frequency of alcohol drinking, amount of alcohol consumed on one occasion or per day, and age upon starting to drink with breast cancer risk among Japanese women. In our analysis, stratified according to use of female hormone, higher alcohol intake was associated with an increased risk among hormone users, but this was not statistically significant. In relation to folate intake, the amount of alcohol consumed per day was marginally associated with breast cancer risk among women with low folate intake. These findings suggest that alcohol intake has no overall impact on breast cancer risk, and that the nutritional factors such as folate intake may modify the alcohol–breast cancer risk relationship. Further studies are required to clarify the association of alcohol intake with breast cancer risk among Japanese women.

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Clinical Trial Notes

Randomized Controlled Trial on Effectiveness of Ultrasonography Screening for Breast Cancer in Women Aged 40–49 (J-START): Research Design

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In cancer screening, it is essential to undertake effective screening with appropriate methodology, which should be supported by evidence of a reduced mortality rate. At present, mammography is the only method for breast cancer screening with such evidence. However, mammography does not achieve sufficient accuracy in breasts with high density at ages below 50. Although ultrasonography achieves better accuracy in Breast Cancer detection even in dense breasts, the effectiveness has not been verified. We have planned a randomized controlled trial to assess the effectiveness of ultrasonography in women aged 40–49, with a design to study 50 000 women with mammography and ultrasonography (intervention group), and 50 000 controls with mammography only (control group). The participants are scheduled to take second round screening with the same modality 2 years on. The primary endpoints are sensitivity and specificity, and the secondary endpoint is the rate of advanced breast cancers.

Key words: breast cancer screening – mammography – ultrasonography – randomized controlled trial

INTRODUCTION

Breast cancer is one of the most common cancers worldwide (1). The age-standardized incidence rate is the first among all female cancers, and it is continuously increasing in Japan (2,3), although Japan has a lower risk of breast cancer in comparison with Western countries. The incidence peaks at ages 45–49, and the mortality peaks at ages 55–59 in Japan (2). In breast cancer screening, it is essential to undertake effective screening with appropriate methodology. Effective screening should be supported by evidence of a reduced mortality rate. At present, mammography (MG) is the only method for breast cancer screening that has such evidence. However, MG does not achieve sufficient screening accuracy in breasts with high mammary gland density. Dense breasts are common at ages below 50 and are more common in Japanese populations than in Western populations (4). As the US Preventive Services Task Force (USPSTF) recommends against routine screen MG in women aged 40–49 years, the issue of breast imaging to screen women aged 40–49 still remains unclear (5).

Since ultrasonography (US) achieves better accuracy in breast cancer detection even in dense breasts (6) and supplemental screening US has the potential to depict early breast cancers not seen on MG (6–8), several single-institution observational studies in screening setting began. As mentioned in the WHO guidelines, 'population-based cancer screening' conducted as a public health program should be undertaken only when there is evidence of a reduced mortality rate (9). Before introducing any new technology in population-based breast cancer screening, it is essential to evaluate the effectiveness. However, randomized controlled trials (RCTs), cohort studies or case–control studies have not been completed to assess the efficacy of screening US to reduce breast cancer mortality, and the effectiveness has not been verified.

Therefore, we have planned an RCT to assess effectiveness of screening US for breast cancer, the Japan Strategic Anti-cancer Randomized Trial (J-START) in 2006. The defined study population is women aged 40–49 years, because this is the age range at which breast cancer peaks in Japan (2) and because a high percentage of Japanese women aged 40s have dense breast. This is a large-scale controlled trial, designed to study 50 000 women with MG and US (intervention group) and 50 000 controls with MG only (control group).

The primary endpoints of this trial are the inter-group comparisons of the sensitivity and specificity, and the secondary endpoint is the inter-group comparison of the accumulated incidence rate of advanced breast cancer during the follow-up period. The most important index in the evaluation of the effectiveness of cancer screening is the mortality rate from the cancer in question in the target population. However, in view of the natural history of breast cancer, the 4-year period scheduled in the strategic study grant is too short to observe a significant inter-group difference. Although the rate of advanced breast cancer could be a surrogate for mortality reduction, it is necessary to have a system that has the long-term follow-up of the survival status of individuals even after the completion of the strategic study, J-START.

This study may have several limitations. First, the screening interval is 2 years, despite evidence that screening MG at age 40–49 years is more effective with annual screening. The recent USPSTF, however, recommends biannual MG screening in view of reducing 'harm', i.e. higher recall rate at age 40–49 years (5). Secondly, the study population, which is so different from that in Western countries, may limit the generalization of study outcomes. Most countries in Asia, however, demonstrate the similar trend of breast cancer incidence as observed in Japan; therefore, this trial may influence their health strategy against breast cancer. Nevertheless, for women aged 40–49 years even in Western countries, there is a limitation of MG screening as the USPSTF recommends against the routine use of screening MG for this age group. Thirdly, the study may be underpowered to provide follow-up data on breast cancer deaths because of the low breast cancer risk of native Japanese women. In this context, as much as 100 000 women are targeted in this trial to ensure the statistical power be sufficient enough in comparison between the two groups.

PROTOCOL DIGEST OF THE STUDY

Purpose

The aim of this study is to assess the effectiveness of screening US for breast cancer in women aged 40–49 (Fig. 1).

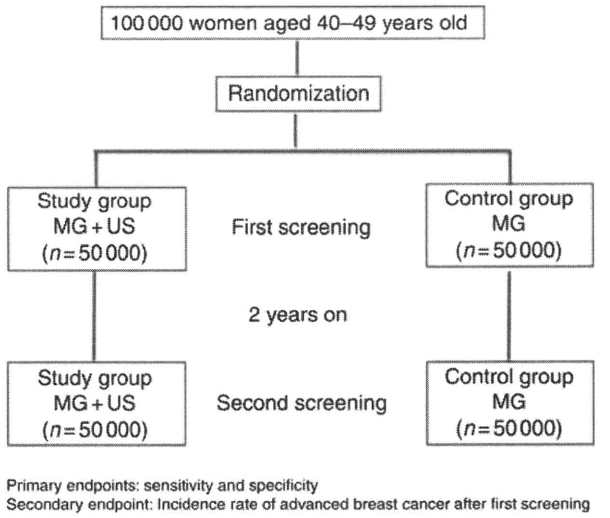

Figure 1. J-START study design. MG, mammography; US, ultrasonography.

Study Setting

This study is a multi-institutional prospective RCT, with 42 participating centers in 23 prefectures in Japan as of 31 March 2011.

Endpoints

The primary endpoints of this trial are sensitivity and specificity, based on the data of each incremental cancer detection rate, false-positives and false-negatives should be forthcoming in 2 years. The secondary endpoint is the rate of advanced breast cancers, as this has been demonstrated in the screening MG RCTs to be a surrogate for mortality reduction (10).

Eligibility Criteria

Inclusion criteria are as follows:

(i) women aged 40–49 years when registered;
(ii) women signed the informed consent to participate in the study.

Exclusion criteria are as follows:

(i) women with a history of breast cancer;
(ii) women with a history of malignant disease other than breast cancer within 5 years;
(iii) women in severe condition, who are not expected to live for 5 years.

Treatment Methods

Patient Assignments

Each participating center confirms the participants' eligibility and screening methods are assigned according to the random number provided by the Japan Clinical Research Supporting Unit (J-CRSU) Data Center. Cluster randomization is also used in some institutions.

Screening Method and Assessment

For the intervention arm, US and MG are performed at the same time. For the control arm, MG is performed. The technologists and the physicians involved in this trial are asked to finish 2-day, 16-h education program for the standardization of US screening for breast cancer. Regarding the procedure in screening with US, the handheld US is performed by a technologist or by a physician, and later, the US image is interpreted by a physician. An interpretation of MG is performed by a physician who is not regulated to be the same doctor interpreting US image or not, although the categorization of the two modalities are defined separately in the protocol. The findings of MG and/or US are subsequently evaluated by authorized screeners and are classified into five categories as follows: Category 1, negative; Category 2, benign finding(s); Category 3, probably benign finding(s); Category 4, suspicious abnormality; and Category 5, malignancy. The women who are rated in Category 3 or higher by the MG and/or US are referred for further diagnostic examinations.

Statistical Analysis

The sample size was calculated on the hypothesis that adjunct US is expected to improve sensitivity of the intervention group compared with the control group. Our previous data demonstrated the lower sensitivity of MG screening, 71% in women aged 40–49, when compared with those in women aged 50–59 and 60–69, 85 and 86%, respectively (11). Assuming that the sensitivity increases from 71 to 86% by adding US to MG, 42 500 subjects for each arm is needed to make it 5% statistical significance (two-sided) with 80% power. Thus, the number of 100 000 subjects (two arms combined) is set to be a targeted sample size to verify the primary endpoint, a sensitivity improvement in the intervention group when compared with the control group.

Follow-up Period

The participants are invited to be screened 2 years after the first recruitment or asked to answer questionnaires of health status, history of receiving other screening program, incidence of breast cancer, and history of hospital consultation with any breast symptoms within 2 years. For evaluating the actual evidence of a reduced mortality rate of the intervention group compared with the control group, there must be needed to establish follow-up strategies for a long time period and systematic, nationwide population-based cancer registries.

Registration of the Protocol

The J-START was registered on the University Hospital Medical Information Network Clinical Trial Registration (UMIN-CTR), Japan (registration number: UMIN000000757), on 2007. Details are available at the following address: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000000910&language=E.

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Conflict of interest statement

None declared.

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Classifying Breast Masses in Volumetric Whole Breast Ultrasound Data: A 2.5-Dimensional Approach

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Abstract. The aim of this paper is to investigate a 2.5-dimensional approach in classifying masses as benign or malignant in volumetric anisotropic voxel whole breast ultrasound data. In this paper, the term 2.5-dimensional refers to the use of a series of 2-dimensional images. While mammography is very effective in breast cancer screening in general, it is less sensitivity in detecting breast cancer in younger women or women with dense breasts. Breast ultrasonography does not have the same limitation and is a valuable adjunct in breast cancer detection. We have previously reported on the clinical value of volumetric data collected from a prototype whole breast ultrasound scanner. The current study focuses on a new 2.5-dimensional approach in analyzing the volumetric whole breast ultrasound data for mass classification. Sixty-three mass lesions were studied. Of them 33 were malignant and 30 benign. Features based on compactness, orientation, shape, depth-to-width ratio, homogeneity and posterior echo were measured. Linear discriminant analysis and receiver operating characteristic (ROC) analysis were employed for classification and performance evaluation. The area under the ROC curve (AUC) was 0.91 using all breast masses for training and testing and 0.87 using the leave-one-mass-out cross-validation method. Clinically significance of the results will be evaluated using a larger dataset from multi-clinics.

Keywords: ultrasound breast mass, classification, geometric feature, echo feature.

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1 Introduction

Mammography is very effective in breast cancer detection. It is the routine technique used in breast cancer screening in women who have no symptom of breast cancer. However, mammography is less sensitivity in detecting breast cancer in younger women or women with dense breasts. This is due to the inherited limitations of x-ray employed in the image acquisition in mammography. Breast ultrasonography is another long-standing technique in breast imaging and is a valuable adjunct in breast cancer detection. Distinguished from mammography, the technique employs acoustic waves and does not have the same limitation as mammography. However, it is not without its shortcomings.

Currently, ultrasound breast examination is routinely performed by an ultrasonographer or ultrasonologist. A small hand-held probe of size about 4 cm is used and the ultraonographer/ ultrasonologist runs the probe over the entire breast or pre-identified regions during an examination. The technique can provide very valuable information in the hands of experienced examiners but is in general time consuming. Results are operator independent and reproducibility is poor. A novel breast scanning system that can acquire the data of the entire breast quickly, systematically and repeatedly with precision will be of great advantage.

We have previously introduced a prototype whole breast ultrasound scanner for auto-acquisition of volumetric breast ultrasound data [1]. Diagnostic value of the data was investigated [2]. The volumetric ultrasound data of a whole breast consist of a stack of two-dimensional images, each depicting an axial slice image of the breast. In exploiting the benefit of volumetric data, three-dimensional analysis was used in our previous study in classifying malignant and benign breast masses [3].

One issue noted in our previous three-dimensional analysis was that the data was anisotropic. Anisotropic data are generally computationally cumbersome. One of the common practices would be to resample the data to create isotropic voxel. However, this would not be a good practice for our volumetric whole breast data as the resolution in one direction (z-direction, normal to the axial plane) is about 8 to 10 times lower than that in the other two directions. The discrepancy is large and a reliable model for interpolation cannot be guaranteed. Another option is to increase the number of data points in the z-direction in the raw data. This could be achieved by reducing the interval between adjacent slice images. Options for slice intervals are 2 mm, 1 mm and 0.5 mm. Corresponding unilateral breast study contains 84, 168 and 336 (axial) images, respectively, with acquisition time increases from 20, to 40 and 80 seconds, respectively. The increase in number of axial unnecessarily burdens the interpreters while longer acquisition time leads to problems such as image blurring due to patient movement. Neither of the above options is desirable in this situation as the first one relied on interpolated slice images of which accuracy of the image details to be employed in the computer-aided image analysis cannot be guaranteed. The second one imposes on a clinical practice to collect extra data which is a burden to the practice at no clear clinical benefits. After taken the above into consideration, this paper investigates the efficacy of a 2.5-dimensional analysis, a step between 2-dimensional and 3-dimensional analyses.

2 Method

2.1 Ultrasound Data

Volumetric full-breast ultrasound data were used in this study. The data included 63 breast masses. Of them 33 were malignant and 30 (16 cysts; 14 fibroadenomas) were benign. The malignant and benign masses were related to 29 and 24 breasts, respectively. All the masses were annotated by a radiologist experienced in breast ultrasound and the malignant masses were proven by biopsy. With the patient in prone position, a diagnostic ultrasound system Prosound-II SSD-5500 (Aloka Co., Ltd, Japan) and a prototype full-breast scanner ASU-1004 (Aloka Co., Ltd, Japan) (Figure 1) were used to acquire the full-breast images. The scanner ASU-1004 was equipped with a 5-10 MHz 6 cm linear probe. Operating in a fixed pattern, the probe scanned an area of 16 × 16 cm^2 in 3 sweeps, covering the full-field of a breast. The original scan images were B-mode breast section images in DICOM format with an overlap margin of 1 cm on each of the 'stitching' side. Volumetric full-breast data were generated by 'stitching' corresponding images in the 3 sweeps together (Figure 2). Details of the scanner can be found in [4-6].

The full-breast ultrasound scans were performed in the period 2003-2004 at the Center of Optical Medicine, Dokkyo University School of Medicine, Tochigi, Japan where a prototype full-breast scanner ASU-1004 was located. The size of each (stitched) B-mode image in the constructed volumetric full-breast data was 694 × 400 pixels with a spatial resolution of 0.23 mm/pixel and a slice-to-slice interval of 2 mm.

The images had a gray scale resolution of 8 bits. For each mass, a series of axial slice images containing that mass is employed in the 2.5-dimensional analysis (Figure 3). Features are measured individually on each slice image. The same feature measured on difference slice images are combined at a later stage.

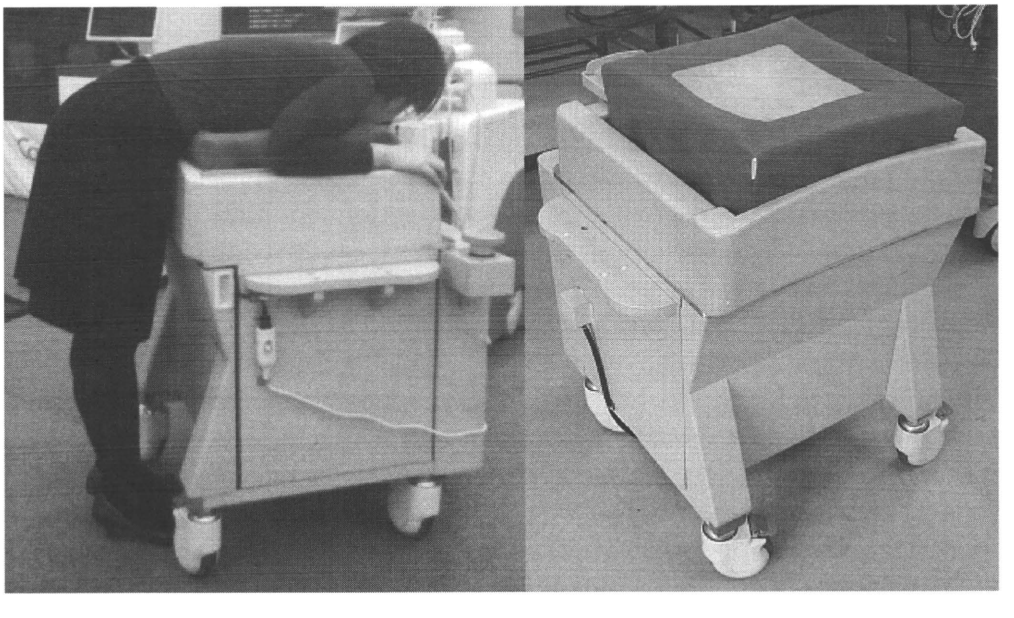

Fig. 1. The prototype full-breast scanner ASU-1004 (right) with a patient in prone position (left)

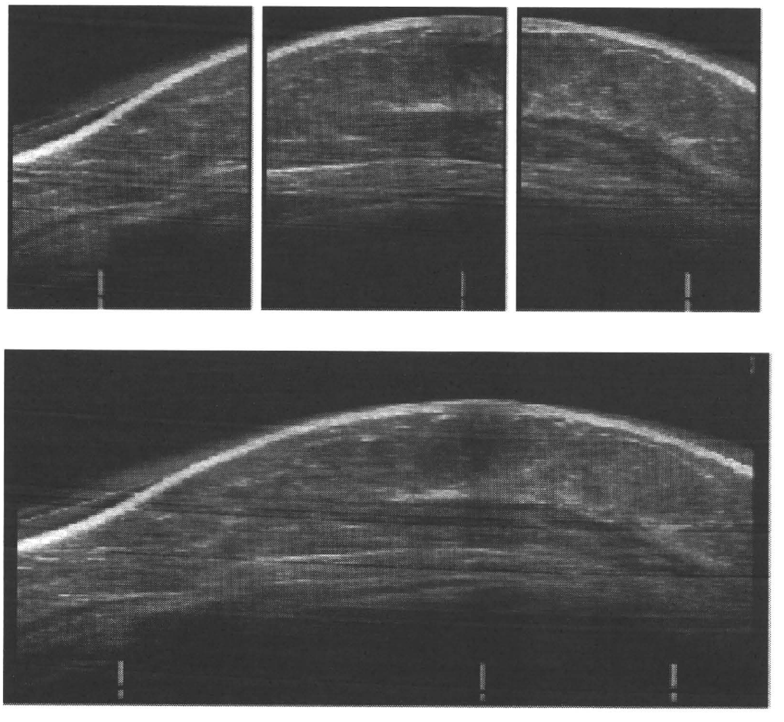

Fig. 2. Corresponding breast section slice images in the 3 sweeps (above) are 'stitched' together to form a slice image in the volumetric full-breast data (below)

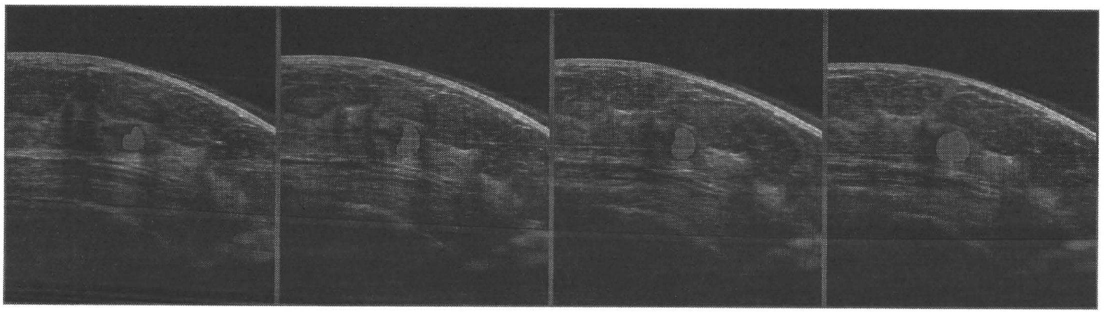

Fig. 3. 2.5-dimensional analysis. In this example, a series of 4 images containing the mass were used in the analysis. The same set of features is measured on each images and is combined at a later stage according to a set rule.

2.2 2.5-Dimensional Analysis

For each mass lesion, a number of axial images containing the mass lesion were identified. The number of associated slice images depends on the size of the mass and the slice-to-slice interval. With the use of a 2 mm slice-to-slice interval and the lesion size ranges from 5 mm to over 3 cm in this study, the number of associated slice image for a mass varies from a minimum of 1 to 2 images to a maximum of over 10 images, with the majority being 4 to 6 images. With the series of slice images containing the mass lesion identified, lesion boundaries were delineated manually and lesions in each of the slice images were segmented.

After the segmentation process, features were measured on the lesions depicted in each of the slice images. Six features were defined. They were compactness, orientation, shape, depth-to-width ratio, homogeneity and posterior analysis. These six features were similar to the features selected in our previous study [3] and were based on the image features that radiologists' found useful and routinely consulted in breast ultrasound images interpretations. A summary of the six features is given in the next paragraph.

In general, compactness (*C*) measures the degree of roundness of an object and is given by

$$C = 4 \times \pi \times A / S^2 \tag{1}$$

where *A* and *S* are the area and circumference of the object, respectively. Benign masses are usually round in shape while malignant masses are more likely to be irregular or oval in shape. Orientation measures the angle (in degrees) between the horizontal axis and the major axis of the ellipse that has the same second-moments as the object and is given by

$$\tan^2 \theta + \frac{M(2,0) - M(0,2)}{M(1,1)} = 0 \tag{2}$$

where *M(p, q)* is the pq^{th}-order moment and is given by

$$M(p,q) = \sum_{i,j} i^p j^q .$$

Depth-to-width (DW) ratio is another feature that can provide information of the orientation of an (elongated) object. This feature can be simply defined as the ratio of the height to the width of the smallest bounding box containing the mass. Homogeneity of the mass is computed using the variance of the intensity inside a mass. Benign masses such as cysts generally display homogeneity (small variance) inside the mass. Posterior echo is also another feature to distinguish benign and malignant lesions. The absence of posterior echo is an indicator of malignant lesion.

The above six features were measured on the lesions in each individual slice images. In other words, the six features were repeatedly measured on a series of mass cross-sectional images separated at a fixed interval of 2 mm.

The 2.5-dimensional analysis is based on features measured in a series of 2-dimensional images. For each breast mass, measurements of the same feature measured on a series of images are combined according to a rule which is feature-specific. For example, the depth-to-width (D/W) ratio measures the depth (vertical extent) of a mass to the width (horizontal extent) of a mass in a 2-dimensional image. Malignant lesions are more rigid and less compressible when subject to external force, hence the D/W ratio of malignant lesions is generally high. On the other hand, benign lesions such as cysts, which are usually filled with fluid or lipids, are more compressible and deformable. Hence, their D/W ratios are generally low. In other words, higher the D/W ratio, more likely is the lesion malignant. So in a 2.5-dimensional analysis, the maximum of the D/W ratios measured on a series of 2-dimensional images of a lesion is the strongest evidence for malignancy. Table 1 listed the rules in combining the multi-slice measurements of the same feature towards 2.5-dimensional analysis assuming strongest evidence for malignancy.

Table 1. Rules for combining multi-slice feature measurements in 2.5-dimensional analysis

FEATURES	*2.5-DIMENSIONAL ANALYSIS*
Compactness	minimum
Orientation	maximum
Depth-to-width ratio	maximum
Posterior echo	minimum
homogeneity	maximum
Shape	maximum

3 Results

Linear discriminant analysis and receiver operating characteristic (ROC) analysis were employed for classification and performance evaluation. Discriminative powers of the six 2.5-dimensional features (combined over slice images) were analyzed in Table 2. The discriminative power of individual feature was indicated by the area under the ROC curve (AUC) obtained when using that feature alone in classifying the mass as benign or malignant. Both the resubstitution AUC using all breast masses for training and testing and the leave-one-mass-out cross-validation AUC are depicted. Table 2 shows that among the six features, three of them have strong discriminative power, namely, orientation, depth-to-width ratio and posterior echo.

When using all the six features for classification, the area under the ROC curve (AUC) was found to be 0.91 using all breast masses for training and testing (resubstitution) and 0.87 using the leave-one-mass-out cross-validation method.

Among a number of classifiers, linear discriminant analysis was chosen for its robustness. Its hyperplane decision surface makes it less susceptible for over-training which is preferable for studies with small samples.

Table 2. Discriminative powers of the six features indicated by the area under the ROC curve (AUC)

FEATURES	*AUC (resubstitution)*	*AUC (leave-one-mass-out)*
Compactness	0.64	0.64
Orientation	0.82	0.79
Depth-to-width ratio	0.83	0.84
Posterior echo	0.84	0.84
homogeneity	0.66	0.50
Shape	0.60	0.58

4 Discussion and Conclusion

The classification based on 2.5-dimensional analysis in this study resulted in high accuracy in discriminating malignant and benign lesions in volumetric breast ultrasound data with anisotropic voxel. AUC indices in this study are in general high and similar to that based on 3-dimensional analysis in our previous study [2]. However, direct comparisons cannot be made. This is because the sample sizes in the two studies were different (63 masses in this study and 36 in the previous 3-d study) and shape feature was introduced in the current 2.5-dimensional analysis but not in the previous 3-dimensional study. In addition, though features definitions are very similar in the two studies, different algorithms were used to compute the features in the two studies. Slight variations in the interpretation of individual features may exist.

Plan for further work in this project is two-folded. (1) a larger database is required to confirm the results in this study. (2) Classification categories will also be extended to include normal breast tissue lumps and other artifacts in the breast which are the false positives found in the detection stage.

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Adiposity, adult weight change and breast cancer risk in postmenopausal Japanese women: the Miyagi Cohort Study

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BACKGROUND: The role of adult weight change in breast cancer (BC) risk is unclear in Japanese women.

METHODS: A total of 10 106 postmenopausal women aged 40–64 years (the Miyagi Cohort) were followed from 1990 to 2003, and 108 BC cases were identified. Hazard ratios (HRs) were estimated according to body mass index (BMI) at the current age and at the of age 20 years, and weight change since age 20 years.

RESULTS: Higher current BMI was associated with an increased risk of BC (*P* for trend = 0.02), whereas higher BMI at the age 20 years was inversely associated with this risk (*P* for trend = 0.002). There was a significant association between weight change since age 20 years and BC risk (*P* for trend = 0.0086). Compared with stable weight, HR was 0.35 for weight loss of 5 kg or more (*P* for weight loss trend = 0.04) and 1.55 for weight gain of 12 kg or more (*P* for weight gain trend = 0.05).

CONCLUSION: Adiposity at younger and current age has differential effects on BC risk among postmenopausal women; weight gain in adulthood being associated with an increased, and weight loss with a decreased risk.

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The incidence of breast cancer (BC) shows variations among countries and although Japan has a lower risk of BC than Western countries, its age-standardised incidence is the highest among female cancers, and it is increasing (Matsuda *et al*, 2008). The increase of BC incidence may be attributed to a change in the proportion of women in the population who have reproductive and anthropometric risk factors (Minami *et al*, 2004). Among such risk factors, the associations between adiposity and BC risk have been extensively investigated, mainly in the Western countries (Lahmann *et al*, 2004; Morimoto *et al*, 2002; Reeves *et al*, 2007). In relation to adiposity, weight gain has also been associated with an increased risk of postmenopausal BC in several prospective studies (Ahn *et al*, 2007; Barnes-Josiah *et al*, 1995; Eliassen *et al*, 2006; Feigelson *et al*, 2004; Lahmann *et al*, 2005). In Japan, however, few prospective studies have evaluated the association with adiposity (Iwasaki *et al*, 2007; Kuriyama *et al*, 2005). Also, data are sparse regarding the effect of body weight change (Hirose *et al*, 1999; Kyogoku *et al*, 1990).

We therefore conducted a population-based cohort study, in which we evaluated the association of adiposity in different periods, that is, at current age and at age 20 years, with BC risk and examined the change in risk resulting from body weight gain and loss since the age of 20 years among postmenopausal Japanese women.

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MATERIALS AND METHODS

Our analysis used the Miyagi Cohort Study, whose design has been described in detail elsewhere (Fukao *et al*, 1995; Kawai *et al*, 2010). Briefly, 25 279 men and 26 642 women aged 40–64 years living in 14 municipalities, selected randomly from among the 62 municipalities in Miyagi Prefecture, Northeastern Japan, were entered into a cohort on 1 June 1990. A self-administered questionnaire on various health aspects was delivered to these subjects between June and August 1990. Usable questionnaires were returned by 22 836 men (90.3%) and 24 769 women (93.0%). After excluding men, women with a history of cancer ($n = 705$), who were premenopausal ($n = 9131$), with undefined menopausal status ($n = 642$) and for whom data on menopausal status were missing ($n = 2927$), 11 364 postmenopausal women remained (Kawai *et al*, 2010). After further excluding women with missing data or extreme values for current height or current weight or weight at age 20 years ($n = 1258$), 10 106 postmenopausal women contributed to this study. The study protocol was approved by the institutional review board of Tohoku University School of Medicine. We considered the return of self-administered questionnaires signed by the subjects to imply their consent to participate in the study.

The questionnaire covered personal history including current height (centimeters) and weight (kilograms) and weight at age 20 years and details of general lifestyle including menstrual and reproductive histories. The self-reported current height and weight data were highly correlated with measured data (correlation coefficient: 0.82 for height and 0.97 for weight) in a subsample of postmenopausal women ($n = 2921$), although we were unable to validate the data for weight at age 20 years.

As a measure of adiposity, body mass index (BMI) was used. The BMI at the current age and at age 20 years, calculated as weight divided by the square of current height ($kg\,m^{-2}$), respectively. To analyze BC risk for adiposity in the different periods, the study women were categorised using quartile points of BMI at age 20 years, respectively: <20.5, ⩾20.5–<22.0, ⩾22.0–<23.8 and ⩾23.8. Subjects with a current BMI of 23.8 and higher were further divided into two groups on the basis of median value in the range between 23.8 and the largest current BMI, as the BMI at the current age was skewed towards a higher value than at age 20 years. Finally, women were categorised as follows: current BMI <20.5, ⩾20.5–<22.0, ⩾22.0–<23.8, ⩾23.8–<25.9 and ⩾25.9; BMI at age 20 <20.5, ⩾20.5–<22.0, ⩾22.0–<23.8 and ⩾23.8. Weight change from age 20 years to the current age was calculated as the difference between current weight and weight at age 20. Subjects were also categorised into seven groups as follows: weight loss of ⩽−5 and >−5 to ⩽−2, stable weight of >−2 to <+2, and weight gain of ⩾+2 to <+5, ⩾+5 to <+8, ⩾+8 to <+12 and ⩾+12. The categorisation of weight loss was based on the median value, and that of weight gain was determined using quintile values.

Women were followed from the start of the study (1 June 1990) until 31 December 2003. The end point of our analysis was BC defined as the topography codes C50.0–C50.9 according to the International Classification of Disease for Oncology, Second Edition, and confirmed by the Miyagi Prefecture Cancer Registry, one of the oldest and most accurate population-based in Japan (Curado *et al*, 2007). In this registry, the percentage registered by death certificates only for BC was 2.5% during 1991–2003. A follow-up committee was also established, consisting of the Miyagi Cancer Society, the Divisions of Community Health of all 14 municipalities, the Department of Health and Welfare, Miyagi Prefectural Government, and the Division of Epidemiology, Tohoku University School of Medicine. The committee periodically reviewed the residential registration record of each municipality. During the study period, 491 women (4.9%) were lost to follow-up because of emigration.

Statistical analysis

The person-years of follow-up were counted for each of the subjects from the start of the study (1 June 1990) until the date of diagnosis of BC, the date of emigration from the study area, the date of death, or the end of follow-up (31 December 2003), whichever occurred first. The mean follow-up period was 12.8 years. The Cox proportional-hazard regression model was used to estimate BC hazard ratios (HRs) and 95% confidence intervals (CIs) according to category of exposure variable, that is, BMI at the current age, BMI at age 20 years and weight change from age 20 years to the current age, and to adjust for confounding variables (Cox, 1972). Linear trends, which were tested using the Cox model by treating each exposure category as a continuous variable, were regarded as significant if *P*-values were <0.05. We considered the following variables as potential confounders: age, education level, cigarette smoking, alcohol drinking, and time spent walking, which are known or suspected risk factors for BC. Menstrual and reproductive factors, exogenous female hormone use, and history of BC in the mother or sisters, some of which had been established as risk factors in our previous study (Kawai *et al*, 2010), were also considered to be adjusted for each other. In the analysis of weight change, height and weight at age 20 years were further adjusted for (Eliassen *et al*, 2006). Missing values for confounders were treated as an additional variable category, and were included in the model. To evaluate any independent effect of BMI during the different periods, analysis adjusting for both BMIs each other was also conducted. All statistical analyses were performed using the SAS software package (version 9.1; SAS Institute, Cary, NC ,USA).

RESULTS

The characteristics of the study subjects are presented in Tables 1 and 2. The subjects with a higher current BMI were less likely to smoke, whereas the subjects with a higher BMI at age 20 years tended to be older and to have a shorter period of education (Table 1). A total of 64.8% of the subjects had gained more than 2 kg since age 20 years (Table 2). The subjects who lost weight were heavier at age 20 years.

During 129 891 person-years of follow-up, 108 BC cases were documented. Table 3 shows the HRs and 95% CIs according to current BMI and BMI at age 20 years. After adjustment for confounding variables, current BMI was marginally associated with an increased BC risk (*P* for trend in multivariate-adjusted model 1 = 0.07). The BMI at age 20 years was inversely associated risk (*P* for trend in multivariate-adjusted model 1 = 0.01). Postmenopausal women with a BMI of ⩾23.8 at age 20 years showed half the risk (multivariate-adjusted HR = 0.44, 95% CI: 0.24–0.81) of women with a BMI of <20.5. Multivariate analysis adjusting for both BMIs each other demonstrated a stronger inverse association for BMI at age 20 years (*P* for trend in multivariate-adjusted model 2 = 0.002). The association of current BMI with risk was statistically significant (*P* for trend = 0.02).

Weight change since the age of age 20 years was significantly associated with the risk (multivariate-adjusted *P* for trend = 0.0086) (Table 4). Compared with women whose weight had been stable (lost or gained <2.0 kg), those who lost 5 kg or more were at a lower risk (multivariate-adjusted HR 0.35, 95% CI: 0.11–1.10). Women with a weight gain of 12 kg or more appeared to have a higher risk (HR 1.55, 95% CI: 0.70–3.45). According to weight loss and gain, weight loss was associated with a decreased risk (*P* for weight loss trend = 0.04), and weight gain with an increased risk (*P* for weight gain trend = 0.05). Although the data are not shown in the table, stratified analysis by the BMI at age 20 years revealed a clearer inverse association with weight loss among women who were heavier at age 20 years (BMI at age 20 years ⩾23.8; *P* for weight loss trend = 0.01).

DISCUSSION

In this population-based cohort study, we found associations between adulthood adiposity and weight change and BC risk among postmenopausal women. Risk differed for BMI between that at current age and that at age 20 years. Weight change from age 20 to current age was significantly associated with risk. These results provide some insight into the significance of adiposity and weight change in terms of BC risk in postmenopausal Japanese women.

This study found a positive association of current BMI with postmenopausal BC risk consistent with previous prospective studies (Iwasaki *et al*, 2007; Kuriyama *et al*, 2005; Lahmann *et al*, 2004; Morimoto *et al*, 2002; Reeves *et al*, 2007), and the fact that postmenopausal obese women have more oestrogens than lean women (Potischman *et al*, 1996), has a central role in BC aetiology. After menopause, oestrogen is synthesised mainly by aromatase in adipose tissue (Bulun *et al*, 2005). Another mechanism is that obese women may be in a state of hyperinsulinemia, insulin being a growth factor for BC cells. Insulin-like growth factor I may also affect risk among heavier women (Muti *et al*, 2002). On the other

Table 1 Characteristics of study population according to body mass index (BMI)

	<20.5	⩽20.5 <22.0	⩽22.0 <23.8	⩽23.8 <25.9	⩽25.9
Current BMI					
Number of subjects	1209	1497	2335	2516	2549
Age (mean, years)	57.2 ± 4.5	57.0 ± 4.4	57.1 ± 4.3	57.2 ± 4.3	57.5 ± 4.2
Occupation (no occupation/housewife, %)	15.4	15.5	17.3	16.6	17.1
Educational level (college/university or higher, %)	12.4	12.8	12.5	11.7	10.3
Alcohol drinking (drinkers, %)	19.5	19.0	18.6	19.1	18.8
Smoking (smokers, %)	10.3	7.6	5.9	5.7	5.8
Walking status (<1 h per day, %)	44.7	46.6	45.1	46.1	49.2
Family history of breast cancer in mother or sisters (%)	1.8	1.7	2.3	2.0	2.0
Age at menarche (mean, years)	15.4 ± 2.1	15.3 ± 1.9	15.3 ± 2.0	15.2 ± 2.0	15.2 ± 2.1
Age at menarche (16 years ⩽, %)	37.2	35.9	36.2	34.7	32.4
Age at natural menopause (mean, years)	49.1 ± 3.8	49.5 ± 3.6	49.4 ± 3.4	49.4 ± 3.7	49.7 ± 3.7
Parity (nulliparous, %)	3.7	2.7	1.8	2.3	2.2
Parity number among parous women (mean)	2.6 ± 1.0	2.6 ± 1.0	2.7 ± 1.0	2.7 ± 1.0	2.8 ± 1.1
Exogenous female hormone use (users, %)	11.7	10.6	9.9	10.8	10.0
Height (mean, cm)	152.4 ± 6.7	151.7 ± 5.2	151.5 ± 5.0	151.5 ± 4.9	150.7 ± 5.3
	<20.5	**⩽20.5 <22.0**	**⩽22.0 <23.8**	**⩽23.8**	
BMI at age 20 years					
Number of subjects	2577	2460	2594	2475	
Age (mean, years)	56.9 ± 4.4	57.1 ± 4.3	57.3 ± 4.3	57.6 ± 4.2	
Occupation (no occupation/housewife, %)	19.0	17.1	16.3	14.0	
Educational level (college/university or higher, %)	14.0	12.7	10.8	9.5	
Alcohol drinking (drinkers, %)	20.0	17.5	18.6	19.6	
Smoking (smokers, %)	7.3	6.0	6.1	6.8	
Walking status (<1 h per day, %)	48.7	45.6	47.0	44.7	
Family history of breast cancer in mother or sisters (%)	2.3	1.5	2.1	2.0	
Age at menarche (mean, years)	15.4 ± 2.0	15.2 ± 1.9	15.3 ± 2.0	15.3 ± 2.1	
Age at menarche (16 years ⩽, %)	36.7	33.3	35.0	34.7	
Age at natural menopause (mean, years)	49.3 ± 3.7	49.4 ± 3.5	49.5 ± 3.7	49.6 ± 3.6	
Parity (nulliparous, %)	3.7	2.0	2.0	1.8	
Parity number among parous women (mean)	2.6 ± 1.0	2.7 ± 1.0	2.7 ± 1.1	2.8 ± 1.1	
Exogenous female hormone use (users, %)	11.6	9.9	10.2	10.1	
Height (mean, cm)	152.9 ± 5.8	151.6 ± 4.7	151.0 ± 5.0	150.2 ± 5.4	

Table 2 Characteristics of study population according to weight change from age 20 to the current age

Characteristics	Weight loss[a]	Stable weight[b]	Weight gain[c]
Number of subjects	2801	758	6547
Age (mean, years)	57.4 ± 4.3	57.1 ± 4.4	57.2 ± 4.3
Occupation (no occupation/housewife, %)	14.6	16.1	17.5
Education level (college/university or higher, %)	10.6	13.6	12.0
Alcohol drinking (drinkers, %)	19.4	18.2	18.9
Smoking (smokers, %)	8.0	6.3	6.0
Walking status (<1 h per day, %)	43.5	44.7	48.1
Family history of breast cancer in mother or sisters (%)	1.6	3.2	2.0
Age at menarche (mean, years)	15.4 ± 2.0	15.1 ± 1.9	15.2 ± 2.0
Age at menarche (16 years ⩽, %)	37.9	30.0	34.3
Age at natural menopause (mean, years)	49.5 ± 3.6	49.3 ± 3.4	49.5 ± 3.6
Parity (nulliparous, %)	2.2	3.0	2.4
Parity number among parous women (mean)	2.7 ± 1.0	2.7 ± 1.0	2.7 ± 1.0
Exogenous female hormone use (users, %)	10.2	12.4	10.3
Height (mean, cm)	150.8 ± 5.5	151.3 ± 5.2	151.7 ± 5.3
Weight at 20 years (mean, kg)	54.7 ± 6.2	51.3 ± 6.1	49.0 ± 5.4
Current body mass index (mean)	21.6 ± 2.3	22.4 ± 2.4	25.2 ± 2.9

Weight change was evaluated for subjects with complete data for height. [a]Weight loss ⩾2 kg. [b]Weight gain or loss <2 kg. [c]Weight gain ⩾2 kg.

hand, a higher BMI at age 20 years was significantly associated with a decreased postmenopausal risk. This inverse association, which has also been observed in the Western countries (Ahn *et al*, 2007; Morimoto *et al*, 2002; Sellers *et al*, 1992; van den Brandt *et al*, 1997), was independent of the effect of current BMI. The Nurses' Health Study recently reported the independent protective effect of body fatness at young age using a pictogram (Baer *et al*, 2010). Although the mechanisms explaining this inverse association are poorly understood, lower serum oestradiol and progesterone levels and anovulation among young obese women may reduce BC risk after menopause (Potischman *et al*, 1996).

There was a significant association between weight change since age 20 and postmenopausal risk. Weight gain was associated with an increased risk, and weight loss with a decreased risk.

Table 3 Hazard ratio (HR) and 95% confidence interval (CI) of breast cancer according to current body mass index (BMI) and BMI at age 20 years

			Age-adjusted model		Multivariate-adjusted model 1[a]		Multivariate-adjusted model 2	
	Person-years	**Cases**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Current BMI								
<20.5	15 327	8	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)[b]
20.5≤ <22.0	19 121	15	1.50	0.64–3.54	1.51	0.64–3.56	1.63	0.69–3.86
22.0≤ <23.8	29 835	24	1.54	0.69–3.43	1.55	0.70–3.46	1.74	0.78–3.90
23.8≤ <25.9	32 575	27	1.59	0.72–3.49	1.64	0.74–3.61	1.86	0.84–4.12
25.9≤	33 033	34	1.97	0.91–4.25	2.04	0.94–4.41	2.54	1.16–5.55
P for trend				0.09		0.07		0.02
BMI at age 20 years								
<20.5	32 880	37	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)[c]
20.5≤ <22.0	31 555	29	0.82	0.50–1.33	0.88	0.54–1.44	0.83	0.51–1.36
22.0≤ <23.8	33 460	28	0.74	0.45–1.21	0.80	0.49–1.31	0.72	0.44–1.19
23.8≤	31 996	14	0.39	0.21–0.72	0.44	0.24–0.81	0.38	0.20–0.70
P for trend				0.003		0.01		0.002

[a]Adjusted for age (continuous variable), alcohol drinking (ever, never), smoking (ever, never), occupation (permanent, no occupation/housewife), walking (<1 h per day, longer than 1 h per day), education level (junior high school or less, high school, college/university or higher), age at menarche (≤13, 14, 15, 16<), age at menopause (≤47, 48≤ ≤50, 51≤ ≤53, 54≤), parity number (0, 1, 2, 3, 4, 5≤), family history of breast cancer (present, absent) and history of exogenous female hormone use (ever, never). [b]Additionally adjusted for BMI at age 20 years (<20.5, 20.5≤ <22.0, 22.0≤ <23.8, 23.8≤). [c]Additionally adjusted for current BMI (<20.5, 20.5≤ <22.0, 22.0≤ <23.8, 23.8≤ <25.9, 25.9≤).

Table 4 Hazard ratio (HR) and 95% confidence interval (CI) of breast cancer according to weight change from age 20 years to the current age

			Age-adjusted model		Multivariate-adjusted model[a]	
Weight change (kg)	**Person-years**	**Cases**	**HR**	**95% CI**	**HR**	**95% CI**
≤−5	19760	5	0.31	0.10–0.94	0.35	0.11–1.10
−5< ≤−2	16128	13	0.98	0.41–2.36	1.05	0.43–2.55
−2< <+2	9714	8	1.00	(Reference)	1.00	(Reference)
+2≤ <+5	18765	11	0.71	0.29–1.77	0.70	0.28–1.75
+5≤ <+8	22857	21	1.12	0.49–2.52	1.09	0.48–2.47
+8≤ <+12	20100	19	1.15	0.50–2.62	1.10	0.48–2.53
+12≤	22567	31	1.67	0.77–3.63	1.55	0.70–3.45
P for trend				0.0002		0.0086
P for weight loss trend				0.03		0.04
P for weight gain trend				0.02		0.05

[a]Adjusted for age (continuous variable), height (<149, 149≤ <152, 152≤ <156, 156≤), body weight at age 20 (continuous variable), alcohol drinking (ever, never), smoking (ever, never), occupation (permanent, no occupation/housewife), walking (<1 h per day, longer than 1 h per day), education level (junior high school or less, high school, college/university or higher), age at menarche (≤13, 14, 15, 16<), age at menopause (≤47, 48≤ ≤50, 51≤ ≤53, 54≤), parity number (0, 1, 2, 3, 4, 5≤), family history of breast cancer (present, absent) and history of exogenous female hormone use (ever, never).

For postmenopausal women who were heavier at age 20 years, a clearer inverse association with weight loss was observed. These results might have been expected from the different associations of risk with BMI at the current age and at age 20 years, as mentioned above. To our knowledge, this is the first prospective cohort study to have evaluated the association between weight change and BC risk among Japanese women. The positive effect of weight gain has been observed in nearly all prospective studies from Western countries (Ahn *et al*, 2007; Barnes-Josiah *et al*, 1995; Eliassen *et al*, 2006; Feigelson *et al*, 2004; Lahmann *et al*, 2005). On the other hand, the relationship of weight loss to risk has not been fully investigated (Eliassen *et al*, 2006; Harvie *et al*, 2005; Hirose *et al*, 1999; Kyogoku *et al*, 1990; Lahmann *et al*, 2005). Although most of the studies have observed a null or non-significant association, a few have demonstrated a significantly decreased postmenopausal risk associated with adult weight loss (Eliassen *et al*, 2006). Our results provide additional evidence for the association with adult weight change, especially weight loss.

Strengths of our study included its prospective design and the high quality of the follow-up. Although this cohort was relatively small scale, participants were recruited from the general population, and BC cases were identified from the population-based cancer registry. Furthermore, the rate of loss to follow-up was low, so selection and information bias were avoided. Limitations included, first, the fact that weights at age 20 years and at current age, and height, were self-reported. The correlations between measured and self-reported current weight and height were high. On the other hand, there were no data for measured weight at age 20years. The self-recalled weight at age 20 years may have been lower or higher than the real weight, thus causing a non-differential misclassification bias. However, it is unlikely that this bias would have seriously distorted the results (Rothman and Greenland, 1998). Second, our results may have been contaminated subclinical effects of BC by cases occurring soon after recruitment. We, therefore, analyzed the data after omitting cases that occurred within 2 years of recruitment, but this yielded almost the same results (data not shown).

This study has found that adiposity at younger and current age has differential effects on BC risk, and that weight change during adulthood is associated with the postmenopausal risk among Japanese women; weight gain was associated with an increased risk, and weight loss with a decreased risk. As body weight is a modifiable lifestyle factor, weight control throughout life appears to be useful in BC.

Epidemiology

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Conflict of interest

The authors declare no conflicts of interest.

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Study Profile

The Ohsaki Cohort 2006 Study: Design of Study and Profile of Participants at Baseline

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ABSTRACT

Background: Large-scale cohort studies conducted in Japan do not always include psychosocial factors as exposures. In addition, such studies sometimes fail to satisfactorily evaluate disability status as an outcome.
Methods: This prospective cohort study comprised 49 603 (22 438 men and 27 165 women) community-dwelling adults aged 40 years or older who were included in the Residential Registry for Ohsaki City, Miyagi Prefecture, in northeastern Japan. The baseline survey, which included psychosocial factors, was conducted in December 2006. Follow-up of death, immigration, cause of death, cancer incidence, and long-term care insurance certification was started on 1 January 2007.
Results: The response rate was 64.2%. In general, lifestyle-related conditions in the study population were similar to those of the general Japanese population; however, the proportion of male current smokers was higher in the cohort. The association between age and the proportion of those reporting psychological distress showed a clear U-shaped curve, with a nadir at age 60 to 69 years in both men and women, although more women were affected by such distress than men. The proportion of those who reported a lack of social support was highest among those aged 40 to 49 years. Most men and women surveyed did not participate in community activities. Among participants aged 65 years or older, 10.9% of participants were certified beneficiaries of the long-term care insurance system at baseline.
Conclusions: The Ohsaki Cohort 2006 Study is a novel population-based prospective cohort study that focuses on psychosocial factors and long-term care insurance certification.

Key words: long-term care insurance; population-based; psychosocial factors; study design; the Ohsaki Cohort 2006 Study

INTRODUCTION

Increasing evidence suggests that, in addition to biomedical factors, a broad range of psychosocial factors influences general health.[1–3] However, large-scale cohort studies performed in Japan may not have sufficiently considered these factors as exposures in evaluating health outcomes.[4–9]

In addition to this tendency to overlook psychosocial exposures, some types of health outcomes, such as disability status, have not been satisfactorily examined in large-scale epidemiological studies in Japan.[4–9] Although there is growing concern about the quality of life of seniors,[10,11] assessment of quality of life—in particular disability status—by means of general population surveys presents many challenges.[12–14] In 2000, the Japanese government implemented a mandatory social long-term care insurance (LTCI) system to promote the independence of seniors by facilitating access to appropriate high-quality services of their choice, whenever and wherever needed.[15,16] Therefore, there is now an opportunity to use LTCI certification status as an alternative to the evaluation of physical and mental disability.

Based on the need for a novel cohort that accounts for the recent diversification in the abovementioned exposures and outcomes, we initiated a large population-based prospective cohort study, the Ohsaki Cohort 2006 Study, the main

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Table 1. Response rate and number of adults in source population, eligible population, and study population

	Aged 40–64 years		Aged ≥65 years		Total
	Men	Women	Men	Women	
No. of source population	23647	22760	12750	18944	78101
No. of eligible population (A)	23359	22639	12606	18631	77235
No. of persons responding to the survey	12967	13849	9690	13704	50210
No. of study population (B)	12833	13679	9605	13486	49603
Response rate (B/A) (%)	54.9	60.4	76.2	72.4	64.2

objective of which is to examine the association between psychosocial factors and both physical and mental disability status. Here, we report the design of the study and the profile of participants at baseline.

METHODS

Study design, setting, and participants

In this prospective cohort study, the source population for the baseline survey comprised community-dwelling individuals aged 40 years or older who were included in the Residential Registry for Ohsaki City, Miyagi Prefecture, northeastern Japan, as of 1 December 2006. The Residential Registry identified 78 101 persons (36 397 men; 41 704 women) in the area.

The baseline survey was conducted from 1 December to 15 December 2006. A questionnaire was distributed by the heads of individual administrative districts to individual households, after which it was collected by mail.

Baseline survey

The baseline questionnaire for persons aged 40 to 64 years requested information on the following, in sequence: (1) history of diseases, (2) family history of diseases, (3) health status over the last year, (4) smoking status, (5) alcohol drinking status, (6) dietary habits,[17] (7) job status and educational status, (8) present and past body weight and height, (9) general health status, (10) sports and exercise,[18,19] (11) psychological distress (using the K6, a 6-item instrument that assesses nonspecific psychological distress developed by Kessler and colleagues),[20–23] (12) social support,[24] (13) participation in community activities, (14) dental status, and (15) reproductive factors (in women).

Question items for persons aged 65 years or older were the same as those for persons aged 40–64, excluding family history of diseases, job status and educational status, present and past body weight and height, and reproductive factors. In addition, we included a frailty checklist (the Kihon Checklist, in Japanese),[25] along with (1) past body weight and height, (2) pain, and (3) daily activities. The Kihon Checklist is a tool developed by the Japanese Ministry of Health, Labour, and Welfare to screen for frailty, and is designed to measure actual task performance.[25]

All people who supplied their name and address, and completed most of the questionnaire, were regarded as eligible; all others were excluded. The reasonableness of data was evaluated according to predetermined rules.

Follow-up

We conducted this prospective cohort study with the cooperation of the Ohsaki City municipal government after obtaining their written agreement. The aim is to follow the cohort participants for mortality and immigration using the Residential Registry of Ohsaki City. We also confirm information regarding LTCI certification status among individuals aged 65 years or older, after obtaining written consent for review of these data. Causes of death are confirmed by review of death certificates, with approval from the Japanese Ministry of Internal Affairs and Communications and the Japanese Ministry of Health, Labour, and Welfare. Cancer incidence is also confirmed by review of data from the Miyagi Prefectural Cancer Registry, with approval from the Miyagi Prefectural Cancer Registry Committee.

Ethical issues

The return of questionnaires completed by the participants was regarded as consent to participate in the study, which involves cross-sectional analysis of baseline survey data and information on subsequent mortality and immigration. We provided an explanatory note on the questionnaire that stated we would follow the cohort participants for mortality and cancer incidence. The study protocol was reviewed and approved by the Ethics Committee of Tohoku University Graduate School of Medicine.

RESULTS

Data on the source population, eligible population, study population, and response rate by age and sex are shown in Table 1. Of the 78 101 people in the source population, we were unable to contact 866, yielding an eligible population of 77 235. Baseline questionnaires were collected from 50 210 persons, and valid responses were received from 49 603 (22 438 men and 27 165 women), who formed the study population of cohort participants. Among the invalid responses, 252 persons aged 65 years or older completed

Table 2. Selected baseline medical and lifestyle-related profiles of study population, by sex and age category

Variables	Age category (years)									
	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	≥85
Men										
No. of participants	1857	2365	2884	3427	2300	2477	2846	2391	1256	635
History of serious disease (%)										
Hypertension	7.7	14.6	18.8	25.4	32.7	37.8	41.9	44.0	39.7	35.3
Diabetes mellitus	3.6	5.2	7.5	11.0	12.8	14.4	16.2	13.6	11.5	10.1
Stroke	0.4	0.6	1.3	2.0	3.4	4.4	5.6	7.1	7.9	8.8
Myocardial infarction	0.1	0.7	1.0	1.8	3.5	4.7	5.9	8.5	9.7	11.5
Cancer	0.8	1.5	2.1	2.8	5.0	7.4	10.4	13.0	12.3	9.8
Current smokers (%)	59.5	56.7	50.6	46.8	40.4	31.4	25.9	21.3	19.2	11.1
Current alcohol drinkers (%)	81.5	80.6	80.7	79.2	77.0	69.1	61.6	53.2	45.3	30.3
Body mass index (%)										
<18.5 kg/m^2	2.7	2.5	1.7	2.0	2.5	3.0	3.7	6.2	11.0	10.9
≥25.0 kg/m^2	35.1	33.8	34.7	34.7	30.8	32.1	29.1	26.3	19.7	16.6
Time spent walking <1 hr/day (%)	69.4	68.4	67.5	67.2	67.3	63.9	67.9	74.2	79.0	85.3
Women										
No. of participants	1935	2488	3025	3638	2593	3070	3623	3303	2021	1469
History of serious disease (%)										
Hypertension	3.3	8.3	15.0	23.5	30.1	37.0	43.0	46.4	47.7	46.1
Diabetes mellitus	0.8	2.6	3.3	6.0	8.4	8.5	10.4	11.6	12.0	10.2
Stroke	0.3	0.2	0.6	0.5	1.1	1.6	2.5	3.8	4.6	6.3
Myocardial infarction	0.1	0.0	0.2	0.5	1.0	1.5	2.9	4.4	6.1	7.2
Cancer	2.0	2.7	4.3	4.7	6.9	6.0	5.9	6.2	6.9	7.9
Current smokers (%)	19.6	15.2	11.0	9.1	7.3	4.7	3.8	2.8	2.5	2.1
Current alcohol drinkers (%)	56.7	49.5	40.3	34.1	29.9	20.7	14.4	11.6	10.8	9.2
Body mass index (%)										
<18.5 kg/m^2	7.5	6.3	4.8	4.2	3.3	3.7	4.8	6.4	9.1	16.1
≥25.0 kg/m^2	20.1	22.6	27.4	28.3	32.2	34.9	35.2	31.9	27.7	22.0
Time spent walking <1 hr/day (%)	74.0	70.3	70.2	71.6	73.4	70.0	72.5	78.8	84.4	91.6

the questionnaires intended for those aged 40 to 64 years. Among the study population, 26 512 persons (53.4%) were aged 40 to 64 years, and 23 091 (46.6%) were aged 65 years or older. The response rate was calculated by dividing the study population by the total eligible population, yielding 64.2%. The response rate for men was 62.4% (22 438/35 965), and was somewhat lower than that for women, at 65.8% (27 165/41 270). By age, the response rate for persons aged 65 years or older was high, at 73.9% (23 091/31 237), while that for persons aged 40 to 64 years was 57.6% (26 512/45 998).

Selected baseline medical and lifestyle-related profiles of the study population

The selected baseline medical and lifestyle-related profiles of the study population are shown in Table 2. The prevalence of a history of serious disease rose with increasing age in both men and women. In men, the distributions of a history of hypertension, diabetes mellitus, and cancer all peaked at age 70 to 79 years. More than 40% of men aged 75 to 79 years had a history of hypertension. About 60% of men, and 20% of women, aged 40 to 44 years currently smoked, and more than 80% of men, and 50% of women, in the same age group currently drank alcohol at baseline, which decreased with increasing age. The proportion of obese individuals, defined as a BMI ≥25.0 kg/m^2, was inversely associated with age in men, but weakly positively associated with age in women, with a peak at age 70 to 79 years. The association between age and the proportion of individuals who were underweight, defined as a BMI <18.5 kg/m^2, was J-shaped for men and U-shaped for women. The association between age and the proportion of those who spent less than 1 hour per day walking was J-shaped for both men and women.

Selected baseline psychosocial profiles of the study population

With regard to psychosocial profiles (Table 3), the association between age and the proportion of participants who had psychological distress showed a clear U-shaped curve in both sexes, with a nadir in those aged 60 to 69 years; psychological distress was more common in women than in men. The proportion of those who reported lack of social support was highest among those in their 40s, and decreased with age for every component of social support in both men and women. More men than women reported lack of social support. About 20% of men in their 40s reported lack of social support for consultation when in trouble. In contrast, the association between age and the proportion of those who did not participate in community activities showed a J-shape curve with a nadir at age 60 to 69 years.

Table 3. Selected baseline psychosocial profiles of study population, by sex and age category

Variables	Age category (years)									
	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	≥85
Men										
Psychological distress[a], yes (%)	7.1	7.4	6.2	5.1	4.7	4.1	4.8	5.7	7.0	6.9
Lack of social support (%)										
(i) To consult when you are in trouble	19.0	20.1	18.0	18.0	18.1	14.5	12.7	13.3	13.1	13.7
(ii) To consult when you are in bad physical condition	15.8	15.7	15.1	13.9	12.6	8.9	8.0	7.7	5.9	7.4
(iii) To help with your daily housework	18.2	18.9	17.8	17.5	18.8	17.6	15.8	16.2	13.0	9.0
(iv) To take you to a hospital	13.5	12.3	11.7	9.5	9.5	7.8	7.6	8.0	6.9	5.3
(v) To take care of you	10.8	11.0	11.6	9.6	10.5	8.8	9.1	9.0	9.9	8.9
No participation in community activities (%)										
(i) Neighborhood association activities	50.1	46.0	45.8	44.6	45.5	42.9	48.0	50.2	59.5	70.6
(ii) Sports or exercise	47.9	49.6	51.6	53.9	49.5	45.8	50.3	55.4	61.7	70.9
(iii) Volunteering	69.3	63.6	61.4	60.4	60.5	56.1	60.8	65.1	75.6	88.7
(iv) Social gatherings	52.7	53.0	50.8	48.5	46.3	40.3	44.9	50.7	61.0	78.9
Women										
Psychological distress[a], yes (%)	9.9	8.7	7.4	6.6	5.4	5.3	6.4	7.5	10.5	13.9
Lack of social support (%)										
(i) To consult when you are in trouble	11.1	10.8	10.2	10.5	9.9	7.9	7.4	7.1	7.7	4.9
(ii) To consult when you are in bad physical condition	11.5	10.8	9.2	9.1	8.9	6.3	5.8	5.1	4.8	2.7
(iii) To help with your daily housework	16.5	15.4	13.5	16.2	16.8	15.3	15.7	13.0	9.7	4.5
(iv) To take you to a hospital	13.3	11.6	7.5	8.8	8.2	8.0	7.8	7.4	5.5	3.4
(v) To take care of you	16.5	15.6	13.4	16.4	17.3	17.8	19.0	17.1	12.9	7.0
No participation in community activities (%)										
(i) Neighborhood association activities	42.3	52.0	57.3	56.3	54.2	53.7	55.8	59.5	69.8	86.8
(ii) Sports or exercise	61.1	58.8	60.5	56.4	51.4	50.0	54.1	62.5	75.0	88.3
(iii) Volunteering	78.8	75.7	73.7	70.1	67.3	67.0	74.3	81.0	88.9	97.4
(iv) Social gatherings	59.5	59.7	60.3	56.9	53.2	51.1	56.2	61.0	74.0	91.9

[a]The K6 was used as an indicator of psychological distress.[20–23]

Table 4. Number (%) of participants certified in the long-term care insurance system of Japan at baseline

Care level	Age category (years)				
	65–69	70–74	75–79	80–84	≥85
Men					
Uncertified	1817 (97.6)	2037 (95.5)	1683 (92.6)	808 (85.0)	316 (65.8)
Support level 1[a]	4 (0.2)	7 (0.3)	13 (0.7)	14 (1.5)	12 (2.5)
Support level 2[a]	4 (0.2)	17 (0.8)	16 (0.9)	22 (2.3)	11 (2.3)
Care level 1[b]	10 (0.5)	21 (1.0)	27 (1.5)	23 (2.4)	47 (9.8)
Care level 2[b]	15 (0.8)	11 (0.5)	25 (1.4)	34 (3.6)	30 (6.3)
Care level 3[b]	3 (0.2)	15 (0.7)	20 (1.1)	28 (2.9)	27 (5.6)
Care level 4[b]	5 (0.3)	18 (0.8)	25 (1.4)	11 (1.2)	18 (3.8)
Care level 5[b]	4 (0.2)	6 (0.3)	9 (0.5)	11 (1.2)	19 (4.0)
Women					
Uncertified	2153 (98.3)	2411 (95.0)	2076 (90.2)	1090 (77.2)	520 (49.4)
Support level 1[a]	4 (0.2)	24 (0.9)	41 (1.8)	49 (3.5)	36 (3.4)
Support level 2[a]	7 (0.3)	31 (1.2)	45 (2.0)	52 (3.7)	59 (5.6)
Care level 1[b]	9 (0.4)	25 (1.0)	57 (2.5)	92 (6.5)	126 (12.0)
Care level 2[b]	3 (0.1)	13 (0.5)	26 (1.1)	48 (3.4)	93 (8.8)
Care level 3[b]	8 (0.4)	10 (0.4)	20 (0.9)	28 (2.0)	83 (7.9)
Care level 4[b]	5 (0.2)	15 (0.6)	22 (1.0)	29 (2.1)	70 (6.7)
Care level 5[b]	2 (0.1)	10 (0.4)	15 (0.7)	24 (1.7)	65 (6.2)

[a]Those who require support for daily activities; a higher number indicates a need for greater support.
[b]Those who require continuous care; a higher number indicates a need for greater continuous care.

LTCI certification at baseline

The percentages of participants aged 65 years or older at baseline who received LTCI certification are shown in Table 4. Among participants in this age group, 16739 (72.5%) provided written consent for our review of the information. Among these seniors, 10.9% had been LTCI-certified as of 15 December 2006. The proportion of those who were LTCI-certified increased linearly in relation to age