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Breast Cancer in Lean Postmenopausal Women Might Have Specific Pathological Features

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Abstract. *Background/Aim: The rate of obesity, an independent risk factor for breast cancer in post-menopausal women, is quite low in Japan, indicating breast cancer in lean women to be more common in the Japanese than in Westerners. However, biological characteristics of such breast cancers have not been adequately investigated. Patients and Methods: We retrospectively investigated clinicopathological breast cancer features of 566 postmenopausal Japanese women, who underwent curative surgery, in relation to patient physique based on the body mass index. Results: There were no differences in several factors examined such as tumour size according to patient physique. On the other hand, mean values of the Ki67 labelling index were significantly higher in lean compared to obese patients (p=0.027). Likewise, HER2-positive tumours were more often observed in lean patients (p=0.051). Conclusion: Lean postmenopausal women had more aggressive tumours, apparently contradicting the widely held view for breast cancer in obese women.*

Postmenopausal breast cancer is widely known to have less aggressive tumour biology than cancers in younger women (1, 2). The hormone receptor-positive rate is high and HER2/neu overexpression is rarer (3, 4). It has also been reported that tumour grade is relatively low and vessel invasion is rare (5, 6). On the other hand, obesity is an independent risk factor for breast cancer occurrence in post-menopausal women (7, 8). Moreover, the breast cancer recurrence risk is higher in post-menopausal patients (9-11). Serum oestradiol is reportedly elevated in obese patients and adipose tissue might contribute to breast cancer development by producing more oestrogen (12, 13).

The breast cancer incidence rate in postmenopausal women is well known to be significantly lower in Asian than in Western countries, although no obvious reasons have yet been identified (14). Age-specific breast cancer incidences in Japan and the UK are shown in Figure 1A. Breast cancer incidence rates decrease with age after menopause in Japan, while the opposite trend is observed in the UK. South Korean women show a trend very similar to that of the Japanese population (15). Meanwhile, obesity rates in adult females are quite low in both Japan and South Korea (Figure 1B). This low rate of obesity might contribute to the low breast cancer incidence in Japan.

The low rate of obesity indicates breast cancer affecting lean women to be more common in the Japanese and other Asian populations than in Western countries. However, biological characteristics of such breast cancers have not been adequately investigated. Studies focusing on lean women are anticipated to provide insights applicable to the prevention and treatment of breast cancer in these women. Differences between lean and obese women can readily be analysed in Japan, where the proportion of lean women is significantly higher than in Western countries.

Based on obesity having an impact on breast cancer development, we hypothesised that biological differences in breast cancer according to patient physique might be more obvious in postmenopausal women. Thus, we retrospectively investigated pathological features of breast cancer in postmenopausal women in relation to their physiques.

Materials and Methods

Patients. We investigated 566 postmenopausal Japanese women over 55 years of age with breast cancer who underwent curative surgery during the 2013 through 2016 period at our Institution, and for whom complete clinical records were available. Clinicopathological features of primary tumours were examined in relation to the body mass index (BMI). According to BMI, a patient's physique was defined as lean (<18.5 kg/m^2 of BMI), normal (18.5-24.9), overweight (25.0-29.9) or obese (≥30). This

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Key Words: Breast cancer, obesity, lean women, postmenopausal.

Table I. *Clinicopathological features of 416 invasive carcinomas without NAC.*

	Lean		Normal		Overweight		Obese		p-Value
n	48		281		68		20		
Age (mean)	67		67		70		68		n.s.
Histology									
IDC (NST)	39	(81%)	236	(84%)	58	(85%)	17	(85%)	n.s.
Others	9	(19%)	45	(16%)	10	(15%)	3	(15%)	
pT (mm, mean)	18		20		21		24	n.s.	
pN+	10	(21%)	59	(21%)	18	(26%)	2	(10%)	n.s.
n≥3	4	(9%)	11	(4%)	7	(10%)	2	(10%)	n.s.
High grade	9	(19%)	37	(13%)	10	(14%)	2	(10%)	n.s.
ER (+)	42	(88%)	239	(85%)	62	(91%)	17	(85%)	n.s.
PgR (+)	40	(83%)	211	(75%)	56	(82%)	17	(85%)	n.s.
HER2 (3+)	12	(25%)	48	(17%)	10	(15%)	1	(5%)	0.051
Ki67 L.I. (mean)	37%		31%		28%		24%		0.027

study was carried out with approval from the ethics committee of Juntendo University Hospital (no: 15-063), and all data were collected after obtaining informed consent from each patient.

Pathological examination and immunohistochemistry. Surgical specimens were pathologically examined at the Juntendo University Hospital by two experienced pathologists. Nuclear grade was judged based on the modified Bloom-Richardson histological grades. Oestrogen receptor (ER) and progesterone receptor (PgR) status were assessed semi-quantitatively and reported as positive when more than 1% of the nuclei of cancer cells showed staining. HER2 was judged as 0 (no staining observed, or membrane staining in <10% of tumour cells), 1+ (faint focal membrane staining in >10% of tumour cells), 2+ (weak to moderate staining of the entire cell membrane in >10% of tumour cells), and 3+ (strong staining of the entire cell membrane in >10% of tumour cells). As to Ki67, a hot spot was chosen under 200× magnification and cells positive for nuclear Ki67 were then counted among 500 cancer cells.

Statistical analysis. Statistical analyses were performed using JMP 11.2.1 statistical software (SAS Institute Inc., Cary, NC, USA). Associations between clinicopathological parameters and patient physique were evaluated using Fisher's exact test. For comparisons of mean values, such as those for age, examinations of unpaired data were carried out employing the two-sided Student's *t*-test. Survival curves were estimated by the Kaplan–Meier method with the log-rank test to assess significance. A p-value <0.05 was considered to indicate a statistically significant difference.

Results

Clinicopathological features of invasive carcinoma according to physique. Mean age was 66 years (range=56-93 years) and proportions of lean and obese patients were 11% and 5%, respectively (Figure 2). Among the 566 patients, there were 497 with invasive carcinoma (88%) and 69 with ductal carcinoma *in situ* (DCIS) (12%). Among the 497 with invasive carcinomas, there were 81 patients who received neoadjuvant chemotherapy (NAC) before surgery. No difference in NAC rates was observed according to patients' physiques (lean: 11%, normal: 17%, overweight: 18% and obese: 13%). Because this study employed surgical specimens, only data from the 416 patients without NAC were further analysed, considering possible changes in biomarkers caused by NAC.

Clinicopathological features of the 416 invasive carcinomas according to physique are shown in Table I. There were no differences in age, histology, tumour size, lymph node metastasis, tumour grade or hormone status. On the other hand, the mean Ki67 labelling index (L.I.) value was significantly higher in lean compared to obese patients (37% *vs.* 24%) (p=0.027). Likewise, HER2 (3+) tumours were more often observed in lean patients (25% *vs.* 5%), although the difference was not statistically significant (p=0.051). The relationship between Ki67 L.I. and HER2 expression was further investigated. HER2 (3+) tumours had a higher Ki67 L.I. value (46%) than HER2 (0-2+) tumours (28%) (p<0.01), indicating a positive correlation between these two factors.

Clinicopathological features of DCIS according to physique. Clinicopathological features of 69 DCIS were investigated. Among factors examined, there were no specific trends according to patients' physiques. The comedo type was relatively uncommon (11%) in lean patients but a firm conclusion cannot be drawn due to the small number of subjects.

Patient outcomes according to physique. Kaplan–Meier curves of lean and obese patients (n=75) with invasive carcinoma, including those who received NAC, are shown in Figure 3. During the median 42-month observation period, 4 patients (5%) developed distant metastases after standard

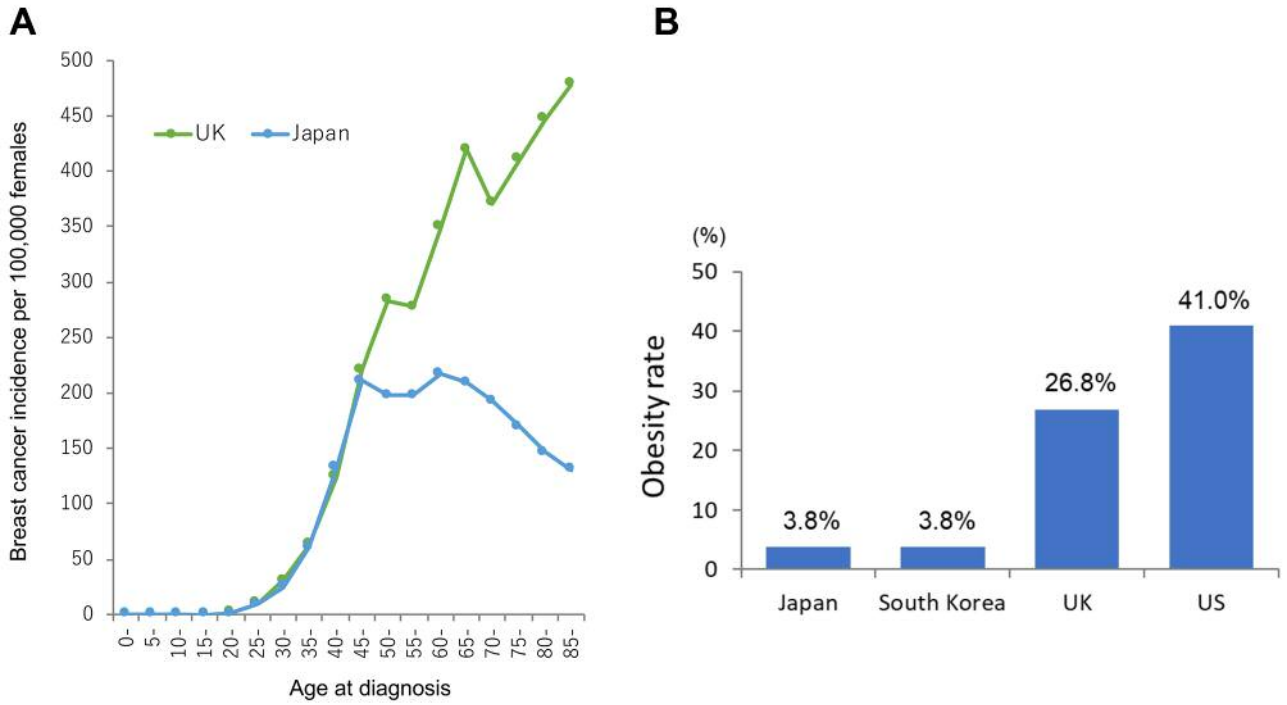

Figure 1. *Comparison of age-specific breast cancer incidences between Japan and U.K. (A) Breast cancer incidence rates per 100,000 females in Japan (2015) and the UK (2013-2015) are shown based on data from the National Cancer Center Japan (available on https://ganjoho.jp/en/index.html) and from Cancer Research UK (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#collapseOne), respectively. (B) Obesity rates in adult females in 2014 are shown. Data from the OECD (Organisation for Economic Co-operation and Development) is available from the website: https://stats.oecd.org/index.aspx?DataSetCode=HEALTH_STAT.*

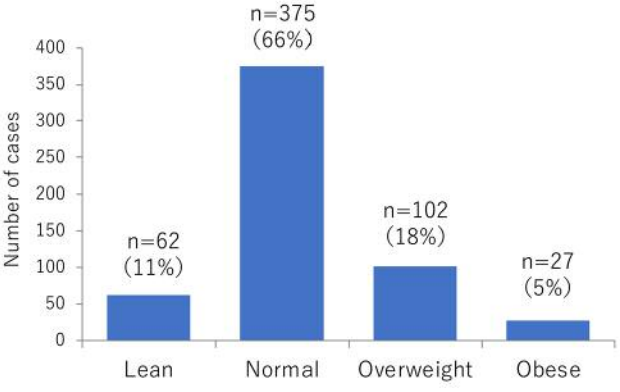

Figure 2. *Distribution of BMI in 568 postmenopausal patients. Distributions of BMI in 568 patients are shown. Based on BMI, patients were categorised into lean (<18.5 kg/m^2 of BMI), normal (18.5-24.9), overweight (25.0-29.9) and obese (≥30), as indicated in the Methods section.*

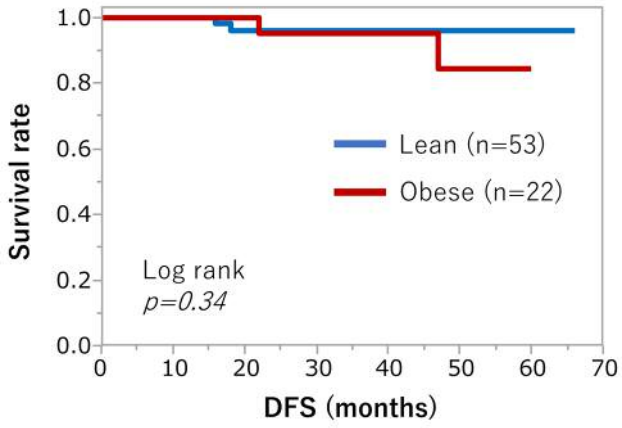

Figure 3. *Kaplan–Meier curves of DFS of lean and obese patients with invasive carcinoma, including those who received NAC, during the median 42-month observation period.*

systemic therapies in these groups. Three of these 4 patients died of their breast cancers. No statistically significant difference in disease-free survival (DFS) was observed between lean and obese patients.

Differences in breast density between lean and obese patients. Finally, we compared mammogram findings evaluated prior to surgery between 48 lean and 20 obese patients with invasive disease to examine differences in the

densities of their background breast tissue according to physique. The rate of high-density breast tissue, was significantly higher in lean than in obese patients (p=0.002).

Discussion

Our data showed that, compared to obese patients, lean postmenopausal women had more malignant tumours. Ki67 L.I. was significantly higher (p=0.027) in these patients and there was also a trend for HER2 (3+) tumours to be more frequently observed in lean patients (p=0.051). Our results appear to contradict the widely held view that obese women have a higher risk of breast cancer development and progression, possibly providing a novel insight into the understanding of the biological differences in breast cancers according to patients' physiques.

Generally, adipose tissue under conditions of obesity is considered to contribute to breast cancer development by producing more oestradiol, especially in postmenopausal women (16). Aromatase levels in the stroma were reportedly high in obese women (17). Meanwhile, inflammation in adipose tissue has been widely recognised as one of the mechanisms promoting breast cancer development (18). Higher aromatase levels were detected in breast tissue with inflammation in postmenopausal women, independently of BMI (17). Interleukin 10, an anti-inflammatory cytokine, reportedly suppressed aromatase levels in human adipose tissue (19). Moreover, blocking inflammation in adipose tissue suppresses breast cancer progression (20). Such an approach, aimed at inhibiting inflammation, might be effective even for ER-negative breast cancer (21).

Lyengar *et al*. recently reported the very interesting findings that menopausal Taiwanese women had pathologically enlarged adipocytes in breast tissue, meaning that more inflammation was involved, despite having a lower BMI than Caucasian women in the United States (22). Our data showed lean patients to more frequently have high-density breast tissue, reflecting lower adipose tissue contents. These observations indicate that lean menopausal women might have a different mechanism of local inflammation independent of obesity. Also, there is evidence that obesity is a negative risk factor for breast cancer in young premenopausal women, even in Western countries (23, 24). Taken together, these data suggest that there might be mechanisms of breast cancer development specific to lean women.

Limitations of the current study include the small sample size and lack of chronological records of patients' physiques. Only BMI at the time of surgery was available in our dataset. As to patient outcomes, there was no difference between lean and obese patients in this study. However, we speculate that a longer observation is needed to draw a meaningful conclusion. Elucidating the mechanisms of lean-specific breast cancer development may require investigating the details of local inflammation.

Our data showed that lean postmenopausal women had more aggressive tumours, apparently contradicting the widely held view that breast cancer in obese women shows biologically higher malignancy. We believe that further investigations focusing on breast cancer in lean women, that would presumably be more feasible in Asian women, will provide useful information for developing new strategies aimed at prevention, screening programs and systemic treatments specifically for lean women.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Conception and design: T. Uomori, Y. Horimoto. Development of methodology: Y. Horimoto. Acquisition of data (enrolled and managed patients, *etc*.): T. Uomori, Y. Horimoto, A. Arakawa, K. Iijima, M. Saito. Analysis and interpretation of data: Y. Horimoto, A. Arakawa. Writing: T. Uomori, Y. Horimoto. Review, and/or revision of the manuscript: K. Iijima, M. Saito.

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