Ph.D. Dissertation of Ji Soo Kim

Association of Body Composition and Its Changes with Metabolic Factors and Cardiovascular Disease Development among Breast Cancer Survivors

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Abstract

Background: With an increasing number of breast cancer survivors, cardiovascular disease (CVD) has emerged as a leading cause of mortality. Increased risk of CVD in breast cancer survivors compared to women without a cancer history is related to cardiotoxic effects of breast cancer treatment and overlapping risk factors of breast cancer and CVD, such as obesity and hormone replacement. However, even after breast cancer diagnosis, the majority gain weight or at least experience changes in body composition, which continues, into breast cancer survivorship. Prior research on breast cancer survivors, let alone breast cancer patients, were limited to investigating association between body mass index (BMI) and mortality, without measuring body composition or CVD. Therefore, this study aimed to address 1) the association between body composition and risk of newly developed CVD; 2) discrepancies in general obesity and abdominal obesity with CVD risk; and 3) the association between changes in body composition with CVD risk and changes in metabolic factors in 5-year breast cancer survivors without prior CVD.

Methods: Using the Korean National Health Insurance Service (NHIS) database, approximately 70,000 5-year breast cancer survivors aged 40 years and above were studied. All participants were followed up from the index date to date of newly diagnosed CVD, date of death, or 31, December, 2020, whichever came first. Participants were divided according to quartiles of percentage of predicted body composition (lean body mass, pLBMP; appendicular skeletal mass, pASMP; and body fat mass, pBFMP), and when evaluating for discrepancies in general obesity and abdominal obesity with CVD risk, according to BMI and waist circumference (WC). Multivariable Cox proportional hazards regression model was used to determine the adjusted hazard ratios (aHR) and 95% confidence intervals (CI) of CVD risk according to the percentage of predicted body composition, type of obesity, and changes in percentage of predicted body composition; changes in metabolic factors (fasting serum glucose, FSG; systolic blood pressure, sBP; diastolic blood pressure, dBP; and total cholesterol, TC)

were determined by multivariable linear regression model. Stratified analysis according to the subgroups of covariates was conducted.

Results: Compared to those with the lowest pLBMP and pASMP, those with the highest pLBMP and pASMP had a 38% and 42% lower risk of CVD, respectively. In contrast, those with the highest pBFMP had a 57% higher risk of CVD compared to those with the lowest pBFMP. Each 1 % increase in pLBMP and pASMP was associated with a decreased risk of CVD (pLBMP, aHR(95% CI) 0.96(0.94–0.98), $p<0.05$ and pASMP, aHR(95% CI) 0.91(0.87–0.95), $p<0.05$, respectively). In contrast, each 1 % increase in pBFMP was associated with a higher risk of CVD (aHR(95% CI) 1.05(1.03–1.07), $p<0.01$). Adjustments for combinations of three confounders showed blood pressure to be the most important mediator for the association of pLBMP, pASMP, and pBFMP with CVD. Compared to those with normal WC and BMI, those who were overweight without abdominal obesity, had abdominal obesity only, and overweight with abdominal obesity, had higher risks of CVD (aHR(95% CI) 1.23(1.02-1.48), 1.51(1.16-1.95), and 1.55(1.31-1.75), respectively) and total stroke (aHR(95% CI) 1.09(0.86-1.38), 1.63(1.20-2.23), and 1.40(1.17-1.68), respectively). In the case of ischemic stroke, subjects with abdominal obesity only and overweight with abdominal obesity showed significantly higher risk (aHR(95% CI) 1.77(1.08-2.88) and 1.84(1.37-2.47), respectively) compared to normal. Compared to those who continued to have low pLBMP and pASMP, those with persistently high pLBMP and pASMP had lower risks of CVD (aHR(95% CI) 0.68(0.53-0.87) and 0.60(0.44-0.81), respectively). In contrast, those with increased (a low to high change) and persistently high pBFMP had higher risks of CVD (aHR(95% CI) 1.51(0.99-2.31) and 1.48(1.15-1.89), respectively), compared to those who maintained a low pBFMP. Pertaining to changes in pLBMP and pASMP, the Low to High group showed decreased systolic and diastolic blood pressure, total cholesterol, and fasting serum glucose, compared to that of the Low to Low group. Pertaining to change in pBFMP, the Low to High group showed increased systolic and diastolic blood pressure, total cholesterol, and fasting serum glucose.

Conclusion: A high percentage of predicted lean body mass and predicted appendicular skeletal mass and a low percentage of predicted body fat mass were associated with lower risk of CVD. Blood pressure showed to be the most important mediator for the association at one timepoint. Furthermore, discrepancies in general and abdominal obesity, observed through BMI and WC, should be considered for preventing CVD and stroke, in particular. Compared to those overweight, those with abdominal obesity only had a higher risk of stroke, especially ischemic stroke. Finally, persistently high muscle mass, represented as pLBMP or pASMP, were associated with lower CVD risk. Preventing an increase in fat mass may be beneficial in preventing CVD in breast cancer survivors. Changes in body composition were accompanied by metabolic changes.

Keywords : Breast cancer survivor; body composition; metabolic factors; cardiovascular disease
Student Number : 2020-33701

Acronyms

CVD, cardiovascular disease; CHD, coronary heart disease; percentage of predicted lean body mass, pLBMP; percentage of predicted appendicular skeletal muscle mass, pASMP; percentage of predicted body fat mass, pBFMP; BMI, body mass index; WC, waist circumference; NHIS, National Health Insurance Service

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I. Introduction

1. Background

Survivors of most site-specific cancers have an increased mid-to long-term risk for one or more cardiovascular diseases (CVD) compared to that of the general population.[1] CVD has emerged as a leading cause of mortality[2], with an increasing number of cancer survivors. The risk of atherosclerosis and cardiovascular diseases (ASCVD) varies by cancer type, and those with bladder, kidney, prostate, colorectal, lung, melanoma, or testicular cancer have a 2.72–10.47 higher 10-year risk of ASCVD.[3] The risk of CVD in breast cancer survivors has also been investigated in previous studies.[4] Results of previous studies showed CVD to be the primary cause of death in older females diagnosed with early-stage breast cancer and the second leading cause of death in breast cancer survivors. The effect of increased risk of stroke, for example, due to cancer is known to be maintained for 7 years after diagnosis.[5]

Increased risk of CVD in breast cancer survivors compared to women without a cancer history is related to cardiotoxic effects of breast cancer treatment and overlapping risk factors of breast cancer and CVD, such as obesity and hormone replacement.[6, 7] After breast cancer diagnosis, the majority gain weight, which continues, especially in premenopausal women, into breast cancer survivorship.[8, 9] Even in the absence of weight gain, changes in body composition consisting of gain in adipose tissue without gain in or with loss of lean tissue have been observed.[10] Chemotherapy also causes alternations in skeletal muscle and creates a predisposition to muscle atrophy and weakness.[11] As a result, CVD burden of post-diagnosis weight gain has been observed to as long as 5 years in Asian patients.[12] Of equal importance, excessive body fat in cancer survivors has been shown to affect the quality of life and disease-free survival.[13]

Various anthropometric and imaging indices of obesity and their relationship with CVD risk have been summarized.[14] While body mass index (BMI) is commonly used to measure obesity, indices of abdominal

adiposity or visceral and subcutaneous adipose tissue at the waist level, such as waist circumference (WC) and waist-to-hip ratio (WHR), have shown to be strong independent predictors of CVD.[14] Few studies have investigated the combined effects of obesity measured by BMI and abdominal obesity measured by WC on CVD in the general population.[15, 16] Body composition has also been associated with risk of metabolic syndrome and CVD in the general population.[17, 18] Body fat percentage has been advocated to be a more accurate measure of obesity than BMI, but imaging modalities such as computerized tomography (CT)[8], dual-energy X-ray absorptiometry (DXA), or bioelectric impendence analysis (BIA) are indispensable for measurement. Therefore, prediction equations using anthropometric measures were validated and used to estimate body composition, including body fat mass (BFM), lean body mass (LBM), and appendicular skeletal muscle mass (ASM).[19]

The paradoxical relationship between obesity and cancer is still not fully understood.[20] As with the obesity paradox, survival rates were improved in overweight and early obese cancer patients, however, there were also observational studies showing that intentional body fat reduction and maintenance of skeletal muscle in overweight and obese cancer survivors have health benefits. Studies conducted on breast cancer patients have also shown varying results. In a study conducted by Shang *et al.* on breast cancer patients in their 50s, BMI loss was found to be a strong predictor of poor prognosis.[21] On the contrary, according to the results of a meta-analysis, weight gain after diagnosis of breast cancer was associated with a high mortality rate, and the risk was higher when weight gain was 10% or more compared to that of weight gain of less than 10%.[22] Besides one study[23], which examined for the association between adipose distribution and CVD, prior research on breast cancer survivors, let alone breast cancer patients, were limited to investigating the association between BMI and mortality, without measuring body composition or CVD. In terms of association between change in BMI and the risk of CVD or CVD mortality, there have been contradicting results.[24] For example, there was no association between change in BMI and risk of CVD in short-term breast

cancer survivors.

2. Research Question

The first research question pertains to whether risk of CVD is increased according to percentage of predicted body composition (lean body mass, appendicular skeletal mass, and body fat mass) in breast cancer survivors. Furthermore, the impact of discrepancies between general obesity and abdominal obesity on CVD is unknown in breast cancer survivors. The final question is whether changes in predicted body composition are associated with risk of CVD and changes in metabolic factors, such as blood pressure, fasting serum glucose, and cholesterol level.

3. Hypothesis and Objective

3.1. Hypothesis

The author hypothesized that a high percentage of fat mass and low percentages of lean body mass and appendicular skeletal mass are associated with higher risk of CVD. Furthermore, it was predicted that general obesity and especially the presence of abdominal obesity would be associated with higher risk of CVD, compared to breast cancer survivors without. Finally, it was predicted that breast cancer survivors with increased or sustained high percentage of lean body mass or appendicular skeletal muscle mass would have lower risk of CVD and that this would be accompanied by changes in metabolic factors such that blood pressure, fasting serum glucose, or cholesterol levels decrease; the converse would be observed in the case of body fat mass.

3.2. Study Objective

This study aimed to address 1) the association between body composition and risk of newly developed CVD; 2) discrepancies in general obesity and abdominal obesity with CVD risk; and 3) the association between changes in body composition with CVD risk and changes in metabolic factors in 5-year breast cancer survivors without prior CVD. Accordingly, the aim was to provide evidence for the holistic health management, in terms of body composition, of breast cancer

survivors in a care continuum.

II. Methods

1. Database

1.1. Korean National Health Insurance Service

The study population was based on the Korean National Health Insurance Service (NHIS) database. The NHIS provides for various forms of health services and collects data for reimbursement purposes. Information from health insurance claims is utilized for research purposes.[25, 26] In this study, information on sociodemographic factors (income level), forms of hospital use (history of radiation therapy), pharmaceutical drug prescriptions (history of chemotherapy and hormone therapy), and results from health screening examinations (health habits, anthropometric measurements, and laboratory tests) were used.

1.2. Ethical Considerations

This study was approved by the Seoul National University Hospital Institutional Review Board (IRB number: 2206-162-1335). The NHIS database was provided through legal procedures after deliberation for only research purposes. The requirement for informed consent from participants was waived as the database is anonymized according to strict confidentiality guidelines.

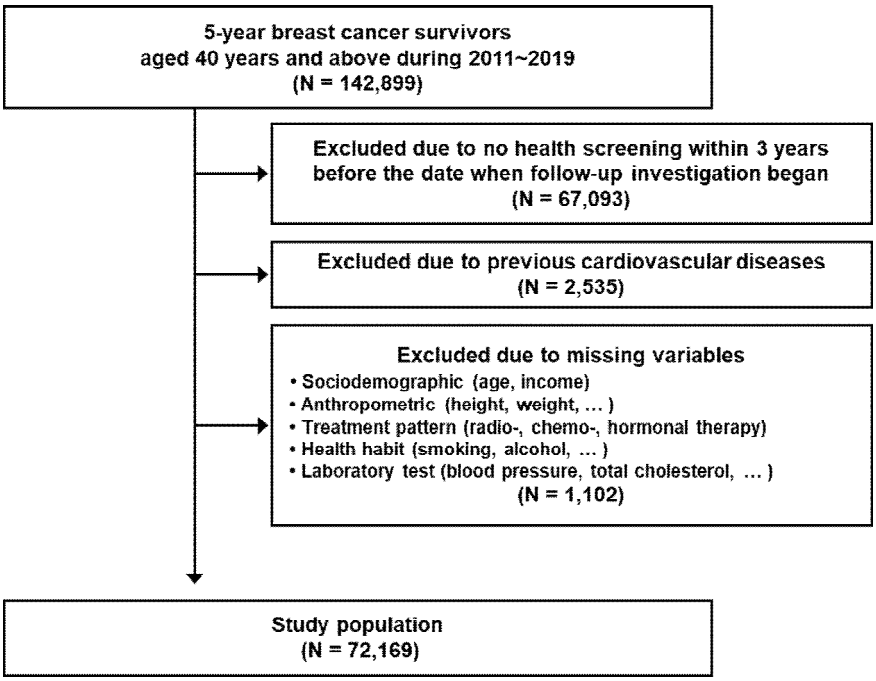
2. Study Population

2.1. Study Subjects for Evaluating Body Composition and CVD Risk

Among 142,899 5-year breast cancer survivors in females aged 40 years or older during 2011~2019, 67,093 participants who did not take the health screening examination during the previous 3 years before the index date (after 5 years from initial breast cancer diagnosis) were excluded. A total of 2,535 participants with previous CVD before the index date were excluded. An additional 1,102 participants who had missing

necessary variables to calculate predictive body composition (age, gender, height, weight, waist circumference, etc.) and covariates (income level, blood pressure, total cholesterol, etc.) were excluded. As a result, the final study population consisted of 72,169 5-year breast cancer survivors (Figure 1). All participants were followed up from the index date to date of newly diagnosed CVD, date of death, or 31, December, 2020, whichever came first.

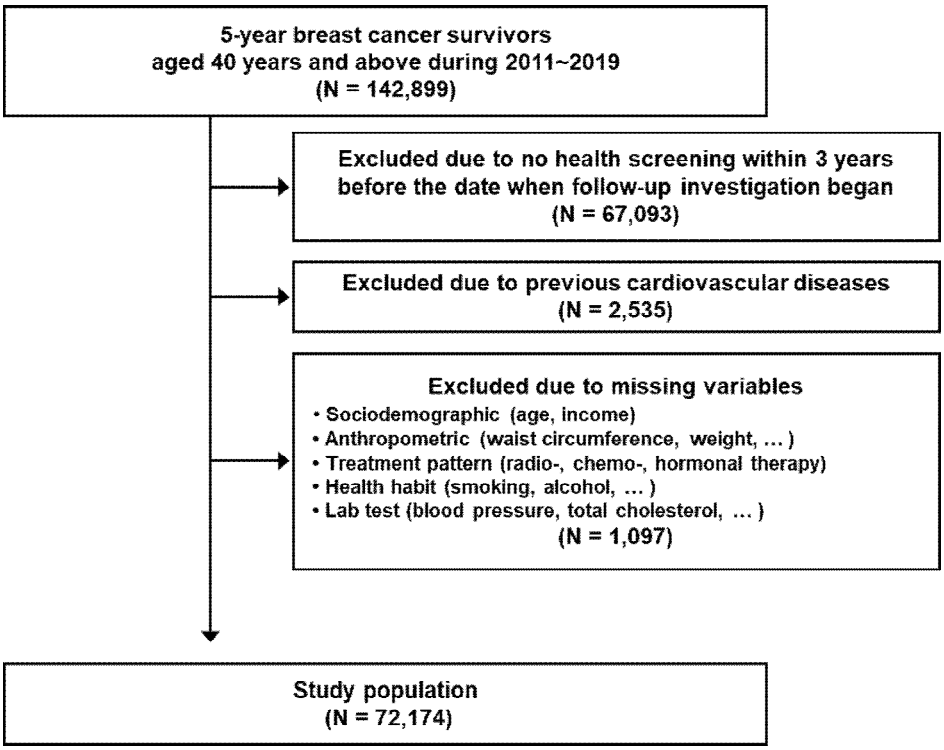
Figure 1. Flow diagram of the study population for evaluating body composition and cardiovascular disease (CVD) risk.



2.2. Study Subjects for Evaluating Discrepancies in General Obesity and Abdominal Obesity with CVD Risk

Among 142,899 5-year breast cancer survivors in females (aged 40 years or older) from 1, January, to 31, December, 2019, 67,093 participants who did not take the national health screening examinations during the previous 3 years before the index date (after 5 years from initial breast cancer diagnosis) were excluded. A total of 2,535 participants with previous CVD before the index date were excluded. An additional 1,097 participants, whose key variables including BMI and WC and covariates were missing, were excluded. Finally, a total of 72,174 5-year breast cancer survivors were included (Figure 2). All participants were followed up from the index date to the follow-up date which came first among the date of newly diagnosed CVD, date of death, or 31, December, 2020.

Figure 2. Flow diagram of the study population for evaluating discrepancies in general obesity and abdominal obesity with CVD risk.

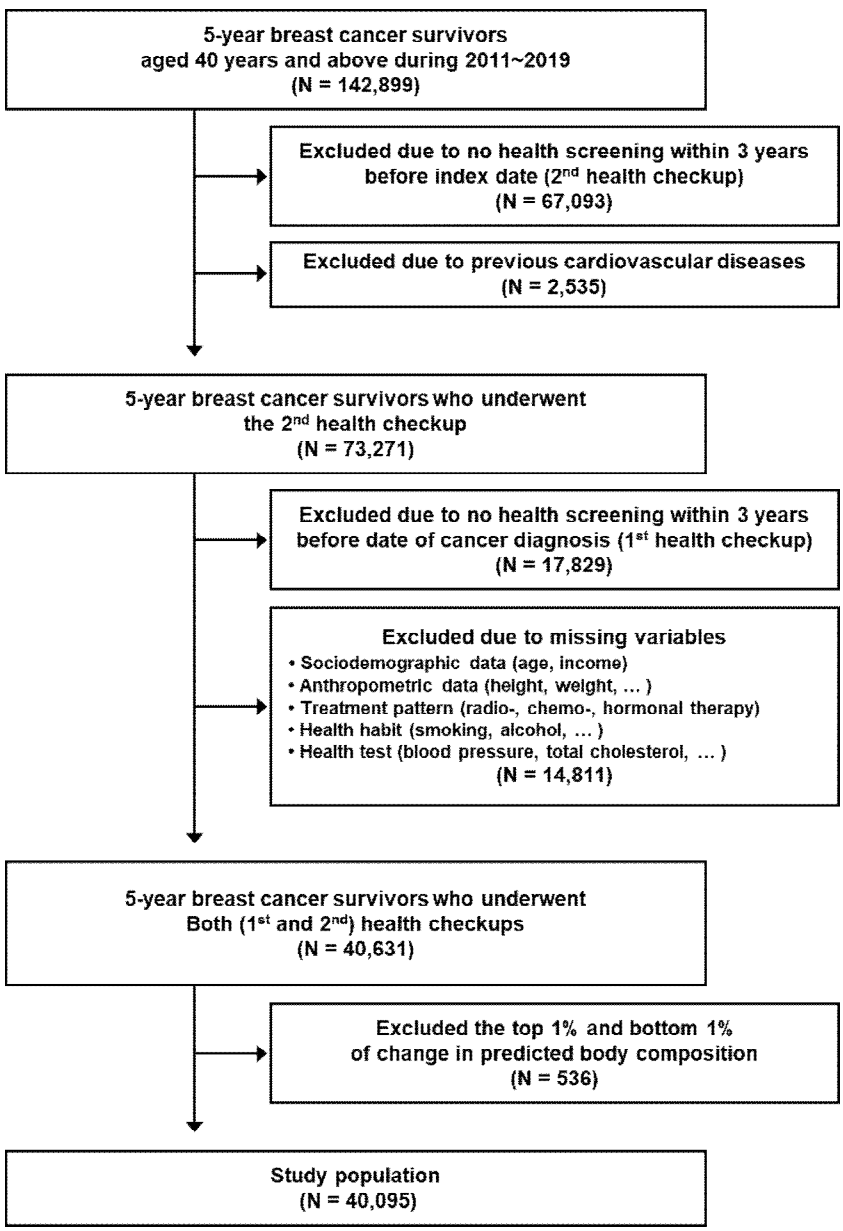


2.3. Study Subjects for Evaluating Changes in Body Composition with CVD Risk and Changes in Metabolic Factors

Among 142,899 5-year breast cancer survivors in females aged 40 years or older during 2011~2019, 67,093 participants who did not take a health screening examination (the second health checkup) during the previous 3 years before the index date (after 5 years from initial breast cancer diagnosis) were excluded. A total of 2,535 participants with previous CVD before the index date were excluded. Furthermore, 17,829 participants were excluded, because they did not take a health screening examination (the first health checkup) during the previous 3 years before the date of initial cancer diagnosis. An additional 14,811 participants who had missing necessary variables to calculate predictive body composition (age, gender, height, weight, waist circumference) and covariates (income level, blood pressure, total cholesterol, etc.) were excluded.

Finally, 536 participants with extreme body composition change (top and bottom 1%) were eliminated as cases of outliers.[27, 28] As a result, the final study population consisted of 40,095 5-year breast cancer survivors (Figure 3). All participants were followed up from the index date to the date of newly diagnosed CVD, date of death, or 31, December, 2020, whichever came first.

Figure 3. Flow diagram of the study population for evaluating body composition with CVD risk and changes in metabolic factors.



3. Key Variables

3.1. Exposure Variable: Predicted Body Composition and Other Anthropometric Measures

Age, gender, weight, height, waist circumference, serum creatine level, smoking status, alcohol consumption, and physical activity were used to evaluate for predicted body composition among a total of 72,169 participants who underwent the health checkup. Predicted mass of body composition (kg) including predicted lean body mass (pLBM), predicted appendicular skeletal muscle mass (pASM), and predicted body fat mass (pBFM) was assessed and calculated using a proven equation.[19] These prediction equations have been previously used in studies related to muscle and fat mass.[17, 29] The prediction equations were developed using multiple linear regressions to predict pASM, pLBM, and pBFM. The correlation coefficient for the variables which were consisted in the equation was then derived. Also, a test of predicted body composition calculated from the equations with actual measurement value showed high predictive power, low bias, and moderate agreement. In this study, age, height, weight, waist circumference, serum creatine level, physical activity, alcohol consumption, smoking status, and their correlation coefficients were used to calculate pLBM, pASM, and pBFM. As there is a difference in pLBM, pASM, and pBFM according to individual height, predicted lean body mass index (pLBMi), predicted appendicular skeletal muscle mass (pASMi), and predicted body fat mass index (pBFMi), which are each divided by the square of height (kg/m^2), were used to compensate for individual height. In addition, the percentage of the index to body mass index (BMI) (the percentage of predicted lean body mass (pLBMP), percentage of predicted appendicular skeletal muscle mass (pASMP), and percentage of predicted body fat mass (pBFMP)), was used since pLBMi, pASMi, and pBFMi are correlated with BMI.[30, 31] The 1st, 2nd, 3rd, and 4th quartile groups were equally divided according to percentage of body composition (pLBMP, pASMP, and pBFMP). The 1st

quartile group pertained to the lowest percentage of body composition and the 4th quartile group, the highest percentage of body composition. In addition, participants were also divided into four groups (Low body fat mass (BFM)-Low lean body mass (LBM), Low BFM-High LBM, High BFM-Low LBM, and High BFM-High LBM) according to whether pLBMi and pBFMi were lower or higher than each median.

For type of obesity based on BMI and WC measurements, 5-year breast cancer survivors, who underwent the national health screening examinations within 3 years before the index date were evaluated. Height, weight, and WC were measured by trained professionals in hospitals at the national health screening examinations, using a standardized protocol. BMI was calculated by dividing weight by the square of height (kg/m^2). According to the World Health Organization (WHO) guidelines, general obesity is defined as a state in which BMI is 25.0 kg/m^2 or more.[32] In addition, 23.0 kg/m^2 in BMI is the alternative standard for overweight in the Asian population.[33] According to the International Diabetes Federation, abdominal obesity was defined as WC higher than 80 cm for women in Asian populations.[34] 5-year breast cancer survivors were then classified according to BMI and WC. 5-year breast cancer survivors were then classified according to BMI and WC: normal (BMI < 23.0 kg/m^2 and WC < 80 cm), overweight without abdominal obesity (BMI $\geq$ 23.0 kg/m^2 and WC < 80 cm), abdominal obesity only (BMI < 23.0 kg/m^2 and WC $\geq$ 80 cm), and overweight with abdominal obesity (BMI $\geq$ 23.0 kg/m^2 and WC $\geq$ 80 cm). For sensitivity analysis, all participants were classified into four groups: normal (BMI < 25.0 kg/m^2 and WC < 80 cm), general obesity without abdominal obesity (BMI $\geq$ 25.0 kg/m^2 and WC < 80 cm), abdominal obesity without general obesity (BMI < 25.0 kg/m^2 and WC $\geq$ 80 cm), and general and abdominal obesity (BMI $\geq$ 25.0 kg/m^2 and WC $\geq$ 80 cm).

To observe changes in body composition, the percentage of predicted lean body mass (pLBMP), percentage of predicted appendicular skeletal muscle mass (pASMP), and percentage of

predicted body fat mass (pBFMP) were derived at both the first and second health checkups. Changes in body composition (pLBMP, pASMP, and pBFMP) were defined as the difference in the percentage of predicted body composition between the second and first health checkups; this value shows the difference in body composition before initial cancer diagnosis and after 5 years of survival from breast cancer. At the first health checkup, the High and Low body composition groups were classified based on pre-defined cut-off values: 65% for pLBMP, 26% for ASMP, and 34% for pBFMP. Similarly, the High and Low groups were classified at the second health checkup with the same cut-off value for respective body compositions.[35] Finally, according to changes in body composition, a total of 40,095 5-year breast cancer survivors were divided into four groups: those who had consistently low body composition (Low to Low), those who had low body composition before initial cancer diagnosis but high body composition after 5 years of survival (Low to High), those who had high body composition before initial cancer diagnosis but low body composition after 5 years of survival (High to Low), and those who had consistently high body composition (High to High).

3.2. Outcome Variable: Cardiovascular Disease

All breast cancer patients based on disease information recorded on the NHIS database were recruited. Breast cancer subjects were collected from 1, January, 2006, to 31, December, 2014, based on the International Classification of Diseases, Tenth Revision (ICD-10; C50) and the special assessment code (V-code that clearly distinguishes cancer patients in Korea; V193 and V194). Among 5-years breast cancer survivors, ICD-10 codes were used to identify CVD (I20–I25, I60–I69), coronary heart disease (CHD; I20–I25), and stroke ((I60–I69), including ischemic stroke and hemorrhagic stroke (I60-I62 and I63, respectively)).[36, 37] Additionally, CVD event was defined as 2 or more days of hospitalization with ICD-10 codes for CVD.

3.3. Outcome Variable: Metabolic Factors

Blood pressure (mmHg), total cholesterol (mg/dL), and fasting serum glucose (mg/dL) are known to cause CVD.[38] The percentage of excess risk mediated (PERM) was used as an indicator to evaluate the impact of these mediators. PERM was calculated by the corresponding equation with aHR of the confounder (blood pressure, total cholesterol, and fasting serum glucose was not adjusted at all) and aHR of the mediator (blood pressure, total cholesterol, and fasting serum glucose were additionally adjusted).[39]

Change in blood pressure (mmHg), total cholesterol (mg/dL), and fasting serum glucose according to changes in body composition was evaluated with adjusted mean and 95% CI, calculated by multiple linear regression after adjustments for the following covariates: age, income, chemotherapy, radiation therapy, hormone therapy, Charlson comorbidity index, smoking status, alcohol consumption, and physical activity.

3.4. Covariates

Participants were evaluated for adjusted hazard ratios (aHR) and 95% confidence intervals (CI) of CVD risk according to the percentage of body composition using multivariable Cox proportional hazards regression model after adjustments for the covariates. The considered covariates included age (continuous, years), income level (categorical, first, second, third, and fourth quartiles), smoking status (categorical, never-, past, and current smokers), alcohol consumption (categorical, 0, 1–2, 3–4, and 5 or more times per week), physical activity (categorical, 0, 1–2, 3–4, and 5 or more times per week), BMI (continuous, kg/m^2), Charlson comorbidity index (continuous), history of chemotherapy (categorical; cyclophosphamide, trastuzumab, doxorubicin, epirubicin, docetaxel, paclitaxel, and cisplatin), history of radiation therapy, history of hormone therapy (categorical; tamoxifen, anastrozole, and letrozole), diastolic blood pressure (continuous, mmHg), systolic blood pressure (continuous, mmHg), total cholesterol (continuous, mg/dL), and fasting

serum glucose (continuous, mg/dL). Income level was derived from the insurance premium. BMI was calculated by dividing body weight by the square of height (kg/m^2). Smoking status, alcohol consumption, and physical activity were assessed by a self-reported questionnaire at the health checkup. The algorithm for calculating Charlson comorbidity index (CCI) was adapted from a previous study.[40] Prescription of anti-cancer drugs known to cause heart disease was collected on the NHIS database.[41] Through the insurance claims, the history of radiation therapy was also collected.[42]

Compared to the 1st quartile group, CVD risk and aHR in the other quartile groups were assessed. Kaplan–Meier curves for risk of CVD according to pLBMP, pASMP, and pBFMP were constructed.

4. Statistical Analysis

4.1. Association of Body Composition and CVD Risk

Statistical significance was defined as p-value<0.05. p-value by Chi-squared test for categorical variables and analysis of variance (ANOVA) for continuous variables were used to determine the risk of CVD. All data collection and statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Stratified analysis was performed with overall according to age, CCI, and treatment pattern (chemotherapy, hormonal therapy, and radiation therapy).

4.2. Association of Discrepancies in General Obesity and Abdominal Obesity with CVD Risk

Chi-squared test for categorical variables and analysis of variance (ANOVA) for continuous variables were used to compare the differences in the distribution of covariates. Statistical significance was defined as p-value<0.05. All data collection and statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Stratified analysis was performed with overall according to type of obesity, age, CCI, and

treatment pattern (chemotherapy, hormone treatment, and radiation therapy).

4.3. Association of Changes in Body Composition with CVD Risk and Changes in Metabolic Factors

Statistical significance was defined as p-value<0.05. p-value by Chi-squared test for categorical variables and analysis of variance (ANOVA) for continuous variables were used to determine the risk of CVD. All data collection and statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Stratified analysis of the association of change in body composition was then performed with overall CVD events according to age, CCI, and treatment pattern (chemotherapy, hormonal therapy, and radiation therapy).

III. Results

1. Association of Body Composition and CVD Risk

Table 1 depicts the descriptive characteristics of the study population according to pLBMP. The mean percentage of predicted lean body mass in the 1st, 2nd, 3rd, and 4th quartile groups were 61.67%, 64.83%, 67.03%, and 70.35%, respectively. Mean ± standard deviation of age in the 1st, 2nd, 3rd, and 4th quartile groups were 59.21 ± 9.54 years, 57.67 ± 9.00 years, 55.87 ± 8.59 years, 53.92 ± 8.35 years, respectively. Most individuals in all quartiles were never-smokers, did not drink alcohol, and underwent chemotherapy, radiation therapy, and hormone therapy.

The risk for CVD according to quartiles of pLBMP, pASMP, and pBFMP is shown in Table 2. Compared to those with the lowest pLBMP, those with the highest pLBMP had a 38% lower risk of CVD. Similarly, compared to those with the lowest pASMP, those with the highest pASMP had a 42% lower risk of CVD. In contrast, those with the highest pBFMP had a 57% higher risk of CVD compared to those with the lowest pBFMP. The risk reduction of CVD tended to be higher according to the higher quartiles of pLBMP and pASMP (both p for trend < 0.001). As pBFMP increased, statistically significant higher risk of developing CVD was observed (p for trend < 0.001). The results after adjusting for additional covariates (Model 2 and 3) and BMI (Model B) were also consistent with the main findings presented in Model 1. Kaplan-Meier curves demonstrated significantly shorter CVD survival for those with the highest quartile of pBFMP and lowest quartile of pLBMP and pASMP (Figure 4). Interestingly, the risk of all-cause mortality tended to be higher according to higher quartiles of pLBMP and pASMP and lower according to higher quartiles of pBFMP (Table 3).

Table 1. Descriptive characteristics of the study population for evaluating body composition and cardiovascular disease (CVD) risk.

	Percentage of predicted lean body mass, quartiles				*p*-value
	1st (lowest)	2nd	3rd	4th (highest)	
Study population, N	18,042	18,042	18,043	18,042	
Percentage [%], mean (SD)	61.67 (1.60)	64.83 (0.67)	67.03 (0.65)	70.35 (1.88)	<0.001
Percentage [%], range	51.37, 63.63	63.63, 65.94	65.94, 68.21	68.21, 86.17	
Age [years], mean (SD)	59.21 (9.54)	57.67 (9.00)	55.87 (8.59)	53.92 (8.35)	<0.001
Age [years], N (%)					<0.001
40-49	2,917 (16.17)	3,354 (18.59)	4,308 (23.88)	5,919 (32.81)	
50-59	6,879 (38.13)	7,788 (43.17)	8,462 (46.90)	8,220 (45.56)	
≥ 60	8,246 (45.70)	6,900 (38.24)	5,273 (29.22)	3,903 (21.63)	
Income, quartiles, N (%)					<0.001
1st (highest)	4,004 (22.19)	4,499 (24.94)	4,789 (26.54)	5,271 (29.22)	
2nd	3,577 (19.83)	3,520 (19.51)	3,406 (18.88)	3,438 (19.06)	
3rd	3,587 (19.88)	3,423 (18.97)	3,372 (18.69)	3,240 (17.96)	
4th (lowest)	6,874 (38.10)	6,600 (36.58)	6,476 (35.89)	6,093 (35.77)	
Smoking, N (%)					<0.001
Never-smoker	17,329 (96.05)	17,440 (96.66)	17,446 (96.69)	17,336 (96.09)	
Past smoker	462 (2.56)	400 (2.22)	373 (2.07)	413 (2.29)	
Current smoker	251 (1.39)	202 (1.12)	224 (1.24)	293 (1.62)	
Alcohol consumption [times per week], N (%)					<0.001
0	16,455 (91.20)	16,220 (89.90)	16,007 (88.72)	15,832 (87.75)	
1-2	1,370 (7.59)	1,560 (8.65)	1,810 (10.03)	1,958 (10.85)	
3-4	158 (0.88)	184 (1.02)	165 (0.91)	181 (1.00)	
≥ 5	59 (0.33)	78 (0.43)	61 (0.34)	71 (0.39)	
Physical activity [times per week], N (%)					<0.001
0	9,401 (52.11)	7,856 (43.54)	6,926 (38.39)	6,221 (34.48)	
1-2	2,484 (13.77)	2,636 (14.61)	2,709 (15.01)	2,994 (16.59)	
3-4	2,381 (13.20)	2,684 (14.88)	3,084 (17.09)	3,291 (18.24)	
≥ 5	3,776 (20.93)	4,866 (26.97)	5,324 (29.51)	5,536 (30.68)	
Appendicular skeletal muscle mass [kg], mean (SD)	16.61 (1.84)	15.39 (1.43)	14.81 (1.31)	14.08 (1.34)	<0.001
Fat mass [kg], mean (SD)	25.02 (3.73)	20.18 (1.75)	17.58 (1.45)	14.35 (1.89)	<0.001
BMI [kg/m^2], mean (SD)	27.76 (2.41)	24.14 (0.86)	22.20 (0.73)	19.89 (1.22)	<0.001

BMI [kg/m^2], N (%)					<0.001
< 23.0	1 (0.01)	1,386 (7.68)	15,273 (84.65)	17,958 (99.53)	
≥ 23.0	18,041 (99.99)	16,656 (92.32)	2,770 (15.35)	84 (0.47)	
Charlson comorbidity index, N (%)					<0.001
≤ 2	6,833 (37.87)	8,225 (45.59)	9,096 (50.41)	9,837 (54.52)	
3-4	7,251 (40.19)	6,936 (38.44)	6,609 (36.63)	6,241 (34.59)	
≥ 5	3,958 (21.94)	2,881 (15.97)	2,338 (12.96)	1,964 (10.89)	
Chemotherapy[a], N (%)	10,133 (56.16)	9,945 (55.12)	9,682 (53.66)	9,736 (53.96)	<0.001
Doxorubicin	4,905 (27.19)	4,604 (25.52)	4,734 (26.24)	5,538 (30.70)	
Cyclophosphamide	9,015 (49.97)	8,986 (49.81)	8,767 (48.59)	8,820 (48.89)	
Paclitaxel	1,954 (10.83)	1,809 (10.31)	1,752 (9.71)	1,627 (9.02)	
Radiation therapy, N (%)	10,622 (58.87)	10,856 (60.17)	10,930 (60.58)	10,880 (60.30)	0.005
Hormone therapy[b], N (%)	12,318 (68.27)	12,430 (68.89)	12,534 (69.47)	12,592 (69.79)	0.010
Tamoxifen	7,297 (40.44)	8,038 (44.55)	8,970 (49.71)	9,563 (56.00)	<0.001
Diastolic blood pressure [mmHg], mean (SD)	77.86 (9.64)	75.22 (9.41)	73.32 (9.43)	71.34 (9.35)	<0.001
Systolic blood pressure [mmHg], mean (SD)	126.33 (14.87)	121.59 (14.50)	117.94 (14.32)	113.99 (13.95)	<0.001
Total cholesterol [mg/dL], mean (SD)	196.36 (39.00)	195.87 (37.48)	193.71 (38.46)	189.24 (36.37)	<0.001
Fasting serum glucose [mg/dL], mean (SD)	103.63 (24.86)	98.38 (20.07)	95.23 (17.12)	92.77 (16.23)	<0.001

p-values calculated via Chi-squared test for categorical variables and analysis of variance (ANOVA) for continuous variables

[a]Treatment patterns including cyclophosphamide, trastuzumab, doxorubicin, epirubicin, docetaxel, paclitaxel, and cisplatin

[b]Treatment patterns including tamoxifen, anastrozole, and letrozole

Acronyms: standard deviation (SD); body mass index (BMI)

Table 2. CVD risk according to quartiles of percentage of predicted body composition.

	Percentage of predicted body composition, quartiles				p_{trend}
	1st (lowest)	**2nd**	**3rd**	**4th (highest)**	
pLBMP					
Study population, N	18,042	18,042	18,043	18,042	
Percentage [%], range	51.37, 63.63	63.63, 65.94	65.94, 68.21	68.21, 86.17	
CVD; events, N (%)	383 (2.12)	331 (1.83)	220 (1.22)	161 (0.89)	
aHR (95% CI) of Model A[a]					
Model 1	1.00 (reference)	0.98 (0.84, 1.13)	0.74 (0.62, 0.87)***	0.62 (0.52, 0.75)***	<0.001
Model 2	1.00 (reference)	1.00 (0.86, 1.16)	0.76 (0.64, 0.90)**	0.65 (0.54, 0.78)***	<0.001
Model 3	1.00 (reference)	1.06 (0.91, 1.23)	0.83 (0.70, 0.99)*	0.74 (0.61, 0.90)**	<0.001
aHR (95% CI) of Model B[b]					
Model 1	1.00 (reference)	1.01 (0.83, 1.23)	0.77 (0.60, 1.01)	0.67 (0.48, 0.94)*	0.004
Model 2	1.00 (reference)	1.04 (0.86, 1.27)	0.81 (0.62, 1.06)	0.71 (0.51, 1.00)	0.010
Model 3	1.00 (reference)	1.05 (0.86, 1.28)	0.83 (0.64, 1.08)	0.74 (0.52, 1.04)	0.017
pASMP					
Study population, N	18,042	18,042	18,043	18,042	
Percentage [%], range	17.04, 25.55	25.55, 26.52	26.52, 27.49	27.49, 46.07	
CVD; events, N (%)	436 (2.42)	312 (1.73)	210 (1.16)	137 (0.76)	
aHR (95% CI) of Model A[a]					
Model 1	1.00 (reference)	0.90 (0.78, 1.04)	0.73 (0.62, 0.87)***	0.58 (0.48, 0.72)***	<0.001
Model 2	1.00 (reference)	0.93 (0.80, 1.08)	0.76 (0.64, 0.91)**	0.61 (0.50, 0.75)***	<0.001
Model 3	1.00 (reference)	0.98 (0.84, 1.13)	0.84 (0.70, 0.99)*	0.70 (0.57, 0.87)**	<0.001
aHR (95% CI) of Model B[b]					
Model 1	1.00 (reference)	0.94 (0.78, 1.12)	0.78 (0.62, 0.98)*	0.64 (0.47, 0.87)**	0.002
Model 2	1.00 (reference)	0.98 (0.82, 1.17)	0.83 (0.66, 1.05)	0.69 (0.51, 0.93)*	0.011
Model 3	1.00 (reference)	0.99 (0.82, 1.18)	0.85 (0.67, 1.07)	0.72 (0.53, 0.98)*	0.022
pBFMP					
Study population, N	18,042	18,042	18,043	18,042	
Percentage [%], range	13.07, 30.85	30.85, 33.13	33.13, 35.36	35.36, 47.60	
CVD; events, N (%)	163 (0.90)	221 (1.22)	326 (1.81)	385 (2.13)	
aHR (95% CI) of Model A[a]					
Model 1	1.00 (reference)	1.17 (0.96, 1.43)	1.51 (1.25, 1.83)***	1.57 (1.30, 1.89)***	<0.001
Model 2	1.00 (reference)	1.17 (0.95, 1.43)	1.50 (1.24, 1.81)***	1.52 (1.26, 1.84)***	<0.001

Model 3	1.00 (reference)	1.12 (0.91, 1.37)	1.38 (1.14, 1.67)**	1.33 (1.09, 1.61)**	0.001
aHR (95% CI) of Model B[b]					
Model 1	1.00 (reference)	1.13 (0.91, 1.40)	1.41 (1.11, 1.80)**	1.39 (0.99, 1.95)	0.015
Model 2	1.00 (reference)	1.12 (0.90, 1.40)	1.40 (1.09, 1.78)**	1.34 (0.95, 1.89)	0.025
Model 3	1.00 (reference)	1.11 (0.89, 1.38)	1.36 (1.07, 1.74)*	1.30 (0.92, 1.83)	0.042

Adjusted hazard ratios were calculated by multivariable Cox proportional hazards regression analysis after adjustments for the following covariates:

[a]Model A: not including BMI

[b]Model B: including BMI

Model 1: age, income, chemotherapy, radiation therapy, hormone therapy, and Charlson comorbidity index

Model 2: Model 1 + smoking, alcohol, and physical activity

Model 3: Model 2 + blood pressures, total cholesterol, and fasting serum glucose

Acronyms: cardiovascular disease (CVD); hazard ratio (HR); confidence interval (CI); percentage of predicted lean body mass (pLBMP); percentage of predicted appendicular skeletal mass (pASMP); percentage of predicted body fat mass (pBFMP)

*p-value<0.05, **p-value<0.01, and ***p-value<0.001

Figure 4. Kaplan-Meier Curve. Survival probability of CVD according to quartiles of percentage of a). predicted lean body mass (pLBMP), b). predicted appendicular skeletal mass (pASMP), and c). predicted body fat mass (pBFMP).

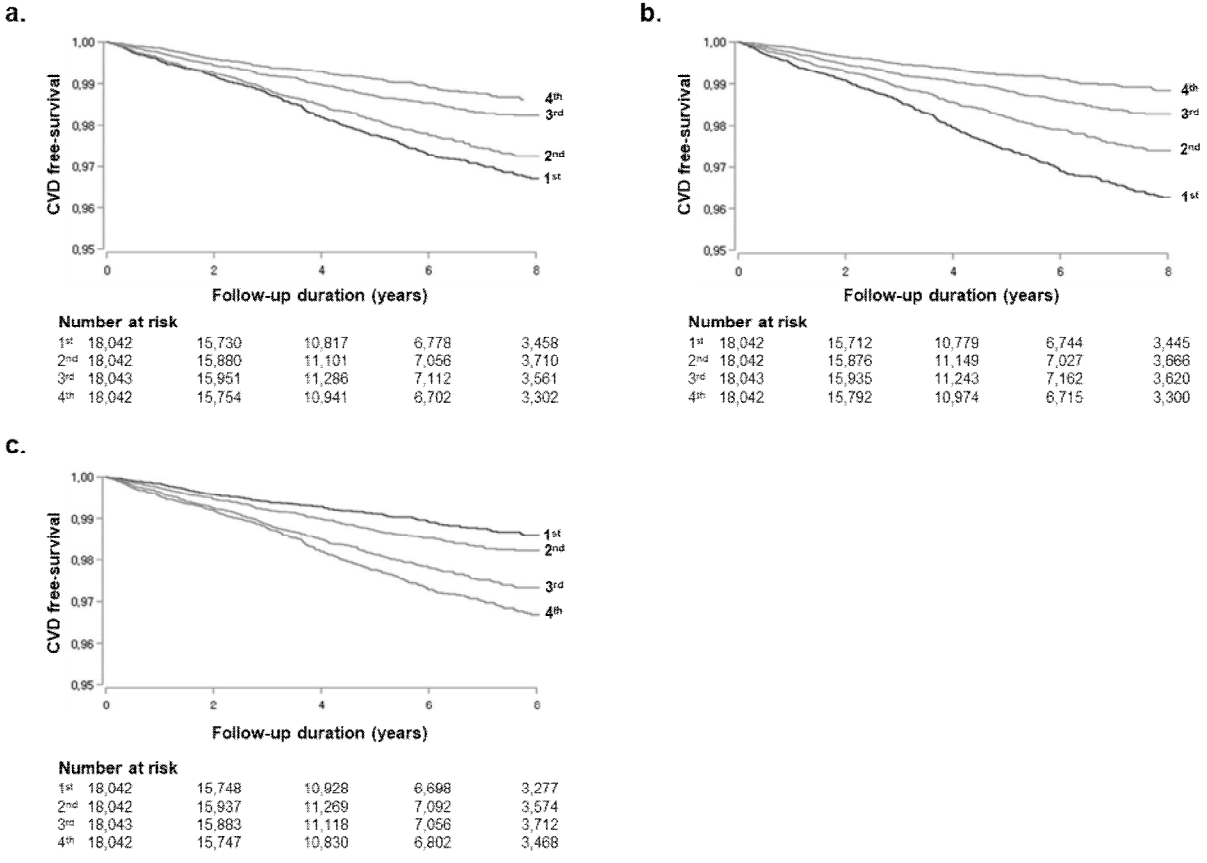


Table 3. Risk of coronary heart diseases (CHD) and subtypes of stroke according to quartiles of percentage of predicted body composition.

	Percentage of predicted body composition, quartiles				
	1st (lowest)	2nd	3rd	4th	p_{trend}
pLBMP					
All-cause mortality; events, N (%)	871 (4.83)	785 (4.35)	657 (3.64)	647 (3.59)	
aHR (95% CI)	1.00 (reference)	1.09 (0.98, 1.20)	1.08 (0.97, 1.19)	1.29 (1.16, 1.43)***	<0.001
CHD; events, N (%)	166 (0.92)	128 (0.71)	61 (0.34)	62 (0.34)	
aHR (95% CI)	1.00 (reference)	0.91 (0.72, 1.14)	0.50 (0.37, 0.67)***	0.60 (0.44, 0.80)***	<0.001
Ischemic stroke; event, N (%)	114 (0.63)	79 (0.44)	58 (0.32)	32 (0.18)	
aHR (95% CI)	1.00 (reference)	0.85 (0.63, 1.13)	0.75 (0.55, 1.04)	0.51 (0.34, 0.75)***	<0.001
Hemorrhagic stroke; events, N (%)	23 (0.13)	32 (0.18)	24 (0.13)	22 (0.12)	
aHR (95% CI)	1.00 (reference)	1.47 (0.87, 2.49)	1.32 (0.75, 2.31)	1.35 (0.75, 2.43)	0.383
pASMP					
All-cause mortality; events, N (%)	1,007 (5.58)	764 (4.23)	612 (3.39)	577 (3.20)	
aHR (95% CI)	1.00 (reference)	1.01 (0.92, 1.11)	1.03 (0.93, 1.15)	1.23 (1.10, 1.37)***	<0.001
CHD; events, N (%)	181 (1.00)	126 (0.70)	62 (0.34)	48 (0.27)	
aHR (95% CI)	1.00 (reference)	0.91 (0.72, 1.15)	0.55 (0.41, 0.75)***	0.54 (0.38, 0.75)***	<0.001
Ischemic stroke; event, N (%)	135 (0.75)	75 (0.42)	47 (0.26)	26 (0.14)	
aHR (95% CI)	1.00 (reference)	0.81 (0.61, 1.09)	0.68 (0.48, 0.96)*	0.51 (0.32, 0.79)**	<0.001
Hemorrhagic stroke; events, N (%)	29 (0.16)	26 (0.14)	29 (0.16)	17 (0.09)	
aHR (95% CI)	1.00 (reference)	1.08 (0.64, 1.84)	1.53 (0.90, 2.60)	1.09 (0.58, 2.05)	0.415
pBFMP					
All-cause mortality; events, N (%)	636 (3.53)	663 (3.67)	784 (4.35)	877 (4.86)	
aHR (95% CI)	1.00 (reference)	0.86 (0.77, 0.96)**	0.85 (0.77, 0.95)**	0.79 (0.71, 0.87)***	<0.001
CHD; events, N (%)	62 (0.34)	60 (0.33)	129 (0.71)	166 (0.92)	
aHR (95% CI)	1.00 (reference)	0.82 (0.58, 1.17)	1.53 (1.12, 2.07)**	1.67 (1.24, 2.25)***	<0.001
Ischemic stroke; event, N (%)	33 (0.18)	56 (0.31)	79 (0.44)	115 (0.64)	
aHR (95% CI)	1.00 (reference)	1.40 (0.91, 2.15)	1.61 (1.07, 2.43)*	1.91 (1.29, 2.84)**	<0.001
Hemorrhagic stroke; events, N (%)	21 (0.12)	27 (0.15)	30 (0.17)	23 (0.13)	
aHR (95% CI)	1.00 (reference)	1.14 (0.65, 2.02)	1.06 (0.60, 1.87)	0.77 (0.42, 1.40)	0.318

Adjusted hazard ratios were calculated by multivariable Cox proportional hazards regression analysis after adjustments for the following covariates: age, income, chemotherapy, radiation therapy, hormone therapy, Charlson comorbidity index, smoking, alcohol, and physical activity

Acronyms: coronary heart diseases (CHD); hazard ratio (HR); confidence interval (CI); percentage of predicted lean body mass (pLBMP); percentage of predicted appendicular skeletal mass (pASMP); percentage of predicted body fat mass (pBFMP)
*p-value<0.05, **p-value<0.01, and ***p-value<0.001

The associations in pLBMP, pASMP, and pBFMP with the risk of CVD stratified by BMI are presented in Table 4. Overall, in Model A, each 1% increase in pLBMP and pASMP was associated with a lower risk of CVD (pLBMP, aHR(95% CI) 0.96(0.94–0.98), $p<0.05$ and pASMP, aHR(95% CI) 0.91(0.87–0.95), $p<0.05$, respectively). In contrast, each 1% increase in pBFMP was associated with a higher risk of CVD (aHR(95% CI) 1.05(1.03–1.07), $p<0.01$). Adjustments for combinations of three confounders showed blood pressure to be the most important mediator for the association of pLBMP, pASMP, and pBFMP with CVD (Figure 5).

In Table 5, the risk of CVD was observed according to groups classified by pLBMi and pBFMi. Compared to those with Low BFM-Low LBM, those with High BFM-Low LBM and High BFM-High LBM had 59% and 35% higher risk of CVD, respectively. Though statistically insignificant, those with High BFM-High LBM had a lower risk of CVD compared to those with High BFM-Low LBM. Results from the stratified analysis on the association of pLBMP, pASMP, and pBFMP with CVD according to subgroups of age, CCI, and treatment pattern were consistent with main findings and are shown in Table 6. Compared to those with the lowest pLBMP and pASMP, those with the highest pLBMP and pASMP, respectively, had significantly lower risk of CVD in all age groups above 40, those with lower CCI, and those who underwent radiation therapy and hormone therapy; however, an interaction was found between age groups and risk of CVD. Highest quartile pBFMP patients in all age groups above 40, those with lower CCI, and those who underwent radiation therapy and hormone therapy had significantly higher risk of CVD compared to that of lowest quartile pBFMP survivors; similarly, an interaction was found between age groups and risk of CVD. A sensitivity analysis based on follow-up years (Table 7) showed similar trends as that of the main results.

Table 4. CVD risk per 1 % increase in percentage of predicted body composition.

	per 1 % increase		
	pLBMP	**pASMP**	**pBFMP**
Overall			
Study population, N	72,169	72,169	72,169
CVD, N	1,095	1,095	1,095
aHR (95% CI)			
Model A[a]	0.96 (0.94, 0.98)***	0.91 (0.87, 0.95)***	1.05 (1.03, 1.07)***
Model B[b]	0.95 (0.90, 1.01)	0.98 (0.90, 1.06)	1.07 (1.00, 1.14)*
BMI (< 23.0 kg/m^2)			
Study population, N	34,618	34,618	34,618
CVD, N	375	375	375
aHR (95% CI)	0.97 (0.93, 1.02)	0.97 (0.88, 1.07)	1.03 (0.99, 1.08)
BMI (≥ 23.0 kg/m^2)			
Study population, N	37,551	37,551	37,551
CVD, N	720	720	720
aHR (95% CI)	0.97 (0.94, 1.01)	0.96 (0.89, 1.03)	1.03 (1.00, 1.07)

Adjusted hazard ratios were calculated by multivariable Cox proportional hazards regression analysis after adjustments for the following covariates: age, income, chemotherapy, radiation therapy, hormone therapy, Charlson comorbidity index, smoking, alcohol, and physical activity.

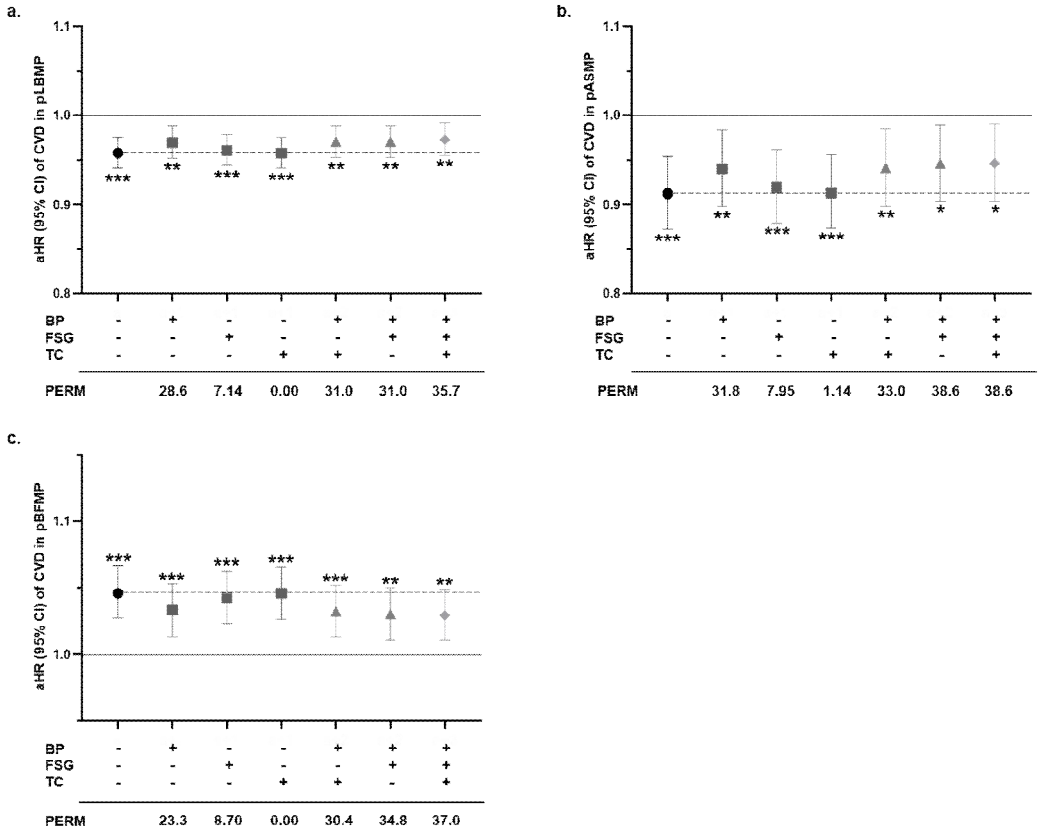
[a]Model A: above covariates and not including BMI

[b]Model B: above covariates and BMI

Acronyms: cardiovascular disease (CVD); hazard ratio (HR); confidence interval (CI); percentage of predicted lean body mass (pLBMP); percentage of predicted appendicular skeletal mass (pASMP); percentage of predicted body fat mass (pBFMP); body mass index (BMI)

*p-value<0.05, **p-value<0.01, and ***p-value<0.001

Figure 5. Mediated factors and excess risk of CVD in percentage of predicted body composition. Percentage of excess risk mediated (PERM, %) and hazard ratios (HR) adjusted for the different combinations of mediators; blood pressure (BP), fasting serum glucose (FSG), and total cholesterol (TC) according to a). pLBMP, b). pASMP, and c). pBFMP.



Solid lines and dash lines indicate HR of the reference group and HR unadjusted for all mediators, respectively.
*p-value<0.05, **p-value<0.01, and ***p-value<0.001

Table 5. CVD risk according to the groups classified by predicted lean body mass (pLBMi) and fat mass index (pLFMi).

		pBFMi [kg/m^2]			
		Low (Range: 1.71, 7.65)		**High** (Range: 7.65, 26.99)	
pLBMi [kg/m^2]	**Low** (Range:11.06, 15.24)	**Low BFM-Low LBM**		**High BFM-Low LBM**	
	High (Range:15.24, 29.13)	**Low BFM-High LBM**		**High BFM-High LBM**	
		Low BFM-Low LBM	**Low BFM-High LBM**	**High BFM-Low LBM**	**High BFM-High LBM**
Study population, N		34,006	2,078	2,078	34,007
pLBMi [kg/m^2], mean (Range)		14.34 (11.06, 15.24)	15.43 (15.24, 17.84)	15.09 (14.33, 15.24)	16.47 (15.24, 29.13)
pBFMi [kg/m^2], mean (Range)		6.36 (1.71, 7,65)	7.41 (3.48, 7.65)	7.87 (7.65, 10.32)	9.42 (7.66, 26.99)
BMI [kg/m^2], mean (SD)		20.89 (1.44)	23.02 (0.40)	23.19 (0.26)	26.15 (2.50)
CVD; events, N (%)		363 (1.07)	28 (1.35)	46 (2.21)	658 (1.93)
aHR (95% CI)		**1.00 (reference)**	1.14 (0.78, 1.68)	1.60 (1.17, 2.17)**	1.35 (1.19, 1.54)***
aHR (95% CI)		-	**1.00 (reference)**	1.40 (0.87, 2.24)	1.18 (0.81, 1.73)
aHR (95% CI)		-	-	**1.00 (reference)**	0.85 (0.63, 1.14)

5-year cancer survivors divided into 4 groups based on pLBMi and pBFMi: the Low BFM-Low LBM group (those who have relatively low fat mass and low lean body mass), the Low BFM-High LBM group (those who have relatively low fat mass and high lean body mass), the High BFM-Low LBM group (those who have relatively high fat mass and low lean body mass), and the High BFM-High LBM group (those who have relatively high fat mass and high lean body mass).

Adjusted hazard ratios were calculated by multivariable Cox proportional hazards regression analysis after adjustments for the following covariates: age, income, chemotherapy, radiation therapy, hormone therapy, Charlson comorbidity index, smoking, alcohol, and physical activity.

Acronyms: cardiovascular disease (CVD); hazard ratio (HR); confidence interval (CI); lean body mass (LBM); body fat mass (BFM); predicted lean body mass index (pLBMi); predicted body fat mass index (pBFMi)

*p-value<0.05, **p-value<0.01, and ***p-value<0.001

Table 6. Stratified analysis of association between CVD risk and predicted body composition according to the subgroups of covariates.

	Predicted body composition, quartiles				p_{trend}	$p_{interaction}$
	1st (lowest)	2nd	3rd	4th		
pLBMP			aHR (95% CI)			
Age [years]						<0.001
40-49	1.00 (reference)	0.79 (0.43, 1.48)	0.53 (0.28, 1.02)	0.40 (0.21, 0.78)**	0.003	
50-59	1.00 (reference)	1.06 (0.80, 1.40)	0.84 (0.62, 1.13)	0.58 (0.41, 0.80)**	<0.001	
≥ 60	1.00 (reference)	0.96 (0.80, 1.15)	0.72 (0.58, 0.90)**	0.76 (0.60, 0.97)*	0.002	
Charlson comorbidity index						0.566
1-3	1.00 (reference)	1.03 (0.85, 1.24)	0.75 (0.60, 0.93)**	0.60 (0.47, 0.76)***	<0.001	
4 or more	1.00 (reference)	0.95 (0.75, 1.21)	0.80 (0.61, 1.05)	0.79 (0.58, 1.07)	0.055	
Treatment pattern						
Radiation therapy						0.570
Yes	1.00 (reference)	0.94 (0.75, 1.19)	0.77 (0.60, 0.99)*	0.62 (0.46, 0.82)**	<0.001	
No	1.00 (reference)	1.04 (0.86, 1.26)	0.76 (0.60, 0.95)*	0.68 (0.53, 0.87)**	<0.001	
Chemotherapy						0.142
Yes	1.00 (reference)	1.23 (0.97, 1.55)	0.93 (0.72, 1.22)	0.79 (0.59, 1.06)	0.064	
No	1.00 (reference)	0.87 (0.71, 1.05)	0.67 (0.54, 0.83)***	0.58 (0.45, 0.74)***	<0.001	
Hormone therapy						0.164
Yes	1.00 (reference)	1.09 (0.90, 1.33)	0.81 (0.64, 1.02)	0.76 (0.57, 0.94)*	0.003	
No	1.00 (reference)	0.89 (0.71, 1.11)	0.71 (0.55, 0.91)**	0.56 (0.42, 0.75)***	<0.001	
pASMP			aHR (95% CI)			
Age [years]						<0.001
40-49	1.00 (reference)	0.41 (0.19, 0.86)*	0.61 (0.33, 1.12)	0.32 (0.16, 0.61)***	0.004	
50-59	1.00 (reference)	0.98 (0.74, 1.31)	0.74 (0.54, 1.00)*	0.60 (0.43, 0.84)**	<0.001	
≥ 60	1.00 (reference)	0.88 (0.74, 1.05)	0.72 (0.57, 0.90)**	0.69 (0.52, 0.92)*	<0.001	
Charlson comorbidity index						0.179
1-3	1.00 (reference)	0.91 (0.75, 1.10)	0.75 (0.60, 0.93)**	0.54 (0.42, 0.70)***	<0.001	
4 or more	1.00 (reference)	0.94 (0.75, 1.19)	0.80 (0.60, 1.06)	0.81 (0.58, 1.13)	0.094	
Treatment pattern						
Radiation therapy						0.368
Yes	1.00 (reference)	0.79 (0.63, 1.00)*	0.69 (0.53, 0.90)**	0.59 (0.44, 0.80)***	<0.001	

No	1.00 (reference)	1.04 (0.85, 1.26)	0.82 (0.65, 1.04)	0.64 (0.48, 0.84)**	0.001	
Chemotherapy						0.390
Yes	1.00 (reference)	1.10 (0.88, 1.39)	0.86 (0.66, 1.13)	0.74 (0.54, 1.00)*	0.034	
No	1.00 (reference)	0.82 (0.67, 0.99)*	0.70 (0.56, 0.88)**	0.55 (0.42, 0.72)***	<0.001	
Hormone therapy						0.307
Yes	1.00 (reference)	0.99 (0.81, 1.21)	0.73 (0.58, 0.92)**	0.71 (0.54, 0.92)**	0.001	
No	1.00 (reference)	0.85 (0.68, 1.06)	0.81 (0.63, 1.04)	0.51 (0.37, 0.71)***	0.001	
pBFMP		aHR (95% CI)				
Age [years]						0.005
40-49	1.00 (reference)	1.83 (0.96, 3.50)	1.39 (0.67, 2.90)	2.55 (1.32, 4.92)**	0.014	
50-59	1.00 (reference)	1.43 (1.02, 1.99)*	1.80 (1.30, 2.48)***	1.70 (1.22, 2.37)**	<0.001	
≥ 60	1.00 (reference)	0.90 (0.68, 1.19)	1.24 (0.97, 1.59)	1.29 (1.01, 1.64)*	0.002	
Charlson comorbidity index						0.235
1-3	1.00 (reference)	1.24 (0.97, 1.59)	1.63 (1.29, 2.06)***	1.62 (1.28, 2.05)***	<0.001	
4 or more	1.00 (reference)	1.01 (0.71, 1.43)	1.22 (0.88, 1.69)	1.29 (0.94, 1.76)	0.042	
Treatment patter						
Radiation therapy						0.472
Yes	1.00 (reference)	1.13 (0.83, 1.53)	1.44 (1.08, 1.92)*	1.53 (1.15, 2.03)**	0.001	
No	1.00 (reference)	1.19 (0.91, 1.56)	1.52 (1.18, 1.95)**	1.50 (1.17, 1.95)**	<0.001	
Chemotherapy						0.156
Yes	1.00 (reference)	1.19 (0.88, 1.62)	1.48 (1.11, 1.97)**	1.27 (0.95, 1.70)	0.076	
No	1.00 (reference)	1.14 (0.87, 1.49)	1.48 (1.15, 1.90)**	1.69 (1.32, 2.17)***	<0.001	
Hormone therapy						0.105
Yes	1.00 (reference)	1.08 (0.82, 1.40)	1.42 (1.11, 1.81)**	1.32 (1.03, 1.69)*	0.008	
No	1.00 (reference)	1.28 (0.94, 1.76)	1.56 (1.16, 2.11)**	1.80 (1.34, 2.40)***	<0.001	

Adjusted hazard ratios were calculated by multivariable Cox proportional hazards regression analysis after adjustments for the following covariates: age, income, chemotherapy, radiation therapy, hormone therapy, Charlson comorbidity index, smoking, alcohol, and physical activity.
Acronyms: cardiovascular disease (CVD); hazard ratio (HR); confidence interval (CI); percentage of predicted lean body mass (pLBMP); percentage of predicted appendicular skeletal mass (pASMP); percentage of predicted body fat mass (pBFMP)
*p-value<0.05, **p-value<0.01, and ***p-value<0.001

Table 7. Sensitivity analysis of association between CVD risk and predicted body composition according to follow-up periods.

	Predicted body composition, quartiles				
	1st (lowest)	2nd	3rd	4th	p_{trend}
Follow-up period ≤ 2 years		aHR (95% CI)			
pLBMP	1.00 (reference)	1.13 (0.88, 1.43)	0.92 (0.71, 1.21)	0.70 (0.52, 0.94)	0.016
pASMP	1.00 (reference)	1.08 (0.85, 1.37)	0.90 (0.69, 1.18)	0.68 (0.50, 0.95)	0.024
pBFMP	1.00 (reference)	1.21 (0.89, 1.64)	1.51 (1.13, 2.02)	1.35 (1.01, 1.81)	0.027
Follow-up period ≤ 4 years		aHR (95% CI)			
pLBMP	1.00 (reference)	1.04 (0.88, 1.25)	0.77 (0.63, 0.94)	0.60 (0.48, 0.75)	<0.001
pASMP	1.00 (reference)	0.96 (0.80, 1.14)	0.75 (0.61, 0.92)	0.57 (0.44, 0.72)	<0.001
pBFMP	1.00 (reference)	1.25 (0.98, 1.60)	1.72 (1.37, 2.15)	1.64 (1.31, 2.06)	<0.001
Follow-up period ≤ 6 years		aHR (95% CI)			
pLBMP	1.00 (reference)	1.00 (0.86, 1.17)	0.73 (0.61, 0.87)	0.58 (0.47, 0.70)	<0.001
pASMP	1.00 (reference)	0.90 (0.78, 1.06)	0.73 (0.61, 0.87)	0.53 (0.43, 0.66)	<0.001
pBFMP	1.00 (reference)	1.27 (1.02, 1.57)	1.70 (1.39, 2.08)	1.73 (1.42, 2.11)	<0.001
Follow-up period ≤ 8 years		aHR (95% CI)			
pLBMP	1.00 (reference)	1.01 (0.88, 1.18)	0.74 (0.63, 0.88)	0.61 (0.50, 0.74)	<0.001
pASMP	1.00 (reference)	0.92 (0.80, 1.07)	0.74 (0.63, 0.88)	0.57 (0.46, 0.70)	<0.001
pBFMP	1.00 (reference)	1.22 (1.00, 1.50)	1.63 (1.35, 1.97)	1.62 (1.34, 1.96)	<0.001

Adjusted hazard ratios were calculated by multivariable Cox proportional hazards regression analysis after adjustments for the following covariates: age, income, chemotherapy, radiation therapy, hormone therapy, Charlson comorbidity index, smoking, alcohol, and physical activity. Acronyms: cardiovascular disease (CVD); hazard ratio (HR); confidence interval (CI); percentage of predicted lean body mass (pLBMP); percentage of predicted appendicular skeletal mass (pASMP); percentage of predicted body fat mass (pBFMP)

2. Association of Discrepancies in General Obesity and Abdominal Obesity with CVD Risk

Table 8 shows the characteristics of the study population. The number of subjects who were normal, overweight without abdominal obesity, had abdominal obesity only, and overweight with abdominal obesity was 31212, 13014, 3409, and 24539, respectively. The mean (standard deviation) ages for normal, overweight without abdominal obesity, abdominal obesity only, and overweight with abdominal obesity were 54.26 (8.22), 55.90 (8.21), 59.20 (9.94), and 59.79 (9.48), respectively. Compared to subjects who were normal or overweight, those who had abdominal obesity had low physical activity. Compared to subjects who were normal, overweight without abdominal obesity, or abdominally obese only, those who were overweight with abdominal obesity had more comorbidities. Most subjects in all four groups received chemotherapy, radiation therapy, or hormone therapy.

The risks for CVD, stroke, and stroke subtypes were compared between normal; overweight without abdominal obesity; abdominal obesity only; and overweight and abdominal obesity (Table 9). Compared to those with normal WC and BMI, those who were overweight without abdominal obesity, had abdominal obesity only, and overweight with abdominal obesity, had higher risks of CVD (aHR(95% CI) 1.23(1.02-1.48), 1.51(1.16-1.95), and 1.55(1.31-1.75), respectively) and total stroke (1.09(0.86-1.38), 1.63(1.20-2.23), and 1.40(1.17-1.68), respectively); this was also evident when models adjusting for additional covariates (Models 2 and 3) were applied. In the case of ischemic stroke, subjects with abdominal obesity only and overweight with abdominal obesity showed significantly higher risk (aHR(95% CI) 1.74(1.07-2.84) and 1.81(1.35-2.43), respectively) compared to normal. Subjects with abdominal obesity only also had higher risk of hemorrhagic stroke, compared to normal, though statistically insignificant.

Table 8. Descriptive characteristics of the study population for evaluating discrepancies in general obesity and abdominal obesity with CVD risk.

	WC < 80 cm		WC ≥ 80 cm		
	BMI < 23.0 kg/m^2	BMI ≥ 23.0 kg/m^2	BMI < 23.0 kg/m^2	BMI ≥ 23.0 kg/m^2	
	Normal	Overweight without abdominal obesity	Abdominal obesity only	Overweight with abdominal obesity	*p* value
Study population, N (%)	31,212	13,014	3,409	24,539	
BMI [kg/m^2], mean (SD)	20.81 (1.45)	24.40 (1.29)	21.91 (0.91)	26.66 (2.67)	
WC [cm], mean (SD)	70.84 (4.72)	75.41 (3.01)	82.44 (2.81)	86.80 (8.31)	
Age [years], mean (SD)	54.26 (8.22)	55.90 (8.21)	59.20 (9.94)	59.79 (9.48)	<0.001
Age [years], N (%)					<0.001
40-49	9,491 (30.4)	2,893 (22.2)	591 (17.3)	3,525 (14.4)	
50-59	14,623 (46.8)	6,266 (48.2)	1,289 (37.8)	9,171 (37.4)	
≥ 60	7,098 (22.7)	3,855 (29.6)	1,529 (44.8)	11,843 (48.3)	
Income, quartiles, N (%)					<0.001
1st (highest)	8,672 (27.8)	3,211 (24.7)	933 (27.4)	5,750 (23.4)	
2nd	5,899 (18.9)	2,508 (19.3)	618 (18.1)	4,976 (20.0)	
3rd	5,719 (18.3)	2,502 (19.2)	628 (18.4)	4,773 (19.4)	
4th (lowest)	10,922 (35.0)	4,793 (36.8)	1,230 (36.1)	9,100 (37.1)	
Smoking status, N (%)					0.003
Never-smoker	30,049 (96.3)	12,601 (96.8)	3,279 (96.2)	23,627 (96.3)	
Past smoker	754 (2.4)	275 (2.1)	73 (2.1)	546 (2.2)	
Current smoker	409 (1.3)	138 (1.1)	57 (1.7)	366 (1.5)	
Alcohol consumption [times per week], N (%)					<0.001
0	27,737 (88.9)	11,559 (88.8)	3,059 (89.7)	22,164 (90.3)	
1-2	3,087 (9.9)	1,268 (9.7)	303 (8.9)	2,040 (8.3)	
3-4	280 (0.9)	134 (1.0)	34 (1.0)	240 (1.0)	
≥ 5	108 (0.4)	53 (0.4)	13 (0.4)	95 (0.4)	
Physical activity [times per week], N (%)					<0.001
0	11,596 (37.2)	5,152 (39.6)	1,535 (45.0)	12,124 (49.4)	
1-2	5,096 (16.3)	1,932 (14.8)	478 (14.0)	3,318 (13.5)	

3-4	5,435 (17.4)	2,085 (16.0)	522 (15.3)	3,399 (13.8)	
≥ 5	9,085 (29.1)	3,845 (29.6)	874 (25.6)	5,698 (23.2)	
Charlson comorbidity index, N (%)					<0.001
≤ 2	16,709 (53.5)	6,381 (49.0)	1,495 (43.8)	9,408 (38.3)	
3-4	10,985 (35.2)	4,887 (37.6)	1,315 (38.6)	9,851 (40.1)	
≥ 5	3,518 (11.3)	1,746 (13.4)	599 (17.6)	5,280 (21.5)	
Treatment pattern, N(%)					
Chemotherapy[a]	16,902 (54.2)	7,411 (57.0)	1,751 (51.4)	13,434 (54.8)	<0.001
Radiation therapy	18,926 (60.6)	8,026 (61.7)	1,969 (57.8)	14,371 (58.6)	<0.001
Hormone therapy[b]	21,827 (69.9)	8,992 (69.1)	2,294 (67.3)	16,766 (68.3)	<0.001
Diastolic BP [mmHg], mean (SD)	115.3 (14.1)	120.5 (14.1)	120.1 (15.0)	125.6 (15.0)	<0.001
Systolic BP [mmHg], mean (SD)	72.1 (9.4)	74.8 (9.3)	74.2 (9.4)	77.3 (9.7)	<0.001
Total cholesterol [mg/dL], mean (SD)	93.4 (16.1)	96.5 (17.5)	98.7 (20.8)	103.1 (24.6)	<0.001
Fasting serum glucose [mg/dL], mean (SD)	190.9 (36.4)	195.8 (36.6)	195.0 (37.5)	196.3 (40.3)	<0.001

p-values calculated via Chi squared test for categorical variables and analysis of variance (ANOVA) for continuous variables

[a]cyclophosphamide, trastuzumab, doxorubicin, epirubicin, docetaxel, paclitaxel, and cisplatin

[b]tamoxifen, anastrozole, and letrozole

Acronyms: standard deviation (SD); body mass index (BMI); waist circumference (WC)

Table 9. Risks of CVD and stroke according to type of obesity.

	WC < 80 cm		WC ≥ 80 cm	
	BMI < 23.0 kg/m^2	BMI ≥ 23.0 kg/m^2	BMI < 23.0 kg/m^2	BMI ≥ 23.0 kg/m^2
	Normal	Overweight without abdominal obesity	Abdominal obesity only	Overweight with abdominal obesity
Study population, N (%)	31,212 (43.25)	13,014 (18.03)	3,409 (4.72)	24,539 (34.00)
BMI [kg/m^2], mean (SD)	20.81 (1.45)	24.40 (1.29)	21.91 (0.91)	26.66 (2.67)
WC [cm], mean (SD)	70.84 (4.72)	75.41 (3.01)	82.44 (2.81)	86.80 (8.31)
Cardiovascular disease				
Events, N (%)	304 (0.97)	172 (1.32)	72 (2.11)	548 (2.23)
Person year [year]	869	410	208	1643
aHR (95% CI)				
Model 1	1.00 (reference)	1.23 (1.02, 1.48)*	1.51 (1.16, 1.95)**	1.55 (1.34, 1.79)***
Model 2	1.00 (reference)	1.23 (1.02, 1.48)*	1.48 (1.14, 1.92)**	1.52 (1.31, 1.75)***
Model 3	1.00 (reference)	1.16 (0.96, 1.40)	1.42 (1.10, 1.85)**	1.36 (1.17, 1.58)***
Stroke				
Events, N (%)	203 (0.65)	101 (0.78)	51 (1.50)	323 (1.32)
Person year [year]	575	304	139	984
aHR (95% CI)				
Model 1	1.00 (reference)	1.09 (0.86, 1.38)	1.63 (1.20, 2.23)**	1.40 (1.17, 1.68)***
Model 2	1.00 (reference)	1.09 (0.86, 1.38)	1.61 (1.18, 2.20)**	1.37 (1.14, 1.65)***
Model 3	1.00 (reference)	1.03 (0.81, 1.31)	1.55 (1.14, 2.12)**	1.24 (1.02, 1.49)*
Hemorrhagic stroke				
Events, N (%)	41 (0.13)	16 (0.12)	8 (0.23)	39 (0.16)
Person year [year]	128	50	24	102
aHR (95% CI)				
Model 1	1.00 (reference)	0.83 (0.47, 1.49)	1.28 (0.60, 2.76)	0.82 (0.52, 1.30)
Model 2	1.00 (reference)	0.83 (0.47, 1.48)	1.27 (0.59, 2.74)	0.81 (0.51, 1.28)
Model 3	1.00 (reference)	0.77 (0.43, 1.38)	1.21 (0.56, 2.62)	0.70 (0.44, 1.12)
Ischemic stroke				
Events, N (%)	66 (0.21)	28 (0.22)	22 (0.65)	166 (0.68)
Person year [year]	206	88	56	534
aHR (95% CI)				

Model 1	1.00 (reference)	0.94 (0.58, 1.41)	1.77 (1.08, 2.88)*	1.84 (1.37, 2.47)***
Model 2	1.00 (reference)	0.91 (0.58, 1.41)	1.74 (1.07, 2.84)*	1.81 (1.35, 2.43)***
Model 3	1.00 (reference)	0.84 (0.54, 1.30)	1.64 (1.01, 2.68)*	1.54 (1.14, 2.08)**

Adjusted hazard ratios were calculated by multivariable Cox proportional hazards regression analysis after adjustments for the following covariates:
Model 1: age, income, chemotherapy, radiation therapy, hormone therapy, and Charlson comorbidity index
Model 2: Model 1 + smoking status, alcohol consumption, and physical activity
Model 3: Model 2 + blood pressures, total cholesterol, and fasting serum glucose
Acronyms: standard deviation (SD); body mass index (BMI); waist circumference (WC); hazard ratio (HR); confidence interval (CI)
*p-value<0.05, **p-value<0.01, and ***p-value<0.001

When subjects with overweight without abdominal obesity were compared with those with abdominal obesity only (Table 10), those with abdominal obesity only had higher risks of CVD and stroke. In particular, those with abdominal obesity only had significantly higher risk of ischemic stroke (aHR(95% CI) 2.04(1.14-3.65)). The results of sensitivity analyses with an adjusted BMI cutoff value (standard: 25.0 kg/m^2) are shown in Table 11 and 12. Similarly, compared to subjects with general obesity without abdominal obesity, those with abdominal obesity without general obesity had higher risk of stroke. Furthermore, 1 cm increase in WC was associated with 1% higher risk of CVD and 3% higher in those with a BMI of less than 25.0 kg/m^2 (Table 13). Based on a stratified analysis of the risk of CVD according to various subgroups, such as age, CCI, and treatment pattern (Table 14), higher risks of CVD in those with abdominal obesity were more evident in those with less comorbidities, and those who received radiation therapy, chemotherapy, or hormone therapy. An interaction was found between age groups and risk of CVD (*p* for interaction 0.027).

Table 10. Risks of CVD and stroke based on presence of abdominal obesity.

	Overweight without abdominal obesity	Abdominal obesity only
Study population, N (%)	13,014 (18.03)	3,409 (4.72)
BMI [kg/m^2], mean (SD)	24.40 (1.29)	21.91 (0.91)
WC [cm], mean (SD)	75.41 (3.01)	82.44 (2.81)
Cardiovascular disease		
Events, N (%)	172 (1.32)	72 (2.11)
Person year [year]	410	208
aHR (95% CI)		
Model 1	1.00 (reference)	1.26 (0.95, 1.68)
Model 2	1.00 (reference)	1.26 (0.69, 1.69)
Stroke		
Events, N (%)	101 (0.78)	51 (1.50)
Person year [year]	304	139
aHR (95% CI)		
Model 1	1.00 (reference)	1.58 (1.12, 2.24)**
Model 2	1.00 (reference)	1.59 (1.12, 2.25)**
Hemorrhagic stroke		
Events, N (%)	16 (0.12)	8 (0.23)
Person year [year]	50	24
aHR (95% CI)		
Model 1	1.00 (reference)	1.52 (0.63, 3.66)
Model 2	1.00 (reference)	1.52 (0.63, 3.66)
Ischemic stroke		
Events, N (%)	28 (0.22)	22 (0.65)
Person year [year]	88	56
aHR (95% CI)		
Model 1	1.00 (reference)	2.04 (1.14, 3.65)*
Model 2	1.00 (reference)	2.07 (1.16, 3.70)*

Adjusted hazard ratios were calculated by multivariable Cox proportional hazards regression analysis after adjustments for the following covariates:

Model 1: age, income, chemotherapy, radiation therapy, hormone therapy, Charlson comorbidity index, smoking status, alcohol consumption,

and physical activity
Model 2: Model 1 + blood pressures, total cholesterol, and fasting serum glucose
Acronyms: standard deviation (SD); body mass index (BMI); waist circumference (WC); hazard ratio (HR); confidence interval (CI)
*p-value<0.05, **p-value<0.01, and ***p-value<0.001

Table 11. Sensitivity analysis (BMI: 25.0 kg/m^2) of association of CVD and stroke with type of obesity.

	WC < 80 cm		WC ≥ 80 cm	
	BMI < 25.0 kg/m^2 **Normal or overweight**	**BMI ≥ 25.0 kg/m^2** **General obesity without abdominal obesity**	**BMI < 25.0 kg/m^2** **Abdominal obesity without general obesity**	**BMI ≥ 25.0 kg/m^2** **General obesity with abdominal obesity**
Study population, N	40,814	3,412	10,600	17,348
BMI [kg/m^2], mean (SD)	21.51 (1.81)	26.10 (1.24)	23.35 (1.21)	27.75 (2.43)
WC [cm], mean (SD)	71.85 (4.74)	76.27 (2.76)	83.15 (3.21)	88.17 (9.30)
Cardiovascular disease				
Events, N (%)	418 (1.02)	58 (1.70)	242 (2.28)	378 (2.18)
Person year [year]	1,156	173	727	1,098
aHR (95% CI)	1.00 (reference)	1.53 (1.16, 2.02)**	1.53 (1.30, 1.80)***	1.43 (1.24, 1.66)***
Stroke				
Events, N (%)	280 (0.69)	24 (0.70)	157 (1.48)	217 (1.25)
Person year [year]	769	79	483	614
aHR (95% CI)	1.00 (reference)	0.96 (0.63, 1.45)	1.52 (1.24, 1.86)***	1.26 (1.05, 1.51)*
Hemorrhagic stroke				
Events, N (%)	55 (0.13)	2 (0.06)	22 (0.21)	25 (0.14)
Person year [year]	170	7	65	62
aHR (95% CI)	1.00 (reference)	0.39 (0.10, 1.62)	1.09 (0.66, 1.81)	0.73 (0.45, 1.19)
Ischemic stroke				
Events, N (%)	84 (0.21)	10 (0.29)	78 (0.74)	110 (0.63)
Person year [year]	262	32	262	328
aHR (95% CI)	1.00 (reference)	1.31 (0.68, 2.52)	2.09 (1.52, 2.87)***	1.79 (1.34, 2.40)***

Adjusted hazard ratios were calculated by multivariable Cox proportional hazards regression analysis after adjustments for the following covariates: age, income, chemotherapy, radiation therapy, hormone therapy, Charlson comorbidity index, smoking status, alcohol consumption, and physical activity.

Acronyms: standard deviation (SD); body mass index (BMI); waist circumference (WC); hazard ratio (HR); confidence interval (CI)

*p-value<0.05, **p-value<0.01, and ***p-value<0.001

Table 12. Sensitivity analysis (BMI: 25.0 kg/m^2) of association of CVD and stroke with type of obesity, based on presence of abdominal obesity.

	General obesity without abdominal obesity	Abdominal obesity without general obesity
Study population, N	3,412	10,600
BMI [kg/m^2], mean (SD)	26.10 (1.24)	23.35 (1.21)
WC [cm], mean (SD)	76.27 (2.76)	83.15 (3.21)
Cardiovascular disease		
Events, N (%)	58 (1.70)	242 (2.28)
Person year [year]	173	727
aHR (95% CI)	1.00 (reference)	1.00 (0.75, 1.34)
Stroke		
Events, N (%)	24 (0.70)	157 (1.48)
Person year [year]	79	483
aHR (95% CI)	1.00 (reference)	1.59 (1.03, 2.45)*
Hemorrhagic stroke		
Events, N (%)	2 (0.06)	22 (0.21)
Person year [year]	7	65
aHR (95% CI)	1.00 (reference)	2.76 (0.65, 1.18)
Ischemic stroke		
Events, N (%)	10 (0.29)	78 (0.74)
Person year [year]	32	262
aHR (95% CI)	1.00 (reference)	1.60 (0.83, 3.11)

Adjusted hazard ratios were calculated by multivariable Cox proportional hazards regression analysis after adjustments for the following covariates: age, income, chemotherapy, radiation therapy, hormone therapy, Charlson comorbidity index, smoking status, alcohol consumption, and physical activity.

Acronyms: standard deviation (SD); body mass index (BMI); waist circumference (WC); hazard ratio (HR); confidence interval (CI)

*p-value<0.05, **p-value<0.01, and ***p-value<0.001

Table 13. CVD risk per 1 kg/m^2 increase in BMI and per 1 cm increase WC.

	Overall	per 1 kg/m^2 increase WC < 80 cm	WC ≥ 80 cm
Study population, N (%)	72,174	44,226 (61.28)	27,948 (38.72)
BMI [kg/m^2], mean (SD)	23.50 (3.23)	21.87 (2.16)	26.08 (2.96)
WC [cm], mean (SD)	77.64 (9.25)	72.19 (4.77)	86.27 (7.97)
Cardiovascular disease			
Events, N (%)	1,096 (1.52)	476 (1.08)	620 (2.22)
aHR (95% CI)	1.04 (1.02, 1.06)***	1.05 (1.01, 1.09)*	1.00 (0.97, 1.03)
	Overall	**per 1 cm increase BMI < 25.0 kg/m^2**	**BMI ≥ 25.0 kg/m^2**
Study population, N (%)	72,174	51,414 (71.24)	20,760 (28.76)
BMI [kg/m^2], mean (SD)	23.50 (3.23)	21.89 (1.86)	27.48 (2.36)
WC [cm], mean (SD)	77.64 (9.25)	74.18 (6.39)	86.21 (9.64)
Cardiovascular disease			
Events, N (%)	1,096 (1.52)	660 (1.28)	436 (2.10)
aHR (95% CI)	1.01 (1.00, 1.01)***	1.03 (1.02, 1.04)***	1.00 (0.98, 1.01)

Adjusted hazard ratios were calculated by multivariable Cox proportional hazards regression analysis after adjustments for the following covariates: age, income, chemotherapy, radiation therapy, hormone therapy, Charlson comorbidity index, smoking status, alcohol consumption, and physical activity.

Acronyms: standard deviation (SD); body mass index (BMI); waist circumference (WC); hazard ratio (HR); confidence interval (CI)

*p-value<0.05, **p-value<0.01, and ***p-value<0.001

Table 14. Stratified analysis of association between CVD risk and type of obesity according to the subgroups of covariates.

	WC < 80 cm		WC ≥ 80 cm		
	BMI < 23.0 kg/m^2	BMI ≥ 23.0 kg/m^2	BMI < 23.0 kg/m^2	BMI ≥ 23.0 kg/m^2	
	Normal	Overweight without abdominal obesity	Abdominal obesity only	Overweight with abdominal obesity	$p_{interaction}$
Age [years]					0.027
40-49	1.00 (reference)	1.68 (0.89, 3.14)	3.57 (1.48, 8.64)**	2.15 (1.23, 3.75)**	
50-59	1.00 (reference)	1.52 (1.14, 2.01)**	1.38 (0.80, 2.36)	1.54 (1.20, 1.98)***	
≥ 60	1.00 (reference)	0.92 (0.70, 1.21)	1.41 (1.03, 1.93)*	1.42 (1.18, 1.71)***	
Charlson comorbidity index					0.147
1-3	1.00 (reference)	1.20 (0.95, 1.52)	1.48 (1.06, 2.06)*	1.61 (1.34, 1.93)***	
4 or more	1.00 (reference)	1.24 (0.90, 1.70)	1.44 (0.95, 2.19)	1.34 (1.05, 1.70)**	
Treatment pattern					
Radiation therapy					0.847
Yes	1.00 (reference)	1.25 (0.95, 1.65)	1.68 (1.14, 2.48)**	1.51 (1.20, 1.88)***	
No	1.00 (reference)	1.20 (0.93, 1.54)	1.35 (0.95, 1.92)	1.50 (1.24, 1.82)***	
Chemotherapy					0.776
Yes	1.00 (reference)	1.18 (0.89, 1.57)	1.76 (1.20, 2.59)**	1.40 (1.12, 1.76)**	
No	1.00 (reference)	1.26 (0.98, 1.61)	1.32 (0.93, 1.87)	1.58 (1.30, 1.91)***	
Hormone therapy					0.235
Yes	1.00 (reference)	1.30 (1.02, 1.66)*	1.50 (1.05, 2.12)*	1.44 (1.18, 1.75)***	
No	1.00 (reference)	1.13 (0.84, 1.52)	1.48 (1.00, 2.17)*	1.60 (1.28, 1.99)***	

Adjusted hazard ratios were calculated by multivariable Cox proportional hazards regression analysis after adjustments for the following covariates: age, income, chemotherapy, radiation therapy, hormone therapy, Charlson comorbidity index, smoking status, alcohol consumption, and physical activity.

*p-value<0.05, **p-value<0.01, and ***p-value<0.001

3. Association of Changes in Body Composition with CVD Risk and Changes in Metabolic Factors

Table 15 shows the characteristics of the study population, based on change in percentage of predicted lean body mass. Mean ages (standard deviation) for Low to Low, Low to High, High to Low, and High to High groups were 59.99(9.18), 58.86(8.71), 56.38(8.56), and 55.25(8.10), respectively. The majority of subjects were never-smokers with rare alcohol consumption and physical activity. In addition, the majority of subjects received chemotherapy, radiation therapy, or hormone therapy.

Cardiovascular risks of the study population were observed, based on change (prior to and 5 years after diagnosis of breast cancer) in pLBMP, pASMP, and pBFMP (Table 16). Compared to those who continued to have low pLBMP and pASMP, those with persistently high pLBMP and pASMP had lower risks of CVD (aHR(95% CI) 0.68(0.53-0.87) and 0.60(0.44-0.81), respectively). In contrast, both the High to Low and High to High pBFMP groups had higher risks of CVD (aHR(95% CI) 1.44(0.98-2.10) and 1.48(1.15-1.89), respectively), compared to those who maintained a low pBFMP. Notably, those with increased (a low to high change) pBFMP had higher risk of CVD (aHR(95% CI) 1.51(0.99-2.31)). This pattern was also evident in Models 2 and 3.

Table 15. Descriptive characteristics of the study population for evaluating body composition with CVD risk and changes in metabolic factors.

	Change in percentage of predicted lean body mass				
	Low % at baseline periods		High % at baseline periods		*p*-value
	Low to Low	Low to High	High to Low	High to High	
Study population, N	16,462	3,497	2,890	17,246	
% at baseline period, means (SD)	62.14 (1.87)	64.00 (0.84)	65.92 (0.81)	67.84 (2.01)	<0.001
% at follow-up period, means (SD)	62.19 (1.89)	66.05 (0.88)	64.01 (0.84)	67.99 (2.08)	<0.001
Change in %, means (SD)	0.05 (1.30)	2.06 (1.10)	-1.91 (1.05)	0.16 (1.56)	<0.001
Change in %, range	-4.93, 4.95	0.00, 4.98	-4.95, -0.02	-4.99, 5.00	
Age [years], mean (SD)	59.99 (9.18)	58.86 (8.71)	56.38 (8.56)	55.25 (8.10)	<0.001
Age [years], N (%)					<0.001
40-49	2,122 (12.9)	495 (14.2)	637 (22.0)	4,511 (26.2)	
50-59	6,405 (38.9)	1,546 (44.2)	1,357 (47.0)	8,252 (47.8)	
≥ 60	7,935 (48.2)	1,456 (41.6)	896 (31.0)	4,483 (26.0)	
Income, quartiles, N (%)					<0.001
1st (highest)	4,094 (24.9)	973 (27.8)	729 (25.2)	5,071 (29.4)	
2nd	3,450 (21.0)	671 (19.2)	564 (19.5)	3,415 (19.8)	
3rd	3,207 (19.5)	702 (20.1)	576 (19.9)	3,207 (18.6)	
4th (lowest)	5,711 (34.7)	1,151 (32.9)	1,021 (35.3)	5,553 (32.2)	
Smoking status, N (%)					<0.001
Never-smoker	15,950 (96.9)	3,422 (97.9)	2,777 (96.1)	16,675 (96.7)	
Past smoker	318 (1.9)	44 (1.3)	80 (2.8)	386 (2.2)	
Current smoker	194 (1.2)	31 (0.9)	33 (1.1)	185 (1.1)	
Alcohol consumption [times per week], N (%)					<0.001
0	14,978 (91.0)	3,247 (92.8)	2,523 (87.2)	15,318 (88.8)	
1-2	1,288 (7.8)	212 (6.1)	319 (11.0)	1,737 (10.1)	
3-4	134 (0.8)	28 (0.8)	37 (1.3)	128 (0.7)	
≥ 5	62 (0.4)	10 (0.3)	11 (0.4)	63 (0.4)	
Physical activity [times per week], N (%)					<0.001
0	7,536 (45.8)	1,381 (39.5)	1,197 (41.4)	5,955 (34.5)	
1-2	2,245 (13.6)	458 (13.1)	419 (14.5)	2,794 (16.2)	
3-4	2,404 (14.6)	545 (15.6)	491 (17.0)	3,131 (18.2)	

≥ 5	4,277 (26.0)	1,113 (31.8)	783 (27.1)	5,366 (31.1)	
BMI [kg/m^2], mean (SD)	26.43 (2.55)	22.44 (0.85)	24.16 (1.01)	20.92 (1.50)	<0.001
BMI [kg/m^2], N (%)					<0.001
< 23.0	186 (1.1)	2,467 (70.6)	209 (7.2)	16,083 (93.3)	
≥ 23.0	16,276 (98.9)	1,030 (29.5)	2,681 (92.8)	1,163 (6.7)	
Charlson comorbidity index, N (%)					<0.001
≤ 2	6,069 (36.9)	1,462 (41.8)	1,377 (47.6)	8,926 (51.8)	
3-4	6,888 (41.8)	1,438 (41.1)	1,100 (38.1)	6,386 (37.0)	
≥ 5	3,505 (21.3)	597 (17.1)	413 (14.3)	1,934 (11.2)	
Chemotherapy[a], N (%)	9,907 (60.2)	2,225 (63.6)	1,650 (57.1)	9,702 (56.3)	<0.001
Doxorubicin	4,608 (28.0)	1,018 (29.1)	743 (25.7)	5,083 (29.5)	<0.001
Cyclophosphamide	9,034 (54.9)	2,036 (58.2)	1,519 (52.6)	9,020 (52.3)	<0.001
Paclitaxel	1,661 (10.1)	363 (10.4)	275 (9.5)	1,454 (8.4)	<0.001
Radiation therapy, N (%)	11,197 (68.0)	2,448 (70.0)	1,940 (67.1)	11,550 (67.0)	0.003
Hormone therapy[b], N (%)	12,163 (73.9)	2,563 (73.3)	2,191 (75.8)	12,820 (74.3)	0.093
Tamoxifen	6,878 (41.8)	1,545 (44.2)	1,582 (54.7)	9,508 (55.1)	<0.001
Diastolic BP [mmHg], mean (SD)	125.0 (14.7)	119.2 (14.9)	120.2 (13.6)	115.5 (14.0)	<0.001
Systolic BP [mmHg], mean (SD)	77.0 (9.5)	73.7 (9.5)	74.9 (9.1)	72.1 (9.3)	<0.001
Total cholesterol [mg/dL], mean (SD)	194.0 (37.9)	191.7 (36.4)	196.5 (37.0)	191.5 (36.8)	<0.001
Fasting serum glucose [mg/dL], mean (SD)	102.5 (23.6)	97.8 (20.57)	96.8 (16.1)	93.7 (15.2)	<0.001

p-values calculated via Chi squared test for categorical variables and analysis of variance (ANOVA) for continuous variables

[a]cyclophosphamide, trastuzumab, doxorubicin, epirubicin, docetaxel, paclitaxel, and cisplatin

[b]tamoxifen, anastrozole, and letrozole

Acronyms: standard deviation (SD); body mass index (BMI); blood pressure (BP)

Table 16. CVD risk according to change in predicted body composition.

	Change in percentage of predicted body composition			
	Low % at baseline periods		High % at baseline periods	
	Low to Low	Low to High	High to Low	High to High
Change in pLBMP				
Study population, N	16,462	3,497	2,890	17,246
Percentage at baseline period [%], means (SD)	62.14 (1.87)	64.00 (0.84)	65.92 (0.81)	67.84 (2.01)
Percentage at follow-up period [%], means (SD)	62.19 (1.89)	66.05 (0.88)	64.01 (0.84)	68.00 (2.08)
CVD; events, N (%)	193 (1.17)	39 (1.12)	25 (0.87)	98 (0.57)
aHR (95% CI)				
Model 1	1.00 (reference)	1.01 (0.72, 1.43)	0.96 (0.63, 1.45)	0.68 (0.53, 0.87)**
	-	-	1.00 (reference)	0.71 (0.46, 1.10)
Model 2	1.00 (reference)	1.04 (0.73, 1.46)	0.97 (0.64, 1.47)	0.69 (0.54, 0.89)**
	-	-	1.00 (reference)	0.72 (0.46, 1.10)
Model 3	1.00 (reference)	1.07 (0.76, 1.52)	0.97 (0.64, 1.48)	0.72 (0.56, 0.94)*
	-	-	1.00 (reference)	0.74 (0.48, 1.16)
Change in pASMP				
Study population, N	20,505	2,597	3,304	13,689
Percentage at baseline period [%], means (SD)	24.77 (0.80)	25.62 (0.31)	26.39 (0.33)	27.12 (0.77)
Percentage at follow-up period [%], means (SD)	24.71 (0.82)	26.38 (0.32)	25.58 (0.34)	27.08 (0.77)
CVD; events, N (%)	257 (1.25)	20 (0.77)	16 (0.48)	62 (0.45)
aHR (95% CI)				
Model 1	1.00 (reference)	0.78 (0.49, 1.23)	0.55 (0.33, 0.92)*	0.60 (0.44, 0.81)***
	-	-	1.00 (reference)	1.09 (0.63, 1.89)
Model 2	1.00 (reference)	0.78 (0.50, 1.24)	0.56 (0.34, 0.93)*	0.61 (0.46, 0.83)**
	-	-	1.00 (reference)	1.10 (0.63, 1.91)
Model 3	1.00 (reference)	0.81 (0.51, 1.28)	0.56 (0.34, 0.94)*	0.65 (0.48, 0.87)**
	-	-	1.00 (reference)	1.15 (0.66, 1.99)
Change in pBFMP				
Study population, N	17,930	2,842	3,439	15,884
Percentage at baseline period [%], means (SD)	31.11 (2.01)	33.05 (0.82)	34.97 (0.80)	36.74 (1.82)
Percentage at follow-up period [%], means (SD)	30.96 (2.07)	34.95 (0.80)	32.92 (0.89)	36.70 (1.84)
CVD; events, N (%)	103 (0.57)	27 (0.95)	37 (1.08)	188 (1.18)
aHR (95% CI)				

Model 1	1.00 (reference)	1.51 (0.99, 2.31)	1.44 (0.98, 2.10)	1.48 (1.15, 1.89)**
	-	-	1.00 (reference)	1.03 (0.72, 1.46)
Model 2	1.00 (reference)	1.50 (0.98, 2.30)	1.43 (0.98, 2.08)	1.44 (1.12, 1.85)**
	-	-	1.00 (reference)	1.01 (0.71, 1.44)
Model 3	1.00 (reference)	1.44 (0.94, 2.21)	1.42 (0.97, 2.07)	1.38 (1.07, 1.78)*
	-	-	1.00 (reference)	0.97 (0.68, 1.39)

Adjusted hazard ratios were calculated by multivariable Cox proportional hazards regression analysis after adjustments for the following covariates:
Model 1: age, income, chemotherapy, radiation therapy, hormone therapy, and Charlson comorbidity index
Model 2: Model 1 + smoking status, alcohol consumption, and physical activity
Model 3: Model 2 + blood pressures, total cholesterol, and fasting serum glucose
Acronyms: cardiovascular disease (CVD); predicted lean body mass percentage (pLBMP); predicted appendicular skeletal mass percentage (pASMP); predicted body fat mass percentage (pBFMP); standard deviation (SD); hazard ratio (HR); confidence interval (CI)
*p-value<0.05, **p-value<0.01, and ***p-value<0.001

Results from the stratified analysis on the association of change in predicted body composition with CVD according to subgroups of age, CCI, and treatment pattern are shown in Table 17. In comparison to the Low to Low group, subjects in the High to High group, aged 60 or above, with less comorbidities, and who had received hormone therapy, had significantly lower (for pLBMP and pASMP) or higher risk (for pBFMP) of CVD. These risks were not affected by subgroups of age, CCI, or treatment pattern (*p* for interaction >0.05).

Figure 6 depicts the changes in metabolic factors in relation to changes in predicted body composition (Table 18). Pertaining to changes in pLBMP and pASMP, the Low to High group showed decreased sBP, dBP, total cholesterol, and FSG, compared to the Low to Low group. Pertaining to change in pBFMP, the Low to High group showed increased sBP, dBP, total cholesterol, and FSG. This pattern was also evident when comparing within those who initially had high pLBMP, pASMP, or pBFMP. Those who maintained high pLBMP and pASMP had decreased metabolic markers compared to those who changed from high to low pLBMP and pASMP; those who maintained high pBFMP had increased metabolic markers compared to those who changed from high to low pBFMP. In the case of change in total cholesterol, total cholesterol decreased less in the High to High group of pLBMP and pASMP, compared to that of the Low to Low group, while total cholesterol decreased more in the High to High group of pBFMP, compared to that of the Low to Low group.

Table 17. Stratified analysis of association between CVD risk and change in predicted body composition according to the subgroups of covariates.

	Percentage of predicted body composition					
	Low % at baseline periods		High % at baseline periods		p_{trend}	$p_{interaction}$
	Low to Low	Low to High	High to Low	High to High		
pLBMP						
Age [years]						0.391
40-49	1.00 (reference)	-	0.70 (0.08, 5.97)	0.56 (0.18, 1.76)	0.252	
50-59	1.00 (reference)	0.96 (0.50, 1.85)	1.08 (0.56, 2.08)	0.76 (0.51, 1.14)	0.203	
≥ 60	1.00 (reference)	1.05 (0.69, 1.60)	0.88 (0.50, 1.55)	0.64 (0.436, 0.90)*	0.011	
Charlson comorbidity index						0.990
1-3	1.00 (reference)	0.99 (0.62, 1.58)	0.97 (0.57, 1.64)	0.71 (0.52, 0.97)*	0.036	
≥ 4	1.00 (reference)	1.10 (0.66, 1.84)	0.98 (0.49, 1.96)	0.70 (0.46, 1.06)	0.113	
Treatment pattern						
Radiation therapy						0.836
Yes	1.00 (reference)	1.03 (0.66, 1.61)	0.95 (0.54, 1.66)	0.74 (0.54, 1.03)	0.083	
No	1.00 (reference)	1.09 (0.64, 1.87)	1.00 (0.53, 1.88)	0.63 (0.42, 0.93)*	0.024	
Chemotherapy						0.789
Yes	1.00 (reference)	1.09 (0.68, 1.73)	1.23 (0.71, 2.12)	0.75 (0.53, 1.07)	0.151	
No	1.00 (reference)	0.98 (0.58, 1.64)	0.71 (0.37, 1.38)	0.63 (0.44, 0.91)**	0.011	
Hormone therapy						0.520
Yes	1.00 (reference)	1.14 (0.76, 1.72)	1.04 (0.63, 1.71)	0.64 (0.47, 0.89)**	0.010	
No	1.00 (reference)	0.85 (0.45, 1.62)	0.80 (0.37, 1.76)	0.78 (0.52, 1.17)	0.225	
pASMP						
Age [years]						0.069
40-49	1.00 (reference)	0.67 (0.08, 5.43)	0.45 (0.06, 3.65)	0.37 (0.12, 1.16)	0.084	
50-59	1.00 (reference)	0.74 (0.36, 1.54)	0.42 (0.18, 0.98)*	0.68 (0.45, 1.02)	0.033	
≥ 60	1.00 (reference)	0.77 (0.42, 1.42)	0.66 (0.34, 1.28)	0.55 (0.35, 0.88)*	0.006	
Charlson comorbidity index						0.305
1-3	1.00 (reference)	0.77 (0.42, 1.39)	0.62 (0.34, 1.13)	0.61 (0.42, 0.88)**	0.005	
≥ 4	1.00 (reference)	0.85 (0.41, 1.74)	0.43 (0.16, 1.18)	0.67 (0.40, 1.11)	0.054	
Treatment pattern						
Radiation therapy						0.520
Yes	1.00 (reference)	0.57 (0.29, 1.12)	0.47 (0.23, 0.97)*	0.61 (0.42, 0.90)*	0.004	

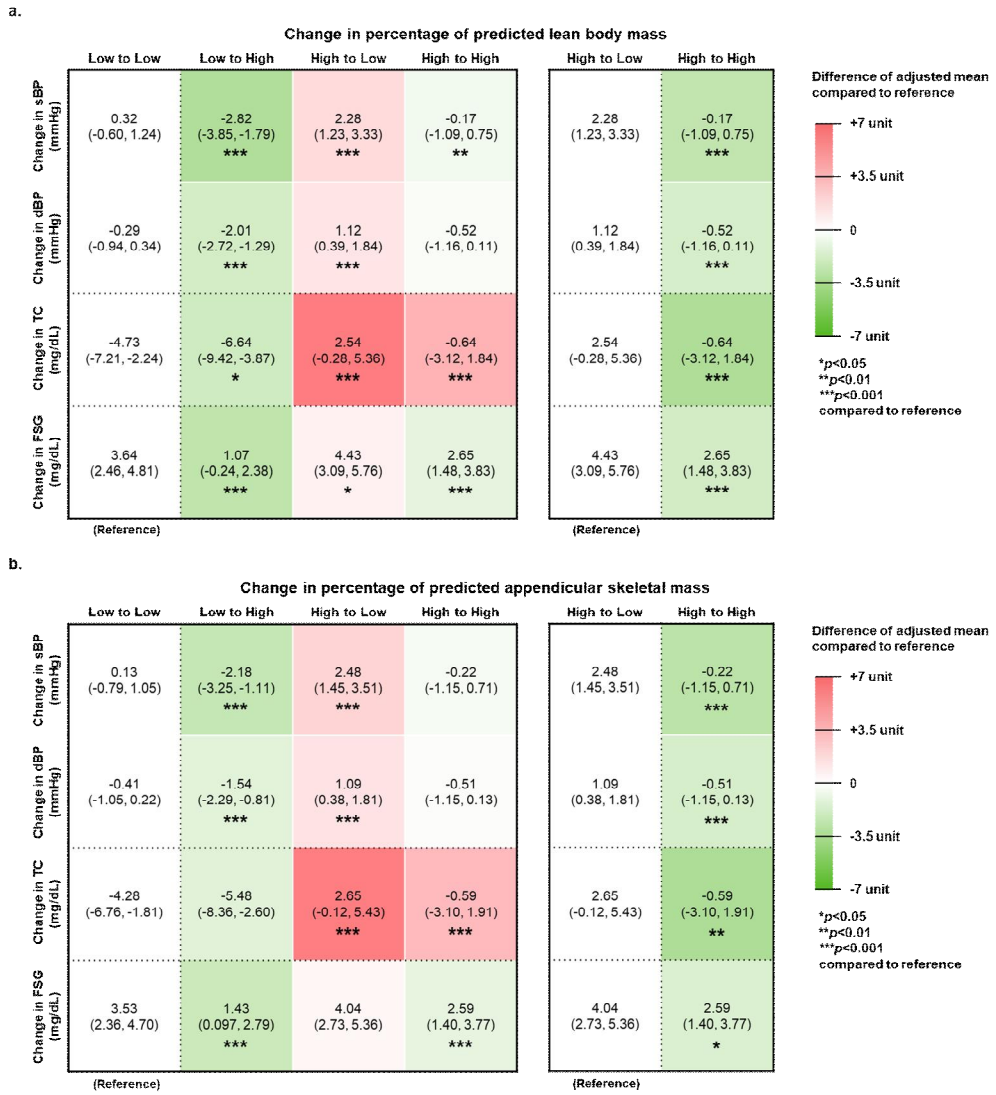
No	1.00 (reference)	1.14 (0.61, 2.15)	0.69 (0.33, 1.42)	0.63 (0.39, 1.01)	0.043	
Chemotherapy						0.988
Yes	1.00 (reference)	0.76 (0.41, 1.41)	0.54 (0.25, 1.17)	0.69 (0.46, 1.03)	0.040	
No	1.00 (reference)	0.84 (0.43, 1.67)	0.58 (0.29, 1.15)	0.54 (0.35, 0.84)**	0.004	
Hormone therapy						0.894
Yes	1.00 (reference)	0.66 (0.36, 1.23)	0.64 (0.35, 1.16)	0.60 (0.41, 0.86)**	0.004	
No	1.00 (reference)	1.04 (0.52, 2.08)	0.40 (0.14, 1.08)	0.65 (0.39, 1.08)	0.042	
pBFMP						
Age [years]						0.350
40-49	1.00 (reference)	1.25 (0.15, 10.46)	3.52 (0.70, 17.76)	1.92 (0.61, 6.06)	0.196	
50-59	1.00 (reference)	1.77 (0.96, 3.28)	1.47 (0.78, 2.78)	1.33 (0.88, 2.01)	0.188	
≥ 60	1.00 (reference)	1.30 (0.70, 2.38)	1.38 (0.84, 2.25)	1.49 (1.08, 2.07)*	0.016	
Charlson comorbidity index						0.900
1-3	1.00 (reference)	1.45 (0.85, 2.46)	1.35 (0.82, 2.23)	1.42 (1.04, 1.94)*	0.036	
≥ 4	1.00 (reference)	1.53 (0.75, 3.11)	1.47 (0.82, 2.65)	1.41 (0.93, 2.12)	0.133	
Treatment pattern						
Radiation therapy						0.892
Yes	1.00 (reference)	1.38 (0.78, 2.42)	1.27 (0.77, 2.09)	1.34 (0.98, 1.86)	0.083	
No	1.00 (reference)	1.68 (0.88, 3.20)	1.73 (0.97, 3.09)	1.57 (1.06, 2.31)*	0.030	
Chemotherapy						0.914
Yes	1.00 (reference)	1.78 (1.01, 3.12)*	1.39 (0.84, 2.32)	1.36 (0.96, 1.92)	0.132	
No	1.00 (reference)	1.20 (0.63, 2.31)	1.46 (0.83, 2.58)	1.54 (1.08, 2.20)*	0.016	
Hormone therapy						0.422
Yes	1.00 (reference)	1.60 (0.95, 2.71)	1.57 (0.98, 2.51)	1.55 (1.14, 2.13)**	0.008	
No	1.00 (reference)	1.31 (0.64, 2.71)	1.22 (0.64, 2.34)	1.26 (0.84, 1.90)	0.287	

Adjusted hazard ratios were calculated by multivariable Cox proportional hazards regression analysis after adjustments for the following covariates: age, income, chemotherapy, radiation therapy, hormone therapy, Charlson comorbidity index, smoking status, alcohol consumption, and physical activity.

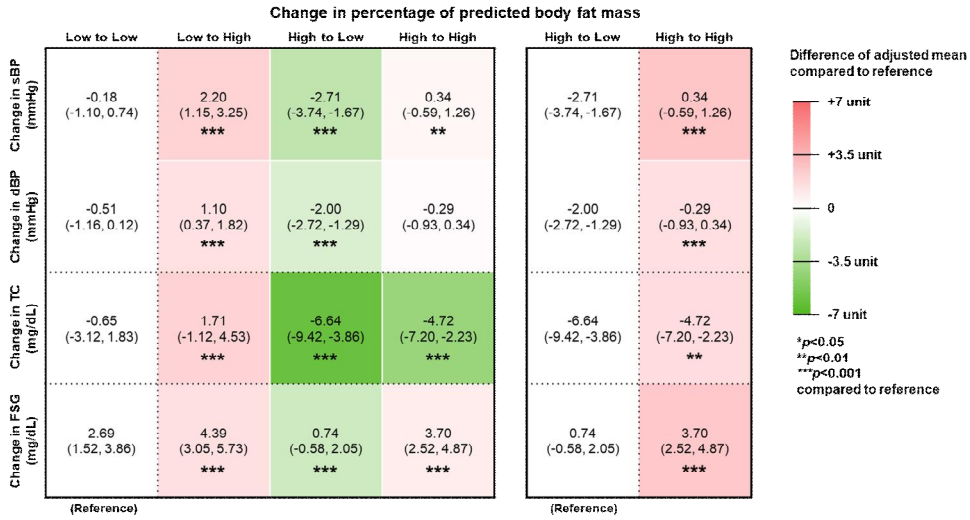
Acronyms: cardiovascular disease (CVD); predicted lean body mass percentage (pLBMP); predicted appendicular skeletal mass percentage (pASMP); predicted body fat mass percentage (pBFMP); hazard ratio (HR); confidence interval (CI)

*p-value<0.05, **p-value<0.01, and ***p-value<0.001 compared to the Low to Low group

Figure 6. Changes in the metabolic factors related to CVD according to predicted body composition. Adjusted mean of change in systolic blood pressure (sBP), diastolic blood pressure (dBP), total cholesterol (TC), and fasting serum glucose (FSG) according to changes in a). pLBMP, b). pASMP, and c). pBFMP.



c.



Adjusted mean and 95% confidence interval (CI) calculated by multiple linear regression after adjustments for the following covariates: age, income, chemotherapy, radiation therapy, hormone therapy, Charlson comorbidity index, smoking status, alcohol consumption, and physical activity. The values inside the table indicate adjusted means and 95% CI. The relative difference of adjusted mean compared to the reference group is expressed in respective heat maps. Red indicates a higher value, whereas green indicates a lower value.

Table 18. Changes in metabolic risk factors according to predicted body composition.

	Change in percentage of predicted body composition			
	Low % at baseline periods		High % at baseline periods	
	Low to Low	Low to High	High to Low	High to High
Change in pLBMP				
Study population[a]	16,458	3,497	2,887	17,243
Change in Systolic BP [mmHg]				
at baseline period, means (SD)	124.9 (15.2)	122.2 (15.1)	118.1 (14.1)	115.8 (13.9)
at follow-up period, means (SD)	125.0 (14.7)	119.2 (14.9)	120.2 (13.6)	115.5 (14.0)
Change in systolic BP, means (SD)	0.1 (16.4)	-3.1 (15.7)	2.2 (14.8)	-0.3 (14.1)
aMean (95% CI)	0.32 (-0.60, 1.24)	-2.82 (-3.85, -1.79)	2.28 (1.23, 3.33)	-0.17 (-1.09, 0.75)
p-value	Reference	<0.001	<0.001	0.004
	-	-	Reference	<0.001
Change in Diastolic BP [mmHg]				
at baseline period, means (SD)	77.1 (10.0)	75.5 (9.8)	73.4 (9.7)	72.1 (9.4)
at follow-up period, means (SD)	77.0 (9.5)	73.7 (9.5)	74.9 (9.1)	72.1 (9.3)
Change in diastolic BP, means (SD)	-0.1 (11.1)	-1.8 (10.4)	1.5 (10.7)	-0.1 (10.0)
aMean (95% CI)	-0.29 (-0.94, 0.34)	-2.01 (-2.72, -1.29)	1.12 (0.39, 1.84)	-0.52 (-1.16, 0.11)
p-value	Reference	<0.001	<0.001	0.061
	-	-	Reference	<0.001
Change in Total cholesterol [mg/dL]				
at baseline period, means (SD)	203.3 (41.0)	202.3 (36.8)	196.7 (36.5)	194.3 (34.5)
at follow-up period, means (SD)	194.0 (37.9)	191.7 (36.4)	196.5 (37.0)	191.5 (36.8)
Change in Total cholesterol, means (SD)	-9.3 (45.6)	-10.6 (40.5)	-0.3 (40.0)	-2.8 (37.6)
aMean (95% CI)	-4.73 (-7.21, -2.24)	-6.64 (-9.42, -3.87)	2.54 (-0.28, 5.36)	-0.64 (-3.12, 1.84)
p-value	Reference	0.012	<0.001	<0.001
	-	-	Reference	<0.001
Change in Fasting serum glucose [mg/dL]				
at baseline period, means (SD)	100.1 (23.4)	98.2 (20.9)	93.7 (17.1)	92.4 (14.8)
at follow-up period, means (SD)	102.5 (23.6)	97.8 (20.7)	96.8 (16.1)	93.7 (15.2)
Change in Fasting serum glucose, means (SD)	2.3 (23.4)	-0.6 (19.1)	3.1 (15.9)	1.3 (15.3)
aMean (95% CI)	3.64 (2.46, 4.81)	1.07 (-0.24, 2.38)	4.43 (3.09, 5.76)	2.65 (1.48, 3.83)
p-value	Reference	<0.001	0.046	<0.001

	-	-	Reference	<0.001
Change in pASMP				
Study population[a]	20,499	2,597	3,302	13,687
Change in Systolic BP [mmHg]				
at baseline period, means (SD)	124.5 (15.3)	120.0 (14.4)	117.0 (13.7)	114.8 (13.5)
at follow-up period, means (SD)	124.3 (14.8)	117.5 (14.5)	119.3 (13.7)	114.4 (13.5)
Change in systolic BP, means (SD)	-0.1 (16.3)	-2.5 (14.9)	2.3 (14.2)	-0.4 (14.0)
aMean (95% CI)	0.13 (-0.79, 1.05)	-2.18 (-3.25, -1.11)	2.48 (1.45, 3.51)	-0.22 (-1.15, 0.71)
p-value	Reference	<0.001	<0.001	0.057
	-	-	Reference	<0.001
Change in Diastolic BP [mmHg]				
at baseline period, means (SD)	76.7 (10.0)	74.6 (9.8)	72.9 (9.5)	71.7 (9.3)
at follow-up period, means (SD)	76.4 (9.5)	73.3 (9.6)	74.5 (9.4)	71.7 (9.3)
Change in diastolic BP, means (SD)	-0.3 (11.0)	-1.3 (10.4)	1.5 (10.4)	0.0 (9.9)
aMean (95% CI)	-0.41 (-1.05, 0.22)	-1.54 (-2.29, -0.81)	1.09 (0.38, 1.81)	-0.51 (-1.15, 0.13)
p-value	Reference	<0.001	<0.001	0.438
	-	-	Reference	<0.001
Change in Total cholesterol [mg/dL]				
at baseline period, means (SD)	203.7 (40.4)	200.6 (36.1)	196.1 (35.0)	191.9 (33.4)
at follow-up period, means (SD)	194.5 (37.9)	192.1 (35.9)	196.3 (37.4)	189.7 (36.3)
Change in Total cholesterol, means (SD)	-9.2 (45.1)	-8.5 (39.2)	0.2 (38.0)	-2.2 (36.8)
aMean (95% CI)	-4.28 (-6.76, -1.81)	-5.48 (-8.36, -2.60)	2.65 (-0.12, 5.43)	-0.59 (-3.10, 1.91)
p-value	Reference	0.166	<0.001	<0.001
	-	-	Reference	<0.001
Change in Fasting serum glucose [mg/dL]				
at baseline period, means (SD)	99.6 (22.9)	96.3 (19.0)	92.9 (15.7)	91.8 (15.7)
at follow-up period, means (SD)	101.7 (23.1)	96.3 (18.6)	95.5 (15.7)	93.0 (14.1)
Change in Fasting serum glucose, means (SD)	2.1 (22.7)	-0.0 (17.5)	2.7 (16.7)	1.2 (14.5)
aMean (95% CI)	3.53 (2.36, 4.70)	1.43 (0.097, 2.79)	4.04 (2.73, 5.36)	2.59 (1.40, 3.77)
p-value	Reference	<0.001	0.160	<0.001
	-	-	Reference	0.023
Change in pBFMP				
Study population[a]	17,927	2,839	3,438	15,881
Change in Systolic BP [mmHg]				

at baseline period, means (SD)	115.9 (13.9)	118.3 (14.2)	122.4 (15.0)	125.0 (15.3)
at follow-up period, means (SD)	115.6 (14.0)	120.3 (13.6)	119.4 (15.0)	125.2 (14.7)
Change in systolic BP, means (SD)	-0.3 (14.2)	2.1 (14.9)	-3.0 (15.6)	0.1 (16.4)
aMean (95% CI)	-0.18 (-1.10, 0.74)	2.20 (1.15, 3.25)	-2.71 (-3.74, -1.67)	0.34 (-0.59, 1.26)
p-value	Reference	<0.001	<0.001	0.003
	-	-	Reference	<0.001
Change in Diastolic BP [mmHg]				
at baseline period, means (SD)	72.2 (9.4)	73.5 (9.7)	75.6 (9.8)	77.2 (10.0)
at follow-up period, means (SD)	72.2 (9.4)	75.0 (9.2)	73.8 (9.5)	77.0 (9.5)
Change in diastolic BP, means (SD)	-0.1 (10.0)	1.5 (10.9)	-1.8 (10.3)	-0.1 (11.1)
aMean (95% CI)	-0.51 (-1.16, 0.12)	1.10 (0.37, 1.82)	-2.00 (-2.72, -1.29)	-0.29 (-0.93, 0.34)
p-value	Reference	<0.001	<0.001	0.060
	-	-	Reference	<0.001
Change in Total cholesterol [mg/dL]				
at baseline period, means (SD)	194.5 (34.5)	197.3 (36.9)	202.3 (37.1)	203.3 (41.0)
at follow-up period, means (SD)	191.7 (36.8)	196.3 (37.1)	191.7 (36.2)	193.9 (38.0)
Change in Total cholesterol, means (SD)	-2.8 (37.7)	-1.1 (40.3)	-10.6 (40.6)	-9.4 (45.7)
aMean (95% CI)	-0.65 (-3.12, 1.83)	1.71 (-1.12, 4.53)	-6.64 (-9.42, -3.86)	-4.72 (-7.20, -2.23)
p-value	Reference	<0.001	<0.001	<0.001
	-	-	Reference	0.013
Change in Fasting serum glucose [mg/dL]				
at baseline period, means (SD)	92.5 (14.8)	93.7 (17.5)	98.4 (21.3)	100.3 (23.5)
at follow-up period, means (SD)	93.9 (15.4)	96.8 (16.4)	97.8 (20.1)	102.7 (23.7)
Change in Fasting serum glucose, means (SD)	1.3 (15.4)	3.1 (1.63)	-0.7 (19.6)	2.4 (23.5)
aMean (95% CI)	2.69 (1.52, 3.86)	4.39 (3.05, 5.73)	0.74 (-0.58, 2.05)	3.70 (2.52, 4.87)
p-value	Reference	<0.001	<0.001	<0.001
	-	-	Reference	<0.001

Adjusted hazard ratios were calculated by multiple linear regression analysis after adjustments for the following covariates: age, income, chemotherapy, radiation therapy, hormone therapy, Charlson comorbidity index, smoking status, alcohol consumption, and physical activity.
[a]N=40,084 (a total of 10 cancer survivors excluded due to missing value at health screening, prior to the date of cancer diagnosis)
Acronyms: standard deviation (SD); blood pressure (BP)

IV. Discussion

1. Key Findings and Contributions

In this nationwide population-based study, it was observed that a high percentage of predicted body fat mass was associated with higher risk of CVD among 5-year breast cancer survivors. Furthermore, a high percentage of predicted lean body mass and predicted appendicular skeletal mass was associated with lower risk of CVD. Each 1% increase in pLBMP and pASMP was associated with a 4% and 9% lower risk of CVD, respectively. Each 1% increase in pBFMP was associated with a 5% higher risk of CVD. In all three components of body composition, blood pressure showed to be the most important mediator for the observed association. This is the first study, in this scale, to show comprehensively that low percentage of body fat mass and high percentage of lean body mass and appendicular skeletal mass are associated with lower risk of CVD among breast cancer survivors.

Furthermore, it was shown that being overweight, abdominally obese, or both is associated with higher risk of CVD and stroke. Also, compared to those overweight, those with abdominal obesity only have a higher risk of stroke, especially ischemic stroke. This is the first study to observe CVD and stroke risk based on discrepancies in BMI and WC among breast cancer survivors.

Finally, having a persistently high predicted LBMP or ASMP among breast cancer survivors was associated with lower CVD risk than a persistently low predicted LBMP or ASMP, respectively. Conversely, persistently high predicted BFMP among breast cancer survivors was associated with higher CVD risk than persistently low predicted BFMP. Additionally, those with a low to high change in pBFMP had a higher risk of CVD than those with persistently low pBFMP. Changes in body composition were accompanied by changes in metabolic markers. This is the first study to demonstrate CVD risk with changes in body composition, by distinguishing muscle mass and fat mass as predicted LBMP, ASMP, and

BFMP in breast cancer survivors.

2. Comparison With Previous Studies

2.1 Association of Body Composition and CVD Risk

The results from previous studies are in accordance with higher risk of CVD associated with a high percentage of predicted body fat mass observed in this study. For example, in a study investigating the association between adipose tissue distribution with CVD risk, each standard deviation increase in visceral and intramuscular adiposity was associated with an increase in CVD risk (aHR(95% CI) 1.15(1.03 to 1.29) and 1.21(1.06 to 1.37), respectively).[23] Similarly, in this study, each 1% increase in pBFMP was associated with a higher risk of CVD (aHR(95% CI) 1.05(1.03–1.07)). Additionally, a relatively recent report observed the association of body mass index, central obesity, and body composition with mortality in Black breast cancer survivors.[43] High body mass index, central obesity (WHR and WC), and body composition (percent body fat and fat mass index) were associated with higher overall mortality (aHR(95% CI) 1.57(1.11-2.22), 1.74(1.26-2.41), and 1.53(1.09-2.15), respectively) and breast cancer-related mortality. However, in this study, association with CVD was not investigated and there were potential confounding variables, because the number of subjects was limited to 1,891, and data on underlying heart disease were not collected.

2.2 Association of Discrepancies in General Obesity and Abdominal Obesity with CVD Risk

Breast cancer survivors who were abdominally obese had higher risk of both CVD and stroke. Though direct comparison is difficult due to lack of previous studies, the results of this study are in accordance with previous findings from a study carried out in the general population. Increasing general and abdominal adiposity, measured through BMI, WC, WHR, and waist-height ratio (WHtR) were associated with significantly

increased risk of total, ischemic, and hemorrhagic stroke in Chinese women aged 40–70 years.[44] Several previous studies have shown that abdominal obesity is positively associated with mortality in cancer patients.[43, 45] However, in various other cohorts, the association was not evident; for example, in a study consisting of elderly women in the United Kingdom, WC was not associated with CVD-related mortality.[46] In a previous study on Korean adults[16], the risk for major adverse cardiovascular events (MACE) for women, in contrast to men, with abdominal obesity was statistically insignificant, even in a sensitivity analysis where abdominal obesity was defined as 90 cm or above. In the Health, Eating, Activity, and Lifestyle (HEAL) Study consisting of a diverse breast cancer survivor cohort, the positive association of WC with breast cancer-specific mortality was not statistically significant.[47]

2.3 Association of Changes in Body Composition with CVD Risk and Changes in Metabolic Factors

The findings this study are consistent with a previous study that examined adiposity from computed tomography (CT) scans taken near diagnosis and subsequent CVD risk in breast cancer survivors.[23] In this previous study, visceral and intramuscular adiposity were associated with increased CVD incidence, though only adiposity was examined and at one time point. Similarly, central obesity was associated with higher all-cause and breast cancer–specific mortality among Black breast cancer survivor[43]; CVD event nor CVD-related mortality was observed in this study. In a cross-sectional study of anthracycline chemotherapy in breast cancer patients, greater thigh muscle fatty infiltration was associated with impaired oxygen extraction, which is a predictor of CVD morbidity and mortality.[48] According to a study that observed for change in BMI and waist circumference between diagnosis and 24 months post-diagnosis in early-stage breast cancer patients, weight change was not associated with risk of CVD, while any elevation in waist circumference was associated with increased risk of CVD.[24] As noted by the author, BMI and

weight change do not fully represent body composition, underscoring the significance of examining body composition and changes in body composition.

Although a low to high change in pBFMP showed a higher risk of CVD than those with persistently low pBFMP, so did that of a high to low change in pBFMP (both were not significant). Having a high body fat mass percentage before initial breast cancer diagnosis or at any timepoint in cancer survivorship may be decisive. Therefore, current results should be interpreted with discretion, and further examination should be carried on CVD risk according to changes in body fat mass percentage respective to muscle mass percentage as well as changes in metabolic markers.

The associations of changes in predicted LBMP, ASMP, and BFMP with CVD risk were statistically significant in the older or healthier individuals, which are consistent with findings from a previous study on young adults.[18] Furthermore, these changes were significant in breast cancer survivors who had a history of hormone therapy. Although cardiovascular effects vary based on the type and combination of hormone therapy, hormone therapy is largely associated with an increased risk of stroke, coronary heart disease, and notably, venous thromboembolism.[2, 49] Therefore, those who received hormone therapy, may benefit, in terms of CVD prevention, from changes in LBMP, ASMP, and BFMP.

3. Mechanism

3.1 Association of Body Composition and CVD Risk

Breast cancer patients experience cardiotoxic agents, and it has been suggested that CVD risk may also be related to anti-estrogen therapy such as aromatase inhibitors.[7] Breast cancer survivors tend to also have other risk factors for CVD. Increased body fat mass may lead to metabolic disturbances related to increased adiposity including insulin resistance, dyslipidemia, and chronic inflammation.[50] Also, visceral fat

has been suggested to alter cardiac autonomic activity in breast cancer survivors.[51] Specifically, diminished parasympathetic activity and heart rate variability have been associated with loss of cholinergic anti-inflammatory pathway, enabling enhanced cytokine responses to the otherwise normal stimuli.[52] Finally, increased intramuscular fat was associated with reduced peak exercise capacity in cancer survivors.[53, 54] This, in addition to breast cancer-related skeletal muscle damage, may have reduced exercise-based opportunities for CVD risk reduction.

Reduced muscle mass, which is prevalent in breast cancer survivors, is a risk factor for mortality in early breast cancer patients.[55, 56] A UK study examined appendicular skeletal muscle mass to have a curvilinear association with CVD events in women.[35] In this study of breast cancer survivors, both lean body mass and appendicular skeletal mass were associated with lower risk of CVD. Though not significant, this was also evident in the lower risk of CVD observed in those with higher lean body mass (High BFM-High LBM) compared to those with lower lean body mass (High BFM-Low LBM) among those with high body fat mass. In breast cancer survivors who had received radiation therapy and hormone therapy, a significantly higher CVD risk was associated with higher pBFMP and lower risk in higher pLBMP and pASMP. The risk of CVD may have been more prominent in the subgroup of radiation therapy due to the significant changes seen in body composition post-radiation.[57] Moreover, the interaction which was found between age groups and risk of CVD, may be due to the limitation of not being able to distinguish menopause status. For example, decreased risk for breast cancer but increased risk for CVD was associated with premenopausal obesity.[7]

Blood pressure, among the three confounders that were adjusted for in combinations, was observed to be the most important mediator for the association of pLBMP, pASMP, and pBFMP with CVD risk. Though further research is warranted to elucidate the mechanism in which body composition and metabolic changes lead to CVD, studies have already examined a close link between body composition and blood pressure. Both lean body mass, the majority constituted by muscle mass, and fat

mass, to a lesser degree, were significant determinants of blood pressure level; relatively high muscle mass was associated with high blood pressure levels in this report.[58] In a study on middle-aged adults, higher visceral adiposity was associated with higher blood pressure level with lower variability, independent of BMI, and this persistently elevated blood pressure may impose cardiac burden.[59]

3.2 Association of Discrepancies in General Obesity and Abdominal Obesity with CVD Risk

The high CVD, including ischemic stroke, risk observed in breast cancer survivors with abdominal obesity only may be attributed to the collective effect of traditional risk factors of CVD and those related to cancer condition. Breast cancer is an independent risk factor of CVD.[60] In the Atherosclerosis Risk In Communities (ARIC) Study, breast cancer survivors had a high risk of heart failure while the risk of stroke was statistically insignificant. However, in a Mendelian randomization study, a causal role of visceral adipose tissue (VAT) in ischemic stroke, as opposed to intracerebral hemorrhage, was suggested.[61] VAT mass was also associated with hypertension, type 2 diabetes, and hyperlipidemia with a possibility of visceral adiposity being more lipolytic and proinflammatory, promoting insulin resistance.[62]

Lower risk of hemorrhagic stroke, though statistically insignificant, was observed in breast cancer survivors who were overweight with and without abdominal obesity, compared to normal; this was also observed in the sensitivity analysis (BMI 25.0 kg/m^2). This may be due to the limitation of not having observed body composition. Also, characteristics of tumor and cancer staging, which were unavailable in this study, were not adjusted for. Long-term survivors from the Shanghai Breast Cancer Survival Study with a WHR of 0.83 had the lowest risk of all-cause mortality, and WHR was associated with late all-cause mortality in a U-shaped pattern[63]; in the same study, the association between WHR and mortality was more apparent in ER-positive patients. Furthermore, Sun *et*

al. showed high WHR (0.84 or above) to be associated with all-cause mortality and luminal mortality in invasive breast cancer participants.[64]

3.3 Association of Changes in Body Composition with CVD Risk and Changes in Metabolic Factors

The metabolic changes associated with changes in body composition have been studied before.[17] Similar findings in breast cancer survivors were observed in our study. Increased or persistently high (compared to a high to low change in) predicted LBMP and ASMP were associated with decreased blood pressure, fasting serum glucose, and total cholesterol. Conversely, increased or persistently high (compared to a high to low change in) predicted BFMP was associated with increased blood pressure, fasting serum glucose, and total cholesterol. Indeed, adipose tissue inflammation includes insulin resistance, alterations in lipid metabolism, and blood pressure regulation, favoring endothelial dysfunction and atherogenesis.[14] Skeletal muscle tissues, another endocrine organ that produces myokines, are also involved immunometabolism or the complex network related to metabolic functions.[65, 66] Myokines such as irisin and fibroblast growth factor-21 (FGF-21) are induced by physical exercise and increase insulin sensitivity and in the case of FGF-21, acts on lipolysis; apelin not only has an anti-inflammatory role but also controls cardiac muscles and blood pressure. However, further research is needed to investigate the joint effects of adiposity and muscle mass, and the crosstalk between respective cytokines.[67]

4. Strengths and Limitations

A major strength of this study is the large study population, considering that it was limited to 5-year breast cancer survivors. Body composition was observed both at one timepoint and changes between two timepoints, in addition to the effect of discrepancies in general and abdominal obesity via traditional anthropometric proxies (BMI and WC). Changes in predicted

body composition were observed as percentages, which may be clinically more meaningful for breast cancer survivors who are particularly susceptible to weight change and were inclusive of both adiposity and muscle mass. In addition, various potential confounders were adjusted for. Though it is unknown whether positive changes in body composition may reverse CVD risk, body composition is not unmodifiable, with lifestyle modification including physical activity and adequate nutrition.

This study is not without limitations. First, prediction equations were used to measure body composition, which may be imperfect. However, a previous large validation study in the same ethnic group was conducted and showed high predictive values, including low bias, high intraclass correlation coefficient, high adjusted R^2, and low standard error of estimate [19]; this allows for applications to large-scale research and epidemiological studies. In addition, in previous studies using the same equations, similar changes in body composition (increase in body fat mass and decrease in appendicular skeletal mass or lean body mass) were associated with increased risk of metabolic syndrome and CVD in young adults.[17, 18] Utilizing prediction questions may not only be less costly, compared to imaging modalities, but also overcome the limitations of applying independent anthropometric indices(cut-offs). Second, the results of this study are limited to Asians and may not represent other ethnicities. Body composition, metabolic syndrome, and the nature of cancer varies among ethnicities. Further research in deciphering individual and inter-racial differences is necessary. Finally, the study was not inclusive of cardiovascular biomarkers associated with adiposity.[68] Therefore, future exploration on delineating associated immunometabolic pathways may provide insight on the progression from changes in body composition to CVD in breast cancer survivors.

V. Conclusion

First, a high percentage of predicted lean body mass and predicted appendicular skeletal mass and a low percentage of predicted body fat mass were associated with lower risk of CVD. Blood pressure showed to be the most important mediator for the association at one timepoint.

Second, discrepancies in general and abdominal obesity, observed through BMI and WC, should be considered for preventing CVD and stroke, in particular. Compared to those overweight, those with abdominal obesity only had a higher risk of stroke, especially ischemic stroke.

Third, persistently high muscle mass, represented as predicted LBMP or ASMP, was associated with lower CVD risk. Preventing an increase in fat mass may be beneficial in preventing CVD in breast cancer survivors, as a part of cancer survivorship. Finally, changes in body composition were accompanied by metabolic changes.

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국문초록

배경 및 목적: 유방암 경험자가 증가함에 따라 심뇌혈관질환이 사망의 주요 원인으로 떠오르고 있다. 암 병력이 없는 여성에 비해 유방암 생존자의 심뇌혈관질환 위험 증가는 유방암 치료의 심장 독성 효과뿐만 아니라 비만과 호르몬 대체와 같은 유방암 및 심뇌혈관질환의 중복 위험 요소와 관련이 있다. 그러나 유방암 진단 후에도 대다수는 체중이 증가하거나 적어도 체성분의 변화를 경험하며, 이는 유방암 생존 기간에도 지속된다. 유방암 생존자에 대한 이전 연구는 체질량지수(BMI)와 사망률 사이의 연관성을 조사하는 데 국한되어 체성분이나 심뇌혈관질환을 측정하지 않았다. 따라서 본 연구는 이전에 심뇌혈관질환이 없었던 5년 유방암 경험자에서 1) 체성분과 새로 발병한 심뇌혈관질환 위험 사이의 연관성; 2) 전신 비만과 복부 비만의 불일치와 심뇌혈관질환 위험의 연관성; 그리고 3) 체성분의 변화와 심뇌혈관질환 위험 및 대사 인자의 변화의 연관성이 어떻게 되는지 분석하고자 한다.

연구 방법: 국민건강보험공단 데이터베이스를 이용하여 40세 이상 5년 유방암 생존자 약 7만명을 대상으로 조사하였다. 인덱스 날짜 기준으로 모든 대상자를 심뇌혈관질환 발생일, 사망일, 또는 2020년 12월 31일 중 가장 먼저 발생한 날짜까지 추적관찰 하였다. 대상자는 예측된 체성분률 (제지방량, pLBMP; 사지골격근육량, pASMP; 체지방량 pBFMP)의 사분위수에 따라 분류되었으며, 심뇌혈관질환 위험이 있는 전신 비만과 복부 비만의 불일치를 평가할 때 BMI와 허리둘레(WC)에 따라 분류하였다. 다변량 콕스 회귀분석

모델을 사용하여 예측된 체성분률, 비만 유형, 및 예측된 체성분률 변화에 따른 심뇌혈관질환 위험도 (adjusted hazard ratio, aHR) 및 95% 신뢰구간 (confidence interval, CI)을 계산하였다. 대사요인(공복 혈당, FSG; 수축기 혈압, sBP; 이완기 혈압, dBP; 그리고 총콜레스테롤, TC) 변화는 다변량 선형 회귀분석 모델을 사용하여 계산하였다. 공변량의 하위 그룹에 따른 층화 분석을 수행하였다.

결과: pLBMP 및 pASMP가 가장 낮은 그룹과 비교하였을 때 pLBMP 및 pASMP가 가장 높은 그룹은 심뇌혈관질환 위험이 각각 38% 및 42% 더 낮았다. 반면 가장 높은 pBFMP를 가진 사람들은 가장 낮은 pBFMP를 가진 사람들에 비해 심뇌혈관질환 위험이 57% 더 높았다. pLBMP 및 pASMP가 1% 증가할 때마다 심뇌혈관질환 위험 감소와 연관되었다 (각각 pLBMP, aHR(95% CI) 0.96(0.94–0.98), $p<0.05$ 그리고 pASMP, aHR(95% CI) 0.91(0.87–0.95), $p<0.05$). 반면 pBFMP가 1% 증가할 때마다 심뇌혈관질환 위험이 증가했다 (aHR(95% CI) 1.05(1.03–1.07), $p<0.01$). 세 가지 교란 요인의 조합에 대한 조정 결과 혈압이 심뇌혈관질환과 pLBMP, pASMP, 및 pBFMP의 연관성에 대한 가장 중요한 매개체임을 확인하였다. WC 및 BMI가 정상인 사람에 비해 복부 비만이 없는 과체중, 복부 비만만 있는 사람, 복부 비만을 동반한 과체중이 심뇌혈관질환 위험 (각각 aHR(95% CI) 1.23(1.02-1.48), 1.51(1.16-1.95), 그리고 1.55(1.31-1.75)) 및 뇌졸중 위험이 (각각 1.09(0.86-1.38), 1.63(1.20-2.23), 그리고 1.40(1.17-1.68)) 더 높았다. 허혈성 뇌졸중의 경우 정상에 비해 복부 비만만 있는 사람과 복부 비만을 동반한 과체중에서 유의하게 더 높은 위험도 (각각 (aHR(95% CI)

1.77(1.08-2.88) 그리고 1.84(1.37-2.47))를 보였다.

pLBMP와 pASMP가 지속적으로 낮은 사람들에 비해 pLBMP와 pASMP가 지속적으로 높은 사람들은 심뇌혈관질환 위험이 더 낮았다 (각각 aHR(95% CI) 0.68(0.53-0.87) 그리고 0.60(0.44-0.81)). 반면 낮은 pBFMP를 유지한 사람들에 비해, pBFMP가 증가(low에서 high 변화)하거나 지속적으로 높은 사람들은 심뇌혈관질환 위험이 더 높았다 (각각 aHR(95% CI) 1.51(0.99-2.31) 그리고 1.48(1.15-1.89)). pLBMP와 pASMP의 변화와 관련하여 Low에서 High 그룹은 Low에서 Low 그룹에 비해 수축기 및 확장기 혈압, 총콜레스테롤, 및 공복혈당이 감소했다. pBFMP의 변화와 관련하여 Low에서 High 그룹은 수축기 및 이완기 혈압, 총콜레스테롤, 및 공복혈당이 증가했다.

결론: 높은 예측된 제지방량 백분율 및 예측된 사지골격근육량 백분율과 낮은 예측 체지방량 백분율은 심뇌혈관질환 위험 감소와 관련이 있었다; 혈압은 (한 시점에서) 연관성의 가장 중요한 매개체로 나타났다. 또한 BMI와 WC를 통해 관찰한 전신 비만과 복부 비만의 불일치는 심뇌혈관질환과 특히 뇌졸중을 예방하기 위해 고려되어야 한다. 과체중과 비교했을 때 복부 비만인 사람들이 뇌졸중, 특히 허혈성 뇌졸중의 위험이 더 높았다. 마지막으로, 지속적으로 높은 근육량은 (pLBMP 또는 pASMP) 낮은 심뇌혈관질환 위험과 관련이 있었다. 체지방 증가를 예방하는 것은 유방암 경험자의 심뇌혈관질환을 예방하는 데 도움이 될 수 있다. 체성분 변화는 대사 변화와 동반되었다.

주요어: 유방암 경험자; 체성분; 대사요인; 심뇌혈관질환

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