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.

Epidemiology

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

ACKNOWLEDGEMENTS

This work was supported by a grant for the Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (grant nos: H20-Kiban C-20590630, H21-Kiban C-21590681) and in part by the third Term Comprehensive Control Research for Cancer (grant no. H18-Senryaku-001, H21-Ippan-003) from the Ministry of Health, Labour and Welfare of Japan.

Conflict of interest
The authors declare no conflicts of interest.

REFERENCES

Ahn J, Schatzkin A, Lacey Jr JV, Albanes D, Ballard-Barbash R, Adams KF, Kipnis V, Mouw T, Hollenbeck AR, Leitzmann MF (2007) Adiposity, adult weight change, and postmenopausal breast cancer risk. *Arch Intern Med* **167:** 2091–2102

Baer HJ, Tworoger SS, Hankinson SE, Willett WC (2010) Body fatness at young ages and risk of breast cancer throughout life. *Am J Epidemiol* **171:** 1183–1194

Barnes-Josiah D, Potter JD, Sellers TA, Himes JH (1995) Early body size and subsequent weight gain as predictors of breast cancer incidence (Iowa, United States). *Cancer Causes Control* **6:** 112–118

Bulun SE, Lin Z, Imir G, Amin S, Demura M, Yilmaz B, Martin R, Utsunomiya H, Thung S, Gurates B, Tamura M, Langoi D, Deb S (2005) Regulation of aromatase expression in estrogen-responsive breast and uterine disease: from bench to treatment. *Pharmacol Rev* **57:** 359–383

Cox DR (1972) Regression models and life-tables (with discussion). *J Roy Statist Soc* **34:** 187–220

Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, Boyle P (2007) *Cancer Incidence in Five Continents*, Vol. IX IARC Scientific Publications No. 160: Lyon

Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE (2006) Adult weight change and risk of postmenopausal breast cancer. *JAMA* **296:** 193–201

Feigelson HS, Jonas CR, Teras LR, Thun MJ, Calle EE (2004) Weight gain, body mass index, hormone replacement therapy, and postmenopausal breast cancer in a large prospective study. *Cancer Epidemiol Biomarkers Prev* **13:** 220–224

Fukao A, Tsubono Y, Komatsu S, Tsuji I, Minami Y, Hisamichi S, Hosokawa T, Kawamura M, Takano A, Sugawara N, Ikeda T, Nishikori M (1995) A cohort study on the relation of lifestyle, personality and biologic markers to cancer in miyagi, japan: study design, response rate and profiles of the cohort subjects. *J Epidemiol* **5:** 153–157

Harvie M, Howell A, Vierkant RA, Kumar N, Cerhan JR, Kelemen LE, Folsom AR, Sellers TA (2005) Association of gain and loss of weight before and after menopause with risk of postmenopausal breast cancer in the Iowa women's health study. *Cancer Epidemiol Biomarkers Prev* **14:** 656–661

Hirose K, Tajima K, Hamajima N, Takezaki T, Inoue M, Kuroishi T, Miura S, Tokudome S (1999) Effect of body size on breast-cancer risk among Japanese women. *Int J Cancer* **80:** 349–355

Iwasaki M, Otani T, Inoue M, Sasazuki S, Tsugane S (2007) Body size and risk for breast cancer in relation to estrogen and progesterone receptor status in Japan. *Ann Epidemiol* **17:** 304–312

Kawai M, Minami Y, Kuriyama S, Kakizaki M, Kakugawa Y, Nishino Y, Ishida T, Fukao A, Tsuji I, Ohuchi N (2010) Reproductive factors, exogenous female hormone use and breast cancer risk in Japanese: the Miyagi Cohort Study. *Cancer Causes Control* **21:** 135–145

Kuriyama S, Tsubono Y, Hozawa A, Shimazu T, Suzuki Y, Koizumi Y, Ohmori K, Nishino Y, Tsuji I (2005) Obesity and risk of cancer in Japan. *Int J Cancer* **113:** 148–157

Kyogoku S, Hirohata T, Takeshita S, Hirota Y, Shigematsu T (1990) Anthropometric indicators of breast cancer risk in Japanese women in Fukuoka. *Jpn J Cancer Res* **81:** 731–737

Lahmann PH, Hoffmann K, Allen N, van Gils CH, Khaw KT, Tehard B, Berrino F, Tjonneland A, Bigaard J, Olsen A, Overvad K, Clavel-Chapelon F, Nagel G, Boeing H, Trichopoulos D, Economou G, Bellos G, Palli D, Tumino R, Panico S, Sacerdote C, Krogh V, Peeters PH, Bueno-de-Mesquita HB, Lund E, Ardanaz E, Amiano P, Pera G, Quiros JR, Martinez C, Tormo MJ, Wirfalt E, Berglund G, Hallmans G, Key TJ, Reeves G, Bingham S, Norat T, Biessy C, Kaaks R, Riboli E (2004) Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer And Nutrition (EPIC). *Int J Cancer* **111:** 762–771

Lahmann PH, Schulz M, Hoffmann K, Boeing H, Tjonneland A, Olsen A, Overvad K, Key TJ, Allen NE, Khaw KT, Bingham S, Berglund G, Wirfalt E, Berrino F, Krogh V, Trichopoulou A, Lagiou P, Trichopoulos D, Kaaks R, Riboli E (2005) Long-term weight change and breast cancer risk: the European Prospective Investigation into Cancer and Nutrition (EPIC). *Br J Cancer* **93:** 582–589

Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T (2008) Cancer incidence and incidence rates in Japan in 2002: based on data from 11 population-based cancer registries. *Jpn J Clin Oncol* **38:** 641–648

Minami Y, Tsubono Y, Nishino Y, Ohuchi N, Shibuya D, Hisamichi S (2004) The increase of female breast cancer incidence in Japan: emergence of birth cohort effect. *Int J Cancer* **108:** 901–906

Morimoto LM, White E, Chen Z, Chlebowski RT, Hays J, Kuller L, Lopez AM, Manson J, Margolis KL, Muti PC, Stefanick ML, McTiernan A (2002) Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). *Cancer Causes Control* **13:** 741–751

Muti P, Quattrin T, Grant BJ, Krogh V, Micheli A, Schunemann HJ, Ram M, Freudenheim JL, Sieri S, Trevisan M, Berrino F (2002) Fasting glucose is a risk factor for breast cancer: a prospective study. *Cancer Epidemiol Biomarkers Prev* **11:** 1361–1368

Potischman N, Swanson CA, Siiteri P, Hoover RN (1996) Reversal of relation between body mass and endogenous estrogen concentrations with menopausal status. *J Natl Cancer Inst* **88:** 756–758

Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D (2007) Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* **335:** 1134

Rothman KJ, Greenland S (1998) *Modern epidemiology*, 2nd edn Lippincott-Raven: Philadelphia

Sellers TA, Kushi LH, Potter JD, Kaye SA, Nelson CL, McGovern PG, Folsom AR (1992) Effect of family history, body-fat distribution, and reproductive factors on the risk of postmenopausal breast cancer. *N Engl J Med* **326:** 1323–1329

van den Brandt PA, Dirx MJ, Ronckers CM, van den Hoogen P, Goldbohm RA (1997) Height, weight weight change, and postmenopausal breast cancer risk: The Netherlands Cohort Study. *Cancer Causes Control* **8:** 39–47

J Epidemiol 2010;20(3):253-258
doi:10.2188/jea.JE20090093

Study Profile

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

Shinichi Kuriyama[1], Naoki Nakaya[1], Kaori Ohmori-Matsuda[1], Taichi Shimazu[1,2], Nobutaka Kikuchi[1], Masako Kakizaki[1], Toshimasa Sone[1], Fumi Sato[1], Masato Nagai[1], Yumi Sugawara[1], Yasutake Tomata[1], Munira Akhter[1,2], Mizuka Higashiguchi[1], Naru Fukuchi[1], Hideko Takahashi[1], Atsushi Hozawa[1], and Ichiro Tsuji[1]

[1]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
[2]Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan

Received June 9, 2009; accepted October 16, 2009; released online April 10, 2010

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

Address for correspondence. Dr. Shinichi Kuriyama, Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, 2-1, Seiryo-machi, Sendai 980-8575, Japan (e-mail: s-kuri@mail.tains.tohoku.ac.jp).

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	23 647	22 760	12 750	18 944	78 101
No. of eligible population (A)	23 359	22 639	12 606	18 631	77 235
No. of persons responding to the survey	12 967	13 849	9690	13 704	50 210
No. of study population (B)	12 833	13 679	9605	13 486	49 603
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, 16 739 (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

category in both men and women; more women were LTCI-certified than men. Among participants aged 85 years or older, about 34% of men and 51% of women were LTCI-certified.

DISCUSSION

To characterize the study population, we compared selected health-related characteristics of the population with those of the Japanese general population, by sex and age, using data from The National Health and Nutrition Survey in Japan, 2005.[26] Among men, the proportion of current smokers was higher in the study population than in the general population. The proportions of current smokers at baseline in the present cohort population by age category were 56.7% to 59.5%, 46.8% to 50.6%, 31.4% to 40.4%, and 21.3% to 25.9% for men in their 40s, 50s, 60s, and 70s, respectively (Table 2); the corresponding figures from the national survey were 44.1%, 42.5%, 34.0%, and 20.0% (≥70 years). In contrast, smoking status among women in the study population was very similar to that in the general population. Other variables, including obesity, underweight, history of serious diseases, alcohol drinking, and time spent walking, were similarly prevalent among middle-aged and elderly men and women in the study population and general population. To take one example, the proportions of men who were obese (BMI of ≥25.0) at baseline in the present cohort population by age category were 33.8% to 35.1%, 34.7%, 30.8% to 32.1%, and 26.3% to 29.1% for those in their 40s, 50s, 60s, and 70s, respectively (Table 2); the corresponding figures from the national survey were 34.1%, 31.4%, 30.7%, and 26.0% (≥70 years), respectively.

We also compared the LTCI certification status of the participants with that of the Japanese population by sex and age.[27] The proportions of those certified at baseline in the present cohort population, by age category, were 2.4%, 4.5%, 7.4%, 15.0%, and 34.2% for men aged 65–69, 70–74, 75–79, 80–84, and ≥85 years (Table 4); the corresponding figures from the estimated national survey were 3.0%, 6.2%, 11.9%, 22.1%, and 45.0%, respectively.[27] The same comparison among women yielded similar results, with smaller proportions in the present cohort population. These observed smaller proportions were not unexpected, because people with disabilities have more difficulties in responding to questionnaires. However, the small magnitude of the difference indicates that the selection bias was not serious.

Our study had some limitations. First, the response rate (64.2%) was not very high. The response rates of men and women aged 40 to 64 years were lower (54.9% and 60.4%, respectively) than those of men and women aged 65 years or older (76.2% and 72.4%, respectively). These relatively low response rates, especially among participants aged 40 to 64 years, should be kept in mind when interpreting the study results. Second, among the psychosocial variables studied, the items regarding job status and educational status, social support, and participation in community activities have not been adequately validated. Third, LTCI certification does not directly indicate an individual's disability status; however, it does reflect the burden of disability on society.[15,16]

We have already conducted a prospective cohort study in the catchment area of Ohsaki Public Health Center. This study began in 1995 and was named the Ohsaki National Health Insurance (NHI) beneficiary's Cohort Study, or the Ohsaki Cohort Study.[5] The primary purpose of that study was to demonstrate quantitatively the economic impact of health-related lifestyles; the Ohsaki Cohort 2006 Study, in contrast, does not assess medical costs. The catchment area of the Ohsaki Public Health Center included Furukawa City, and the towns of Nakaniida, Onoda, Miyazaki, Shikama, Matsuyama, Sanbongi, Kashimadai, Iwadeyama, Naruko, Wakuya, Tajiri, Kogota, and Nango. Among these areas, the city of Furukawa, and the towns of Matsuyama, Sanbongi, Kashimadai, Iwadeyama, Naruko, and Tajiri were consolidated to form the city of Ohsaki on 31 March 2006. The population of the present study and that investigated in the Ohsaki Cohort overlap by about one-third.

In conclusion, we have begun a large population-based prospective study that focuses on psychosocial factors and LTCI certification status. The psychological factors include measurements of job status and educational status, psychological distress,[20–23] social support,[24] participation in community activities, and the Kihon Checklist.[25] LCTI certification is followed up as an alternative to individual disability status, and as a measure of the economic burden of disability on society.

ACKNOWLEDGEMENTS

This study was supported by Health Sciences Research Grants (H19-Seisaku-Ippan-026, H18-Choju-Ippan-014, H21-Choju-Ippan-001) from the Japanese Ministry of Health, Labour and Welfare, and a Grant-in-Aid for Scientific Research (B) (21390200) from the Japan Society for the Promotion of Science.

The authors thank Yoshiko Nakata, Mika Wagatsuma, Naoko Sato, and Yuki Takeda for their technical assistance.

REFERENCES

1. Berkman LF, Kawachi I. Social Epidemiology. New York: Oxford University Press; 2000.
2. Cannuscio C, Block J, Kawachi I. Social capital and successful aging: the role of senior housing. Ann Intern Med. 2003;139:395–9.
3. Prince M, Patel V, Saxena S, Maj M, Maselko J, Phillips MR, et al. No health without mental health. Lancet. 2007;370:859–77.
4. Fukao A, Tsubono Y, Komatsu S, Tsuji I, Minami Y, Hisamichi S, et al. Cohort study on the relation of lifestyle, personality and

biologic markers to cancer in Miyagi, Japan: Study design, response rate and profiles of the cohort subjects. J Epidemiol. 1995;5:153–7.
5. Tsuji I, Nishino Y, Ohkubo T, Kuwahara A, Ogawa K, Watanabe Y, et al. A prospective cohort study on National Health Insurance beneficiaries in Ohsaki, Miyagi Prefecture, Japan: Study design, profiles of the subjects and medical cost during the first year. J Epidemiol. 1998;8:258–63.
6. Nagata C, Takatsuka N, Kurisu Y, Shimizu H. Decreased serum total cholesterol concentration is associated with high intake of soy products in Japanese men and women. J Nutr. 1998;128:209–13.
7. Tsubono Y, Nishino Y, Komatsu S, Hsieh CC, Kanemura S, Tsuji I, et al. Green tea and the risk of gastric cancer in Japan. N Engl J Med. 2001;344:632–6.
8. Watanabe S, Tsugane S, Sobue T, Konishi M, Baba S. Study design and organization of the JPHC study. Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases. J Epidemiol. 2001;11 Suppl:S3–7.
9. Ohno Y, Tamakoshi A; JACC Study Group. Japan collaborative cohort study for evaluation of cancer risk sponsored by monbusho (JACC study). J Epidemiol. 2001;11:144–50.
10. Fried LP, Guralnik JM. Disability in older adults: evidence regarding significance, etiology, and risk. J Am Geriatr Soc. 1997;45:92–100.
11. Tsuji I. Nobasou Kenko Jumyo (Extending Healthy Life Expectancy). Tokyo: Iwanami Shoten; 2004 (in Japanese).
12. Hyder AA, Rotllant G, Morrow RH. Measuring the burden of disease: healthy life-years. Am J Public Health. 1998;88:196–202.
13. Gold MR, Stevenson D, Fryback DG. HALYS and QALYS and DALYS, Oh My: similarities and differences in summary measures of population health. Annu Rev Public Health. 2002;23:115–34.
14. Grosse SD, Lollar DJ, Campbell VA, Chamie M. Disability and disability-adjusted life years: not the same. Public Health Rep. 2009;124:197–202.
15. Tsutsui T, Muramatsu N. Care-needs certification in the long-term care insurance system of Japan. J Am Geriatr Soc. 2005;53:522–7.
16. Tsutsui T, Muramatsu N. Japan's universal long-term care system reform of 2005: containing costs and realizing a vision. J Am Geriatr Soc. 2007;55:1458–63.
17. Ogawa K, Tsubono Y, Nishino Y, Watanabe Y, Ohkubo T, Watanabe T, et al. Validation of a food-frequency questionnaire for cohort studies in rural Japan. Public Health Nutr. 2003;6:147–57.
18. Suzuki I, Kawakami N, Shimizu H. Reliability and validity of a questionnaire for assessment of energy expenditure and physical activity in epidemiological studies. J Epidemiol. 1998;8:152–9.
19. Shimizu H. A supplementary comment on "Reliability and validity of a questionnaire for assessment of physical activity in epidemiological studies" published in Journal of Epidemiology, 1998. J Epidemiol. 2002;12:54.
20. Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SL, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychol Med. 2002;32:959–76.
21. Furukawa TA, Kessler RC, Slade T, Andrews G. The performance of the K6 and K10 screening scales for psychological distress in the Australian National Survey of Mental Health and Well-Being. Psychol Med. 2003;33:357–62.
22. Kessler RC, Barker PR, Colpe LJ, Epstein JF, Gfroerer JC, Hiripi E, et al. Screening for serious mental illness in the general population. Arch Gen Psychiatry. 2003;60:184–9.
23. Furukawa TA, Kawakami N, Saitoh M, et al. The performance of the Japanese version of the K6 and K10 in the World Mental Health Survey Japan. Int J Methods Psychiatr Res. 2008;17:152–8.
24. Muraoka Y, Ikichi A, Ihara K. The physical and psychological and social background factor of elderly depression in the community. Ronen Seishin Igaku Zasshi. 1996;7:397–407 (in Japanese).
25. Suzuki N, Makigami K, Goto A, Yokokawa H, Yasumura S. Comparison of ability-based and performance-based IADL evaluation of community-dwelling elderly using the Kihon Checklist and TMIG Index of Competence. Nippon Ronen Igakkai Zasshi. 2007;44:619–26 (in Japanese).
26. The Research Group on Health and Nutrition Information. The National Health and Nutrition Survey in Japan, 2005. Tokyo: Dai-ichi Publishing; 2007.
27. Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare. Survey of long-term care benefit expenditures in 2006. Tokyo: Health and Welfare Statistics Association; 2008 (in Japanese).

Dose-escalation phase I study in metastatic breast cancer patients with combination of paclitaxel and tegafur·uracil

AKIHIKO OSAKI[1,7], SHOSHU MITSUYAMA[2], JUN-ICHI KUREBAYASHI[3], HIROSHI SONOO[3], REIKI NISHIMURA[4], TOSHIHIRO KOGA[5], SHIGERU MURAKAMI[1] and SHINJI OHNO[6]

[1]Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima-shi, Hiroshima 734-8551; [2]Kitakyushu Municipal Medical Center, Kitakyushu-shi, Fukuoka 802-0077; [3]Department of Breast and Thyroid Surgery, Kawasaki Medical School, Kurashiki-shi, Okayama 701-019; [4]Department of Surgery, Kumamoto Municipal Hospital, Kumamoto-shi, Kumamoto 862-0909; [5]Hirose Hospital, Fukuoka-shi, Fukuoka 810-0004; [6]Department of Breast Oncology, National Kyushu Cancer Center Hospital, Fukuoka-shi, Fukuoka 811-1395, Japan

Received April 24, 2009; Accepted August 7, 2009

DOI: 10.3892/ol_00000008

Abstract. The study present the results of the dose-setting study of concomitant weekly administration of paclitaxel and tegafur·uracil (UFT) for metastatic breast cancer. Eligible patients who entered the study underwent two or more courses of weekly paclitaxel + UFT therapy as the protocol therapy. The initial dose (level 1) was paclitaxel, 80 mg/m^2 and UFT, 400 mg/day. At level 2, paclitaxel remained the same, but UFT was increased to 600 mg/day. At level 3, only paclitaxel was increased to 90 mg/m^2. Twelve patients were enrolled in this study between September 2000 and September 2002. Three patients were assigned to level 1. Grade 3 liver dysfunction (increased aspartate aminotransferase and alanine aminotransferase) was noted in one patient and grade 4 neutropenia was noted in one patient, showing that dose-limiting toxicity was detected in 2/3 patients. In accordance with the protocol, UFT was fixed at 400 mg/day and paclitaxel was decreased to 60 mg/m^2 at level -1, and then increased to 70 mg/m^2 at level 0. The overall effective rate after completion of two courses was 33% (3/9) including one case of complete response and two cases of partial responses. The remaining patients presented with stable diseases and no patient had progressive disease. In this study, weekly paclitaxel with concomitant UFT was administered. The recommended doses of paclitaxel and UFT were determined to be 70 mg/m^2 and 400 mg/day, respectively. As the toxicity profile shows, the highest toxicity level of this regimen was neutropenia and liver dysfunction, and dose-limiting toxicity was neutropenia.

Correspondence to: Dr Akihiko Osaki, *Present address:* [7]Department of Breast Oncology, Saitama Medical University, 1397-1 Yamane, Hidaka-shi, Saitama 350-1298, Japan
E-mail: aosaki@saitama-med.ac.jp

Key words: uracil and tegafur, paclitaxel, phase I, metastatic breast cancer

Introduction

An anthracycline-containing regimen represents the first-line palliative chemotherapy (1-3). However, it is necessary to develop non-anthracycline combination regimens to provide salvage therapy in metastatic breast cancer patients who have relapsed during or after anthracycline-containing combinations. Although new salvage chemotherapy using (or in combination with) novel anticancer drugs has been studied (4-6), survival benefits and higher response rates are often countered by increased toxicity and complexity of regimen. An effective combination chemotherapy regimen that is both simple and has lesser toxicity would be valuable.

Paclitaxel is highly effective for both breast cancer without previous treatment (7) and breast cancer previously treated with anthracycline (8). Findings in a Japanese late phase II study showed the effective rate in metastatic breast cancer patients to be 33.7% (21/62) (9). Clinical evaluation of weekly regimens was frequently performed. Higher effects with mild adverse events compared to those of the approved dosage/application method, comprising an every-three-week regimen, have also been reported (10). These regimens can be administered on an outpatient basis, which is an advantage.

5-Fluorouracil is used in combination with anthracycline anticancer drugs and cyclophosphamide for the treatment of breast cancer and is administered by bolus injection in many cases. However, continuous intravenous infusion is the best administration method because the effect of 5-fluorouracil is time-dependent and increases with the duration of exposure of tumor cells (11). Several reports have shown that continuous intravenous infusion was effective for colon carcinoma.

Thus, we paid attention to tegafur·uracil (UFT) because its oral administration obtains area under the curve comparable to that obtained by continuous intravenous infusion of 5-fluorouracil. UFT is an anticancer drug developed in Japan and consists

of the masked compound of 5-fluorouracil (tegafur) and uracil. UFT inhibits the rate-limiting decomposition enzymes of 5-fluorouracil that is dihydropyrimidine dehydrogenase (DPD). UFT has tegafur and uracil at a molar ratio of 1:4. The effects of UFT alone on local progressive and metastatic breast cancer were reported to be 32 (12) and 39% (13), respectively.

This study presents the results of the dose-setting study of concomitant weekly administration of paclitaxel and UFT for metastatic breast cancer.

Patients and methods

The eligibility criterion of this study was the presence of a measurable or evaluable lesion. Other criteria included: a two-week or longer drug withdrawal after previous therapy, adequate bone marrow function, liver function and renal function, 75-year-old or younger age, an expected survival of 3 months or longer, performance status 0-2 and the absence of active double cancer. Informed consent was obtained in writing from the patients enrolled in the study.

Eligible patients who entered the study underwent 2 or more courses of weekly paclitaxel + UFT therapy as the protocol therapy. One course of this regimen took 4 weeks. Paclitaxel was infused intravenously for 60 min on days 1, 8 and 15, and UFT was orally administered daily for 21 days, followed by drug withdrawal for 1 week. As premedication for hypersensitive reactions, dexamethasone 20 mg d.i.v., diphenhydramine 500 mg p.o. and ranitidine 50 mg i.v. were administered 30 min before paclitaxel administration.

The dose escalation schedule was set as: the initial dose (level 1) was paclitaxel, 80 mg/m^2 and UFT, 400 mg/day. At level 2, paclitaxel remained the same, but UFT was increased to 600 mg/day. At level 3, only paclitaxel was increased to 90 mg/m^2. When the initial dose was determined to be the maximum tolerated dose (MTD), level 0 and level -1 were set as follows: at level 0 and level -1, the dose of UFT was fixed at 400 mg/day and paclitaxel was changed to 70 mg/m^2 at level 0 and 60 mg/m^2 at level -1 (Table I). Dose-limiting toxicity (DLT) was defined in accordance with the National Cancer Institute Common Toxicity Criteria. The criteria were: grade 4 thrombocytopenia, grade 3 pyrexial neutropenia (≥38˚C), grade 4 neutropenia that persists for ≥4 days, grade 3-4 peripheral neuropathy and grade 3-4 non-hematological toxicity (excluding depilation, nausea and vomiting). One dose level was assigned to a cohort of 3 patients and when no DLT was noted, the study proceeded to the next dose level. When DLT was noted in 1/3, 3 additional patients were assigned to the same level. When DLT was noted in ≥2 patients at the same dose level, the dose was determined to be MTD. A one-level lower dose than MTD was selected as the recommended dose (RD) for the phase II study.

Table I. Dose escalation scheme.

Dose level	Paclitaxel (mg/m^2)	UFT (mg/body)
-1	60	400
0	70	400
1	80	400
2	80	600
3	90	600

Table II. Patient characteristics.

Characteristics	No. of patients	%
No. of patients entered	12	
Age, year		
Median	53	
Range	40-73	
Performance status		
0	10	83.3
1	2	16.7
2	0	0.0
Menopausal status		
Pre-	3	25.0
Post-	9	75.0
No. of metastatic sites involved		
1	8	66.7
2	4	33.3
Hormone receptor status		
Estrogen or progesterone		
Positive receptor	7	58.3
Negative receptor	5	41.7
Unknown	0	0.0
Prior chemotherapy		
Prior adjuvant chemotherapy	9	75.0
Prior chemotherapy for metastatic disease	8	66.7
Prior anthracycline	10	83.3
Prior taxane	4	33.3

Table III. Toxicity according to dosing level.

Level	PTX/UFT	No. of patients	DLT	No. of patients with DLT
-1	60/400	5	-	0
0	70/400	4	-	0
1	80/400	3	Liver dysfunction, neutropenia	2

PTX, paclitaxel; DLT, dose-limiting toxicity; UFT, uracil and tegafur.

Table IV. Toxicity profiles.

	Grade									
	0		1		2		3		4	
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%
Leukocytopenia	7	64	1	9	1	9	2	18	-	
Neutropenia	7	64	1	9	1	9	-		2	18
Thrombocytopenia	11	100	-		-		-		-	
Fever	11	100	-		-		-		-	
Diarrhea	11	100	-		-		-		-	
Alopecia	-		7	64	4	36	-		-	
Neurosensory	6	55	5	45	-		-		-	
Skin	11	100	-		-		-		-	
Stomatitis	10	91	1	9	-		-		-	
Arthralgia	10	91	1	9	-		-		-	
Myalgia	11	100	-		-		-		-	
Liver dysfunction	10	91	-		-		-		1	9
Hypersensitivity reaction	10	91	-		1	9	-		-	
Fatigue	9	82	2	18	-		-		-	
Appetite loss	9	82	2	18	-		-		-	
Nausea	9	82	2	18	-		-		-	
Headache	9	82	2	18	-		-		-	
Flushing	8	73	3	27	-		-		-	

Results

Twelve patients were enrolled in this study between September 2000 and September 2002. The median age of the patients was 52.8 years of age (42-67 years) and the performance status (ECOG) was 0 in the 12 patients (Table II). Eleven patients had metastatic breast cancer and 1 patient had local progressive breast cancer. Patients with metastatic breast cancer had previously undergone chemotherapy and 6 of them were on chemotherapy including anthracycline.

Three patients were assigned to level 1. Grade 3 liver dysfunction (increased apartate aminotransferase and alanine aminotransferase) was noted in 1 patient and grade 4 neutropenia was noted in 1 patient, showing that DLT was detected in 2/3 patients. In accordance with the protocol, UFT was fixed at 400 mg/day and paclitaxel was decreased to 60 mg/m^2 at level -1 and then increased to 70 mg/m^2 at level 0.

Five patients were assigned to level -1, and 2 of the patients were handled as dropouts. One dropout developed grade 3 neutropenia in the first course and postponed administration of the drugs. Recovery, however, was delayed and the protocol therapy was discontinued. The safety evaluation committee advised the addition of 1 patient to confirm safety and 1 patient was thus added. However, the fourth patient was also judged as a dropout, since hypersensitive reaction developed immediately after initial administration of paclitaxel. Thus, 5 patients were enrolled. No DLT was noted in 3 patients judged evaluable and the study proceeded to the next step. At level 0 no DLT was noted in any patient. One patient was judged to be a dropout due to grade 4 neutropenia. However, persistence of neutropenia for 4 days or longer could not be confirmed (Table III). Based on these findings, MTD in this protocol was paclitaxel, 80 mg/m^2 and UFT, 400 mg/day; RD was paclitaxel, 70 mg/m^2 and UFT, 400 mg/day.

Table V. Overall tumor response.

Tumor response	Dose level		
	-1 (n=3)	0 (n=3)	1 (n=3)
CR	0	0	0
PR	0	2	1
SD	3	1	2
PD	0	0	0
CR+PR	0	2 (66.7%)	1 (33.3%)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table IV shows the frequency of the main adverse events. DLT was neutropenia, but was complicated in 1 patient at level 1 and liver dysfunction occurred in 1 patient at level 1. The incidence of grade 3-4 neutropenia was 18%.

Non-hematological drug-related toxicities were rarely severe and remained easily manageable except liver dysfunction, noted in 1 patient at level 1. Toxicities included alopecia (overall incidence 100%), neuropathy neurosensory (45%), stomatitis (9%), arthralgia (9%), fatigue (18%), appetite loss (18%), nausea (18%), headache (18%) and flushing (27%).

The overall effective rate after completion of 2 courses was 33% (3/9) including three cases of partial responses. The remaining patients presented with stable diseases (SD) and no patient had progressive disease. At dose levels, the effective rate at level 0, which was RD, was 66.7% (2/3) and continuity was also high (Table V). In continuous administration, partial responses were confirmed in some patients after 7 courses and complete response was confirmed in the remaining patients after 4 courses. Regarding the regional effects, the effect was noted in the liver, cervical lymph nodes and local skin.

Discussion

Our starting hypothesis is that administrating paclitaxel on a weekly basis not only improves the tolerability but in combination with oral UFT may also improve the anticancer effect. The results of our phase I trial, show both of these aspects. At the phase II recommended dose, the regimen was well tolerated and was associated with promising anticancer activity (14).

As chemotherapy for progressive/recurrent breast cancer, the current first choice is combination chemotherapy using multiple drugs, including anthracycline anticancer drugs. After taxan anticancer drugs were introduced, the efficacy of taxans for patients who became resistant to anthracyclines has been reported. Comparative studies, as well as studies on the combination of these anticancer drugs are underway.

Furthermore, weekly administration of paclitaxel in comparison with the standard every-three-week administration was recently investigated. Seidman *et al* performed a phase II clinical study of the weekly administration of paclitaxel in anthracycline-resistant breast cancer patients and obtained a high effective rate of 53% (10). Weekly administration was also reported in Japan, where adverse events (peripheral neuropathy and inhibition of the bone marrow) were milder and the effect was higher than those with every-three-week administration (15). According to Kimura *et al*, when 80 mg/m^2 paclitaxel was administered for 3 weeks followed by one-week withdrawal, a high effective rate of 71.4% was obtained (16).

5-Fluorouracil is included in combination regimens with cyclophosphamide, doxorubicin and 5-fluorouracil (CAF), as well as cyclophosphamide, epirubicin and 5-fluorouracil (CEF), and is administered intravenously. In contrast, oral 5-fluorouracil anticancer drugs are frequently administered in Japan. UFT is an oral anticancer drug consisting of tegafur and uracil. UFT inhibits the rate-limiting decomposition enzyme DPD, and is called dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine (DIF). The effective rate of UFT was found to be 32% (16/50) in a Japanese phase II study (10).

Basic investigations of the combination of paclitaxel and UFT using a lung-metastasized breast cancer model have been reported. The concomitant administration of the two drugs inhibited cancer growth without increasing toxicity. Thus, the duration of growth inhibition by paclitaxel alone was short (7-14 days) and re-growth occurred during the administration period, while the combination with UFT inhibited cancer growth for an extensive period of time. Repeated administration of paclitaxel has been reported to induce MDR and resistance, but 5-fluorouracil does not cross-react with MDR. Thus, the combination of paclitaxel and 5-fluorouracil is a useful one. In addition, DPD activity is higher in metastatic than in primary lesions, suggesting that a DIF UFT is an appropriate 5-fluorouracil anticancer drug in combination with paclitaxel.

In this study, weekly paclitaxel with concomitant UFT was administered. The recommended doses of paclitaxel and UFT were determined to be 70 mg/m^2 and 400 mg/day, respectively. As the toxicity profile shows, the major toxicity of this regimen was neutropenia and liver dysfunction, and DLT was neutropenia. Although hypersensitive reaction was noted after the initial administration of paclitaxel in 1 patient, no peripheral nerve toxicity attributable to paclitaxel occurred. This was a phase I study that aimed to determine the recommended dose. However, the number of patients enrolled was small and the effective rate at RD was 66.7% (2/3), suggesting the usefulness of this regimen.

Based on the results of this study, a phase II study is being performed at the recommended dose determined in the phase I study in patients previously treated with anthracycline. Results of this phase II study are anticipated.

References

1. A'Hern RP, Smith IE and Ebbs SR: Chemotherapy and survival in advanced breast cancer: the inclusion of doxorubicin in Cooper type regimens. Br J Cancer 67: 801-805, 1993.
2. Fossati R, Confalonieri C, Torri V, Ghislandi E, Penna A, Pistotti V, Tinazzi A and Liberati A: Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. J Clin Oncol 16: 3439-3460, 1998.
3. Paterson AH, Szafran O, Cornish F, Lees AW and Hanson J: Effect of chemotherapy on survival in metastatic breast cancer. Breast Cancer Res Treat 1: 357-363, 1981.
4. Pentheroudakis G, Razis E, Athanassiadis A, Pavlidis N and Fountzilas G: Paclitaxel-carboplatin combination chemotherapy in advanced breast cancer: accumulating evidence for synergy, efficacy, and safety. Med Oncol 23: 147-160, 2006.
5. Polyzos A, Tsavaris N, Kosmas C, Gogas H, Toufexi H, Kosmidis C, Markopoulos C, Giannopoulos A, Papadopoulos O, Stamatiadis D and Kouraklis G: Full dose paclitaxel plus vinorelbine as salvage chemotherapy in anthracycline-resistant advanced breast cancer: a phase II study. J Chemother 15: 607-612, 2003.
6. Seo JH, Oh SC, Choi CW, Kim BS, Shin SW, Kim YH, Kim JS, Kim AR, Lee JB and Koo BH: Phase II study of a gemcitabine and cisplatin combination regimen in taxane resistant metastatic breast cancer. Cancer Chemother Pharmacol 59: 269-274, 2007.
7. Holmes FA, Walters RS, Theriault RL, Forman AD, Newton LK, Raber MN, Buzdar AU, Frye DK and Hortobagyi GN: Phase II trial of taxol, an active drug in the treatment of metastatic breast cancer. J Natl Cancer Inst 83: 1797-1805, 1991.
8. Seidman AD, Reichman BS, Crown JP, Yao TJ, Currie V, Hakes TB, Hudis CA, Gilewski TA, Baselga J, Forsythe P, *et al*: Paclitaxel as second and subsequent therapy for metastatic breast cancer: activity independent of prior anthracycline response. J Clin Oncol 13: 1152-1159, 1995.
9. Ito Y, Horikoshi N, Watanabe T, Sasaki Y, Tominaga T, Okawa T, Tabei T, Kuraishi Y, Tamura K, Abe R, Kitajima M, Yamaguchi S, Kobayashi T, Koyama H, Orita K, Takashima S, Nomura Y and Ogawa M: Phase II study of paclitaxel (BMS-181339) intravenously infused over 3 hours for advanced or metastatic breast cancer in Japan. BMS-181339 Breast Cancer Study Group. Invest New Drugs 16: 183-190, 1998.
10. Seidman AD, Hudis CA, Albanell J, Tong W, Tepler I, Currie V, Moynahan ME, Theodoulou M, Gollub M, Baselga J and Norton L: Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. J Clin Oncol 16: 3353-3361, 1998.

11. Lokich JJ, Ahlgren JD, Gullo JJ, Philips JA and Fryer JG: A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program Study. J Clin Oncol 7: 425-432, 1989.
12. Ota K, Taguchi T and Kimura K: Report on nationwide pooled data and cohort investigation in UFT phase II study. Cancer Chemother Pharmacol 22: 333-338, 1988.
13. Tashiro H, Nomura Y and Ohsaki A: A double blind comparative study of tegafur (FT) and UFT (a combination of tegafur and uracil) in advanced breast cancer. Jpn J Clin Oncol 24: 212-217, 1994.
14. Passardi A, Maltoni R, Milandri C, Cecconetto L, Massa I, Zoli W, Tesei A, Fabbri F, Nanni O and Amadori D: Phase I study of paclitaxel and uracil plus tegafur combination in patients with pretreated metastatic breast cancer: drug sequencing based on preclinical modelling studies. Oncology 72: 118-124, 2007.
15. Kim R, Osaki A and Toge T: Feasibility and therapeutic efficacy of weekly 1-h low-dose paclitaxel infusion for relapsed breast cancer. Oncol Rep 10: 145-150, 2003.
16. Kimura M, Koida T and Yanagita Y: Weekly administration of paclitaxel for advanced or metastatic breast cancer-short-course premedications for outpatients. Gan To Kagaku Ryoho 27: 1703-1708, 2000.

COMMENTS AND RESPONSES

Screening for Breast Cancer

TO THE EDITOR: In 2009, the U.S. Preventive Services Task Force (USPSTF) recommended that starting regular screening mammography before the age of 50 years should be an individual decision that takes patient context into account, including the patient's values regarding specific benefits and harms (1, 2). As a metric, Nelson and colleagues (3) calculated the number needed to invite (NNI) to screening to prevent 1 death from breast cancer by conducting a meta-analysis of several trials. They concluded that the net benefit is smaller for women aged 40 to 49 years with a larger NNI than for women aged 50 to 59 years. However, they did not consider different follow-up periods when comparing NNI by age group. For women aged 40 to 49 years, the average follow-up varied from 10.7 to 16.8 years in 8 trials included in the meta-analysis, whereas follow-up varied from 12.9 to 18.1 years for women aged 50 to 59 years in 5 trials and from 14.3 to 15.5 years for women aged 60 to 69 years in 2 trials. Shorter follow-ups for women aged 40 to 49 years will lead to lower cumulative mortality, which results in an overestimation of NNI.

We aimed to estimate the NNI adjusted by the follow-up period in each available study to compare NNIs between different age groups. We applied similar methods and included similar mammography trials to those used in Nelson and colleagues' meta-analysis (3). We conducted a meta-analysis of the trials to estimate the pooled relative risk (RR) from a random-effects model under a Bayesian analysis by using the WinBUGS package (MRC Biostatistics Unit, Cambridge, and Imperial College School of Medicine, London, United Kingdom) (4). We included 8 trials (5–10), 5 trials (5, 9, 10), 2 trials (5), and 1 trial (5) for women aged 40 to 49 years, 50 to 59 years, 60 to 69 years, and 70 to 74 years, respectively. The NNI to screening to prevent 1 breast cancer death was defined by the USPSTF as the inverse of the absolute risk reduction. Here, the risk was the mortality rate during follow-up (death per person). In considering the follow-up period of studies, we estimated NNI by using the mortality rate per year (death per person-year). The estimated NNI was based on a 1-year follow-up. Thus, when we compared the NNI on the assumption that the follow-up was x years, we divided the estimated NNI by x. We tried to estimate the NNIs on the assumption of 10-, 15-, and 20-year follow-ups.

The pooled RRs and NNIs for reducing breast cancer mortality in Nelson and colleagues' report and our estimates calculated by using the same condition are shown in the **Table**. Pooled RRs with adjustment for the follow-up were similar for all age groups. On the contrary, the NNIs differed depending on the assumed follow-up, that is, 10, 15, and 20 years. On the assumption of a 10-year follow-up, the estimated NNIs for women aged 40 to 49 and 50 to 59 years were 2399 (95% CI, 1195 to 8550) and 1708 (CI, 452 to 10 215), respectively. The longer the assumed follow-up, the smaller the estimated NNIs for all age groups. More important, the differences in NNIs between women aged 40 to 49 years and those aged 50 to 59 years were smaller in our analysis than in Nelson and colleagues' report.

When comparing NNIs, the follow-up period directly affects the results. The NNIs are necessarily greater in shorter follow-ups, which means that, if not adjusted for follow-up, the NNI can be overestimated for younger age groups with relatively shorter follow-ups. The USPSTF recommendations for mammography screening stated that an NNI of 1904 for women aged 40 to 49 years was too high, yet an NNI of 1339 for women aged 50 to 59 years was adequate (2). However, when we adjusted for the follow-up of the trials, the estimated NNIs for women aged 40 to 49 years were 1599 with a 15-year follow-up and 1199 with a 20-year follow-up. Whatever the conclusion, it should not be based on biased estimates of NNIs for reducing breast cancer mortality by age group.

Table. **Pooled RRs and NNIs for Breast Cancer Mortality From Mammography Screening Trials for All Ages***

Age	RR for Breast Cancer Mortality (95% CI)	NNI to Prevent 1 Breast Cancer Death (95% CI)
Reported value by USPSTF		
40–49 y	0.85 (0.75–0.96)	1904 (929–6378)
50–59 y	0.86 (0.75–0.99)	1339 (322–7455)
60–69 y	0.68 (0.54–0.87)	377 (230–1050)
70–74 y	1.12 (0.73–1.72)	NA
Our estimates under the same condition as USPSTF		
40–49 y	0.85 (0.75–0.96)	1908 (957–7339)
50–59 y	0.83 (0.69–0.99)	1229 (299–7490)
60–69 y	0.69 (0.54–0.87)	388 (64–4438)
70–74 y	1.2 (0.71–2.09)	NA
Adjusted by follow-up		
10-year follow-up		
40–49 y	0.85 (0.75–0.96)	2399 (1195–8550)
50–59 y	0.82 (0.69–0.98)	1708 (452–10 215)
60–69 y	0.68 (0.53–0.86)	520 (36–2907)
70–74 y	1.23 (0.71–2.14)	NA
15-year follow-up		
40–49 y	–	1599 (797–5700)
50–59 y	–	1139 (302–6810)
60–69 y	–	347 (24–1938)
70–74 y	–	NA
20-year follow-up		
40–49 y	–	1199 (598–4275)
50–59 y	–	854 (226–5107)
60–69 y	–	260 (18–1453)
70–74 y	–	NA

NA = not available; NNI = number needed to invite to screening; RR = relative risk; USPSTF = U.S. Preventive Services Task Force.
* Six trials, including the Canadian National Breast Screening Study-2, were used.

Saika Kumiko, PhD
Saito Hiroshi, MD, PhD
Ohuchi Noriaki, MD, PhD
Sobue Tomotaka, MD, PhD, MPH
National Cancer Center
Tokyo 104-0045, Japan

Potential Conflicts of Interest: None disclosed.

References

1. US Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;151:716-26, W-236. [PMID: 19920272]
2. U. S. Preventive Services Task Force. Screening for breast cancer. November

2009. Accessed at www.uspreventiveservicestaskforce.org/uspstf/uspsbrca.htm on 7 September 2010.

3. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L; U.S. Preventive Services Task Force. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;151:727-37. [PMID: 19920273]

4. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS—a Bayesian modeling framework: concepts, structure, and extensibility. Stat Comput. 2000;10:325-37.

5. Nyström L, Andersson I, Bjurstam N, Frisell J, Nordenskjöld B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet. 2002;359:909-19. [PMID: 11918907]

6. Habbema JD, van Oortmarssen GJ, van Putten DJ, Lubbe JT, van der Maas PJ. Age-specific reduction in breast cancer mortality by screening: an analysis of the results of the Health Insurance Plan of Greater New York study. J Natl Cancer Inst. 1986; 77:317-20. [PMID: 3461193]

7. Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years. Ann Intern Med. 2002;137:305-12. [PMID: 12204013]

8. Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L; Trial Management Group. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. Lancet. 2006;368:2053-60. [PMID: 17161727]

9. Bjurstam N, Björneld L, Warwick J, Sala E, Duffy SW, Nyström L, et al. The Gothenburg Breast Screening Trial. Cancer. 2003;97:2387-96. [PMID: 12733136]

10. Tabar L, Fagerberg G, Chen HH, Duffy SW, Smart CR, Gad A, et al. Efficacy of breast cancer screening by age. New results from the Swedish Two-County Trial. Cancer. 1995;75:2507-17. [PMID: 7736395]

IN RESPONSE: We agree with Dr. Saika and colleagues that adjustment for follow-up time when estimating the NNI to mammography screening to prevent 1 breast cancer death provides more comparable results across age groups. However, the purpose of our meta-analysis was primarily to determine the effectiveness of mammography screening in reducing breast cancer mortality among women in their 40s, not to determine differences between age groups. Estimates of NNI are a way to illustrate magnitudes of effect that may be more relevant to clinical applications than RRs for some audiences. These estimates were calculated in the 2002 review (1), and we provided them in the updated review for consistency. Results indicate imprecise point estimates with overlapping confidence intervals that do not differentiate the 3 age groups in both the unadjusted NNI estimates and the estimates adjusted for follow-up provided by Dr. Saika and colleagues.

In general, NNI estimates would be expected to decrease with longer follow-ups for any event that accumulates over time, and Dr. Saika and colleagues results are consistent with this. However, their results are also a consequence of dividing the NNI estimates by the follow-up period, thereby imposing an inverse relationship by definition rather than allowing the data to reveal such a relationship. Their calculations also assume that the mortality rate is the same across all follow-ups, which may not be accurate, and for 20 years after screening, a period for which data are not yet available.

The USPSTF enlisted a more rigorous approach than using NNI estimates to evaluate ages to initiate and discontinue screening by commissioning statistical models from the Cancer Intervention and Surveillance Modeling Network (CISNET) (2). The USPSTF final recommendations (3) were based on its determination of the balance of benefits and harms of screening mammography for specific age groups from multiple data sources detailed in our evidence review and the CISNET report (2). Our NNI estimates were only 1 piece of this puzzle.

Also, to clarify, we included the Canadian National Breast Screening Study-2 (4) in our analysis of women age 50 to 59 years, although the reference in our review was incorrectly cited as the Canadian National Breast Screening Study-1.

Heidi D. Nelson, MD, MPH
Benjamin K. Chan, MS
Oregon Evidence-based Practice Center, Oregon Health & Science University
Portland, OR 97239-3098

Potential Conflicts of Interest: None disclosed.

References

1. Humphrey LL, Helfand M, Chan BK, Woolf SH. Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2002;137:347-60. [PMID: 12204020]

2. Mandelblatt JS, Cronin KA, Bailey S, Berry DA, de Koning HJ, Draisma G, et al; Breast Cancer Working Group of the Cancer Intervention and Surveillance Modeling Network. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. Ann Intern Med. 2009;151:738-47. [PMID: 19920274]

3. U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;151:716-26. [PMID: 19920272]

4. Miller AB, To T, Baines CJ, Wall C. Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50-59 years. J Natl Cancer Inst. 2000;92:1490-9. [PMID: 10995804]

The Need for Biomedically and Contextually Sound Care Plans in Complex Patients

TO THE EDITOR: Weiner and colleagues (1) provide evidence that error-free treatment plans are rarely created for patients with biomedical and contextual complexity (9%) and are not commonly created for those with contextual (22%) or biomedical (38%) complexity alone. This is not surprising given that primary care physicians are already expected to devote 1.5 times their available patient contact hours to providing preventive, long-term care, and acute medical services (2). Nonetheless, implementing improved skills in error-free or, at least, error-reduced care plans for the complex 1% to 5% of patients who use one quarter to one half of health resources (3) will be essential for patient-centered medical homes and accountable care organizations to succeed in augmenting quality care and lowering health-related costs (4). Barriers to improvement in these most needy patients, whose care is expensive, can be removed only through consistent identification and outcome-changing intervention, including contextual life-situation support.

Weiner and colleagues thus raise a practical, system-based question in this time of health reform: Can already overtaxed clinicians be expected to personally uncover and create individualized care plans in patients with biomedical and contextual complexity? Logically, to do so would require decreasing the number of patients per physician panel, thereby increasing available patient contact time; expanding the number of treatment-level clinicians (for example, physicians, physician assistants, nurse practitioners); or adding spe-

cialized support personnel to clinician teams, such as case managers (5), who can assist treating practitioners in individualizing biopsychosocial and health system support for complex patients.

As physicians intimately involved in augmenting the care of patients with health complexity, we see Weiner and colleagues' findings as a clinical challenge for physicians who wish to practice quality medicine. Perhaps a greater challenge, however, is for those involved in enhancing system-level care delivery (for example, in designing patient-centered medical homes or accountable care organizations) to create financially sustainable practice environments that allow practitioners time to consistently address biomedical and contextual needs in patients with complicated life and health situations.

Roger G. Kathol, MD
Mary H. Kathol, MD
Cartesian Solutions
Burnsville, MN 55337

Potential Conflicts of Interest: The authors own a health complexity and physical and mental health integration medical management company.

References

1. Weiner SJ, Schwartz A, Weaver F, Goldberg J, Yudkowsky R, Sharma G, et al. Contextual errors and failures in individualizing patient care: a multicenter study. Ann Intern Med. 2010;153:69-75. [PMID: 20643988]
2. Bindman AB, Forrest CB, Britt H, Crampton P, Majeed A. Diagnostic scope of and exposure to primary care physicians in Australia, New Zealand, and the United States: cross sectional analysis of results from three national surveys. BMJ. 2007;334:1261. [PMID: 17504790]
3. Zuvekas SH, Cohen JW. Prescription drugs and the changing concentration of health care expenditures. Health Aff (Millwood). 2007;26:249-57. [PMID: 17211035]
4. McClellan M, McKethan AN, Lewis JL, Roski J, Fisher ES. A national strategy to put accountable care into practice. Health Aff (Millwood). 2010;29:982-90. [PMID: 20439895]
5. Kathol RG, Perez R, Cohen JS. The Integrated Case Management Manual: Assisting Complex Patients Regain Physical and Mental Health. New York: Springer; 2010.

IN RESPONSE: A finding of our study that surprised us was that although physicians who spent more time with patients were more likely to probe for biomedical or contextual red flags, they were not more likely to provide contextually appropriate care. For example, in the case of a patient whose health literacy problems accounted for an inability to dose his diabetes medications correctly, physicians more often identified the literacy issue during longer visits but were not more likely to appropriately intervene. Physicians who intervened, however, did not on average have longer visits. Physicians who avoid contextual errors seem to think differently, considering context not as an afterthought but instead as a part of the clinical reasoning process. We recently studied an educational intervention that suggests such reasoning processes can be effectively taught (1).

Drs. Kathol and Kathol propose that if physicians had more time and specialized support personnel, such as case managers and midlevel providers, they would be more likely to provide contextually appropriate care. Although we did not find that additional time alone helped, the combination of additional time and a medical home environment might substantially improve care. Physicians who, during longer visits, unmasked health literacy problems as the root cause of a patient's poor diabetes control may simply have concluded that there was nothing they could do about it, without having, for instance, a diabetes educator who could assist. We share the concern that the major challenge for physicians involved in enhancing system-level care delivery is designing financially sustainable practice environments that support physicians who have developed the cognitive skills to individualize care, with the resources and tools needed to do so.

Saul J. Weiner, MD
Jesse Brown Veterans Affairs Medical Center and University of Illinois at Chicago
Chicago, IL 60612

Alan Schwartz, PhD
University of Illinois at Chicago
Chicago, IL 60680

Potential Conflicts of Interest: None disclosed.

Reference

1. Schwartz A, Weiner SJ, Harris IB, Binns-Calvey A. An educational intervention for contextualizing patient care and medical students' abilities to probe for contextual issues in simulated patients. JAMA. 2010;304:1191-7. [PMID: 20841532]

CORRECTION

Correction: Acute Sinusitis

In the recent In the Clinic on acute sinusitis (1), the figure title on page ITC3-2 was incorrect. The correct title is: "Diffuse pansinusitis with mucosal thickening and polyposis in the anterior sinuses." This has been corrected in the online version.

Reference

1. Wilson JF. In the clinic. Acute sinusitis. Ann Intern Med. 2010;153:ITC3-1-15. [PMID: 20820036]

Cancer Science
The official journal of the Japanese Cancer Association JCA

Comparison of core needle biopsy (CNB) and surgical specimens for accurate preoperative evaluation of ER, PgR and HER2 status of breast cancer patients

Kentaro Tamaki,[1,2,3,4] Hironobu Sasano,[2] Takanori Ishida,[1] Minoru Miyashita,[1] Motohiro Takeda,[1] Masakazu Amari,[1] Nobumitsu Tamaki[3] and Noriaki Ohuchi[1]

[1]Department of Surgical Oncology, Tohoku University Graduate School of Medicine, Miyagi; [2]Department of Pathology, Tohoku University Hospital, Miyagi; [3]Department of Breast Surgery, Nahanishi Clinic, Okinawa, Japan

(Received January 26, 2010/Revised May 8, 2010/Accepted May 18, 2010/Accepted manuscript online May 25, 2010/Article first published online June 15, 2010)

The roles of core needle biopsy (CNB) have become well established as an important preoperative diagnostic method for breast lesions. We examined the concordance of histological types, nuclear grades, hormone receptors, and human epidermal growth factor receptor 2 (HER2) status between CNB and surgical specimens in 353 cases. In addition, we analyzed the correlation between the number of CNB specimens obtained and accuracy of histological factors in order to explore the optimal number of CNB specimens. Between CNB and surgical specimens, concordance rates of histological type, nuclear grade, estrogen receptor (ER), and progesterone receptor (PgR) status (cut-off 0–<1%, 1–10%, and 10%<), and HER2 were 84.4%, 81.3%, 92.9%, and 89.3%, respectively. In 52 of 353 patients who were histopathologically diagnosed as ductal carcinoma *in situ* (DCIS) by CNB, final diagnosis was changed in to invasive ductal carcinoma (IDC) in surgical specimens. Statistically significant differences were detected in the discrepancy of the following factors between CNB and subsequent surgical specimens: histological types, nuclear grade, and PgR, between patients who received four or more cores and those who had received three or less cores. In addition, a similar tendency was also detected in estrogen receptor (ER) and HER2 as in the above, and the cases that received four cores reached to 100% concordance in diagnosis between CNB and surgical specimens. Therefore, the optimal numbers of CNB were considered four at least in assessing the histological type, invasion, nuclear grade, hormone receptor status, and HER2 status of individual patients in the preoperative setting. (*Cancer Sci* 2010; 101: 2074–2079)

The incidence of breast cancer is increasing worldwide, which is partly considered to be due to mass screening programs resulting in the discovery of clinically occult breast lesions.[1] In these lesions, relatively a more cautious approach is required to obtain appropriate tissue samples for preoperative pathological analysis. Roles of core needle biopsy (CNB) have become well established as an important diagnostic tool for both palpable and non-palpable breast lesions and it is considered the method of choice for tissue sampling.[2,3] In addition, CNB is less invasive than excision biopsy and generally provided more reliable information compared to fine needle aspiration biopsy cytology (FNAC), especially for providing architectural or histological information. For instance, an absolute sensitivity of ultrasound guided FNAC was 83.1% and that of CNB was 96.7%.[4] Accurate preoperative diagnosis of a breast lesion has recently considered essential for designing an optimal treatment algorithm in order to achieve a definite diagnosis without delay and with minimal biopsies.

The cases receiving preoperative systemic therapy have increased in order to reduce the tumor volume and eliminate possible micrometastasis for the patients with locally advanced breast carcinoma. Therefore, clinical demands on pathologists to provide not only histological diagnosis but also prognostic information for patients, including the determination of estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) for treatment planning, have markedly increased for clinicians in institutions of many parts of the world.[2] The information obtained from CNB may be the only information available for determining the candidates for preoperative or neoadjuvant treatment.[2] However, the information obtained from CNB must reasonably reflect that in the whole tissue for determining a treatment strategy for these patients. Results of previous studies demonstrated that the concordance rate between CNB and surgical specimens were 61.7–99% for ER, 61.5–97.1% for PgR, and 80–96% for HER2, respectively.[1,2,5–7] However, it is also true that these studies evaluated only 100 cases at most with a limited statistical power to detect discordance, and results differed significantly between these studies.[5,6] Therefore, in this study, we examined the concordance rate of nuclear grades, hormone receptors, and HER2 status between CNB and surgical specimens in 353 Japanese patients with breast carcinoma.

There have been controversies as to the optimum number of the CNB specimens to be taken from the patients in order to obtain accurate information of whole carcinoma tissues. Three or four cores were initially recommended as the most appropriate or optimum number of the specimens in a pioneer stereotactic study, employing needles of different calibers and excursion.[8] Another study also demonstrated relatively a high correlation of histological parameters between CNB and surgical specimens with only two cores.[9] To the best of our knowledge, no studies have reported the correlation between the number of cores obtained and the status of hormone receptors and HER2 status in the whole specimens. Therefore in this study, we examined the correlation between the number of cores and the accuracy of histological types, nuclear grade, hormone receptors, and HER2 status, and attempted to establish the optimal number of cores taken from the patients in preoperative settings.

Materials and Methods

We examined 353 Japanese female patients with breast carcinoma without neoadjuvant chemotherapy who underwent CNB and surgical resection from January 2002 and June 2009 at the Department of Breast and Endocrine Surgery, Tohoku University Hospital in Sendai, Japan. We received informed consents from all the patients and the protocol for this study was

[4]To whom correspondence should be addressed.
E-mail: nahanisikenta@yahoo.co.jp

doi: 10.1111/j.1349-7006.2010.01630.x

approved by the Ethics Committee at Tohoku University Graduate School of Medicine. The median age of the patients was 57 years (range, 27–85 years). All the core biopsies were performed under ultrasound guidance using a 16-gauge true-cut needle with an automated biopsy device.

We performed staining with hematoxylin–eosin (H&E) and immunohistochemicals for ER, PgR, and HER2 at the Department of Pathology, Tohoku University Hospital. After CNB and surgical resection of the primary tumors, the specimens were fixed in 10% formalin, embedded in paraffin, cut into 4-μm thick sections, and placed on the glue-coated glass slides. For determining the hormone receptor status, we employed the avidin–streptavidin immunoperoxidase method using the clone 6F11 antibody (Ventana, Tucson, AZ, USA) for ER and the clone 6 antibody (Ventana) for PgR in an automated immunostainer (Benchmark System; Ventana). A standardized immunohistochemistry kit (HercepTest for Immunoenzymatic Staining; Dako, Copenhagen, Denmark) was used for HER2 staining. Hematoxylin–eosin (H&E) and IHC staining were performed by a single and experienced technician. Positive controls for ER, PgR, and HER2 were breast carcinoma, whereas negative controls for immunostaining were hepatocellular carcinoma.

Two of the authors independently evaluated CNB samples and surgical specimens twice on different days. They were also blinded to the findings of CNB and surgical specimens, respectively. If there were discrepancies, they reached a final decision using evaluations from the third experienced pathologist. Olympus BX 50 and 20 X objectives (Tokyo, Japan) were used for the analysis. We examined the comparison between CNB samples and surgical specimens for the following parameters: histological types, nuclear grades, ER, PgR, HER2, correlation between the number of cores and status of hormone receptors, and HER2 status in operative specimens. Histopathological evaluations were based on World Health Organization (WHO) histological classification of tumors of the breast[10] and Rosen's Breast Pathology.[11] The nuclear grade was evaluated according to the Japan National Surgical Adjuvant Study of Breast Cancer (NSAS-BC) protocol.[12] By combining the nuclear atypia and mitotic counts, nuclear grades were defined as the summation of scores for the nuclear atypia (1 for low degree atypia; 2 for intermediate-degree atypia; 3 for high-degree atypia) with the scores for the mitotic counts per 10 high-power fields (×40 objective lens) (1 for 0–4 mitoses; 2 for 5–9 mitoses; 3 for 10 mitoses).[12] The nuclear grade was 1, 2, and 3 when the summation of scores for the nuclear atypia and those for mitotic counts were 2–3, 4, and 5–6, respectively.[12] Estrogen receptor (ER) and PgR were determined by nuclear staining graded from 0 to 8 using the Allred score.[13] The results were categorized as positive when the total score (TS), expressed as the sum of the proportion score (PS) and immunointensity score (IS),[13] was 3 or more.[13] In addition, we also evaluated the number of ER- and PgR-positive tumor cells according to the following criteria: cut-off 0–<1%, 1–10%, and 10%<, which was demonstrated by Arihiro *et al.*[14] We also defined the positive hormone receptor status as follows: cut-off 1%≤, discussed at the 11th St Gallen (Switzerland) expert consensus meeting on the primary treatment of early breast cancer in March 2009,[15] and cut-off 10%≤, defined by the J-score system.[14,16] In addition, with regard to HER2 evaluation of 225 cases excluding ductal carcinoma *in situ* (DCIS) diagnosed by CNB or surgical specimen, membranous staining was graded as the following: score 0–1+, 2+, and 3+.[2,6] A score of 0 was defined as no staining observed or membrane staining in <10% of tumor cells, and 1+ as faint/-barely perceptible membrane staining detected in more than 10% of the tumor cells.[2,17] Scoring of 2+ was assigned when there was weak to moderate complete membrane staining in >10% tumor cells; whereas 3+ consisted of uniform, intense membrane staining of >10% tumor cells.[2,17]

Statistical analysis, such as the one-factor ANOVA and simple regression analysis, were performed using StatMate III for Windows version 3.18 (ATMS, Tokyo, Japan). The agreement on the histological types, nuclear grade, hormone receptors, and HER2 status was tested using the kappa test.[18] Results obtained were considered significant at $P < 0.05$.

Results

Concordance of histological type between CNB samples and surgical specimens. The concordance rate of histological types between CNB and surgical specimens was 84.4% (298 of 353 cases) with a kappa value of 0.70 (Table 1). Concordance rates, defined as the number of CNB samples divided by surgical specimens of the following histological types, invasive ductal carcinoma (IDC), DCIS, invasive lobular carcinoma (ILC), and mucinous carcinoma, were as follows: 99.5% (196/197), 58.6% (75/128), 92.9% (13/14), and 100% (14/14), respectively (Table 1).

Concordance of nuclear grades. The concordance rate of nuclear atypia was 76.8% (271/353), including 41 cases with a score of 1, 191 cases with 2, and 39 cases with 3, with a kappa value of 0.55 (Table 2a). The concordance rate of mitotic counts was 82.2% (290/353), including 191 cases of with a score of 1, 57 cases with 2, and 42 cases with 3, with a kappa value of 0.69 (Table 2b). In addition, the concordance rate of nuclear grades was 81.3% (287/353), including 209 cases of with a score of 1, 38 cases with 2, and 40 cases with3, with a kappa value of 0.64 (Table 2c).

Comparison of ER and PgR status between CNB and surgical specimens. The agreement of ER status defined by the following criteria: cut-off 0–<1%, 1–10%, and 10%< was 92.9% (328/353), including 58 cases of cut-off 0–<1%, 12 cases of cut-off 1–10%, and 258 cases of cut-off 10%<, with a kappa value of 0.82 (Table 3a). The agreement of ER-positive or -negative status was as follows: 94.1% (332/353) for the Allred Score, 94.9% (335/353) for the proportion; cut-off level of 1%≤ and 96.0% (339/353) for the proportion; cut-off level of 10%≤, respectively. Sensitivity was 95.2% (279/293) for the Allred Score, 95.8% (277/289) for the cut-off level of 1%, and 96.8% (271/280) for the cut-off level of 10%≤, respectively. However, specificity was 88.3% (53/60) for the Allred Score, 90.6% (58/64) for the cut-off level of 1%≤, and 93.2% (68/73) for the cut-off level of 10%≤, respectively. In addition, positive predictive values (PPV) were 97.6% (279/286) for the Allred Score, 97.9% (277/283) for the cut-off level of 1%≤, and 98.2% (271/276) for the cut-off level of 10%≤, respectively.

The agreement of PgR status was 77.9% (275/353), including 105 cases of cut-off 0–<1%, 40 cases of cut-off 1–10%, and 125 cases of cut-off 10%<, with a kappa value of 0.66 (Table 3b). The concordance ratio of positive and negative was as follows: 86.1% (304/353) for the Allred Score, 89.5% (316/353) for the cut-off level of 1%≤, and 88.7% (313/353) for the cut-off level

Table 1. Analysis of the concordance of histological type between CNB and surgical specimens

		Surgical specimens			
		DCIS	IDC	ILC	Mucinous
CNB	DCIS	75	52	0	1
	IDC	0	196	1	0
	ILC	0	1	13	0
	Mucinous	0	0	0	14

CNB, core needle biopsy; DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; mucinous, mucinous carcinoma.

Table 2. Analysis of the concordance of (a) nuclear atypia, (b) mitotic counts, and (c) nuclear grade between core needle biopsy (CNB) and surgical specimens

(a)

		Surgical specimens			
		Low	Intermediate	High	Total
CNB	Low	41	37	4	82
	Intermediate	11	191	26	228
	High	0	4	39	43
	Total	52	232	69	353

(b)

		Surgical specimens			
		Score 1	Score 2	Score 3	Total
CNB	Score 1	191	18	1	210
	Score 2	13	57	17	87
	Score 3	1	13	42	56
	Total	205	87	60	353

(c)

		Surgical specimens			
		Grade 1	Grade 2	Grade 3	Total
CNB	Grade 1	209	21	4	234
	Grade 2	12	38	20	70
	Grade 3	1	8	40	49
	Total	222	67	64	353

Table 3. Analysis of the concordance of (a) ER and (b) PgR between CNB and surgical specimens

(a) ER

		Surgical specimens			
		0–<1%	1–10%	10%<	Total
CNB	0–<1%	58	7	5	70
	1–10%	0	12	9	21
	10%<	0	4	258	262
	Total	58	23	272	353

(b) PgR

		Surgical specimens			
		0–<1%	1–10%	10%<	Total
CNB	0–<1%	106	21	5	132
	1–10%	0	40	23	63
	10%<	0	29	129	158
	Total	106	90	157	353

CNB, core needle biopsy; ER, estrogen receptor; PgR, progesterone receptor.

of 10%≤, respectively. Sensitivity was 84.6% (219/259) for the Allred Score, 88.7% (211/238) for the cut-off level of 1%≤, and 89.4% (185/207) for the cut-off level of 10%≤, respectively. However, specificity was 90.4% (85/94) for the Allred Score, 91.3% (105/115) for the cut-off level of 1%≤, and 87.7% (128/146) for the cut-off level of 10%≤, respectively. In addition, PPV were 96.1% (219/228) for the Allred Score, 95.5% (211/221) for the cut-off level of 1%≤, and 91.1% (185/203) for the cut-off level of 10%≤, respectively.

Concordance of HER2 status between CNB and surgical specimens. Agreement of the HER2 status defined by the following criteria: cut-off 0,1+, 2+, and 3+ was 89.3% (201/225 invasive carcinomas) including 182 cases of cut-off 0,1+, seven cases of cut-off 2+, and 12 cases of cut-off 3+, with a kappa value of 0.64 (Table 4).

Table 4. Analysis of the concordance of HER2 status between CNB and surgical specimens

		Surgical specimens			
		0–1+	2+	3+	Total
CNB	0–1+	182	6	0	188
	2+	4	7	10	21
	3+	0	4	12	16
	Total	186	17	22	225

CNB, core needle biopsy; HER2, human epidermal growth factor receptor 2.

Analyses of discordant cases. The discordance of histological types was 55 of 353 cases. Among 52 cases which were originally diagnosed as DCIS by CNB, and subsequently changed to IDC by surgical specimens, 63.5% (33 of 52) were T1mic and T1a. The discordance of nuclear grade, ER, PgR, and HER2 was 66 of 353, 25 of 353, 78 of 353, and 24 of 225 cases, respectively (Tables 1–4). We defined major discordance as the discordance of two grades or two scores, and minor discordance as the discordance of one grade or one score. Major discordance of nuclear grade, ER, and PgR accounted for 5 of 66, 5 of 25, and 5 of 78 cases, respectively (Tables 2,3). As for HER2 status, all of 24 discordant cases corresponded with minor discordance (Table 4). Some of these discordances were due to technical problems, for instance, there was only one core and insufficient sample volume caused difficulty in histopathological diagnoses. In the case of only one sampling core that was 100 μm in diameter with a very small amount of carcinoma tissue, accurate diagnosis was difficult. Five discordant cases of histological types, four major and two minor discordant cases of nuclear grades, three major and two minor discordant cases of ER and PgR, and two discordant cases of HER2 status were due to the technical problem described above. On the other hand, all of the other cases were due to intratumoral heterogeneity.

Correlation between the concordance rates and number of consecutive cores. One to five cores were obtained in clinical settings as follows: one core in 158 cases, two cores in 119 cases, three cores in 33 cases, four cores in 17 cases, and five cores in 26 cases. The concordance rate of histological types from one core to five cores was 82.3% (130/158), 83.2% (99/119), 84.8% (28/33), 88.2% (15/17), and 100% (26/26), respectively (Fig. 1a). The concordance rate of nuclear grades from one to five cores was 74.7% (118/158), 84.9% (101/119), 81.8% (27/33), 88.2% (15/17), and 100% (26/26) (Fig. 1b). The concordance rate of ER status was 91.1% (144/158) for one core, 95.8% (114/119) for two cores, 97.0% (32/33) for three cores, 100% (17/17) for four cores, and 100% (26/26) for five cores, respectively (Fig. 2a). The concordance rate of PgR was 88.6% (140/158) for one core, 87.4% (104/119) for two cores, 93.9% (31/33) for three cores, 100% (17/17) for four cores, and 100% (26/26) for five cores, respectively. In addition, the concordance rate of HER2 was 85.6% (83/97) for one core, 88.4% (61/69) for two cores, 91.3% (21/23) for three cores, 100% (15/15) for four cores, and 100% (21/21) for five cases, respectively (Fig. 2b). As for histological types, nuclear grades, and PgR, there were statistically significance between patients who received four or more cores and those who had received three or less cores ($P = 0.035$, $P = 0.012$, and $P = 0.020$, respectively). A similar tendency was also detected in ER and HER2 but did not reach statistical significance ($P = 0.087$ and $P = 0.053$, respectively).

doi: 10.1111/j.1349-7006.2010.01630.x