Table 1 Characteristics of the study participants

		N	%
Education level	Junior high school	3	0.8
	High school	96	25.5
	Junior college*	154	41.0
	University, graduate school	105	27.9
	No reply	18	4.8
Marital status	Married, living with a partner	280	74.5
	Unmarried, widow, divorced	78	20.7
	No reply	18	4.8
Work status	Employed	308	81.9
	Unemployed	49	13.0
	No reply	19	5.1
Study allocation**	Intervention group	198	52.7
	Control group	162	43.1
	No reply	16	4.3

The mean age of the participants was 43.8 years (SD = 3.1). *Junior college includes vocational school and technical college. **Participants were randomly assigned to the intervention group (screening by mammography and ultrasound) or control group (screening only by mammography) in the Japan STrategic Anti-cancer Randomized controlled Trial (J-START).

78.2 (95% CI, 68.6 to 87.8). Participants generally understood most question items well. However, the accuracy rates for some items were low. Specifically, there were accuracy rates of 14.6% for Question A4 on the "Experimental nature of study", 14.1% for Question A8 on "Potential risks or discomforts", 34.6% for Question A9 on "Benefit to self", and 33.0% for Question A13 on "Compensation".

Subjective understanding

The results of the subjective understanding (QuIC Part B) are shown in Table 3. The average QuIC Part B score was 82.2 (95% CI, 69.3 to 95.1). However, for Question B11 on "Compensation", "Who will pay for treatment if you are injured or become ill because of participation in J-START?", the combined percentage of participants who indicated that "I understood very well" and "I generally understood" was only 44.7%. For Question B6 on "Potential risks or discomforts", the total percentage of participants who indicated that "I understood very well" and "I generally understood" was 78.2%. This question item corresponded to Question A8 on "Potential risks or discomforts". It is worth noting that, although objective understanding of this item was low, subjective understanding was high.

Assessment of explanatory materials and information-providing procedures

In order to examine how various information-providing procedures used during the IC process related to participants' understanding, we asked participants about their prior knowledge and asked them to give their impression of the materials used for explanation and verbal description, and to evaluate each procedure (Table 4). Although informational leaflets explaining the trial had been mailed to the participants in advance, 279 (74.2%) indicated that they did not have any prior knowledge of J-START. The participants highly valued the informational leaflets and the educational videos explaining the trial. These were regarded as "Helpful for understanding" by 266 (70.7%) and 277 participants (73.7%), respectively. Three hundred and forty-six participants (92.0%) reported that their understanding had been confirmed by the research coordinator at the end of the oral description during the IC process. It would be expected that, at the time of that interaction, the research coordinator would become cognizant of the participant's questions and points of confusion, but we do not know what sort of communication took place later in this study. Only 10 participants (2.7%) indicated that they sought further explanation of the trial at that time.

Factors associated with low objective understanding

Table 5 shows the association between factors at the time of the IC process and the four objective understanding items with low accuracy rates; that is, A4, A8, A9, and A13 of QuIC Part A. The medical centre showed a correlation with two questions: Question A8 on "Potential risks or discomforts" ($P = 0.009$) and Question A13 on "Compensation" ($P < 0.0001$). The existence of prior knowledge of the RCT or J-START itself was statistically significant only for Question A4 on "Experimental nature of study", (RCT, $P = 0.002$; J-START, $P = 0.003$). The educational video showed a correlation with the two questions A8 on "Potential risks or discomforts" ($P = 0.003$) and A13 on "Compensation" ($P = 0.001$). Sufficient opportunity to ask a question showed correlations with Question A8 on "Potential risks or discomforts" ($P = 0.025$), Question A9 on "Benefit to self" ($P = 0.023$), and Question A13 on "Compensation" ($P = 0.049$), while enough time to achieve understanding showed correlations with Question A8 on "Potential risks or discomforts" ($P = 0.007$) and Question A13 on "Compensation" ($P = 0.013$). The atmosphere at the venue when the decision to participate was made showed correlations with Question A9 on "Benefit to self" ($P = 0.001$) and Question A13 on "Compensation" ($P = 0.043$), but for each case there was a low percentage of participants who felt the atmosphere made it hard to refuse to participate. No statistically significant correlation was found between the degree of understanding and the following factors: education level, marital status, work status, informational leaflet, whether the research staff confirmed whether the participant understood, or whether the participant wanted to ask further questions at the time of IC.

Table 2 Percentage of participants by QuIC Part A score: an objective understanding of J-START

		QuIC items	QuIC scores			No reply
			1	2	3	
A1.	Nature of research	When I signed the consent form for J-START, I knew that I was agreeing to participate in a clinical trial	0.3	5.6	92.6*	1.6
A2.	Purpose of research	The main goal of J-START is improving breast cancer screening for future generations	0.0	2.7	95.7*	1.6
A3.	Duration of procedures	I have been informed about the duration of J-START	4.8	30.3	63.3*	1.6
A4.	Experimental nature of study	All tests in J-START are standardized	14.6*	26.1	57.5	1.9
A5.	Purpose of research	The major purpose of J-START is to assess the effectiveness of ultrasound screening for breast cancer among Japanese women aged 40–49 years	1.1	10.6	86.7*	1.6
A6.	Purpose of research	Neither the mammography screening nor the combined use of mammography and ultrasound screening have been proven as the best screening method for Japanese women aged 40–49 years	0.8	25.3	72.3*	1.6
A7.	Procedures to be followed	After I agreed to participate in J-START, my examination was chosen randomly between mammography screening or combined use of mammography and ultrasound screening	1.9	11.4	85.1*	1.6
A8.	Potential risks or discomforts	Compared with standard breast cancer screening, J-START does not carry any additional risks or discomforts	14.1*	35.6	48.7	1.6
A9.	Benefits to self	I might not receive any direct medical benefits from my participation in J-START	25.5	38.3	34.6*	1.6
A10.	Benefits to others	By participating in J-START, I am helping the researchers gather information that might benefit future breast cancer screening procedures	0.3	10.4	87.8*	1.6
A11.	Confidentiality	Because I am participating in a clinical trial, it is possible that the study sponsor, various government agencies, or others who are not directly involved in my care will review my medical records	3.7	33.2	61.4*	1.6
A12.	Alternatives to participation	My doctors did not offer me any alternative breast cancer screening procedures beyond J-START.	87.8*	9.3	1.3	1.6
A13.	Compensation	The consent form I signed indicates who will pay for treatment if I am injured or become ill as a result of participation in this clinical trial	14.9	50.3	33.0*	1.9
A14.	Study contacts	The informed consent form listed study contact persons	4.8	19.7	73.7*	1.9
A15.	Voluntary nature of participation	If I had not wanted to participate in this clinical trial, I could have declined to sign the consent form	1.1	11.4	85.6*	1.9
A16.	Voluntary nature of participation	I must remain in the clinical trial, even if I decide that I would like to withdraw someday	60.1*	30.1	8.2	1.6

Quality of Informed Consent (QuIC) is a scale for assessing participants' understanding of clinical trials. Part A assesses objective understanding and Part B assesses subjective understanding. QuIC Part A possible responses are 1 (quite disagree), 2 (unsure) and 3 (totally agree) [6]. *Correct answer. J-START, Japan STrategic Anti-cancer Randomized controlled Trial.

Discussion

The present study aimed to evaluate the degree of participants' understanding of an RCT and investigate the associated factors. We administered questionnaires to 376 healthy Japanese women on the day of enrolment at five study sites using a Japanese version of the QuIC. Although healthy volunteers generally well understood J-START, there were some domains in need of improvement. Until the present study, there have been no reports on either the understanding of an RCT targeting the general population of healthy women or reports concerning evaluations using international and validated scales in Japan. The present study has demonstrated hints of improvement in the IC process in an RCT that targeted the general population of healthy people. The participants generally provided correct responses to the majority of the questions. Furthermore, the QuIC scores in the present survey were comparable to the scores in the preceding studies [14-16,18]. The results of the present study revealed a tendency for the degree of subjective understanding to be higher than the degree of objective understanding, which is similar to the findings of earlier studies. The higher degree of subjective understanding can be thought to be related to the ease of understanding the IC and/or a feeling of satisfaction with the amount of information, but the reason for discrepancy with the degree of objective understanding warrants further study. Thus, the purpose of IC seems to have largely been achieved. However, among the items specified by the US Federal Regulation (Chapter 45, Part 46) that should be explained to individuals eligible for participation in a clinical trial, "Experimental nature of study", "Potential risks or discomforts", "Benefit to self", and "Compensation" were not correctly understood by some participants. In previous studies, "Experimental nature of study" [1,8,14,18], "Potential risks or discomfort"

Table 3 Percentage of participants by QuIC Part B score: a subjective understanding of J-START

		QuIC questions	QuIC scores					No reply
			1	2	3	4	5	
B1.	Nature of research	This breast cancer screening involves a research component	1.1	2.1	3.7	39.6	51.6	1.9
B2.	Purpose of research	What the researchers are trying to understand in J-START	0.3	1.1	1.6	36.7	59.0	1.3
B3.	Duration of procedures	How long you will be in J-START	1.9	7.2	9.0	33.8	46.8	1.3
B4.	Procedures to be followed	The tests and procedures you will undergo	1.1	0.8	2.7	30.6	62.2	2.7
B5.	Experimental nature of study	Which of these tests and procedures are experimental	1.1	4.3	7.5	38.6	39.4	9.3
B6.	Potential risks or discomforts	The potential risks or discomforts associated with participating in J-START	1.9	4.5	13.8	34.8	43.4	1.6
B7.	Benefits to self	The potential benefit to you for participating in J-START	2.1	1.9	14.4	42.0	37.8	1.9
B8.	Benefits to others	How your participation in this clinical trial might benefit future patients	0.3	0.3	2.4	31.4	64.1	1.6
B9.	Alternatives to participation	The alternative to participation in the clinical trial	0.8	1.3	6.4	28.5	61.4	1.6
B10.	Confidentiality	The effect of clinical trial participation on the confidentiality of your medical records	0.5	0.0	3.2	30.1	64.9	1.3
B11.	Compensation	Who will pay for treatment if you are injured or become ill due to participation in J-START	14.9	19.4	18.4	21.8	22.9	2.7
B12.	Study contacts	Whom you should contact if you have questions or concerns regarding J-START	4.5	6.4	11.7	31.9	43.9	1.6
B13.	Voluntary nature of participation	The fact that participation in J-START is voluntary	0.5	0.3	0.3	17.8	79.8	1.3
B14.	Overall	Overall, how well did you understand your specified clinical trial when you signed the consent form?	0.8	2.4	4.5	65.7	25.3	1.3

Quality of Informed Consent (QuIC) is a scale for assessing participants' understanding of clinical trial procedures. Part A assesses objective understanding and Part B assesses subjective understanding [6]. QuIC Part B responses were as follows: 1 for "did not understand", 2 for "almost did not understand", 3 for "neither understood nor didn't understand", 4 for "generally understood", and 5 for "understood very well". J-START, Japan STrategic Anti-cancer Randomized controlled Trial.

[8,14,18,20],"Benefit to self" [5], and "Compensation" [14,18] were reported to be difficult for participants to understand. Therefore, strategies need to be developed to facilitate better understanding of these items among participants.

It is necessary to consider the current status of breast cancer screening in Japan, giving consideration to these three factors: "Experimental nature of the study", "Potential risks or discomforts", and "Compensation". Regarding "Experimental nature of the study" and "Potential risks or discomforts", because of the comfort level and familiarity derived from the fact that ultrasonography is a well-known method, participants are unlikely to understand that a trial is conducted due to the lack of any established intervention, and that there are potential risks or discomforts involved. Moreover, regarding "Compensation", participants might not have paid attention to the explanation of compensation for any problems about intervention. Mammography, which is currently used for breast cancer screening, is known to sometimes cause pain from the compression of a breast, as well as minor exposure to x-rays during imaging. Ultrasonography is generally perceived to be more comfortable than mammography. Therefore, it might be difficult to imagine that health problems could be caused by ultrasonography. Moreover, because breast ultrasonography has already been employed as a breast cancer screening method for opportunistic screening (for example, complete physical examination), a perception of this procedure as a well-established screening method might not reflect the true situation. In fact, scientific evidence for breast ultrasonography as a method for mass screening has remained under investigation in J-START since 2007. Because the procedure has been employed as an effective screening method in routine practice in breast surgery departments, the present survey might have included participants who had previously undergone ultrasonography as a component of their medical care.

There were three possible reasons for participants' misunderstanding of IC, which have been referenced in previous studies. First, the explanatory materials might have been difficult to understand [21,22]. Second, the comprehension ability of participants might have been insufficient [4,23]. Third, the information-providing procedures used during the IC process might have varied between medical centres [9].

First, in relation to difficult explanatory materials, well-considered wording [22] and explanations using

Table 4 Questionnaire on participants' impression of the informed consent process

Item	Categories	N	%
Prior knowledge			
Did you know about "RCTs" before participating in J-START?	Yes	108	28.7
	No	268	71.3
Did you know about J-START before the informed consent procedure?	Yes	97	25.8
	No	279	74.2
Helpfulness of media			
Did the information leaflet help you understand J-START?	Helpful	266	70.7
	Unsure	62	16.5
	No	48	12.8
Did the educational video help you understand J-START?	Helpful	277	73.7
	Unsure	25	6.7
	No	74	19.7
Evaluations of the verbal delivery of the information during the informed consent procedure			
Did the research staff confirm your understanding?	Yes	346	92.0
	Unsure	17	4.5
	No	9	2.4
	Missing	4	1.1
Did you need further information?	Yes	10	2.7
	Unsure	58	15.4
	No	299	79.5
	Missing	9	2.4
I had sufficient opportunity to ask questions	Yes	338	89.9
	Unsure	14	3.7
	No	20	5.3
	Missing	4	1.1
I had enough time to understand information	Yes	259	68.9
	Unsure	102	27.1
	No	12	3.2
	Missing	3	0.8
Did you find it easy to refuse participation?	Yes	285	75.8
	Unsure	60	16.0
	No	23	6.1
	Missing	8	2.1

J-START, Japan STrategic Anti-cancer Randomized controlled Trial; RCT, randomized controlled trial.

written, paper-based information (for example, leaflets and booklets) appear to improve understanding of RCTs [21]. Further, it is preferable to provide information with a combination of several materials [24]. When we prepared the informational leaflets and the educational video, we sought to use simple words and considered a combination of materials. The resultant material was also approved by the institutional ethical review board. As shown in Table 4, the majority of the participants indicated that the explanatory materials were "Helpful for understanding". This demonstrates that the explanatory materials were perceived to be sufficiently easy to understand. Table 5 indicates that prior knowledge influenced misunderstanding of "Experimental nature of the study", but prior knowledge had not always been given by our leaflet, and the educational video did not help correct misconceptions. In a study simulating a situation in which children and their parents undergo the IC process, it was reported that multimedia materials with visual and auditory information are preferable to paper-based information and could be expected to improve understanding, particularly among parents [25]. Other studies have indicated that a simplified IC form with emphasis added by verbal description [26], and user testing, which examines not only the wording of leaflets, but also the layout and paper thickness, in order to design interesting materials for participants to read, leads to improved explanatory materials and better understanding [27]. However, in systematic reviews of understanding of RCTs [28] and of trials and ICs [29], it was reported that multimedia informational materials were not as effective for improving participants' understanding as test-feedback quizzes or discussion of the IC process [28,29]. The result of our survey corroborated the systematic reviews. Improving face-to-face communication would foster better understanding than improving written materials.

Second, regarding the comprehension ability of participants, approximately 70% of the participants in the present study graduated from vocational school, junior college, or above (Table 1). Because the illiteracy rate in Japan is low due to the 9 years of mandatory education, insufficient comprehension ability is an unlikely explanation.

Regarding the third possible reason for participants' misunderstanding of IC, there were, unfortunately, significant gaps or inconsistencies between the IC information-providing procedures of the different medical centres (Table 5). Regrettably, we did not have the data on how IC was obtained from each of the participants. For the standardized information dissemination process in J-START, the manual included specific procedures concerning IC and the use of materials, and held several training sessions for the research coordinators, who had previous experience working at a medical centre (for example, nurses and public health nurses). To avoid misconceptions arising from verbal communication, explanatory materials were also integrated into the IC process. Despite this, a certain number of participants reported as being unsure about these materials. However, we did not have the IC process data, and it was not clear that the process was lost or the participants did not read or watch. Given that explanatory materials are reported to improve participants' understanding [8], the differences in understanding observed in the present study might be attributable to insufficient use

Table 5 Factors associated with low comprehension scores of QuIC Part A items

	A4. Experimental nature of study				A8.Potential risks or discomforts				A9. Benefit to self				A13. Compensation			
	Quite disagree*	Unsure	Totally agree	*P*	Quite disagree*	Unsure	Totally agree	*P*	Quite disagree	Unsure	Totally agree*	*P*	Quite disagree	Unsure	Totally agree*	*P*
Medical centres																
Site A	3.5%	7.1%	12.7%	0.54	3.0%	6.5%	13.8%	0.009	5.7%	8.7%	8.9%	0.927	0.8%	6.5%	16.0%	<0.0001
Site B	1.1%	3.3%	5.4%		2.7%	4.1%	3.0%		3.2%	3.5%	3.0%		2.2%	6.0%	1.6%	
Site C	6.5%	9.2%	22.2%		4.3%	14.3%	19.2%		9.2%	14.6%	14.1%		7.6%	21.7%	8.7%	
Site D	3.0%	4.1%	8.9%		3.5%	6.8%	5.7%		3.8%	7.0%	5.1%		1.6%	9.8%	4.6%	
Site E	0.8%	3.0%	9.2%		0.8%	4.6%	7.8%		4.1%	5.1%	4.1%		3.0%	7.3%	2.7%	
Prior knowledge: had you known about "RCTs" before you took part in J-START?																
Yes	6.2%	9. 8%	13.0%	0.002	5.4%	10.5%	13.0%	0.266	6.5%	11.9%	10.5%	0.613	4.1%	16.0%	8.9%	0.629
No	8.7%	16.8%	45.5%		8.9%	25.7%	36.5%		19.5%	27.0%	24.6%		11.1%	35.2%	24.7%	
Prior knowledge: had you known about J-START before the informed consent?																
Yes	6.5%	7.1%	12.5%	0.003	3.5%	8.7%	13.8%	0.703	6.2%	11.4%	8.4%	0.529	4.1%	13.8%	8.1%	0.851
No	8.4%	19.5%	46.1%		10.8%	27.6%	35.7%		19.7%	27.6%	26.8%		11.1%	37.4%	25.5%	
Helpfulness of media: Educational video was an aid to understanding J-START																
Yes	9.8%	19.8%	44.2%	0.538	9.5%	24.6%	39.5%	0.003	19.2%	27.0%	27.3%	0.517	9.2%	35.5%	29.0%	0.001
No	1.1%	1.4%	4.1%		0.3%	4.3%	2.2%		1.4%	3.5%	1.9%		1.1%	4.3%	1.1%	
Unsure	4.1%	5.4%	10.3%		4.6%	7.3%	7.8%		5.4%	8.4%	6.0%		4.9%	11.4%	3.5%	
Evaluations of the verbal delivery of the information: I had sufficient opportunity to ask questions																
Yes	14.1%	23.9%	51.8%	0.411	14.1%	30.8%	44.9%	0.025	25.1%	33.5%	31.1%	0.023	13.3%	44.4%	32.0%	0.049
No	0.8%	2.7%	6.8%		0.3%	5.4%	4.6%		0.8%	5.4%	4.1%		1.9%	6.8%	1.6%	
Evaluations of the verbal delivery of the information: I had enough time to understand information																
Yes	9.8%	17.9%	40.7%	0.828	9.2%	21.6%	37.6%	0.007	18.1%	25.7%	24.6%	0.729	9.2%	32.8%	26.3%	0.013
No	5.2%	8.7%	17.9%		5.1%	14.6%	11.9%		7.8%	13.2%	10.5%		6.0%	18.4%	7.3%	
Evaluations of the verbal delivery of the information: Did you find it easy to say no?																
Yes	11.7%	18.7%	45.0%	0.409	10.5%	25.4%	39.5%	0.137	22.4%	25.7%	27.3%	0.001	13.0%	36.0%	26.3%	0.043
No	3.3%	7.9%	13.6%		3.8%	10.8%	10.0%		3.5%	13.2%	7.8%		2.2%	15.2%	7.3%	

*Correct answer. J-START, Japan STrategic Anti-cancer Randomized controlled Trial; RCT, randomized controlled trial.

of the materials. A previous systematic review reported that having a long discussion time with a team member and a neutral educator was effective for participants' understanding, and it worked even over the telephone [29]. In J-START, this type of discussion was not programmed officially. If we could have had the opportunity to include such a discussion, IC and accompanying materials might have been delivered more effectively. In order to more effectively perform the IC process, we must create opportunities for the team members to have frequent discussions with the educator, with the topic of discussion to include better information-providing procedures.

A limitation of the present study was that not all of the J-START study sites were included. However, the validity of the QuIC was evaluated and the reliability of the questionnaire was tested. Significantly more participants in the intervention group returned the questionnaires than in the control group. Therefore, the present findings were not derived from random sampling with respect to which participants received an explanation of J-START. Unfortunately, we had to use the most convenient sampling method, and could not collect data on non-responders without authorization.

Conclusions

Healthy volunteers generally well understood the RCT in which they participated. The results of the present study suggest that when an RCT on a minimally invasive intervention is conducted, both the researchers who provide explanations and the participants might neglect the following four items: the fact that interventions under investigation have not been standardized, the possible benefits and disadvantages of participating in the trial, and compensation in case of injury resulting from participation. In order to facilitate participants' understanding, it is necessary to provide training for the research team members to reduce differences in information-providing procedures between medical centres and to endeavour to provide consistent information and conditions.

Abbreviations

IC: informed consent; J-START: Japan STrategic Anti-cancer Randomized controlled Trial; QuIC: Quality of Informed Consent; RCT: randomized controlled trial.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YNS and YFZ co-conceived the study, designed the protocol, conducted research and performed data collection, and YNS drafted the manuscript. YFZ and MKi participated in the design of the study and performed the statistical analysis. MKi, MKa, TI, SK, and NO helped to draft the manuscript. NO supervised all aspects of this study. All authors read and approved the final manuscript. YNS and YFZ contributed equally to this work.

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Author details

[1]Division of Surgical Oncology J-START research unit, Tohoku University Graduate School of Medicine, 2-1, Seiryo-machi, Aoba-ku, Sendai, Japan. [2]Division of Molecular Epidemiology, Tohoku University Graduate School of Medicine, 2-1, Seiryo-machi, Aoba-ku, Sendai, Japan. [3]Department of Advanced Breast Cancer Imaging, Tohoku University Graduate School of Medicine, 2-1, Seiryo-machi, Aoba-ku, Sendai, Japan. [4]Department of Preventive Medicine and Epidemiology, Tohoku Medical Megabank Organization, Tohoku University, 2-1, Seiryo-machi, Aoba-ku, Sendai, Japan. [5]Department of Breast Oncology, Miyagi Cancer Centre Hospital, 47-1 Nodayama, Medeshima-Shiode, Natori, Miyagi, Japan. [6]Division of Molecular Epidemiology, Environment and Genome Research Centre, Tohoku University Graduate School of Medicine, 2-1, Seiryo-machi, Aoba-ku, Sendai, Japan. [7]Division of Disaster Public Health, International Research Institute for Disaster Science, Tohoku University Graduate School of Medicine, 2-1, Seiryo-machi, Aoba-ku, Sendai, Japan.

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Original Article

Height, Body Mass Index (BMI), BMI Change, and the Risk of Estrogen Receptor-Positive, HER2-Positive, and Triple-Negative Breast Cancer Among Women Ages 20 to 44 Years

Masaaki Kawai, MD, PhD; Kathleen E. Malone, PhD; Mei-Tzu C. Tang, PhD; and Christopher I. Li, MD, PhD

BACKGROUND: The evidence regarding correlations between various anthropometric characteristics and breast cancer risk among young women is mixed, and few studies have assessed these associations by subtype. **METHODS:** This was a population-based, case-control study of 779 women with estrogen receptor (ER)-positive breast cancer; 182 women with ER-negative/human epidermal growth factor-2 (HER2)-negative/progesterone receptor-negative (triple-negative [TN]) breast cancer; and 60 women with ER-negative/HER2-overexpressing, invasive breast cancer ages 20 to 44 years who were diagnosed from 2004 to 2010 in the Seattle-Puget Sound metropolitan area; as well as 939 cancer-free controls. Associations between height and body mass index (BMI) at different time points in relation to breast cancer risk were assessed using polytomous logistic regression. **RESULTS:** Height, BMI at age 18 years, and BMI at the reference date were not related to the risks of ER-positive, TN, or HER2-overexpressing breast cancer. Changes in BMI from age 18 years to the reference date were not related to the risk of either ER-positive or HER2-overexpressing breast cancer. However, compared with women who had a BMI change from 0 to 4.9 kg/m^2 from age 18 years to the reference date, those who experienced a BMI increase ≥10 kg/m^2 during the same interval had a 2.0-fold (95% confidence interval, 1.2-fold to 3.3-fold increase) increased risk of TN breast cancer. For women with ER-positive disease, there was some evidence that parity modified the effect of BMI change ($P_{interaction}$ = .002), because a BMI increase of ≥10 kg/m^2 was associated with a reduced risk of ER-positive disease only among nulliparous women (odds ratio, 0.3; 95% confidence interval, 0.2-0.6). **CONCLUSIONS:** The correlations appear to differ substantially between BMI change and the risks of TN breast cancer and ER-positive breast cancer. ***Cancer*** **2014;120:1548-56.** © *2014 American Cancer Society.*

KEYWORDS: breast cancer, height, body mass index, estrogen receptor, triple-negative, premenopausal.

INTRODUCTION

The correlations between anthropometric factors and breast cancer risk have been studied extensively among young women.[1] Briefly, height is positively associated[2,3] and body mass index (BMI) is negatively associated[3,4] with the risk of breast cancer among premenopausal women. Fewer studies have evaluated the impact of weight gain, but, of those that focused on young women, four[5-8] of the five[4-8] studies observed no relation between weight gain and breast cancer risk. However, among the studies that evaluated associations between BMI,[9-19] height,[9,12,15,16] and the risk of different breast cancer subtypes defined by joint estrogen receptor (ER)/progesterone receptor (PR) status, the majority observed no association between BMI and the risk of either ER-positive/PR-positive[9-14] or ER-negative/PR-negative[9-19] breast cancer, and no association was observed between height and the risk of either ER-positive/PR-positive[9,12,16] or ER-negative/PR-negative[9,12,16] breast cancer. Six studies evaluated associations between anthropometric factors and the risk of different breast cancer subtypes defined by ER/PR and human epidermal growth factor receptor 2 (HER2-*neu* [HER2]) status among young women.[20-25] Those studies yielded inconsistent results, and 5 of the 6 studies were hindered by small sample sizes, with the numbers of ER-negative/PR-negative/HER2-negative (triple-negative [TN]) women who were included ranging from only 19 to 119.[20-24] The largest study included 187 TN women and observed no association between BMI and the risk of TN breast cancer.[25] Given the distinct biologies of different breast cancer subtypes, they also likely have unique etiologies,[26,27] and prior studies have identified differences in magnitudes and directions in risk associated with various reproductive and lifestyle characteristics across molecular subtypes of breast cancer.[28,29] Studying potentially modifiable risk factors for these cancers in young women is particularly important, given that the proportions of 2 of the more aggressive subtypes, TN and HER2-overexpressing (ER-negative/HER2-positive) breast cancers, are inversely associated with

Corresponding author: Masaaki Kawai, MD, PhD, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., M4-C308, Seattle, WA 98109; Fax: (206) 667-5948; mkawai@fhcrc.org

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington

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age.[21] Toward this goal, we evaluated the associations between height, BMI, and BMI change and the risk of different molecular subtypes of breast cancer in a population-based, case-control study of women ages 20 to 44 years.

MATERIALS AND METHODS

The design and methods used in this population-based, case-control study have been described previously.[30] Briefly, the study was designed specifically to characterize risk factors for breast cancer among young women who were diagnosed with invasive breast cancer between January 2004 and June 2010. Eligible cases were women ages 20 to 44 years who had no prior history of in situ or invasive breast cancer and were living in the 3-county Seattle-Puget Sound metropolitan area (King, Pierce, and Snohomish counties). Potentially eligible cases were identified thorough the Cancer Surveillance System, the population-based tumor registry that serves the 13 counties of western Washington state and participates in the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Of the 1359 eligible cases identified, 1056 women (78%) were interviewed. Of those who were not enrolled (n = 303), 82% refused to be interviewed, 10% could not be located, and 8% died before the interview could be conducted. We obtained basic information on breast cancer diagnosis and a variety of tumor characteristics from the cancer registry and from a centralized review of pathology reports. That review included the collection of data on tumor histology and disease stage and on ER, PR, and HER2 status. Positive ER and PR status was defined as positive staining of $\geq$1% of cells and negative staining of 0% to <1% of positive cells. Positive HER2 status was based on an immunohistochemistry (IHC) score of 3+ and/or a fluorescence in situ hybridization (FISH)-positive result, and negativity was defined as an IHC score of 0 or 1+ and/or a FISH-negative result. Cases with a 2+ HER2 IHC result without a FISH result were considered to have unknown HER2 status. This information was used to group cases into 3 defined groups: ER-positive (approximating the luminal A and B subtypes), ER-negative/HER2-positive (HER2-overexpressing type), and ER-negative/PR-negative/HER2 negative (triple-negative [TN], approximating the basal-like subtype and unclassified). This approach has been used in our previous work.[30] The 28 cases (2.7%) for whom data on ER, PR, and/or HER2 status were missing were excluded.

We used a combination of list-assisted (purchased, randomly generated telephone numbers) and Mitofsky-Waksberg (telephone numbers randomly generated ourselves using a clustering factor of 5)[31] random digit dialing methodologies to identify potential controls from the general population of female residents of King, Pierce, and Snohomish counties. Women in the control group were frequency matched within 5-year age groups to women in the case group using 1-step recruitment. Of the 1489 eligible controls identified, 943 (63%) were interviewed by this method.

Data Collection

The study protocol was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board, and written informed consent was obtained from all study participants. Cases and controls were interviewed in their homes by a trained interviewer and were asked about their reproductive history, demographics, physical activity, alcohol drinking, cigarette smoking, medical history, history of breast cancer screening, and family history of breast cancer. In addition, women were queried regarding their weight at age 18 years (not counting times when women were pregnant or nursing), height, and weight 1 year before their reference date. Our questioning was limited to exposures that occurred before each participant's reference date. The reference date/age used for each woman with breast cancer was her diagnosis date/age. Control reference dates/ages were assigned to reflect the expected distribution of reference dates/ages among the cases. The mean time between the reference date and the interview date was 18 months for cases and 20 months for controls, and the median times were 16 months and 19 months, respectively. This was consistent with our goal of trying to interview women within 2 years of their reference date. Data on height were missing for 4 controls and 7 cases (5 ER-positive and 2 TN cases). Therefore, our final analytic data set consisted of 939 controls, 779 ER-positive cases, 60 ER-negative/HER2-positive cases, and 182 TN cases.

Statistical Analysis

Our primary exposures of interest were height at reference age, BMI at age 18 years, BMI at reference date, and change in BMI from age 18 years to the reference date. Weight at reference age (in kg) was the weight 1 year before the reference age. Height and weight also were measured at the time of the interview by the trained interviewer. We used measured values of height at the time of the interview and self-reported values of weight at the reference age and weight at age 18 years to calculate exposures. When physically measured height at the interview

was not available, self-reported height was used (n = 111 cases, n = 132 controls). When self-reported weight at reference age was not available, physically measured weight at the interview was used (n = 113 cases, n = 150 controls). BMI at the reference age (in kg/m^2) was calculated as weight 1 year before reference date (kg) divided by height squared at reference age (meters). BMI at age 18 years (kg/m^2) was calculated as weight at age 18 years (kg) divided by height squared at reference age (meters). A high level of correlation was observed between self-reported and physically measured anthropometric characteristics (continuous variables: height, Spearman correlation [r] = 0.96; weight, r = 0.88; quartile categorizations: height, r = 0.91; weight, r = 0.85). For height, BMI at age 18 years, and BMI at reference age, our primary analysis was based on the quartile distributions of these anthropometric characteristics among our control population, in which the lowest quartile served as the reference category. In addition, for BMI at reference date, we evaluated risk according to clinically relevant categories (BMI $\leq$24.9 kg/m^2, 25.0-29.9 kg/m^2, or $\geq$30.0 kg/m^2). We did not use these same categories for BMI at age 18 years because there were few obese women (n = 20 controls, n = 18 cases). For BMI change from age 18 years to the reference date, we grouped women into 4 categories (BMI change: <0.0 kg/m^2, 0.0-4.9 kg/m^2, 5.0-9.9 kg/m^2, or $\geq$10.0 kg/m^2), in which those in the BMI change category 0.0 to 4.9 kg/m^2 served as the reference group. These evenly spaced categories were selected for ease of interpretation. We used polytomous logistic regression to calculate odds ratios (ORs) and their associated 95% confidence intervals (CIs) to compare ER-positive, TN, and ER-negative/HER2-positive breast cancer cases versus controls. All analyses were conducted using Stata/SE version 13 (StataCorp LP, College Station, Tex). All models were adjusted for age (in 5-year categories) and reference year (continuous), because controls were matched to cases on these factors. Several potential confounders and effect modifiers of the relation between each anthropometric factor and breast cancer risk were assessed, including race/ethnicity, education, first-degree family history of breast cancer, duration of oral contraceptive use, parity number, age at first live birth among parous women, age at menarche, alcohol consumption, smoking history, physical activity, and mammography screening history. Age at first live birth and race/ethnicity changed our risk estimates by greater than 10% when added to the model; so our final statistical models were adjusted for age, reference year, age at first live birth, and race/ethnicity. Parity was identified as a statistically significant effect modifier of the relation between BMI change and the risk of ER-positive breast cancer based on likelihood ratio testing (P values for interaction [$P_{interaction}$]< .05 for ER-positive breast cancer). In the analysis that was stratified by parity, we collapsed women with BMI changes of <0.0 kg/m^2 and changes from 0.0 to 4.9 kg/m^2 into a single category, and those in the $\leq$4.9 kg/m^2 category served as the reference group. P values for trend were (P_{trend}) calculated by treating each categorical variable as an ordered, continuous variable. In addition, estimates of trend for continuous values were calculated by treating each variable as a continuous variable. For BMI change from age 18 years to reference age, the trend calculated was limited to those whose BMI stayed the same or increased over this interval. We conducted Wald tests to estimate case-case differences in risk between our ER-positive and TN case groups.

RESULTS

Compared with women in the control group, women in the case groups as a whole were less likely to be non-Hispanic white and were more likely to have a first-degree family history of breast cancer, to be nulliparous, and to ever have had a screening mammogram (Table 1). Compared with the ER-positive women, the TN women were somewhat more likely to be younger, to be African American, and to have a younger age at first live birth; and they were less likely to have graduate or professional school education and to ever have had a screening mammogram. The HER2-positive women were more likely to be younger, to have a younger age at first live birth, and to never have had a screening mammogram.

There was some suggestion that women in the upper 3 height quartiles had slightly elevated risks of ER-positive breast cancer and slightly decreased risks of HER2-positive breast cancer compared with women in the lowest height quartile, but neither trend was statistically significant (Table 2). There was some suggestion that women in the upper 3 BMI quartiles at age 18 years had decreased risks of TN breast cancer compared with women in the lowest BMI quartile, but this trend also was not statistically significant. In contrast, a BMI change from age 18 years to the reference date of $\geq$10.0 kg/m^2 was associated with a 2.0-fold (95% CI, 1.2-3.3) increased risk of TN breast cancer (P_{trend} = .02), but not with the risk of either ER-positive or ER-negative/HER2-positive breast cancer. When analyzed on a continuous scale, BMI change from age 18 years to the reference date was associated with an increased risk of TN breast cancer per 1.0 kg/m^2-unit increase in BMI (OR, 1.07; 95% CI, 1.02-1.11).

TABLE 1. Distribution of Selected Characteristics Among Controls and Cases and Among Estrogen Receptor (ER)-Negative/Progesterone Receptor (PR)-Negative/Human Epidermal Growth Factor Receptor 2 (HER2)-Negative, ER-Negative/HER2-Positive, and ER-Positive Breast Cancer Subtypes

						Subtypes						
	Controls, n = 940		Total Cases, n = 1021			ER−/ PR−/ HER2−, n = 182		ER−/ HER2+, n = 60		ER+, n = 779[a]		
Characteristic	No.	%	No.	%	*P*[b]	No.	%	No.	%	No.	%	*P*[b]
Age, y												
20-29	25	3	24	2		7	4	2	3	15	2	
30-34	86	9	83	8		22	12	6	10	55	7	
35-39	267	28	279	27		58	32	22	37	199	26	
40-44	562	60	635	62	.7	95	52	30	50	510	66	.03
Reference y												
2004-2005	306	33	290	28		61	34	17	28	212	27	
2006-2007	361	38	356	35		57	31	25	42	274	35	
2008-2010	273	29	375	37	.001	64	35	18	30	293	38	.007
Race/ethnicity												
Non-Hispanic white	768	82	798	79		142	78	48	80	608	79	
African American	34	4	53	5		17	9	4	7	32	4	
Asian/Pacific Islander	82	9	119	12		14	8	6	10	99	13	
Native American	19	2	27	3		7	4	1	2	19	2	
Hispanic white	35	4	19	2	.01	2	1	1	2	16	2	.003
Missing	2		5			0		0		5		
Education												
≤High school	98	10	121	12		24	13	8	13	89	11	
>High school/some college	306	33	335	33		65	36	16	27	254	33	
College graduate	354	38	375	37		69	38	23	38	283	36	
Graduate/professional school	181	19	190	19	.8	24	13	13	22	153	20	.7
Missing	1		0			0		0		0		
First-degree family history of breast cancer												
No	815	90	790	80		140	79	48	81	602	80	
Yes	92	10	198	20	<.001	38	21	11	19	149	20	<.001
Missing	33		33			4		1		28		
Duration of oral contraceptives use, y												
Never	103	11	118	12		15	8	11	18	92	12	
<5.0	338	36	362	36		59	33	22	37	281	36	
5.0-9.9	218	23	206	20		39	22	11	18	156	20	
≥10	278	30	328	32	.4	66	37	16	27	246	32	.4
Missing	3		7			3		0		4		
Parity, no.												
Nulliparous	191	20	270	26		50	27	11	18	209	27	
1	194	21	206	20		34	19	14	23	158	20	
2	366	39	374	37		68	37	23	38	283	36	
≥3	189	20	170	17	.01	30	16	12	20	128	16	.1
Missing	0		1			0		0		1		
Age at first live birth among parous women, y												
<25	219	29	242	32		57	43	17	35	168	30	
25-29	225	30	243	32		35	27	20	41	188	33	
30-34	205	27	181	24		30	23	8	16	143	25	
≥35	100	13	83	11	.2	10	8	4	8	69	12	.04
Missing	0		1			0		0		1		
Age at menarche, y												
<12	190	20	225	22		44	24	11	18	170	22	
12-13	521	55	581	57		100	55	42	70	439	56	
≥14	227	24	214	21	.2	38	21	7	12	169	22	.2
Missing	2		1			0		0		1		
Alcohol consumption, average no. of alcohol drinks/wk												
Never	227	24	243	24		45	25	23	38	175	23	
0-1.4	234	25	238	23		34	19	15	25	189	24	

TABLE 1. *Continued*

Characteristic	Controls, n = 940		Total Cases, n = 1021			Subtypes: ER−/PR−/HER2−, n = 182		ER−/HER2+, n = 60		ER+, n = 779[a]		
	No.	%	No.	%	P^b	No.	%	No.	%	No.	%	P^b
1.4-3.7	235	25	254	25		49	27	9	15	196	25	
≥3.7	237	25	278	27	.7	53	29	13	22	212	27	.2
Missing	7		8			1		0		7		
Smoking status at reference date												
Never	639	68	648	64		111	61	42	70	495	64	
Current	139	15	170	17		37	20	10	17	123	16	
Former	160	17	202	20	.1	34	19	8	13	160	21	.2
Missing	2		1			0		0		1		
Physical activity, average h of any physical activity at reference age/wk												
0	448	48	485	48		87	48	31	52	367	47	
≤4	319	34	359	35		72	40	21	35	266	34	
>4	171	18	175	17	.8	22	12	8	13	145	19	.4
Missing	2		2			1		0		1		
Ever had a screening mammogram												
Never	478	51	433	42		84	46	34	57	315	40	
Ever	462	49	588	58	<.001	98	54	26	43	464	60	<.001

Abbreviations: −, negative; +, positive.
[a] These were patients who had ER-positive breast cancer regardless of PR/HER2 status.
[b] *P* values were determined with the chi-square test.

Parity modified the association between BMI change and the risk of ER-positive breast cancer ($P_{interaction}$ = .002) (Table 3). Nulliparous women and women whose BMI increased by 5.0 to 9.9 kg/m^{2}or by ≥10 kg/m^2 had decreased risks of ER-positive breast cancer (OR, 0.5 [95% CI, 0.3-0.9] and OR, 0.3 [95% CI, 0.2-0.6], respectively) compared with women whose BMI changed <5.0 kg/m^2 (P_{trend}<.001). BMI change was not related to the risk of ER-positive breast cancer among parous women. Parity did not statistically significantly modify the relation between BMI change and TN breast cancer ($P_{interaction}$ = .11), although there was some suggestion that the observed increase in risk was primarily limited to parous women.

DISCUSSION

In this population-based, case-control study of women ages 20 to 44 years, we observed that height, BMI at reference date, and BMI at age 18 years were not associated with the risk of any of the 3 breast cancer subtypes evaluated. However, an increase in BMI since age 18 years was associated with an increased risk of TN breast cancer, primarily among parous women, as well as a reduced risk of ER-positive breast cancer that was limited to nulliparous women. This report adds to the limited literature[20-25] addressing these relations. Comparing our results with those from previous studies is challenging, particularly because only 1 study specifically evaluated changes in BMI.[20]

Among the studies that characterized risk according to ER/PR status, some observed that BMI at diagnosis[15-19] and BMI at age 18 years[15] were associated inversely with the risk of ER-positive/PR-positive breast cancer; however, similar to our results, the majority of those studies observed no association between BMI and the risk of either ER-positive/PR-positive[9-14] or ER-negative/PR-negative[9-19] breast cancer. Five case-control studies[20-23,25] and 1 cohort study[24] assessed risk according to joint ER/PR/HER2 status. The results across those studies generally were null for each breast cancer subtype. Three[20-22] of the 4 studies[20-23] that evaluated luminal A cancer risk, two[20,23] of the 3 studies[20,22,23] that evaluated luminal B cancer risk, all 4 of the studies[20,22-24] that evaluated HER2-overexpressing breast cancer risk, and five[20,21,23-25] of the 6 studies[20-25] that evaluated TN/basal-like cancer risk reported no associations between different aspects of BMI and cancer risk. Thus, there are no consistently observed positive or negative associations between BMI and different breast cancer subtypes.

Given the paucity of available evidence on the relations between anthropometric factors and different breast

TABLE 2. Association of Height, Body Mass Index (BMI) at Age 18 Years, BMI at Reference Year, BMI Change, and Breast Cancer Risk

							Subtypes												
	Controls, n = 940		Cases, n = 1021				ER−/PR−/HER2−, n = 182				ER−/HER2+, n = 60				ER+, n = 779[a]				$P_{Heterogeneity}$ (ER−/PR−/HER2− vs ER+)
Variable	No.	%	No.	%	OR[b]	95% CI	No.	%	OR[b]	95% CI	No.	%	OR[b]	95% CI	No.	%	OR[b]	95% CI	
Height, m																			
<1.60	185	20	181	18	1.0	Ref	30	16	1.0	Ref	17	28	1.0	Ref	134	17	1.0	Ref	
1.60 to <1.64	240	26	290	28	1.3	0.9-1.8	54	30	1.4	0.8-2.4	15	25	0.9	0.4-2.1	221	28	1.3	0.9-1.9	
1.64 to <1.70	261	28	275	27	1.1	0.8-1.5	48	26	0.9	0.5-1.6	14	23	0.6	0.2-1.4	213	27	1.2	0.9-1.7	
≥1.70	254	27	275	27	1.1	0.8-1.5	50	27	1.0	0.6-1.8	14	23	0.7	0.3-1.7	211	27	1.2	0.8-1.7	
P_{trend}						.99				.53				.28				.63	.37
Continuous, per 5 cm					1.04	0.96-1.13			1.03	0.88-1.20			0.84	0.66-1.07			1.06	0.97-1.16	
BMI at age 18 y, kg/m^2																			
<18.8	238	26	299	29	1.0	Ref	56	31	1.0	Ref	15	25	1.0	Ref	228	29	1.0	Ref	
18.8 to <20.4	233	25	257	25	0.9	0.7-1.2	47	26	0.7	0.4-1.2	15	25	1.0	0.5-2.3	195	25	0.9	0.7-1.3	
20.4 to <22.2	224	24	237	23	1.0	0.7-1.3	37	20	0.7	0.4-1.2	16	27	1.0	0.4-2.3	184	24	1.0	0.8-1.4	
≥22.2	232	25	221	22	0.9	0.6-1.1	41	23	0.7	0.4-1.2	14	23	1.0	0.4-2.3	166	21	0.9	0.6-1.2	
P_{trend}						.41				.17				.93				.65	.28
Continuous, kg/m^2					0.99	0.96-1.03			0.95	0.89-1.01			0.97	0.89-1.07			1.00	0.97-1.04	
BMI at reference y, kg/m^2																			
<21.7	235	25	295	29	1.0	Ref	47	26	1.0	Ref	13	22	1.0	Ref	235	30	1.0	Ref	
21.7 to <24.2	231	25	235	23	0.9	0.7-1.2	37	20	0.9	0.5-1.5	20	33	1.4	0.6-3.1	178	23	0.8	0.6-1.2	
24.2 to <28.3	241	26	253	25	0.9	0.7-1.3	42	23	0.8	0.5-1.4	9	15	0.8	0.3-1.9	202	26	1.0	0.7-1.3	
≥28.3	232	25	238	23	0.9	0.7-1.2	56	31	1.2	0.7-2.0	18	30	1.2	0.5-2.8	164	21	0.8	0.6-1.2	
P_{trend}						.68				.62				1.00				.5	.38
Continuous, kg/m^2					1.00	0.98-1.02			1.02	0.98-1.05			1.01	0.96-1.06			1.00	0.98-1.02	
BMI at reference y, kg/m^2																			
<25	526	56	600	59	1.0	Ref	99	54	1.0	Ref	37	62	1.0	Ref	464	60	1.0	Ref	
25 to <30	241	26	243	24	1.0	0.8-1.3	43	24	1.0	0.6-1.5	9	15	0.6	0.3-1.3	191	25	1.0	0.8-1.4	
≥30	172	18	178	17	1.1	0.8-1.4	40	22	1.2	0.7-2.0	14	23	1.1	0.5-2.3	124	16	1.0	0.7-1.4	
P_{trend}						.81				.5				.88				.94	.54
BMI change from age 18 y to reference y, kg/m^2																			
<0	89	10	91	9	0.9	0.6-1.4	14	8	1.3	0.6-2.7	3	5	0.7	0.2-2.5	74	10	0.9	0.6-1.3	
0 to <5.0	456	49	535	53	1.0	Ref	80	44	1.0	Ref	33	55	1.0	Ref	422	55	1.0	Ref	
5.0 to <10.0	259	28	251	25	0.9	0.7-1.1	52	29	1.2	0.7-1.9	12	20	0.6	0.3-1.4	187	24	0.9	0.7-1.1	
≥10.0	123	13	137	14	1.1	0.8-1.5	35	19	2.0[c]	1.2-3.3	12	20	1.1	0.5-2.6	90	12	0.9	0.7-1.3	
P_{trend}[d]						.90				.02				.88				.46	.007
Continuous, kg/m^2[d]					1.01	0.98-1.04			1.07	1.02-1.11			1.02	0.96-1.09			0.99	0.97-1.02	

Abbreviations: −, negative; +, positive; CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; PR, progesterone receptor; Ref, reference category.

[a] These were patients who had ER-positive breast cancer regardless of PR/HER2 status.

[b] ORs were adjusted by age at reference, reference year, race/ethnicity, and age at first birth.

[c] $P < 0.05$.

[d] The BMI change was ≥0 kg/m^2.

TABLE 3. Association of Body Mass Index Change and the Risk of Estrogen Receptor-Positive Stratified by Parity

	Controls, n = 927		Cases								
			ER−/PR−/HER2−, n = 181				ER+, n = 771[a]				
Parity Status	No.	%	No.	%	OR[b]	95% CI	No.	%	OR[b]	95% CI	$P_{Heterongeneity}$
Nulliparous: Never had a live birth											
BMI change from age 18 y to reference y, kg/m^2											
<5.0	112	59	30	60	1.0	Ref	154	74	1.0	Ref	
5.0 to <10.0	48	25	16	32	1.3	0.6-2.6	38	18	0.5[c]	0.3-0.9	
≥10.0	29	15	4	8	0.5	0.2-1.5	15	7	0.3[c]	0.2-0.6	
P_{trend}						.4				<.001	.08
Continuous, kg/m^2				0.97	0.91-1.04			0.93	0.89-0.97		
Parous: Ever had a live birth											
BMI change from age 18 y to reference y, kg/m^2											
<5.0	433	59	64	49	1.0	Ref	342	61	1.0	Ref	
5.0 to <10.0	211	29	36	27	1.2	0.8-1.9	148	26	0.9	0.7-1.2	
≥10.0	94	13	31	24	2.1[c]	1.3-3.4	75	13	1.0	0.7-1.4	
P_{trend}						.008				.7	.0045
Continuous, kg/m^2				1.06	1.02-1.10			1.00	0.97-1.02		
$P_{interaction}$						.11				.002	

Abbreviations: −, negative; +, positive; BMI, body mass index; CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; OR, odds ratio; PR, progesterone receptor; Ref, reference group.

[a] These were patients who had ER-positive breast cancer regardless of PR/HER2 status.

[b] ORs were are adjusted by age at reference, reference year, and race/ethnicity.

[c] $P < 0.05$.

cancer subtypes, our results need to be interpreted cautiously. It is believed that the inverse association between BMI and premenopausal breast cancer risk overall is primarily hormonally driven. The greater frequency of anovulatory and irregular menstrual cycles in women with higher BMI results in reduced endogenous estrogen production.[32] The inverse association between BMI change and the risk of ER-positive breast cancer only among nulliparous women may reflect the finding that the profound changes in breast tissue induced by pregnancy outweigh the effects of BMI on breast cancer risk.[33] Although there is some evidence that BMI is inversely related to hormone receptor-positive breast cancer, as described above, the results from studies evaluating the relation between BMI and hormone receptor-negative disease are largely null. The biologic mechanisms underlying the relations observed between BMI change and TN breast cancer are largely unknown. Obesity does exert a range of biologic effects beyond its influence on hormones that potentially could explain this finding. For example, BMI is positively related to insulin-like growth factor-I levels,[34] and it has been demonstrated that insulin-like growth factor-I enhances breast cancer cell growth irrespective of hormone receptor status.[35] Thus, if our observation is confirmed, then further exploration of the biologic underpinnings of this association is needed.

It is important to acknowledge the limitations of this study. Given our case-control design, recall bias is a potential concern. However, beyond identifying case-control differences, we also observed significant case-case differences. Given that recall across case groups should not differ appreciably, the impact of recall bias on our results probably is minimal. With respect to exposure assessment, we used both self-reported and measured height and weight, and there was high correlation between these measures. We also conducted sensitivity analyses of our BMI data restricted to those women with measured weights and then restricted to those with self-reported weights, and our results did not change appreciably with either restriction (data not shown). However, our BMI change variable required recall of body weight at age 18 years and, thus, is potentially subject to recall bias. However, again, our analyses did demonstrate both case-control differences and case-case differences, suggesting that any differences in recall are likely to be nondifferential with only the potential to bias risk estimates toward the null.[36]

In conclusion, the results from this population-based case-control study of young women add to recent

evidence indicating that height, current BMI, and BMI at age 18 years are not associated with the risk of breast cancer subtypes defined by ER/PR/HER2 status. BMI change from age 18 years was positively related to the risk of TNBC and was inversely related to the risk of ER-positive breast cancer only among nulliparous women. These results require confirmation, and the underlying biologic mechanisms are largely unknown.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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Family history, body mass index and survival in Japanese patients with stomach cancer: a prospective study

Yuko Minami[1,2], Masaaki Kawai[1,3], Tsuneaki Fujiya[4], Masaki Suzuki[5], Tetsuya Noguchi[5], Hideaki Yamanami[4], Yoichiro Kakugawa[4] and Yoshikazu Nishino[2]

[1] Division of Community Health, Tohoku University Graduate School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi, Japan
[2] Division of Cancer Epidemiology and Prevention, Miyagi Cancer Center Research Institute, 47-1 Nodayama, Medeshima-Shiode, Natori, Miyagi, Japan
[3] Department of Surgical Oncology, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, Japan
[4] Department of Surgery, Miyagi Cancer Center Hospital, 47-1 Nodayama, Medeshima-Shiode, Natori, Miyagi, Japan
[5] Department of Gastroenterology, Miyagi Cancer Center Hospital, 47-1 Nodayama, Medeshima-Shiode, Natori, Miyagi, Japan

Family history and nutritional status may affect the long-term prognosis of stomach cancer, but evidence is insufficient and inconsistent. To clarify the prognostic factors of stomach cancer, we conducted a prospective study of 1,033 Japanese patients with histologically confirmed stomach cancer who were admitted to a single hospital between 1997 and 2005. Family history of stomach cancer and pretreatment body mass index (BMI) were assessed using a self-administered questionnaire. Clinical data were retrieved from a hospital-based cancer registry. All patients were completely followed up until December, 2008. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated according to family history in parents and siblings and BMI category. During a median follow-up of 5.3 years, 403 all-cause and 279 stomach cancer deaths were documented. Although no association with family history was observed in the patients overall, analysis according to age group found an increased risk of all-cause death associated with a history in first degree relatives (HR = 1.61, 95% CI: 0.93–2.78, $p = 0.09$) and with a parental history (HR = 1.86, 95% CI: 1.06–3.26) among patients aged under 60 years at diagnosis. BMI was related to all-cause and stomach cancer death among patients aged 60 and over, showing a J-shaped pattern (HR of all-cause death = 2.28 for BMI < 18.5; HR = 1.61 for 25 $\leq$ *vs.* $\geq$ 23.0 to < 25.0 kg/m^2). A family history of stomach cancer, especially parental history, may affect mortality among younger stomach cancer patients, whereas nutritional status may be a prognostic factor in older patients.

Despite a dramatic decline in recent years, stomach cancer remains a major cause of cancer death in Japan, being the second leading cause in men and the fourth in women.[1] A number of environmental factors are known to be related to the development of the disease,[2–6] while at the same time, familial aggregation has long been observed.[7] Many previous studies have revealed that the presence of a family history of stomach cancer is associated with an increased risk of the disease,[8,9] but there are few data to indicate the degree to which the familial factor influences the disease-specific prognosis and overall survival. Only a few population-based prospective studies conducted in Japan[10,11] have found that a positive family history of stomach cancer increases the risk of stomach cancer death. Meanwhile, some studies from Asian countries have obtained opposite results. For example, a recent large-scale study conducted in Korea reported that a family history of stomach cancer was associated with improved survival in patients with advanced cancer.[12] These inconsistent results may be attributable to differences among the studies in terms of the subject selection procedure, definition of family history and treatment of potential confounders, and thus the true effects of family history on survival of stomach cancer patients still remain unclear.

Conversely, some population-based studies have analyzed the relationship between obesity and the risk of stomach cancer death,[13–15] and adverse effects of obesity on early surgical outcome have also been reported.[16–19] Body mass index (BMI) at the time of diagnosis, which reflects the nutritional status of stomach cancer patients, may influence survival.[20,21] Evaluations of the effects of being overweight or underweight can be essential for identifying prognostic factors of stomach cancer. However, the effect of BMI on long-term outcome has received little attention.[18,22–24]

The aim of this study is to examine whether a positive family history of stomach cancer and BMI at the time of diagnosis influence the survival of stomach cancer patients. Lifestyle and clinical data for stomach cancer patients were

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Correspondence to: Yuko Minami, Division of Community Health, Tohoku University Graduate School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8575, Japan, Tel: +81-22-717-7479, E-mail: adym@med.tohoku.ac.jp

What's new?
How do family history and body mass index affect prognosis of stomach cancer? In this study, the authors collected data from more than 1,000 stomach cancer patients and documented deaths over a 5-year period. Family history had no apparent impact when considering all patients, but among patients under 60, family history increased the risk of death. Similarly, among patients over age 60, being overweight increased the chance of death.

obtained from a questionnaire survey and a hospital-based cancer registry at a single hospital in Japan, and a long-term follow-up survey was conducted.

Material and Methods

Study subjects

Between January 1997 and December 2005, 1,283 patients aged 30 years and over were newly diagnosed as having malignant gastric tumors at the Miyagi Cancer Center Hospital (MCCH). All of these patients were requested to complete a self-administered questionnaire at the time of their initial admission. After diagnosis, they were registered in the hospital-based cancer registry and followed up. This cancer registry records clinical and pathological findings and information on antineoplastic treatments for all patients with malignant tumors admitted to the MCCH. The MCCH is located in Natori City, situated in the southern part of Miyagi Prefecture, and functions as a hospital for both cancer and benign disease.

Of the 1,283 newly diagnosed patients with malignant gastric tumors, 1,210 (94.3%) completed the questionnaire. From among these 1,210 patients, 14 with submucosal malignant tumor and 47 without pathological data were excluded, giving 1,149 patients with histologically confirmed stomach cancer. After further excluding 76 patients with a history of cancer other than stomach cancer, 1,073 patients were identified for the present study. This study was approved by the ethical review board of the Miyagi Cancer Center (Protocol Identification Number 23–7, May 20, 2011).

Ascertainment of exposures and follow-up

Exposures, that is, family history of stomach cancer and BMI, were obtained from the aforementioned questionnaire survey, which covered items on demographic characteristics, referral status, personal history including family history of cancers, current height (centimeters) and weight (kilograms), and general lifestyle factors including smoking and alcohol drinking. The purpose of the survey was stated on the cover page of the questionnaire. We considered the return of self-administered questionnaires signed by the patients to imply their consent to participate in the study.

With regard to family history of stomach cancer, patients were asked in the questionnaire: "Choose someone who had the history of stomach cancer." The response categories were: father, mother, brothers or sisters and spouse. History of stomach cancer in first-degree relatives including father, mother and siblings was defined as a positive family history. BMI, that is, pretreatment BMI, was calculated based on self-reported weight and height as described in the questionnaire: weight divided by the square of current height (kg/m^2). Thirty-eight patients for whom BMI data were missing were excluded from the study, leaving 1,035 subjects. The self-reported current height and weight data were highly correlated with measured data (correlation coefficient: 0.96 for height and 0.93 for weight) in a subsample ($n = 716$) of the study subjects.

Patients were followed until December 2008. The MCCH cancer registry conducted active follow-up by accessing hospital visit records, resident registration cards and permanent domicile data. Information on the date and cause of death was obtained with permission from the Ministry of Justice. The 1,035 subjects were completely followed up. Details of the questionnaire survey and follow-up procedure have already been described elsewhere.[3,25]

Statistical analysis

The end point of our analysis was all-cause death and stomach cancer death according to the International Classification of Disease for Oncology, Tenth Edition (ICD-10). Survival time was calculated for each patient from the date of diagnosis until the date of death or the end of follow-up (December 31, 2008). Among deceased patients, 2 patients who died within 30 days after the index operation were defined as operative mortality cases and excluded.[26] Finally, a total of 1,033 patients were included in the analysis.

The Cox proportional hazards regression model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality due to all-causes and stomach cancer.[27] We first evaluated HRs in relation to family history of stomach cancer and BMI among the subjects overall. The HRs for family history were evaluated according to history in siblings only and in the father or mother (parental history), along with overall history in first-degree relatives. For analysis of BMI, subjects were stratified according to the following BMI categories (<18.5 kg/m^2, ≥ 18.5 to <23 kg/m^2, ≥ 23 to <25.0 kg/m^2, ≥ 25.0 kg/m^2). These BMI categories correspond to the cut-off points proposed by the World Health Organization (WHO). The BMI value of 23 kg/m^2 was the median for the analyzed population. The BMI category ≥ 23 to <25.0 kg/m^2 was selected as the reference. Second, age-specific all-cause mortality according to family history was calculated. Based on the distribution of the mortality rates by

age at diagnosis, the subjects were divided into two groups (younger and older age groups) and analysis stratified by age group was performed. In these analyses, we considered the following variables to be potential confounders: age, sex, referral status (from screening, other), stage, histological type (adenocarcinoma, other), occupation (profession or office work, other), smoking (never, ever) and alcohol drinking (never, ever). Curative resection (no, yes) was also considered as a confounder. Among these confounders, clinical data including stage, histological type and curability were retrieved from the MCCH cancer registry. Endoscopic or surgical treatment has been used for resection of cancer lesions. Curability was evaluated mainly on the basis of the Japanese Classification of Gastric Carcinoma 12th and 13th edition.[28] In the evaluation of curability for endoscopic treatment, judgment of clinicians was also taken into account. Subjects whose curability was undetermined were regarded as noncurative. Subjects who had undergone neither endoscopic nor surgical treatment were placed in the noncurative group. Staging (I, II, III, IV) was performed using the UICC TNM classification 5th and 6th editions. In our study, pathological stage was ordinarily coded and clinical stage was coded for cases with unknown pathological stage. Missing values for confounders were treated as an additional variable category, and included in the model.

To investigate the heterogeneity in risk for BMI according to family history, analysis stratified by family history was also performed.

Results were regarded as significant if the two-sided p values were <0.05. All statistical analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC).

Results

During a median follow-up period of 5.3 years, 403 all-cause and 279 stomach cancer deaths were observed.

Table 1 shows the characteristics of the study subjects according to exposure variables, that is, family history of stomach cancer and BMI. There was not a large difference in background characteristics among the groups in terms of family history of stomach cancer; however, subjects with a family history in siblings only tended to have early-stage cancers. In terms of BMI, the proportion of stage IV cancers in the BMI <18.5 group was higher than in any of the other BMI groups. The proportion of curative resections was low in lean subjects with a BMI of <18.5. The distributions of smokers and alcohol drinkers were almost the same across all BMI categories.

Table 2 shows the risk of mortality in relation to family history and BMI among the subjects overall. A family history of stomach cancer in first-degree relatives was not associated with either all-cause death or stomach cancer death. A history in either sibling only or in the father or mother was not associated with mortality risk. Lower BMI was associated with a higher risk of all-cause death in the sex, age and stage-adjusted model. After adjustment for confounding variables, a similar association was observed. Further adjustment for curative resection (no, yes) did not change the magnitude of the association for BMI (BMI <18.5, HR = 1.85; BMI ≥18.5 to <23.0, HR = 1.55; p for trend in BMI <25.0 = 0.0004). BMI was also related to stomach cancer death. In a multivariate-adjusted model including curative resection, lower BMI was significantly associated with an increased risk of stomach cancer death and a significant linear association was also observed (p for trend in BMI <25.0 = 0.03).

Table 3 shows age-specific all-cause mortality in relation to family history. In the 30–39-year age group, no patients had a family history of stomach cancer, and therefore we were unable to consider the effect of family history in this group. However, a higher mortality rate was observed among subjects with a parental history of stomach cancer in both the 40–49- and 50–59-year age groups, compared with subjects without such a family history. The mortality rate ratio (present in father or mother *vs.* absent) was over one in both the 40–49- (ratio = 1.20) and 50–59-year age groups (ratio = 1.46). Conversely, the corresponding ratio in the group aged 60 years and over was around one or under. Thus, the risk of all-cause death associated with a parental history may possibly change at around the age of 60.

Table 4 presents the distribution of causes of death according to age group (<60 years and ≥60 years). The proportion of stomach cancer death was higher in subjects under 60-years old (88.3%) than in those aged 60 years and over (64.0%). Conversely, the proportion of deaths due to vascular disease or pneumonia was higher in subjects aged 60 years and over.

Table 5 shows the risk of mortality according to age group (<60 years and ≥60 years). Based on the findings presented in Tables 3 and 4, this stratification appears to be reasonable. After adjustment for confounding variables including curative resection, history of stomach cancer in first-degree relatives was associated with an increased risk of all-cause death among subjects aged under 60 years (HR = 1.61, 95% CI: 0.93–2.78); however, statistical analysis failed to demonstrate significance ($p = 0.09$). Evaluation according to a history in siblings only and in the father or mother revealed that a parental history of stomach cancer was significantly associated with an increased risk of all-cause death in subjects aged under 60 years (HR = 2.05, 95% CI: 1.17–3.59). Further adjustment for curative resection also showed a significant association (HR = 1.86, 95% CI: 1.06–3.26). The association of parental history with the risk of stomach cancer death in subjects aged under 60 years was not statistically significant (HR = 1.68, 95% CI: 0.90–3.12). Among subjects aged 60 years and over, the association of family history with the risk of mortality was unity for both all-cause and stomach cancer death. As for BMI, no association with the risk of all-cause death was observed in subjects aged under 60 years, whereas the risk of all-cause death among subjects aged 60 years and over was statistically significant in both the lower and higher

Table 1. Characteristics of study subjects at baseline according to exposure variable

		Family history of stomach cancer			Body mass index (kg/m^2)			
Factor	All subjects	Absent	Present in siblings only	Present in father or mother	<18.5	18.5≤ <23.0	23.0≤ <25.0	25.0≤
Number of subjects (n)	1033	763	85	185	82	454	236	261
Age group, n (%)								
<60 years	289 (28.0)	223 (29.2)	11 (12.9)	55 (29.7)	21 (25.6)	138 (30.4)	70 (29.7)	60 (23.0)
≥60 years	744 (72.0)	540 (70.8)	74 (87.1)	130 (70.3)	61 (74.4)	316 (69.6)	166 (70.3)	201 (77.0)
Age (years), mean ± sd	65.8 ± 11.3	65.5 ± 11.7	69.6 ± 8.1	65.4 ± 10.4	66.6 ± 11.9	65.6 ± 11.8	65.6 ± 11.6	66.0 ± 10.0
Sex, n (%)								
Male	721 (69.8)	539 (70.6)	55 (64.7)	127 (68.7)	52 (63.4)	318 (70.0)	173 (73.3)	178 (68.2)
Female	312 (30.2)	224 (29.4)	30 (35.3)	58 (31.3)	30 (36.6)	136 (30.0)	63 (26.7)	83 (31.8)
Referral status, n (%)								
From screen	246 (23.8)	187 (24.5)	18 (21.2)	41 (22.2)	14 (17.1)	86 (18.9)	67 (28.4)	79 (30.3)
Other	787 (76.2)	576 (75.5)	67 (78.8)	144 (77.8)	68 (82.9)	368 (81.1)	169 (71.6)	182 (69.7)
Occupation, n (%)								
Professional or office work	222 (21.5)	173 (22.7)	13 (15.3)	36 (19.5)	15 (18.3)	92 (20.3)	57 (24.2)	58 (22.2)
Industrial work	385 (37.2)	295 (38.6)	24 (28.3)	66 (35.6)	28 (34.1)	194 (42.7)	79 (33.5)	84 (32.2)
Agriculture, forestry, or fishery	192 (18.6)	132 (17.3)	20 (23.5)	40 (21.6)	16 (19.5)	75 (16.5)	44 (18.6)	57 (21.8)
Others[1]	104 (10.1)	64 (8.4)	16 (18.8)	24 (13.0)	9 (11.0)	45 (9.9)	26 (11.0)	24 (9.2)
Missing	130 (12.6)	99 (13.0)	12 (14.1)	19 (10.3)	14 (17.1)	48 (10.6)	30 (12.7)	38 (14.6)
Smoking, n (%)								
Never	405 (39.2)	294 (38.5)	40 (47.1)	71 (38.4)	33 (40.2)	172 (37.9)	91 (38.6)	109 (41.8)
Ever	601 (58.2)	449 (58.9)	44 (51.8)	108 (58.4)	46 (56.1)	277 (61.0)	136 (57.6)	142 (54.4)
Missing	27 (2.6)	20 (2.6)	1 (1.1)	6 (3.2)	3 (3.7)	5 (1.1)	9 (3.8)	10 (3.8)
Alcohol drinking, n (%)								
Never	402 (38.9)	294 (38.5)	37 (43.5)	71 (38.4)	31 (37.8)	177 (39.0)	91 (38.6)	103 (39.5)
Ever	581 (56.3)	435 (57.0)	44 (51.8)	102 (55.1)	46 (56.1)	255 (56.1)	133 (56.3)	147 (56.3)
Missing	50 (4.8)	34 (4.5)	4 (4.7)	12 (6.5)	5 (6.1)	22 (4.9)	12 (5.1)	11 (4.2)
Stage of cancer, n (%)								
I	690 (66.8)	498 (65.3)	64 (75.3)	128 (69.2)	34 (41.5)	293 (64.5)	169 (71.6)	194 (74.3)
II	77 (7.5)	57 (7.5)	6 (7.1)	14 (7.6)	6 (7.3)	37 (8.1)	21 (8.9)	13 (5.0)
III	76 (7.4)	63 (8.2)	3 (3.5)	10 (5.4)	6 (7.3)	42 (9.3)	17 (7.2)	11 (4.2)
IV	174 (16.8)	131 (17.2)	12 (14.1)	31 (16.7)	32 (39.0)	73 (16.1)	26 (11.0)	43 (16.5)
Unknown	16 (1.5)	14 (1.8)	0 (0.0)	2 (1.1)	4 (4.9)	9 (2.0)	3 (1.3)	0 (0.0)