Association of Mammary Gland Disease With Metabolic Syndrome Factors in Japanese Women—Case-Control Study Based on Health Screening Results

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Sakika Sumida[1], Tadayuki Iida[2], Masao Yoshikawa[3] and Kaoru Nagaoka[3]

[1]Department of Radiology, Yoshida General Hospital, Akitakata, Japan. [2]Department of Physical Therapy, Faculty of Health and Welfare, Prefectural University of Hiroshima, Mihara, Japan. [3]Preventive Medicine Promotion Research Center, Nisshin, Japan.

ABSTRACT

BACKGROUND: The association of obesity with breast cancer is clear. Although body mass index (BMI) is used as an indicator of obesity, its accuracy remains questionable. Although, there factors for diagnosing metabolic syndrome are caused by obesity, the association with breast cancer has not been clarified.

METHODS: Women who underwent breast cancer screening with mammography and measurements of metabolic syndrome factors, including waist circumference, blood glucose, triglycerides, HDL (high-density lipoprotein) cholesterol levels, and systolic and diastolic pressure, twice within a 2-year period were enrolled (n = 314), with a final sample size of 256. To determine the presence of mammary gland disease, 2 expert physicians interpreted radiogram findings, with category 3 or higher shown by mammography considered to indicate an abnormality.

RESULTS AND CONCLUSIONS: Waist circumference at the initial measurement was marginally significant as a risk factor for onset of mammary gland disease (odds ratio [OR] = 1.036, $P = .045$) and thus was concluded to be a risk factor for disease onset. Although not significant, a 2-year increase in systolic and diastolic blood pressure has been presumed to be risk factors (systolic: OR = 1.020, $P = .085$, diastolic: OR = 1.040, $P = .065$), while high levels of HDL cholesterol have been presumed to protect against the disease (OR = 0.982, $P = .064$). Based on these results, waist circumference and blood pressure are speculated to be related to development of mammary gland disease.

KEYWORDS: Mammary gland disease, metabolic syndrome factors, breast cancer screening

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CORRESPONDING AUTHOR: Tadayuki Iida, Department of Physical Therapy, Faculty of Health and Welfare, Prefectural University of Hiroshima, 1-1 Gakuen-cho, Mihara 723-0053, Hiroshima, Japan. Email: iida@pu-hiroshima.ac.jp

Introduction

According to the National Cancer Center of Japan, the number of breast cancer cases in 2016 in Japan was 73 997, with an increase to 91 605 noted in 2020. The Ministry of Health, Labor and Welfare of Japan has been conducting activities for raising awareness of breast cancer screening, although the rate of consultation has remained low. Obesity is defined as a state of excessive fatty tissue caused by hypertrophy that leads to an increase in that tissue, and the association between breast cancer and obesity in Japanese women has been clarified in recent years, with the westernization of dietary habits considered to be an important cause.[1]

Adipocytes produce estrogen based on male hormones (androgens) secreted by the adrenal cortex. Hypertrophy and increased adipose tissue are thought to promote exposure to estrogen and are closely related to the development of breast cancer. On the contrary, adipose tissue induces production and secretion of a variety of adipose cytokines. Furthermore, it has been reported that hypertrophy and increased adipose tissue can cause heterogeneous secretion of adipocytokines, which have effects on mammary tissue that can lead to breast cancer.[2] Thus, it is considered that hypertrophy and increased fatty tissue enhance exposure to estrogen, indicating their close relationship with breast cancer development. Uneven levels of secreted adipocytokines also elevate insulin sensitivity, facilitate glucose metabolism, and suppress blood pressure increase by a vasodilating effect.[3,4] As a result, hypertrophy and increased fatty tissue induce abnormal glucose metabolism and hypertension, causing advancement of metabolic syndrome.[5,6] Although, there factors for diagnosing metabolic syndrome are caused by obesity, the association with breast cancer has not been clarified.

Studies of breast cancer that use body mass index (BMI) generally define obesity as the presence of excess fatty tissue. Four previous case-control studies reported that increases in BMI and hormones were significantly associated with increased risk for breast cancer.[7-10] However, each of those cross-sectional studies examined the association with BMI at the time of breast cancer onset. While it has been established that BMI represents excessive fatty tissue, it may be inaccurate to use only

that to determine an increased state of adipose tissue.[11] Although breast cancer studies have been conducted with BMI used to determine adipose tissue increase, to the best of our knowledge the association of metabolic syndrome caused by an increase in adipose tissue with breast cancer has not been investigated. Furthermore, because an increase in adipose tissue can cause metabolic syndrome, those effects on breast cancer should be investigated in a longitudinal manner.

This study was conducted to clarify the relationship between metabolic syndrome index in healthy individuals and breast disease so as to raise awareness of the importance of daily life activities for prevention of disease onset. This was a longitudinal examination of the association of metabolic syndrome factors, including waist circumference, glucose level, blood pressure, triglycerides, and HDL (high-density lipoprotein) cholesterol in blood, as well as blood pressure with development of mammary gland disease such as breast cancer using data obtained in routine health checkup examinations.

Materials and Methods

Examination procedure

From 2010 to 2013, each of the participants (n = 314) was examined twice (initial and 2 years later), with physical characteristics and blood markers of metabolic syndrome noted, and also underwent breast cancer screening. Of those enrolled in this study, 89 participated in screening tests conducted in 2010 (first) and 2012 (2 years later) and 225 underwent screening in 2011 (first) and 2013 (2 years later). Mammograms and blood tests were performed during a voluntarily desired physical examination, where weight and height were measured for physical characteristics and blood markers for metabolic syndrome, and screening for breast cancer was also performed. Each was given a full explanation of the study content and methods in advance, and written consent was obtained.

This study is a nonrandomized trial for all women health checkups at one medical examination center. Of a total of 6249 breast cancer screenings conducted from 2010 to 2013, 4376 cases were classified as category 1 based on mammogram findings in the first year, while 2504 were selected for breast cancer screening 2 years later. It was assumed that the examinees had no abnormalities at the time of the initial examination. The number of examinees who underwent a biochemical examination at the same time as the mammography examination was 314. Of those, 89 participated in screening tests in 2010 (first) and 2012 (2 years later), and 225 underwent screening tests in 2011 (first) and 2013 (2 years later). Of 301 females with anomalies detected in the first screening and who responded to a questionnaire, 80 were assigned to the case group following the second examination. In addition, 221 females with no abnormalities detected and consistent with the case group in terms of age (±2 years) and BMI (±2 kg/m^2) were designated as the control group. Thus, each individual in the case group was matched with at least 2 individuals in the control group for range of age (±2 years) and BMI (±2 kg/m^2). Later, 36 in the control group were excluded because of missing test data or with data outside of the matching values; thus, the total number of participants in the control group was 185 (Figure 1). The sample size was determined according to waist circumference and presence/absence of breast cancer using G-power.[12,13] Based on the findings of studies conducted by Elías et al.[14] on the relationship between control participants without breast cancer and breast cancer survivors, and in consideration of results showing M1 = 88.52 (mean score of control group), SD1 = 9.61, M2 = 93.65 (mean score of breast cancer survivor group), and SD2 = 10.48, as well as one-sided $\alpha = 0.05$ and power = 90%, the sample size per group was determined to be 80, for a total sample size of 265.

This study was approved by the Ethics Committee of Hiroshima Koseiren Yoshida General Hospital (approval number 201607) and was performed in accordance with the Declaration of Helsinki.

Physical characteristics

For physical characteristics, age, height, body weight, and waist circumference were determined. The BMI was calculated on the basis of height and weight. Systolic and diastolic pressure, known to be major risk factors for circulatory disease, were used for blood pressure evaluation.

Metabolic syndrome factors

Among the metabolic syndrome factors examined, blood testing to determine glucose, triglyceride, and HDL cholesterol levels was performed as a biochemical examination using a HITACHI DM-JACS device. For the reagents, Determiner L GLU HK was used for blood glucose, Determiner L TG for triglycerides, and MetaboLead HDL-C for HDL cholesterol measurements. All reagents were provided by Kyowa Medex Co, Ltd (presently, Hitachi Chemical Diagnostics Systems Co, Ltd).

Breast cancer screening

An MGU-100D mammographic device (Toshiba Medical Systems Corporation; presently, Canon Medical Systems Corporation), which met the criteria of the Japan Radiological Society, was used for breast cancer screening. Mammography examinations were conducted at a certified facility, which has been accredited by the Japan Central Organization on Quality Assurance for Breast Cancer Screening (specified nonprofit organization). The screening criteria were fulfilled on the basis of evaluations of mammography equipment, actual radiograms, and radiation dose for the purpose of enhancing and maintaining screening precision. For determining abnormal status, we used the 5-category assessment of final malignancy shown in the Mammography Screening Guidelines based on the Breast

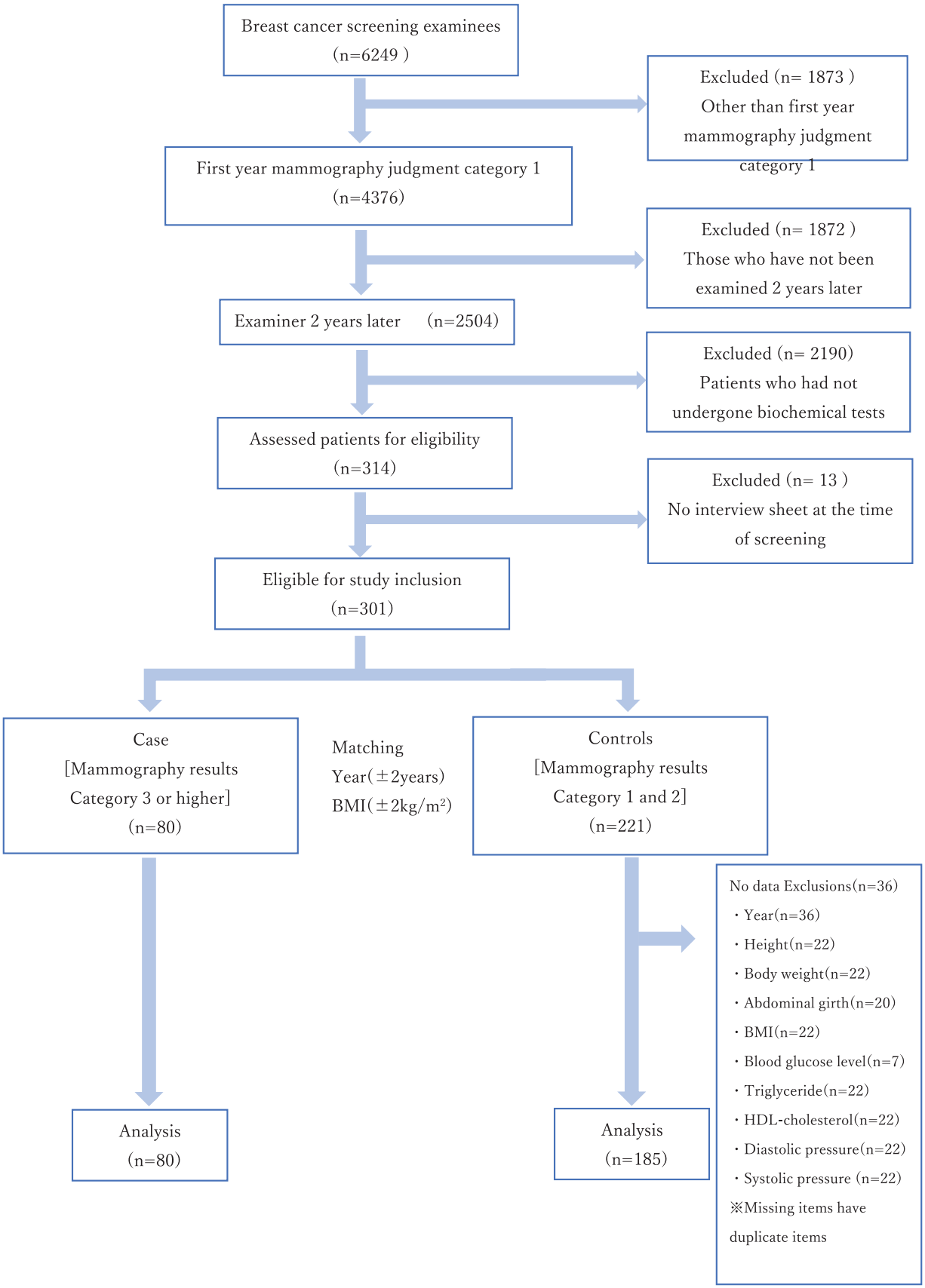

Figure 1. Flow diagram of this case-control study.

Imaging Reporting and Data System (BI-RADS) prepared by the American College of Radiology (ACR). For judgment of a mammography examination in the BI-RADS category, category 0 (insufficient examination: additional diagnostic imaging

required = close examination required), or categories 1 and 2 (normal and benign: recommended management for regular mammography examination) were used. In Japan, the conventional mammography guideline category, which expresses the degree of malignancy, has been renamed as "examination mammography category" and examination category 3 or higher requires a close examination. In other words, according to Japanese mammography guidelines, examination categories 3, 4, and 5 correspond to BI-RADS examination category 0. Two qualified physicians with experience with mammogram interpretation (B1) certified by the Japan Central Organization on Quality Assurance of Breast Cancer Screening were in charge of the breast cancer screening examinations and 2 radiogram interpretations, first and second, were used for grading. Participants classified as category 1 or 2 in the mammography results obtained 2 years after the initial screening were considered as other than abnormality detected, while those classified as category 3 or higher were considered to be abnormality detected related to onset of mammary gland disease.

Statistical Analysis

Age, physical characteristics, and metabolic syndrome factors, including waist circumference, glucose, triglyceride, and HDL cholesterol level, as well as systolic and diastolic pressure, were recorded, with the normality of the initial test values confirmed by use of a histogram and Kolmogorov-Smirnov test results ($P > .05$). Values from the initial measurements were subtracted from those obtained 2 years later for determining changes, with normality tested and confirmed in the same manner ($P > .05$). Mean and standard deviation values were calculated for each test item. Furthermore, age, height, weight, and waist circumference, blood glucose, triglyceride, and HDL cholesterol levels, and diastolic and systolic pressure were compared between included and excluded participants using Student t test.

Results obtained in the breast cancer screening test were used as dependent variables for examining the association of risk factors with binominal logistic regression analysis. Before selecting the explanatory variables, the correlations of waist circumference, glucose, triglyceride, and HDL cholesterol blood levels, and systolic and diastolic pressure determined at the initial measurement were examined using Pearson correlation coefficient, with a strong correlation between systolic and diastolic pressure noted ($r = 0.806$, $P < .001$). Accordingly, in model 1, waist circumference, glucose, triglyceride, HDL cholesterol, and systolic pressure were used as explanatory variables, while in model 2, systolic pressure was replaced with diastolic pressure. For both models 1 and 2, the effect of age was taken into consideration by using that at the initial screening as a regulating factor. Furthermore, for changes in waist circumference, blood glucose, triglyceride, and HDL cholesterol levels, and systolic and diastolic pressure, the correlation of each variable was examined using Pearson correlation coefficient. As a result, a strong correlation between changes in systolic and diastolic pressure was demonstrated ($r = 0.635$, $P < .001$). In model 3, changes in waist circumference, blood glucose, triglyceride, HDL cholesterol, and systolic pressure were used as explanatory variables. By taking into consideration the association of those at the initial measurement, each was used as a regulator factor. In model 4, change in systolic pressure was replaced with diastolic pressure, while the other explanatory and regulator factors were the same as in Model 3. For all of these tests, a risk ratio $\leqslant 5\%$ was considered to indicate statistical significance. For statistical analysis, SPSS 25.0J (KBM Japan, Tokyo) was used. The level of significance was set at $P < .05$.

Results

Physical characteristics and biochemical test results as metabolic syndrome factors for participants included and excluded from analysis conducted in the period from 2010 to 2013 are shown in Table 1. There were no significant differences between the 265 included participants and 36 excluded regarding height, weight, BMI, or waist circumference, glucose, triglyceride, or HDL cholesterol in blood, or diastolic pressure, whereas significant differences were confirmed for age and systolic pressure. In the participants classified as other than abnormality detected, systolic pressure was significantly lower at the second as compared with the initial measurement. Comparisons of the examined metabolic syndrome factors between the initial measurements and those obtained 2 years later are shown in Table 2. In the group with an abnormality detected, HDL cholesterol level was significantly higher at the second measurement. In all participants, waist circumference was significantly higher and systolic pressure significantly lower at the second measurement.

Results of binominal logistic regression analysis based on grading of breast cancer screening findings as an objective variable are shown in Tables 3 and 4. Those presented in Table 3 indicate an association of metabolic syndrome factors noted at the initial assessment on development of mammary gland disease 2 years later. Using model 1, waist circumference showed a significant association (odds ratio = 1.036, $P = .045$), while that of HDL cholesterol levels tended to be associated as protective factor, but this association was not statistically significant (odds ratio = 0.982, $P = .064$). In model 2, waist circumference again showed a significant association (odds ratio = 1.036, $P = .044$) and HDL cholesterol levels tended to be associated as protective factor, but this association was not statistically significant (odds ratio = 0.982, $P = .064$). Results presented in Table 4 demonstrate the association of changes in the examined metabolic syndrome factors at 2 years after the initial examination on development of mammary gland disease. With model 3, which included waist circumference, glucose, triglyceride, and HDL cholesterol levels in blood, as well as systolic pressure at the initial measurement, change in systolic pressure tended to be associated as risk factor, but this association was not statistically

Table 1. A comparison of sociodemographic and biochemical factors among included and excluded participants.

	N	INCLUDED PARTICIPANTS			EXCLUDED PARTICIPANTS (INCLUDING LACK OF DATA)				*P* VALUE	NORMAL REFERENCE VALUE
		MEAN	SD	MIN-MAX	N	MEAN	SD	MIN-MAX		
Age (y)	265	47.8	(8.0)	35.0-78.0	36	56.5	(11.6)	38.0-77.0	<.001	–
Height (cm)	265	158.6	(5.3)	144.1-174.0	22	156.5	(5.5)	147.2-167.7	.071	–
Body weight (kg)	265	53.2	(8.2)	40.1-108.3	22	53.1	(6.2)	40.6-64.7	.980	–
Waist circumference (cm)	265	76.9	(8.9)	60.0-122.5	20	80.3	(8.9)	64.5-95.8	.107	90
BMI (kg/m^2)	265	21.2	(3.2)	16.2-45.1	22	21.8	(2.9)	16.6-28.9	.393	18.5-25
Blood glucose (mg/dL)	265	90.0	(11.0)	66.0-171.0	7	86.7	(5.8)	79.0-92.0	.430	<110
Triglycerides (mg/dL)	265	80.6	(48.5)	27.0-428.0	22	82.0	(38.7)	40.0-213.0	.897	<150
HDL cholesterol (mg/dL)	265	76.8	(16.0)	33.0-130.0	22	79.2	(11.5)	56.0-97.0	.493	>40
Systolic pressure (mmHg)	265	115.3	(16.0)	82.0-181.0	22	123.0	(15.4)	106.0-160.0	.030	<130
Diastolic pressure (mmHg)	265	68.5	(11.2)	43.0-100.0	22	71.4	(8.2)	60.0-91.0	.239	<85

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein.
P value: Student *t* test between included and excluded participants. Normal reference value: Value determined by Member of the Metabolic Syndrome Diagnostic Criteria Review Committee.

significant (odds ratio = 1.020, *P* = .085). With model 4, which replaced systolic pressure with diastolic pressure, change in diastolic pressure tended to be associated as risk factor, but this association was not statistically significant (odds ratio = 1.040, *P* = .065).

Discussion

It is considered that obesity, namely, expanded waist circumference, and BMI are associated with onset of breast cancer, the causal relationship of metabolic syndrome factors, including waist circumference with risk for breast cancer development, has yet to be elucidated. The present results confirmed that waist circumference is a significant risk factor associated with development of mammary gland disease, with risk increasing as the circumference becomes larger. In Japan, voluntary health examinations are conducted for prevention of metabolic syndrome and breast cancer, and the results supported by evidence from the findings presented here show that a large abdominal circumference is a risk factor for later disease in otherwise healthy factors.[6] It has been speculated that hypertrophy and increase in number of adipocytes due to obesity can have effects to facilitate adipokine secretion.[15] Along with adipocyte accumulation, secretion of leptin, in contrast to that of adiponectin, increases the level of leptin in blood, which promotes vascularization and tumor proliferation. Furthermore, it has been reported that an increase in leptin level in blood induces production of vascular endothelial cell growth factor to promote growth of endothelial cells in tumor vessels, resulting in tumor enlargement, which has effects on mammary gland tissue epithelium and interstitium.[16] The incidence of breast cancer was increased in association with a decrease in blood adiponectin level of adipokine can be a cause of carcinogenesis.

On the contrary, because adipocytes produce estrogen by use of the male hormone androgen secreted from the adrenal cortex, it is considered that exposure to estrogen might have a close relationship with onset of breast cancer. Estrogen is known to be associated with development of mammary gland diseases, including those with a benign nature.[17] Together, these findings indicate that hypertrophy and an increase in number of adipocytes associated with larger waist circumference may lead to increased risk of mammary gland disease.

High levels of HDL cholesterol have been presumed to be a possible protective factor in the development of mammary gland disease, but have not shown a significant association. The relationship between its anti-inflammatory effect and metabolic mechanisms is speculated. Fiorenza et al[18] suggested that low HDL cholesterol level, a risk factor for cardiovascular disease development, is related to cancer occurrence in a variety of sites. In another study, hypo-HDL-cholesterolemia (50 mg/dL) was shown to be related to onset of breast as well as prostate cancer.[19] Furberg et al[20] investigated the association between breast cancer and HDL cholesterol level both before and after menopause, and their results support the notion that a high HDL cholesterol level is associated with decreased risk of breast cancer development, which was confirmed by the present results. Should HDL cholesterol be involved in immune stimulation and inhibition of inflammatory response, it is possible that an increased level might inhibit malignant tumor

Table 2. Comparisons of metabolic syndrome factors (waist circumference, glucose, triglycerides, HDL cholesterol in blood, systolic pressure, and diastolic pressure) between initial measurements and values obtained 2 years later.

PARTICIPANTS WITH OTHER THAN ABNORMALITY DETECTED (N = 185)	INITIAL			2 YEARS LATER			DIFFERENCE BETWEEN SECOND AND INITIAL MEASUREMENTS			*P* VALUE
	MEAN	SD	MIN-MAX	MEAN	SD	MIN-MAX	MEAN	SD	MIN-MAX	
BMI (kg/m^2)	20.9	(2.9)	16.2 to 45.1	21.0	(3.0)	15.2 to 46.7	0.03	(0.8)	−4.3 to 2.6	.598
Waist circumference (cm)	76.3	(8.1)	60.0 to 119.0	77.2	(8.6)	60.5 to 128.5	0.85	(4.0)	−12.0 to 14.2	.161
Blood glucose (mg/dL)	90.3	(8.4)	85.0 to 119.0	90.6	(8.8)	85.0 to 120.0	0.30	(7.4)	−4.0 to 23.0	.584
Triglycerides (mg/dL)	79.8	(42.9)	27.0 to 347.0	83.4	(42.5)	19.0 to 269.0	3.60	(36.6)	−204.0 to 140.0	.182
HDL cholesterol (mg/dL)	78.3	(16.3)	44.0 to 125.0	78.4	(16.6)	42.0 to 129.0	0.07	(9.6)	−24.0 to 35.0	.921
Systolic pressure (mmHg)	115.8	(16.5)	82.0 to 181.0	113.8	(14.5)	85.0 to 166.0	−2.04	(12.0)	−39.0 to −10.0	.022
Diastolic pressure (mmHg)	68.8	(11.3)	43.0 to 97.0	67.9	(11.0)	44.0 to 111.0	−0.85	(8.3)	−27.0 to 24.0	.161
PARTICIPANTS WITH ABNORMALITY DETECTED (N = 80)	INITIAL			2 YEARS LATER			DIFFERENCE BETWEEN SECOND AND INITIAL MEASUREMENTS			*P* VALUE
	MEAN	SD	MIN-MAX	MEAN	SD	MIN-MAX	MEAN	SD	MIN-MAX	
BMI (kg/m^2)	21.7	(3.7)	16.5 to 35.3	21.7	(3.7)	17.2-34.6	0.07	(1.1)	−4.8 to 3.1	.588
Waist circumference (cm)	78.4	(10.3)	62.1 to 122.5	79.2	(10.5)	60.5-115.7	0.75	(4.8)	−15.0 to 13.5	.164
Blood glucose (mg/dL)	89.3	(15.5)	82.0 to 171.0	89.2	(12.9)	82.0-153.0	−0.06	(8.0)	−3.0 to 25.0	.945
Triglycerides (mg/dL)	82.5	(59.8)	27.0 to 428.0	83.1	(66.9)	32.0-585.0	0.59	(33.2)	−115.0 to 157.0	.875
HDL cholesterol (mg/dL)	73.4	(14.7)	33.0 to 130.0	75.5	(15.7)	36.0-125.0	2.05	(8.3)	−26.0 to 21.0	.030
Systolic pressure (mmHg)	114.2	(14.8)	86.0 to 163.0	114.8	(15.5)	92.0-173.0	0.63	(11.2)	−24.0 to −6.3	.618
Diastolic pressure (mmHg)	67.9	(11.2)	49.0 to 100.0	69.1	(12.3)	47.0-112.0	1.20	(8.8)	−29.0 to 24.0	.226
TOTAL (N = 265)	INITIAL			2 YEARS LATER			DIFFERENCE BETWEEN SECOND AND INITIAL MEASUREMENTS			*P* VALUE
	MEAN	SD	MIN-MAX	MEAN	SD	MIN-MAX	MEAN	SD	MIN-MAX	
BMI (kg/m^2)	21.2	(3.2)	16.2 to 45.1	21.2	(3.2)	15.2 to 46.7	0.04	(0.9)	−4.8 to 3.1	.449
Waist circumference (cm)	76.9	(8.9)	60.0 to 122.5	77.8	(9.2)	60.5 to 128.5	0.82	(4.2)	−15.0 to 14.2	.002
Blood glucose (mg/dL)	90.0	(11.0)	66.0 to 171.0	90.2	(10.2)	69.0 to 153.0	0.19	(7.6)	−32.0 to 4.0	.685
Triglycerides (mg/dL)	80.6	(48.5)	27.0 to 428.0	83.3	(51.0)	19.0 to 585.0	2.69	(35.5)	−204.0 to −157.0	.219
HDL cholesterol (mg/dL)	76.8	(16.0)	33.0 to 130.0	77.5	(16.4)	36.0 to 129.0	0.67	(9.2)	−26.0 to 35.0	.240
Systolic pressure (mmHg)	115.3	(16.0)	82.0 to 105.0	114.1	(14.8)	85.0 to 102.0	-1.23	(11.8)	−39.0 to −9.0	<.001
Diastolic pressure (mmHg)	68.5	(11.2)	43.0 to 100.0	68.3	(11.4)	44.0 to 112.0	-0.23	(8.5)	−29.0 to 24.0	.653

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein.
P value: Paired t test between initial and 2 years later. Other than abnormality detected: Participants classified as category 1 or 2 in the mammography results obtained 2 years after the initial screening. Abnormality detected: Participants with a normal initial screening and a mammogram result classified as category 3 or higher after 2 years.

Table 3. Association of metabolic factors at initial measurement on onset of mammary gland disease 2 years later.

		ODDS RATIO	95% CI	*P* VALUE
Model 1	Waist circumference (cm)	1.036	1.001-1.073	.045
	Blood glucose (mg/dL)	0.987	0.960-1.016	.371
	Triglycerides (mg/dL)	0.999	0.992-1.005	.717
	HDL cholesterol (mg/dL)	0.982	0.963-1.001	.064
	Systolic pressure (mmHg)	0.997	0.977-1.017	.737
Model 2	Waist circumference (cm)	1.036	1.001-1.072	.044
	Blood glucose (mg/dL)	0.987	0.959-1.015	.345
	Triglycerides (mg/dL)	0.999	0.992-1.005	.736
	HDL cholesterol (mg/dL)	0.982	0.963-1.001	.064
	Diastolic pressure (mmHg)	0.995	0.969-1.022	.729

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein.
Model was adjusted for: model 1: age at a initial measurement, model 2: age at a initial measurement. *P* value: Binominal logistic regression analysis with dependent variable to use results obtained in the breast cancer screening.

Table 4. Association of metabolic syndrome factors over 2-year period on onset of mammary gland disease.

		ODDS RATIO	95% CI	*P* VALUE
Model 3	Change in waist circumference (cm)	1.020	0.953-1.090	.571
	Change in blood glucose (mg/dL)	0.982	0.940-1.020	.401
	Change in triglycerides (mg/dL)	0.999	0.991-1.010	.830
	Change in HDL cholesterol (mg/dL)	1.010	0.979-1.050	.445
	Change in systolic pressure (mmHg)	1.020	0.997-1.050	.085
Model 4	Change in waist circumference (cm)	1.010	0.948-1.090	.673
	Change in blood glucose (mg/dL)	0.978	0.937-1.020	.323
	Change in triglycerides (mg/dL)	0.999	0.990-1.010	.769
	Change in HDL cholesterol (mg/dL)	1.010	0.974-1.040	.631
	Change in diastolic pressure (mmHg)	1.040	0.998-1.080	.065

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein.

Model was adjusted for: model 3: age, waist circumference, blood glucose, triglycerides, HDL cholesterol, and systolic pressure at initial measurement; model 4: age, waist circumference, blood glucose, triglycerides, HDL cholesterol, and diastolic pressure at initial measurement. *P* value: Binominal logistic regression analysis with dependent variable to use results obtained in the breast cancer screening.

development.[21] As for mastopathy and fibroadenoma, benign mammary gland diseases, it is considered likely that associated inflammation is induced by a change in estrogen secretion by mammary gland epithelial cells.[22] When considering the present findings, it is possible that even benign mammary gland diseases are suppressed by the anti-inflammatory effect of HDL cholesterol.

Changes in systolic and diastolic blood pressure have been presumed to be risk factors for the development of mastopathy, but have not shown a significant association. However, this may be related to reactive oxygen species associated with elevated blood pressure. Hypertension is known to be a pathological condition associated with vascular endothelial disorder and one of its causes, and previous studies have shown that a variety of physiological active substances are produced in and secreted by vascular endothelium.[23,24] Once vascular endothelium becomes impaired, the balance of active oxygen is disrupted, resulting in breakdown of the vascular structure. Another study showed that oxidative reaction caused by active oxygen disturbed intravascular cells and the resultant oxidant stress elevated blood pressure,[25] while other findings indicated that a blood pressure increase causes further oxidant stress.[26] Furthermore, it is known that DNA undergoes oxidative damage caused by oxidant stress,[27,28] while others have shown that tetradecanoyl phorbol,

a carcinogen formed as a result of DNA damage, induces activation of breast cancer cells.[29-31] Therefore, it is likely that an increased concentration of active oxygen impairs mammary gland cells, leading to onset of mammary gland disease.

In this study, participants who received breast cancer screening and showed a mammography grade of 3 or higher underwent detailed examinations at Atami Hospital Department of Surgery, International University of Health and Welfare, Japan. Those results showed that approximately 12% of the category 3 participants and approximately 55.5% of those classified as category 4 had a malignant tumor, while the ratio of benign tumors was 60.5% for category 3 and 30% for category 4, indicating that category 3 cases are a mixture of benign and malignant tumors.[32] When a multifocal genetic mutation occurs in normal epithelial cells, they become precancer cells, and with excessive proliferation of those, a benign tumor is formed.[33] This study was not designed to clarify the mechanism of tumorigenesis from a benign to malignant tumor. However, based on our understanding that a benign tumor has the possibility of malignant alteration, we consider that careful examination of routine screening data of metabolic syndrome factors, such as waist circumference, blood pressure, and HDL cholesterol level, in participants with mammary gland disease graded as category 3 or higher might lead to effective treatments for control of breast cancer onset.

For this study, 2 accredited physicians provided the mammogram interpretations; thus, internal validity was considered high even though screening was performed with mammography alone. While potential confounders, such as smoking,[34] age at menarche,[35] physical activity,[36] and food type,[37] and gene (BRCA1/2),[38] have been noted, those were not considered as factors in this study and not included in the analysis. In a future study, we intend to include those items in the questionnaire to verify their relationship.

The physical constitution of the present participants was similar to that of participants of the same age in another survey conducted in Japan.[39] Furthermore, the measurements were approximately the same as those excluded from analysis. Accordingly, the results of the present study, at least from the viewpoint of physical constitution, are considered to be valid to represent young women in Japan. In addition, the participants were not inpatients at health care settings and care facilities, but rather those who voluntarily underwent health examinations. Because this study was a nonrandomized study of all women who underwent a health examination, it cannot be denied that it may include healthy people and people with high health consciousness. And recent studies have pointed out the relevance of ovarian stem cells in the treatment of breast cancer, which is expected not only to prevent but also to cure the above.[40-42]

On the contrary, a significant difference was noted between the analyzed participants and those excluded regarding systolic pressure. Because the mean age of those excluded was higher, it is likely that age was as a factor and possible that participants with higher blood pressure levels were excluded. The systolic pressure value of those excluded was 123.05 mmHg, while the standard value in diagnostic criteria for metabolic syndrome is 130 mmHg or lower. Whether systolic pressure had an effect on the present results is unknown, though that at the initial measurement was not associated with risk determination. Accordingly, we think that systolic pressure in the participants excluded from this analysis did not exert a significant effect on the results. When we used data from the present participants (n = 265) to conduct a cross-sectional survey of BMI and mammary gland disease, the odds ratio of BMI at the onset of mammary gland disease was found to be 1.08 (95% confidence interval: 0.998-1.18, $P = .056$). In the future, we intend to perform similar investigations with a longer follow-up period.

Conclusions

This was a longitudinal study of the association of metabolic syndrome factors (waist circumference, glucose, triglyceride, HDL cholesterol levels in blood, blood pressure) with development of mammary gland disease, including breast cancer using routine test data obtained for 265 participants who underwent breast cancer screening by mammography twice in a 2-year period from 2010 to 2013. A significant association of waist circumference with mammary gland disease was confirmed, as participants with greater waist circumference had an increased risk of mammary gland disease development. Furthermore, high levels of HDL cholesterol have been presumed to be a possible protective factor in the development of mammary gland disease, with a higher level found to lower the risk. Changes in systolic and diastolic blood pressure have been presumed to be risk factors for the development of mastopathy and it is likely that an increase in blood pressure over the 2-year period between examinations increased the risk of mammary disease. The results of the current longitudinal study showing an association between metabolic syndrome factors and risk of breast cancer in healthy individuals are considered to be useful to promote lifestyle-related improvements for preventing disease onset.

Declarations

Ethical Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and performed after receiving approval from the Hiroshima Welfare Ren Yoshida General Hospital Ethics Committee (approval number 201607). Informed consent was obtained from all individual participants included in the study. Each was given a full explanation of the study content and methods in advance, and their written consent was obtained. Obtained data and materials were used only for the present study, and are available only to researchers who participated in the study project.

Consent for Publication

None.

Author Contributions

TI developed the study protocol, and KN, SS, and MY obtained measurements and interview results. All authors contributed to writing the manuscript and TI revised the text. Each provided critical contributions to interpretation of the data and associated comments. The final version was approved by all of the authors.

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Availability of Data and Materials

None.

ORCID iD

Tadayuki Iida https://orcid.org/0000-0003-4934-3576

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