Association between body mass index combined with high-sensitivity C-reactive protein and the risk of postmenopausal breast cancer: A prospective cohort study

RUNXUE JIANG[1*], JIANGLUN SHEN[1*], XIA WANG[2], SHUOHUA CHEN[3], SHOULING WU[3] and HAIFENG CAI[1]

[1]Department of Oncology Surgery, Tangshan People's Hospital, Tangshan, Hebei 063000, P.R. China;
[2]Department of Gynaecology, Tangshan Hongci Hospital, Tangshan, Hebei 063000, P.R. China;
[3]Health Department of Kailuan (Group), Kailuan General Hospital, Tangshan, Hebei 063000, P.R. China

Received April 4, 2024; Accepted June 20, 2024

DOI: 10.3892/mco.2024.2762

Abstract. The present study aimed to assess the risk of postmenopausal breast cancer in women based on a combination of body mass index (BMI) and high-sensitivity C-reactive protein (hs-CRP) levels. A total of 20,400 participants were investigated as part of the 'Kailuan Study' clinical trial. Participants were classified into four groups based on BMI (BMI ≥24 or <24 kg/m^2) and hs-CRP level (hs-CRP ≥3 or <3 mg/l). Cox proportional hazards models were used to evaluate the association between the combination of BMI and hs-CRP and the risk of postmenopausal breast cancer. A total of 19,540 participants met the inclusion criteria. The median follow-up time was 14.97 years, with a cumulative follow-up period of 283,599.43 person-years. Among the participants, 269 individuals were diagnosed with postmenopausal breast cancer. Individuals with a high BMI (BMI ≥24 kg/m^2) and a high hs-CRP level (hs-CRP ≥3 mg/) had a greater risk of postmenopausal breast cancer compared with individuals with a low BMI (BMI <24 kg/m^2) and a low hs-CRP level (<3 mg/l) (hazard ratio, 1.75; 95% confidence interval, 1.25-2.47). The sensitivity analysis showed findings consistent with the primary results. In conclusion, the combination of high BMI and high hs-CRP level is associated with an increased risk of postmenopausal breast cancer. The present study is part of the Kailuan Study. Trial registration number: ChiCTRTNCR11001489 (Chinese Clinical Trial Registry, https://www.chictr.org.cn/showproj.html?proj=8050). Date of registration: 19/07/2015.

Correspondence to: Dr Runxue Jiang or Professor Haifeng Cai, Department of Oncology Surgery, Tangshan People's Hospital, 65 Shengli Road, Tangshan, Hebei 063000, P.R. China
E-mail: cnhbjirx@163.com
E-mail: tangshanchf@163.com

*Contributed equally

Key words: postmenopausal breast cancer, body mass index, high-sensitivity C-reactive protein, combination, cohort study

Introduction

Breast cancer currently has the highest incidence among all malignant tumours worldwide, with >2.26 million new cases in 2020 (1). The main risk factors for breast cancer include genetic mutations (2) and non-genetic risk factors, such as smoking, alcohol consumption, hormonal contraception, hormone replacement therapy, dense breasts, reproductive history, lack of physical activity and unhealthy weight (3-6).

Obesity is a significant contributor to various chronic diseases (7). Body mass index (BMI) is commonly used to assess if an individual is overweight or obese. The association between unhealthy BMI and breast cancer risk has been extensively studied (8-12). The impact of BMI on breast cancer risk varies depending on menopausal status. Obesity significantly increases the risk of postmenopausal breast cancer (10-12). However, a study published in 2019 (13) suggested that BMI alone may not accurately indicate breast cancer risk, as postmenopausal women with normal weight may still have an increased risk if they have high levels of body fat. Therefore, it is important to identify high-risk subgroups based on different BMI categories.

Increasing evidence supports the role of inflammation in cancer development and progression (14). C-reactive protein (CRP) is a commonly used inflammatory biomarker (15). Several studies have shown a positive association between CRP levels and breast cancer risk (16-18). A French study also revealed a positive association between CRP levels and postmenopausal breast cancer risk in obese women (19). The associations between unhealthy body weight (being overweight or obese), inflammation and the risk of postmenopausal breast cancer require further investigation. Therefore, a prospective cohort study was conducted as part of the Kailuan study to explore the impact of the combination of BMI and hs-CRP levels on breast cancer risk.

Materials and methods

Study cohort. The Kailuan Study is a large cohort study conducted in the Kailuan community population; its main objective is to identify the risk factors for chronic diseases,

such as cancer. The Kailuan Community is located in the city of Tangshan in Northern China. Between July 2006 and December 2007, a total of 101,510 adults from the Kailuan community participated in the initial survey. Since 2006, they have consistently completed questionnaires and health assessments every 2 years. The questionnaire collected information on demographic characteristics, medical comorbidities, medication history, lifestyle choices and more. All participants were closely monitored until death, and the design and methodology of the Kailuan Study have been described in previous studies (20,21). The BMI and hs-CRP data of the Kailuan Study participants were obtained at baseline (between July 2006 and December 2007). The continuous follow-up data, including breast cancer diagnoses, was analysed from the establishment of the cohort to the present. Also in the present study, the associations between BMI, hs-CRP levels and breast cancer incidence were investigated. The inclusion criteria for the study were as follows: i) Female participants who participated in the baseline survey of the Kailuan Study; and ii) those who signed the informed consent form. The exclusion criteria were as follows: i) A history of malignancy; and ii) incomplete BMI or hs-CRP data. This study was approved by the Ethics Committee of Kailuan General Hospital (Tangshan, Hebei; approval no. KS-2006-5) and conducted in accordance with The Declaration of Helsinki.

Collection of exposure information. Using a standardised protocol through questionnaire interviews and health examinations, well-trained physicians or nurses collected data at baseline, including sociodemographic characteristics (age, occupation, education, income and marital status), lifestyle characteristics (smoking, alcohol consumption, salt intake, sitting time, physical activity and high-fat diet), history of previous diseases (hypertension, diabetes mellitus and malignant tumour), history of drug treatment (treatment with statins, antihypertensive drugs and glucose-lowering drugs), family history of cancer, physical examination data (height and weight) and blood test data (hs-CRP level). The height and weight of the participants, who removed their hats and shoes, and wore thin clothes, were measured. BMI was calculated as follows: BMI=weight (kg)/height (m^2). Subjects were instructed to fast for 8 to 12 h the night before, and then early morning fasting blood samples (3-5 ml venous blood) were collected to measure serum hs-CRP using a high-sensitivity nephelometry test (Cias Latex CRP-H, Kanto Chemical Co. Inc.).

Definition of variables. According to the Working Group on Obesity in China, normal weight is defined as a BMI <24 kg/m^2, and abnormal weight is defined as a BMI ≥24 kg/m^2 (22). When hs-CRP was ≥ 3 mg/l, the subjects were identified as having low-grade inflammation (23). The participants were divided into four groups based on their BMI and hs-CRP levels as follows: i) $BMI^{low}CRP^{low}$ group (BMI <24 kg/m^2 and hs-CRP <3 mg/l); ii) $BMI^{low}CRP^{high}$ group (BMI <24 kg/m^2 and hs-CRP ≥3 mg/l); iii) $BMI^{high}CRP^{low}$ (BMI ≥24 kg/m^2 and hs-CRP <3 mg/l); and iv) $BMI^{high}CRP^{high}$ (BMI ≥24 kg/m^2 and hs-CRP ≥3 mg/l).

Smoking status was defined as smoking one or more cigarettes per week in for ≥1 year, and subjects were classified as never smokers, former smokers or current smokers. Alcohol consumption was defined as drinking at least one alcoholic drink per month for >6 months, and subjects were classified as never drinkers, former drinkers or current drinkers. Physical activity was classified as never, occasionally or frequently (four times/week or more, for ≥20 min/session).

Collection of endpoint event information. The starting point of the follow-up was the time when the participants were recruited to the Kailuan Cohort (July 2006 to December 2007). The follow-up endpoints were newly diagnosed breast cancer, death or administrative censoring (December 31, 2021), whichever occurred first. First, information on the medical records of individuals was obtained through the Tangshan City Health Insurance System, after obtaining patient consent. Professionally trained investigators then went to the hospitals where the subjects were treated to collect medical history information. The diagnosis of breast cancer was confirmed and refined by clinicians via pathology, imaging (including magnetic resonance imaging, computed tomography and colour Doppler ultrasonography) and blood biochemical examinations. Tumour cases were sorted according to the International Classification of Diseases, Tenth Revision (24), and breast cancer was coded as C50. Information on fatal events was obtained from the Kailuan Group and Tangshan City Social Insurance System.

Statistical analysis. Continuous variables are presented as the mean ± standard deviation, and one-way analysis of variance (ANOVA) with Tukey's post hoc test was used to compare the differences among the groups. Categorical variables are described as the number of cases (percentages) and were compared using the χ^2 test. Multivariate Cox proportional hazards models were applied to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) to estimate the impact of BMI and CRP alone and in combination on the risk of breast cancer. A cross-product interaction term between BMI and CRP level was introduced into the model, and the statistical multiplicative interaction was assessed using the likelihood ratio test. Sensitivity analysis was conducted by applying Cox proportional hazards models to evaluate the consistency of the findings after excluding participants who developed breast cancer within the first 2 years of follow-up, those who received previous treatment with statins, those who received previous treatment with antihypertensive drugs or those who received previous treatment with glucose-lowering drugs.

All the statistical tests were considered statistically significant at P<0.05 (two-sided). SAS 9.4 (SAS Institute, Inc.) was used for the statistical analysis.

Results

Baseline characteristics. A total of 20,400 female individuals participated in the 2006-2007 baseline survey, of which 115 with a history of malignancy and 745 lacking baseline BMI and/or hs-CRP data were excluded. Overall, 19,540 female participants were included in the statistical analysis. The flow diagram of this study is shown in Fig. 1. The mean age of the observed subjects was 48.95±11.47 years. The cumulative follow-up time is expressed in person-years, which is calculated by adding the individual exposure times of each cohort

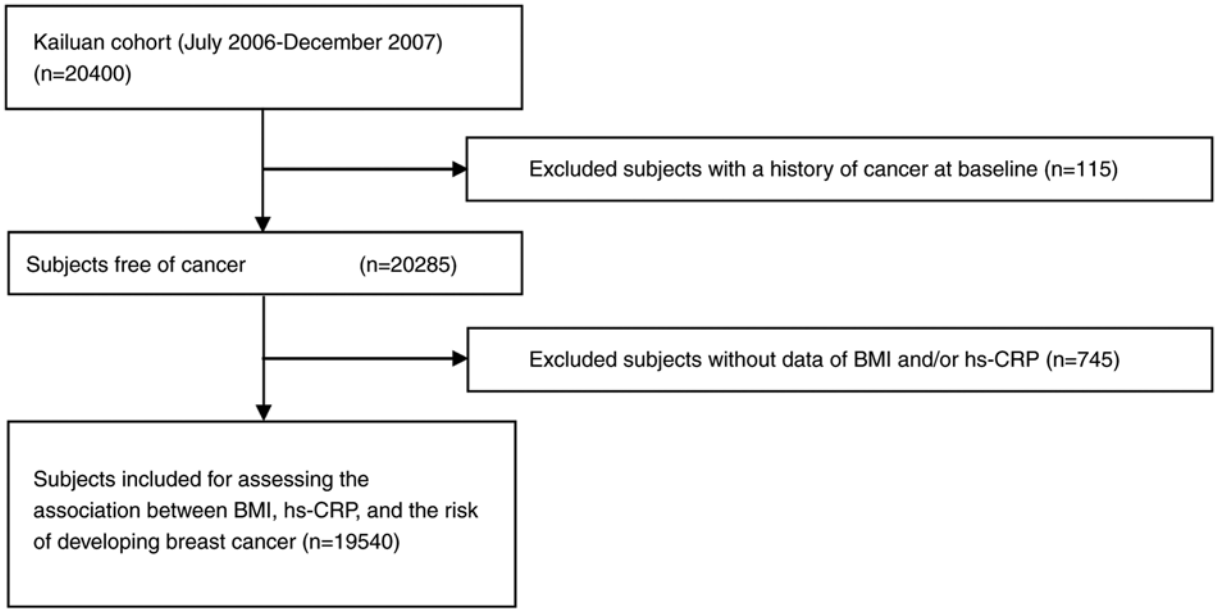

Figure 1. Flow diagram of the study population. BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein.

member. In this study the cumulative follow-up period was 283,599.43 person-years, the median duration of follow-up was 14.97 years [interquartile range (IQR), 14.68-15.18 years] and 269 patients with new-onset postmenopausal breast cancer were identified in this study.

All participants were classified into four groups ($BMI^{low}CRP^{low}$, n=7,655; $BMI^{low}CRP^{high}$, n=1,406; $BMI^{high}CRP^{low}$, n=7,668; and $BMI^{high}CRP^{high}$, n=2,811) in accordance with BMI and hs-CRP levels. Significant differences were found between the groups for age, smoking status, alcohol consumption, occupation, education level, income, marital status, salt intake, sitting time, physical activity, high-fat diet and family history of cancer. The baseline characteristics of the participants are presented in detail in Table I.

Associations of BMI and hs-CRP with the risk of postmenopausal breast cancer. Multivariate Cox proportional hazards models were used to evaluate the associations between BMI or hs-CRP level alone and the risk of postmenopausal breast cancer. Compared with the BMI^{low} and hs-CRP^{low} groups, after adjustment for age, smoking status, alcohol consumption, occupation, education level, income, marital status, salt intake, sitting time, physical activity, high-fat diet and family history of cancer, the HR (95% CI) of participants in the BMI^{high} group was 1.44 (1.11-1.85); the BMI^{high} group had a significantly increased risk of postmenopausal breast cancer. Moreover, a significantly increased and borderline risk for postmenopausal breast cancer according to BMI and CRP per IQR increase was observed in multivariate analyses (HR, 1.23; 95% CI, 1.06-1.43; and HR, 1.03; 95% CI, 0.99-1.07, respectively). Furthermore, no significant interaction was detected between BMI and the hs-CRP level (P=0.102) (Table II).

Effect of BMI combined with hs-CRP on the risk of postmenopausal breast cancer. Compared with individuals in the $BMI^{low}CRP^{low}$ group, participants in the $BMI^{high}CRP^{high}$ group had a significantly increased risk of postmenopausal breast cancer, with a HR (95% CI) of 1.70 (1.21-2.39; P=0.002; adjusted for age) and 1.75 (1.25-2.47; P=0.001; further adjusted for smoking status, alcohol consumption, occupation, education level, income, marital status, salt intake, sitting time, physical activity, high-fat diets and family history of cancer) (Table III).

Sensitivity analysis. The results of the sensitivity analysis were consistent with the study findings. The risk of breast cancer was significantly greater in the $BMI^{high}CRP^{high}$ group than that in the $BMI^{low}CRP^{low}$ group after excluding participants who developed breast cancer within the first 2 years of follow-up, those who received treatment with statins, those who received treatment with antihypertensive drugs or those who received treatment with glucose-lowering drugs (Table IV).

Discussion

To the best of our knowledge, the present study is the first prospective cohort study to explore the associations between BMI and hsCRP levels and the risk of postmenopausal breast cancer. The findings showed that abnormal weight (BMI ≥24 kg/m^2) and low-grade inflammation (hs-CRP ≥3 mg/l) synergistically increased the risk of postmenopausal breast cancer. The results of this study suggest the importance of controlling weight and inflammation for the prevention of postmenopausal breast cancer.

In the present study, the subjects were first grouped by BMI. Compared with women with a normal BMI (BMI <24 kg/m^2), women with a high BMI (BMI ≥24 kg/m^2) had a 1.44-fold greater risk of postmenopausal breast cancer, which was statistically significant. In addition, a significant association was observed between BMI (per IQR increase) and the risk of incident postmenopausal breast cancer according to multivariate analyses. The association between BMI and breast cancer risk has been widely studied. A randomised controlled trial conducted in America revealed that obesity

Table I. Baseline characteristics of the participants by BMI and hs-CRP status.

Characteristics	Total cohort (n=19,540)	$BMI^{low}CRP^{low}$ (n=7,655)	$BMI^{low}CRP^{high}$ (n=1,406)	$BMI^{high}CRP^{low}$ (n=7,668)	$BMI^{high}CRP^{high}$ (n=2,811)	P-value
Mean age ± SD, years	48.95±11.47	45.51±11.80	48.95±12.57	50.64±10.24	53.68±10.41	<0.001
Smoking status, n (%)						<0.001
Never	19,084 (97.67)	7,540 (98.50)	1,376 (97.87)	7,455 (97.22)	2,713 (96.51)	
Former	86 (0.44)	23 (0.30)	4 (0.28)	36 (0.47)	23 (0.82)	
Current	370 (1.89)	92 (1.20)	26 (1.85)	177 (2.31)	75 (2.67)	
Alcohol consumption, n (%)						<0.001
Never	18,229 (93.29)	7,064 (92.28)	1,309 (93.10)	7,202 (93.92)	2,654 (94.41)	
Former	85 (0.44)	45 (0.59)	4 (0.28)	21 (0.27)	15 (0.53)	
Current	1,226 (6.27)	546 (7.13)	93 (6.61)	445 (5.80)	142 (5.05)	
Occupation, n (%)						<0.001
White collar	2,667 (13.65)	1,199 (15.66)	220 (15.65)	888 (11.58)	360 (12.81)	
Blue collar	16,873 (86.35)	6,456 (84.34)	1,186 (84.35)	6,780 (88.42)	2,451 (87.19)	
Education level, n (%)						<0.001
Illiteracy and primary	1,066 (5.46)	209 (2.73)	80 (5.69)	493 (6.43)	284 (10.10)	
Middle school	16,434 (84.10)	6,310 (82.43)	1,114 (79.23)	6,670 (86.98)	2,340 (83.24)	
College and above	2,040 (10.44)	1,136 (14.84)	212 (15.08)	505 (6.59)	187 (6.65)	
Income in Yuan per person per month, n (%)						<0.001
<600	3,658 (18.72)	1,386 (18.11)	205 (14.58)	1,565 (20.41)	502 (17.86)	
≥600 to <1,000	14,083 (72.07)	5,592 (73.05)	1,017 (72.33)	5,507 (71.82)	1,967 (69.98)	
≥1,000	1,799 (9.21)	677 (8.84)	184 (13.09)	596 (7.77)	342 (12.17)	
Marital status, n (%)						<0.001
Single	1175 (6.01)	532 (6.95)	85 (6.05)	374 (4.88)	184 (6.55)	
Married/cohabiting	18365 (93.99)	7,123 (93.05)	1,321 (93.95)	7,294 (5.12)	2,627 (93.45)	
Salt intake, n (%)						<0.001
Light	1838 (9.41)	741 (9.68)	148 (10.53)	674 (8.79)	275 (9.78)	
General	16390 (83.88)	6,488 (84.76)	1,174 (83.50)	6,397 (83.42)	2,331 (82.92)	
Heavy	1312 (6.71)	426 (5.56)	84 (5.97)	597 (7.79)	205 (7.29)	
Sitting time in h/day, n (%)						<0.001
<4	14375 (73.57)	5,541 (72.38)	1,077 (76.60)	5,654 (73.74)	2,103 (74.81)	
≥4 to <8	4433 (22.69)	1,773 (23.16)	292 (20.77)	1,760 (22.95)	608 (21.63)	
≥8	732 (3.75)	341 (4.45)	37 (2.63)	254 (3.31)	100 (3.56)	
Physical activity, n (%)						<0.001
Never	976 (4.99)	356 (4.65)	89 (6.33)	348 (4.54)	183 (6.51)	
Occasionally	15,932 (81.54)	6,426 (83.95)	1,178 (83.78)	6,099 (79.54)	2,229 (79.30)	
Frequently	2,632 (13.47)	873 (11.40)	139 (9.89)	1221 (15.92)	399 (14.19)	
High-fat diet, n (%)						<0.001
Seldom	1,867 (9.55)	790 (10.32)	130 (9.25)	695 (9.06)	252 (8.96)	
Occasionally	16,698 (85.46)	6,531 (85.32)	1,222 (86.91)	6,535 (85.22)	2,410 (85.73)	
Frequently	975 (4.99)	334 (4.36)	54 (3.84)	438 (5.71)	149 (5.30)	
Family history of cancer, n (%)						0.007
No	18,653 (95.46)	7,337 (95.85)	1,359 (96.66)	7,284 (94.99)	2,673 (95.09)	
Yes	887 (4.54)	318 (4.15)	47 (3.34)	384 (5.01)	138 (4.91)	

hs-CRP, high-sensitivity C-reactive protein; BMI, body mass index; BMI^{low}, BMI <24 kg/m^2; BMI^{high}, BMI ≥24 kg/m^2; CRP^{low}, hs-CRP <3 mg/l; CRP^{high}, hs-CRP ≥3 mg/l.

was associated with an increased risk of invasive breast cancer in postmenopausal women (10). A study based on the Korean National Health Insurance System Cohort showed that the risk of invasive breast cancer in postmenopausal women with a BMI

Table II. HRs for the association of BMI or hs-CRP levels with breast cancer risk.

Groups	Total cases, n	Cumulative follow-up period, person-years	Newly diagnosed postmenopausal breast cancer cases during the follow-up period, n	Model 1[a]		Model 2[b]	
				HR (95% CI)	P-value	HR (95% CI)	P-value
BMI							
BMI^{low}	9,061	132,205.44	93	Reference		Reference	
BMI^{high}	10,479	151,393.99	176	1.41 (1.09-1.82)	0.008	1.44 (1.11-1.85)	0.006
BMI (per IQR)				1.22 (1.05-1.42)	0.008	1.23 (1.06-1.43)	0.006
hs-CRP							
CRP^{low}	15,323	223,383.77	194	Reference		Reference	
CRP^{high}	4,217	60,215.66	75	1.26 (0.96-1.65)	0.097	1.28 (0.97-1.67)	0.078
hs-CRP (per IQR)				1.03 (0.99-1.07)	0.148	1.03 (0.99-1.07)	0.130
P-value for interaction[c]					0.106		0.102

[a]Model 1 was adjusted for age; [b]model 2 was further adjusted for smoking status, alcohol consumption, occupation, education level, income, marital status, salt intake, sitting time, physical activity, high-fat diet and family history of cancer. [c]Interaction between BMI and hs-CRPhs-CRP, high-sensitivity C-reactive protein; BMI, body mass index; BMI^{low}, BMI <24 kg/m2; BMI^{high}, BMI ≥24 kg/m2; CRP^{low}, hs-CRP <3 mg/l; CRP^{high}, hs-CRP ≥3 mg/l; HR, hazard ratio; CI, confidence interval; IQR, interquartile range.

Table III. HRs for the association of BMI and hs-CRP with breast cancer risk.

Groups	Total cases, n	Cumulative follow-up period, person-years	Newly diagnosed postmenopausal breast cancer cases during the follow-up period, n	Model 1[a]		Model 2[b]	
				HR (95% CI)	P-value	HR (95% CI)	P-value
$BMI^{low}CRP^{low}$	7,655	111,931.87	80	Reference		Reference	
$BMI^{low}CRP^{high}$	1,406	20,273.57	13	0.80 (0.44-1.44)	0.455	0.81 (0.45-1.45)	0.470
$BMI^{high}CRP^{low}$	7,668	111,451.90	114	1.23 (0.92-1.65)	0.154	1.25 (0.94-1.67)	0.129
$BMI^{high}CRP^{high}$	2,811	39,942.09	62	1.70 (1.21-2.39)	0.002	1.75 (1.25-2.47)	0.001

[a]Model 1 was adjusted for age; [b]model 2 was further adjusted for smoking status, alcohol consumption, occupation, education level, income, marital status, salt intake, sitting time, physical activity, high-fat diet and family history of cancer. hs-CRP, high-sensitivity C-reactive protein; BMI, body mass index; BMI^{low}, BMI <24 kg/m^2; BMI^{high}, BMI ≥24 kg/m^2; CRP^{low}, hs-CRP <3 mg/l; CRP^{high}, hs-CRP ≥3 mg/l; HR, hazard ratio; CI, confidence interval.

of 23-25, 25-30 or ≥30 kg/m^2 increased linearly compared with that in women with a BMI of 18.5-23 kg/m^2 (11). In another prospective cohort study of Taiwanese women, the risk of breast cancer increased with increasing BMI in the enrolled women after menopause. Obesity significantly promoted the development of late-onset breast cancer after menopause (12). The present findings regarding the association between BMI and postmenopausal breast cancer incidence were consistent with those of previous research (10-12). Although obesity is considered a risk factor for postmenopausal breast cancer by a number of studies (10-12), there is also contrasting data in an Asian study. Wang *et al* (25) conducted a case-control study and found that obesity is significantly associated with breast cancer in premenopausal women, but not in postmenopausal women. These differences in findings may be related to differences in the ethnicities of the subjects and the study design.

In the present study, regardless of BMI status, participants were grouped according to the presence (hs-CRP ≥3 mg/l) or absence (hs-CRP <3 mg/l) of low-grade inflammation. Multivariate analysis revealed that subjects with low-grade inflammation (hs-CRP level ≥3 mg/l) showed a slightly increased risk of developing postmenopausal breast cancer (HR, 1.28; 95% CI, 0.97-1.67), but this did not reach statistical significance. A study with a small sample

Table IV. Sensitivity analyses of the association of BMI and hs-CRP with breast cancer risk.

A, Excluding participants who developed breast cancer within the first 2 years of follow-up

Variable	Total cases, n	Cumulative follow-up period, person-years	Newly diagnosed postmenopausal breast cancer cases during the follow-up period, n	HR (95% CI)	P-value
$BMI^{low}CRP^{low}$	7,649	111,925.59	74	Reference	
$BMI^{low}CRP^{high}$	1,405	20,273.40	12	0.81 (0.44-1.49)	0.496
$BMI^{high}CRP^{low}$	7,658	111,441.44	104	1.26 (0.93-1.70)	0.140
$BMI^{high}CRP^{high}$	2,802	39,936.28	53	1.67 (1.16-2.40)	0.006

B, Excluding participants who received treatment with statins

Variable	Total cases, n	Cumulative follow-up period, person-years	Newly diagnosed postmenopausal breast cancer cases during the follow-up period, n	HR (95% CI)	P-value
$BMI^{low}CRP^{low}$	7,607	111,243.02	80	Reference	
$BMI^{low}CRP^{high}$	1,397	20,137.34	13	0.81 (0.45-1.45)	0.476
$BMI^{high}CRP^{low}$	7,561	109,886.11	112	1.25 (0.93-1.66)	0.147
$BMI^{high}CRP^{high}$	2,741	39,023.44	61	1.76 (1.25-2.48)	0.001

C, Excluding participants who received treatment with antihypertensive drugs

Variable	Total cases, n	Cumulative follow-up period, person-years	Newly diagnosed postmenopausal breast cancer cases during the follow-up period, n	HR (95% CI)	P-value
$BMI^{low}CRP^{low}$	7,310	107,103.25	73	Reference	
$BMI^{low}CRP^{high}$	1,305	18,843.53	13	0.91 (0.50-1.64)	0.748
$BMI^{high}CRP^{low}$	6,435	93,839.22	97	1.32 (0.97-1.79)	0.079
$BMI^{high}CRP^{high}$	2,211	31,670.16	48	1.77 (1.22-2.56)	0.003

D, Excluding participants who received treatment with glucose-lowering drugs

Variable	Total cases, n	Cumulative follow-up period, person-years	Newly diagnosed postmenopausal breast cancer cases during the follow-up period, n	HR (95% CI)	P-value
$BMI^{low}CRP^{low}$	7,535	110,385.64	78	Reference	
$BMI^{low}CRP^{high}$	1,376	19,847.30	13	0.84 (0.46-1.51)	0.553
$BMI^{high}CRP^{low}$	7,379	107,507.05	106	1.23 (0.92-1.66)	0.168

Table IV. Continued.

Variable	Total cases, n	Cumulative follow-up period, person-years	Newly diagnosed postmenopausal breast cancer cases during the follow-up period, n	HR (95% CI)	P-value
$BMI^{high}CRP^{high}$	2,664	37,964.06	59	1.79 (1.26-2.53)	0.001

The model was adjusted for age, smoking status, alcohol consumption, occupation, education level, income, marital status, salt intake, sitting time, physical activity, high-fat diets and family history of cancer. hs-CRP, high-sensitivity C-reactive protein; BMI, body mass index; BMI^{low}, BMI <24 kg/m^2; BMI^{high}, BMI ≥24 kg/m^2; CRP^{low}, hs-CRP <3 mg/l; CRP^{high}, hs-CRP ≥3 mg/l; HR, hazard ratio; CI, confidence interval.

size conducted in Norway showed a positive association between prediagnostic hs-CRP and the risk of breast cancer among postmenopausal women (16). Wang *et al* (17) found through a case-control study in the Nurses' Health Study that the risk of breast cancer was increased in individuals in the highest vs. the lowest quintile of CRP levels. A further meta-analysis (including 5,371 cases from 11 studies) then revealed an increased risk in women in the highest vs. lowest category of CRP. Guo *et al* (26) also found that elevated CRP levels were associated with increased breast cancer risk in a meta-analysis (26). However, a French case-control study showed that although no association was observed between CRP levels and overall breast cancer risk or breast cancer risk in women with a normal BMI, a significantly increased risk of breast cancer (odds ratio, 1.92; 95% CI, 1.20-3.08) in overweight and obese women (BMI ≥25 kg/m^2) with CRP ≥2.5 mg/l was found compared with that in patients with CRP <1.5 mg/l (19). Therefore, being overweight or obese may be associated with inflammation that promotes postmenopausal breast cancer.

To the best of our knowledge, the effect of the co-occurrence of BMI^{high} and CRP^{high} status on the risk of breast cancer has not been reported in previous studies. The present study analysed the effect of the combination of BMI and CRP level on the occurrence of postmenopausal breast cancer, aiming to identify subgroups at increased risk. The study found that high BMI combined with increased CRP levels has a greater influence on the incidence of new-onset postmenopausal breast cancer compared with normal BMI (BMI <24 kg/m^2) and CRP levels (hs-CRP <3 mg/l). These results were robust after adjusting for confounding factors. Questions were raised as to whether there were some subjects at baseline who already had breast cancer but had not been diagnosed or were in the preclinical phase of the disease, and whether the baseline data results of BMI and CRP of these subjects were affected by the preclinical disease, causing a reverse causal relationship between the independent and dependent variables. Another query was whether the long-term use of certain medications interfered with the impact of BMI and CRP on the occurrence of breast cancer in certain chronic disease patients. Therefore, in order to eliminate this reverse causal relationship and potential impact of certain medications, a sensitivity analysis was conducted after excluding participants who developed breast cancer within the first 2 years of follow-up, those who received treatment with statins, those who received treatment with antihypertensive drugs or those who received treatment with glucose-lowering drugs. The risk of postmenopausal breast cancer was significantly greater in the $BMI^{high}CRP^{high}$ group than that in the $BMI^{low}CRP^{low}$ group, thus demonstrating the reliability of the main study results.

Although the pathophysiological mechanisms by which BMI combined with low-grade inflammation increases the risk of postmenopausal breast cancer remain unknown, some preliminary explanations based on previous studies may be inferred. In obese individuals, cells in adipose tissue undergo changes in number, phenotype and secretion that affect systemic metabolism, leading to hyperglycemia and insulin resistance, promoting local inflammation and shaping the tumour microenvironment (27,28). Adipose tissue produces numerous bioactive factors, including steroid hormones, growth factors, proinflammatory mediators and adipokines (27). Most of these factors promote the expression of aromatase. In adipose tissue, aromatase can induce the synthesis of large amounts of estrogens that sustain breast cancer cell growth (28,29). In obese individuals, proinflammatory mediators, such as leptin, CCL2, IL-1b, IL-6, and TNF-α, are released by dysfunctional adipose cells, inducing the recruitment and differentiation of monocytes/macrophages (30). Macrophages within adipose tissue aggregate into inflammatory foci, where they release proinflammatory mediators that sustain an inflammatory feedback loop (30,31). Several inflammatory mediators, such as adipokines, CRP and IL-6, are elevated in patients with breast cancer with white adipose tissue inflammation (32).

The primary strength of the present study is that it is a prospective cohort study with long-term follow-up. In addition, serum hs-CRP levels were measured in accordance with standard procedures to minimise detection bias. Moreover, the physical examination data (e.g., height and weight) were obtained by well-trained physicians or nurses using a standardised protocol rather than based on the subjects' self-reports, thereby avoiding misclassification bias. Nevertheless, this cohort study had some limitations. First, certain information is lacking, such as information on other

chronic inflammatory factors, including interleukins, the use of hormone therapy, age at first pregnancy and the number of children, which may be confounding factors. Second, only baseline BMI and CRP data were used to analyse their effects on postmenopausal breast cancer risk, and time-dependent changes in BMI and CRP during follow-up were not considered. Third, the limited number of patients with breast cancer and the statistical differences in covariates among the groups in this study may have limited the ability to conduct interaction analyses. Although there are certain limitations, it is undeniable that this study involved a long-term rigorous follow-up, and the results presented after statistical analysis and covariate adjustment are worth reporting. It is hoped that in-depth subsequent studies with assessment of the molecular mechanism, a larger cohort, a longer follow-up time, a dynamic state of the independent variable and more covariates will be conducted to explore the risk of developing breast cancer in women.

In conclusion, the present study showed that the combination of BMI and inflammation significantly increased the risk of developing postmenopausal breast cancer. The findings of this study will help researchers identify other high-risk individuals who should be targeted for focused screening and prevention of breast cancer.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data that support the findings of this study are available from the Kailuan Study, but restrictions apply to the availability of these data, which were used under the licence for the current study and are not publicly available. The data are available from the authors upon reasonable request and with permission from the Kailuan Study.

Authors' contributions

RJ, JS, XW, SW and HC were responsible for study conception, design, validation, formal analysis, investigation and writing of the original draft. RJ, JS, XW and SC performed data acquisition, analysis and interpretation. RJ, SW and HC assisted with the methodology, review and editing the manuscript, and funding acquisition. All the authors have read and approved the final manuscript. RJ, SW and HC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study was conducted in accordance with The Declaration of Helsinki and approved by the Ethics Committee of Kailuan General Hospital (approval no. KS-2006-5). All participants provided written informed consent to participate in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Coignard J, Lush M, Beesley J, O'Mara TA, Dennis J, Tyrer JP, Barnes DR, McGuffog L, Leslie G, Bolla MK, *et al*: A case-only study to identify genetic modifiers of breast cancer risk for BRCA1/BRCA2 mutation carriers. Nat Commun 12: 1078, 2021.
3. Al Ajmi K, Lophatananon A, Mekli K, Ollier W and Muir KR: Association of Nongenetic factors with breast cancer risk in genetically predisposed groups of women in the UK Biobank cohort. JAMA Netw Open 3: e203760, 2020.
4. Cohen SY, Stoll CR, Anandarajah A, Doering M and Colditz GA: Modifiable risk factors in women at high risk of breast cancer: A systematic review. Breast Cancer Res 25: 45, 2023.
5. Nelson HD, Zakher B, Cantor A, Fu R, Griffin J, O'Meara ES, Buist DS, Kerlikowske K, van Ravesteyn NT, Trentham-Dietz A, *et al*: Risk factors for breast cancer for women aged 40 to 49 years: A systematic review and meta-analysis. Ann Intern Med 156: 635-648, 2012.
6. John EM, Phipps AI, Hines LM, Koo J, Ingles SA, Baumgartner KB, Slattery ML and Wu AH: Menstrual and reproductive characteristics and breast cancer risk by hormone receptor status and ethnicity: The breast cancer Etiology in minorities study. Int J Cancer 147: 1808-1822, 2020.
7. Safaei M, Sundararajan EA, Driss M, Boulila W and Shapi'i A: A systematic literature review on obesity: Understanding the causes & consequences of obesity and reviewing various machine learning approaches used to predict obesity. Comput Biol Med 136: 104754, 2021.
8. Laudisio D, Muscogiuri G, Barrea L, Savastano S and Colao A: Obesity and breast cancer in premenopausal women: Current evidence and future perspectives. Eur J Obstet Gynecol Reprod Biol 230: 217-221, 2018.
9. Torres-de la Roche LA, Steljes I, Janni W, Friedl TWP and De Wilde RL: The association between obesity and premenopausal breast cancer according to intrinsic Subtypes-a systematic review. Geburtshilfe Frauenheilkd 80: 601-610, 2020.
10. Neuhouser ML, Aragaki AK, Prentice RL, Manson JE, Chlebowski R, Carty CL, Ochs-Balcom HM, Thomson CA, Caan BJ, Tinker LF, *et al*: Overweight, obesity, and postmenopausal invasive breast cancer risk: A secondary analysis of the Women's Health initiative randomized clinical trials. JAMA Oncol 1: 611-621, 2015.
11. Park JW, Han K, Shin DW, Yeo Y, Chang JW, Yoo JE, Jeong SM, Lee SK, Ryu JM and Park YM: Obesity and breast cancer risk for pre- and postmenopausal women among over 6 million Korean women. Breast Cancer Res Treat 185: 495-506, 2021.
12. Chen MJ, Wu WY, Yen AM, Fann JC, Chen SL, Chiu SY, Chen HH and Chiou ST: Body mass index and breast cancer: Analysis of a nation-wide population-based prospective cohort study on 1 393 985 Taiwanese women. Int J Obes (Lond) 40: 524-530, 2016.
13. Slomski A: BMI not a good proxy for breast cancer risk. JAMA 321: 735, 2019.
14. Iyengar NM, Gucalp A, Dannenberg AJ and Hudis CA: Obesity and cancer mechanisms: Tumor microenvironment and inflammation. J Clin Oncol 34: 4270-4276, 2016.
15. Gabay C and Kushner I: Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 340: 448-454, 1999.
16. Frydenberg H, Thune I, Lofterød T, Mortensen ES, Eggen AE, Risberg T, Wist EA, Flote VG, Furberg AS, Wilsgaard T, *et al*: Pre-diagnostic high-sensitive C-reactive protein and breast cancer risk, recurrence, and survival. Breast Cancer Res Treat 155: 345-354, 2016.

17. Wang J, Lee IM, Tworoger SS, Buring JE, Ridker PM, Rosner B and Hankinson SE: Plasma C-reactive protein and risk of breast cancer in two prospective studies and a meta-analysis. Cancer Epidemiol Biomarkers Prev 24: 1199-1206, 2015.
18. Price TR, Friedenreich CM, Robson PJ, Li H and Brenner DR: High-sensitivity C-reactive protein, hemoglobin A1c and breast cancer risk: A nested case-control study from Alberta's Tomorrow Project cohort. Cancer Causes Control 31: 1057-1068, 2020.
19. Dossus L, Jimenez-Corona A, Romieu I, Boutron-Ruault MC, Boutten A, Dupré T, Fagherazzi G, Clavel-Chapelon F and Mesrine S: C-reactive protein and postmenopausal breast cancer risk: Results from the E3N cohort study. Cancer Causes Control 25: 533-539, 2014.
20. Li X, Chen H, Wang G, Feng X, Lyu Z, Wei L, Wen Y, Chen S, Wu S, Hang D, *et al*: Metabolic syndrome components and the risk of colorectal cancer: A Population-based prospective study in Chinese men. Front Oncol 9: 1047, 2019.
21. Liu T, Song C, Zhang Y, Siyin ST, Zhang Q, Song M, Cao L and Shi H: Hepatitis B virus infection and the risk of gastrointestinal cancers among Chinese population: A prospective cohort study. Int J Cancer 150: 1018-1028, 2022.
22. Zhou BF and Cooperative Meta-Analysis Group of the Working Group on Obesity in China. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults-study on optimal cut-off points of body mass index and waist circumference in Chinese adults. Biomed Environ Sci 15: 83-96, 2002.
23. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO III, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, *et al*: Markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for healthcare professionals from the centers for disease control and prevention and the American Heart Association. Circulation 107: 499-511, 2003.
24. Utter GH, Atolagbe OO and Cooke DT: The use of the international classification of diseases, tenth revision, clinical modification and procedure classification system in clinical and health services research: The devil is in the details. JAMA Surg 154: 1089-1090, 2019.
25. Wang X, Li L, Gao J, Liu J, Guo M, Liu L, Wang W, Wang J, Xing Z, Yu Z and Wang X: The association between body size and breast cancer in Han Women in Northern and Eastern China. Oncologist 21: 1362-1368, 2016.
26. Guo L, Liu S, Zhang S, Chen Q, Zhang M, Quan P, Lu J and Sun X: C-reactive protein and risk of breast cancer: A systematic review and meta-analysis. Sci Rep 5: 10508, 2015.
27. Renehan AG, Zwahlen M and Egger M: Adiposity and cancer risk: New mechanistic insights from epidemiology. Nat Rev Cancer 15: 484-498, 2015.
28. Crespi E, Bottai G and Santarpia L: Role of inflammation in obesity-related breast cancer. Curr Opin Pharmacol 31: 114-122, 2016.
29. Irahara N, Miyoshi Y, Taguchi T, Tamaki Y and Noguchi S: Quantitative analysis of aromatase mRNA expression derived from various promoters (I.4, I.3, PII and I.7) and its association with expression of TNF-alpha, IL-6 and COX-2 mRNAs in human breast cancer. Int J Cancer 118: 1915-1921, 2006.
30. Wagner M, Samdal Steinskog ES and Wiig H: Adipose tissue macrophages: The inflammatory link between obesity and cancer? Expert Opin Ther Targets 19: 527-538, 2015.
31. Gilbert CA and Slingerland JM: Cytokines, obesity, and cancer: New insights on mechanisms linking obesity to cancer risk and progression. Annu Rev Med 64: 45-57, 2013.
32. Iyengar NM, Zhou XK, Gucalp A, Morris PG, Howe LR, Giri DD, Morrow M, Wang H, Pollak M, Jones LW, *et al*: Systemic correlates of white adipose tissue inflammation in early-stage breast cancer. Clin Cancer Res 22: 2283-2289, 2016.