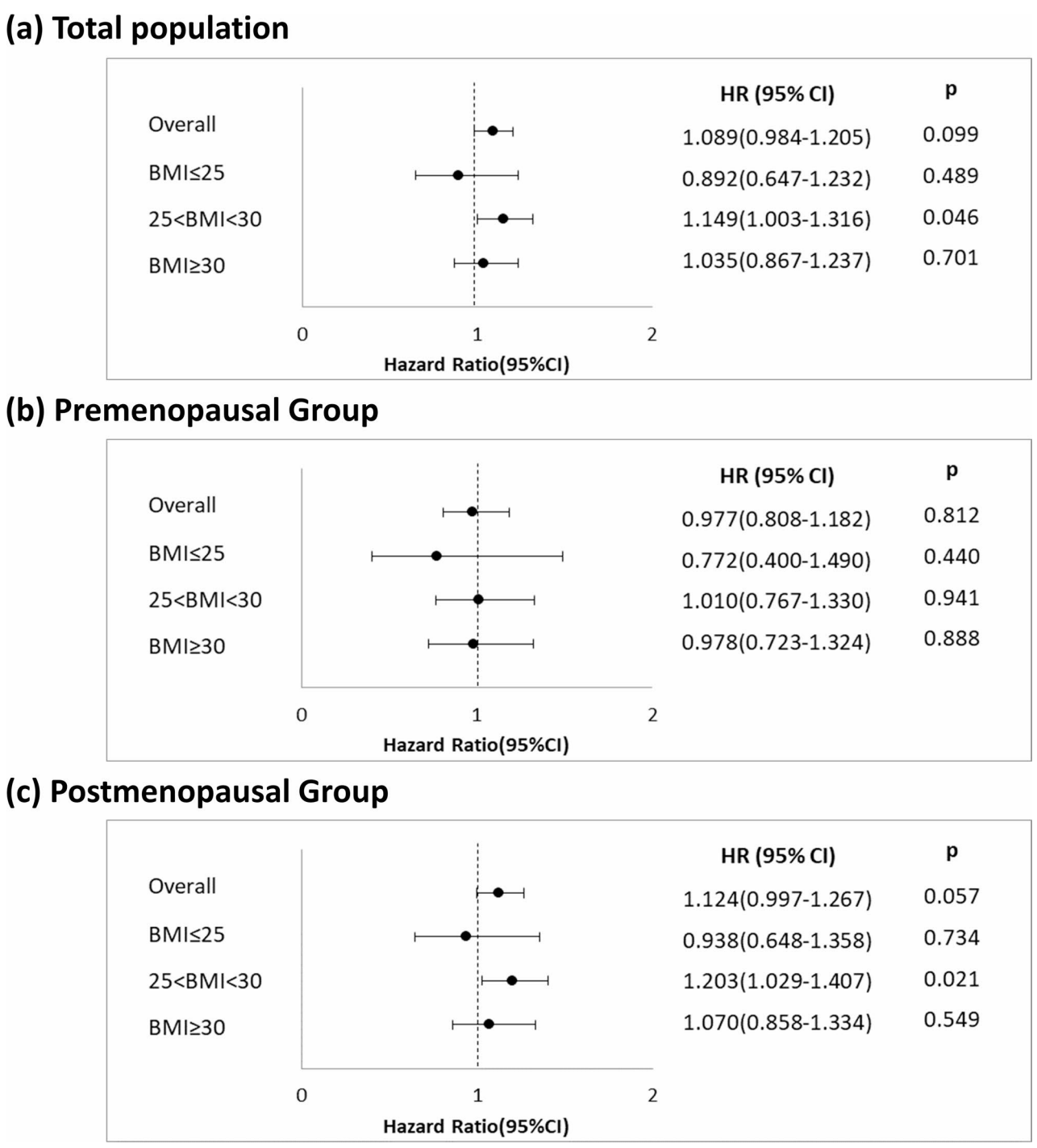

Fig. 3 Forest plot of breast cancer risk by MASLD status across BMI and menopausal subgroups. **a** In the total population, MASLD was not significantly associated with breast cancer risk (HR 1.089; $p=0.099$), except in women with BMI 25–30 kg/m^2 (HR 1.149; $p=0.046$); **b** In the premenopausal group, MASLD was not associated with a significantly overall risk of breast cancer (HR 0.977; $p=0.812$); **c** In the postmenopausal group, MASLD showed a borderline association with breast cancer risk (HR 1.124; $p=0.057$), with a significant increase observed only in those with BMI 25–30 kg/m^2 (HR 1.203; $p=0.021$)

to cancer risk should not be overlooked. Public health efforts to improve metabolic health may reduce not only liver and cardiovascular disease but also cancer risk in selected subgroups. Further research should assess whether MASLD-targeted strategies can be integrated into cancer prevention for midlife women.

Conclusion

In this large, population-based cohort of middle-aged Korean women, MASLD was not significantly associated with overall breast cancer risk. However, an elevated risk was observed in specific subgroups, particularly among postmenopausal women with moderate obesity. These findings highlight the importance of jointly considering metabolic and hormonal factors in breast cancer risk assessment and support the need for further prospective studies.

Abbreviations

NAFLD	Nonalcoholic fatty liver disease
MASLD	Metabolic dysfunction-associated steatotic liver disease
NHIS	National health insurance service
IRB	Institutional review board
ICD-10	International classification of disease-10
METs	Metabolic equivalents
CCI	Charlson comorbidity index
FLI	Fatty liver index
HSI	Hepatic steatosis index
BMI	Body mass index
GGT	Gamma-glutamyl transferase
WC	Waist circumference
HR	Hazard ratio
CIs	Confidence intervals

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13058-025-02211-6.

Supplementary Material 1

Supplementary Material 2

Author contributions

CY had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization, JAL, JML, CY; Data curation, HL, SJ; Investigation, JL, HL, SJ, DK, JC and CY; Methodology, JL, HL, SJ, JC and CY; Resources, HL, SJ; Formal analysis, JL and CY; Supervision, YL, SB, and WP; Funding, JML; Writing-original draft, JL and CY.

Funding

This study was supported by a faculty research grant of department of surgery of Yonsei University College of Medicine.

Data availability

All data generated or analyzed during this study are included in this research article and supplementary information files. However, the original data are prohibited from being exported outside due to NHI policy.

Declarations

Consent for publication

All authors have given consent for publication.

Informed consent

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study protocol was approved by the Institutional Review Board (Local IRB number: KC23ZISI0410) of Seoul St. Mary's Hospital. The need for informed consent was waived by the IRB due to the retrospective study design.

Competing interests

The authors declare no competing interests.

Received: 23 July 2025 / Accepted: 19 December 2025
Published online: 07 January 2026

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