

ORIGINAL ARTICLE

Body Mass Index Is Not Associated with Treatment Outcomes of Breast Cancer Patients Receiving Neoadjuvant Chemotherapy: Korean Data

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Purpose: The effects of body mass index on pathologic complete response and survival have not been reported in Korean patients with breast cancer. The purpose of this study was to evaluate the predictive or prognostic value of obesity in breast cancer receiving neoadjuvant chemotherapy. **Methods:** A total of 438 stage II or III breast cancer patients treated with neoadjuvant chemotherapy were enrolled and analyzed retrospectively. **Results:** In the study, 319 patients (72.8%) were normal weight, 100 patients (22.8%) were overweight, and 19 patients (4.3%) were obese. Baseline clinicopathologic characteristics were not different among the groups, except for age. There were no differences in pathologic complete response rate between the groups (9.7% in normal weight, 10.0% in overweight, 5.3% in obese;

$p=0.804$). Neither overweight nor obese patients showed a significant difference in relapse-free survival compared to normal weight patients ($p=0.523$ and $p=0.931$, respectively). Also, no significant difference in overall survival ($p=0.520$ and $p=0.864$, respectively) was observed. **Conclusion:** Obesity or higher body mass index was not significantly associated with pathologic complete response and survival in Korean patients with breast cancer who received neoadjuvant chemotherapy. Our results suggest that the prognostic impact of body mass index is different from that of Western patients.

Key Words: Breast neoplasms, Neoadjuvant therapy, Obesity, Prognosis

INTRODUCTION

In general, obesity has been regarded as a poor prognostic factor for breast cancer [1,2]. Several mechanisms have been raised to explain the association between obesity and poor prognosis. Some reports suggested that obesity leads to poor prognosis by increasing circulating plasma level of estrogen,

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This study was supported in part by grants of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A110448), and the Seoul National University Brain Fusion Program 2010 Research Grant to S.A. Im.

Received: June 15, 2012 Accepted: November 9, 2012

insulin and insulin-like growth factor that promote tumor growth [3,4]. Obese patients tend to have larger tumors and more positive nodes [5,6].

However, there are contradictory reports indicating that obesity is not associated with the prognosis of breast cancer [7]. The prognostic role of obesity is still controversial, because systemic under-treatment of obese patients, not obesity itself, might contribute to the poor prognosis, and it is difficult to strictly adjust tumor characteristics and other prognostic factors that could affect positive results [8]. Furthermore, the effect of obesity on the prognosis of breast cancer might vary according to ethnicity [9]. Compared with Western breast cancer patients, Korean patients have shown a higher portion of breast cancer in patients aged less than 35 years [10,11] which is considered a poor prognostic factor. Young, Korean breast cancer patients tend to have a lower body mass index (BMI) [12], and these ethnic differences may affect the prognostic effect of obesity.

To date, there are 2 Western reports that identify the posi-

tive predictive or prognostic value of the obesity in locally advanced breast cancer patients receiving neoadjuvant chemotherapy (NAC) [13,14]. However, the effects of obesity on pathologic complete response (pCR) to NAC and survival have not been reported in Asian patients. The purpose of this study was to evaluate the predictive or prognostic value of obesity in Korean breast cancer patients treated with NAC.

METHODS

Patients and treatment

From April 1994 to August 2008, a total of 438 patients with stage II or III breast cancer received NAC at Seoul National University Hospital. These patients were enrolled consecutively and analyzed retrospectively. Among the 438 patients, 370 patients received docetaxel+doxorubicin as a NAC regimen. Thirty-three patients received doxorubicin+cyclophosphamide, and 15 patients received paclitaxel+gemcitabine+trastuzumab. Twenty patients received other taxane or anthracycline based regimens. After completion of NAC, the patients underwent curative surgery, either breast-conserving surgery or mastectomy. This study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (H-1002-051-310).

phamide, and 15 patients received paclitaxel+gemcitabine+trastuzumab. Twenty patients received other taxane or anthracycline based regimens. After completion of NAC, the patients underwent curative surgery, either breast-conserving surgery or mastectomy. This study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (H-1002-051-310).

Pathology

The conventional pathologic factors, including biological factors (estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor receptor 2 [HER2]), were examined with immunohistochemistry. Immunohistochemistry was performed as previously described [15,16]. The molecular phenotypes of breast cancer were classified into luminal A, luminal B, HER2, and triple-negative breast cancer (TNBC) [17]. TNBC was defined as ER(-), PR(-), and

Table 1. Correlation between obesity and initial clinical variables

Characteristic	Total (n=438) No. (%)	NW (n=319) No. (%)	OW (n=100) No. (%)	OB (n=19) No. (%)	p-value*
Age (yr)	45.3±9.6	44.1±9.3	48.5±10.1	48.4±9.0	<0.001
<35	50 (11.4)	42 (13.2)	8 (8.0)	0 (0.0)	0.102
≥35	388 (88.6)	277 (86.8)	92 (92.0)	19 (100.0)	
Pathologic characteristics					
Invasive ductal carcinoma	416 (95.0)	304 (95.3)	93 (93.0)	19 (100.0)	0.388
Others [†]	22 (5.0)	15 (4.7)	7 (7.0)	0 (0.0)	
Initial clinical stage					
IIA	19 (4.3)	12 (3.8)	6 (6.0)	1 (5.3)	0.064
IIB	78 (17.8)	56 (17.6)	20 (20.0)	2 (10.5)	
IIIA	208 (47.5)	163 (51.1)	37 (37.0)	8 (42.1)	
IIIB	67 (15.3)	39 (12.2)	25 (25.0)	3 (15.8)	
IIIC	61 (13.9)	46 (14.4)	11 (11.0)	4 (21.1)	
Unknown	5 (1.1)	3 (0.9)	1 (1.0)	1 (5.3)	
Neoadjuvant regimen					
DA	370 (95.0)	271 (85.0)	84 (84.0)	15 (78.9)	0.416
AC	33 (7.5)	24 (7.5)	7 (7.0)	2 (10.5)	
PGH	15 (3.4)	11 (3.4)	2 (2.0)	2 (10.5)	
Others	20 (4.6)	13 (4.1)	7 (7.0)	0 (0.0)	
Inflammatory breast cancer					
Yes	35 (8.0)	23 (7.2)	10 (10.0)	2 (10.5)	0.613
No	403 (92.0)	296 (92.8)	90 (90.0)	17 (89.5)	
Type of surgery					
Mastectomy	193 (44.1)	171 (53.6)	62 (62.0)	12 (63.2)	0.273
Breast-conserving	245 (55.9)	148 (46.4)	38 (38.0)	7 (36.8)	
Adjuvant hormonal therapy					
Yes	197 (45.2)	145 (45.7)	42 (43.0)	10 (52.6)	0.646
No	239 (54.8)	172 (54.3)	58 (58.0)	9 (47.4)	
Adjuvant radiation therapy					
Yes	376 (85.8)	279 (87.5)	83 (80.0)	14 (73.7)	0.160
No	62 (14.2)	40 (12.5)	17 (17.0)	5 (26.3)	

NW = normal/underweight; OW = overweight; OB = obese; DA = docetaxel + doxorubicin; AC = doxorubicin + cyclophosphamide; PGH = paclitaxel + gemcitabine + trastuzumab.

*p-value is based on ANOVA test for the comparison of age, and chi-square test for the comparison of other variables; [†]Includes invasive lobular carcinoma, mucinous carcinoma, metaplastic carcinoma, micropapillary carcinoma, and large cell carcinoma.

HER2(-). Luminal A phenotype was defined as ER(+) or PR(+) and HER2(-) tumor, and luminal B phenotype was defined as ER(+) or PR(+) and HER2(+). ER(-), PR (-) and HER2(+) tumor was classified as HER2 phenotype. pCR was defined as the complete disappearance of invasive carcinoma in both breast and axillary lymph nodes after NAC. Residual ductal carcinoma *in situ* was included in the pCR category.

Statistics

BMI was calculated by dividing weight in kilograms by the square of height in meters. BMI was measured at the time of diagnosis, and categorized using the definition of the World Health Organization [18]: BMI < 25 kg/m² was categorized as normal/underweight (NW); BMI 25.0 to 29.9 kg/m² was cate-

gorized as overweight (OW); BMI ≥ 30 kg/m² was categorized as obese (OB).

The association between obesity and response to NAC was investigated in terms of pCR, relapse-free survival (RFS), and overall survival (OS). RFS was determined as the interval between the initiation of NAC and the date when disease relapse or progression was first documented, or the date of death from any cause. OS was measured from the date NAC was initiated to the date of death.

The chi-square test or analysis of variance (ANOVA) was used to compare the differences in clinicopathologic features between groups. Logistic regression analysis was used to determine the correlation between BMI and pCR. Receiver-operating characteristics (ROC) analysis was performed to

Table 2. Correlation between obesity and pathologic variables

Characteristic	Total (n=438) No. (%)	NW (n=319) No. (%)	OW (n=100) No. (%)	OB (n=19) No. (%)	p-value
pCR					
No	396 (90.4)	288 (90.3)	90 (90.0)	18 (94.7)	0.804
Yes	42 (9.6)	31 (9.7)	10 (10.0)	1 (5.3)	
Nuclear grade					
I	22 (5.0)	15 (4.7)	6 (6.0)	1 (5.3)	0.460
II	89 (20.3)	73 (22.9)	13 (13.0)	3 (15.8)	
III	264 (60.3)	184 (57.7)	68 (68.0)	12 (63.2)	
Unknown	63 (14.4)	47 (14.7)	13 (13.0)	3 (15.8)	
Histologic grade					
I	10 (2.3)	9 (3.0)	0 (0.0)	1 (5.3)	0.463
II	138 (31.5)	105 (34.4)	28 (28.0)	5 (26.3)	
III	205 (46.8)	142 (46.6)	53 (53.0)	10 (52.6)	
Unknown	85 (19.4)	49 (16.1)	19 (19.0)	3 (15.8)	
ER					
Negative	228 (52.1)	165 (51.7)	54 (54.0)	9 (47.4)	0.847
Positive	210 (47.9)	154 (48.3)	46 (46.0)	10 (52.6)	
PR					
Negative	294 (67.1)	213 (66.8)	67 (67.0)	14 (73.7)	0.823
Positive	144 (32.9)	106 (33.2)	33 (33.0)	5 (26.3)	
HER2					
0	168 (38.4)	124 (38.9)	38 (38.0)	6 (31.6)	0.949
+	94 (21.5)	68 (21.3)	21 (21.0)	5 (26.3)	
++	79 (18.0)	56 (17.6)	18 (18.0)	5 (26.3)	
+++	94 (21.5)	68 (21.3)	23 (23.0)	3 (15.8)	
Unknown	3 (0.7)	3 (0.9)	0 (0.0)	0 (0.0)	
Subtype					
Luminal A	168 (38.4)	123 (38.6)	37 (37.0)	8 (42.1)	0.982
Luminal B	45 (10.3)	32 (10.0)	11 (11.0)	2 (10.5)	
HER2	95 (21.7)	68 (21.3)	22 (22.0)	5 (26.3)	
TNBC	127 (29.0)	93 (29.2)	30 (30.0)	4 (21.1)	
Unknown	3 (0.7)	3 (0.9)	0 (0.0)	0 (0.0)	
Recurrence					
No recurrence	326 (74.4)	239 (74.9)	72 (72.0)	15 (78.9)	0.533
Locoregional	20 (4.6)	14 (4.4)	4 (4.0)	2 (10.5)	
Distant	92 (21.0)	66 (20.7)	24 (24.0)	2 (10.5)	

NW = normal/underweight; OW = overweight; OB = obese; pCR = pathologic complete response; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer.

determine a cut-off for the hold for the prediction of pCR. Survival function was estimated using the Kaplan-Meier product limit method. Survival comparisons between each group were made using log-rank tests. The Cox proportional hazard model (PHM) was used for prognostic significance of obesity in each group. The performance of Cox PHM was quantified in terms of the discrimination performance. Discrimination was evaluated using the C statistic with Harrell's concordance index (C-index) [19], which is similar in concept to the area under the ROC curve in the logistic model, however appropriate for censored data. All reported *p*-values were two-sided, with the level of significance established at *p* < 0.05. STATA statistical software version 11.0 (STATA Co., College Station, USA) was used for statistical analyses.

RESULTS

Obesity and clinicopathologic characteristics

The median age of the cohort was 45 years (range, 20-84 years). Three hundred nineteen patients (72.8%) were classi-

fied as NW, 100 patients (22.8%) were OW, and 19 patients (4.3%) were OB. Baseline clinicopathologic characteristics were not different among each group, except for age (Table 1). NW patients were younger than OB or OW patients (mean age, 44.1 ± 9.3 in NW, 48.5 ± 10.1 in OW, 48.4 ± 9.0 in OB, *p* < 0.001). BMI, as continuous variable, was correlated with age (Pearson's correlation coefficient = 0.275, *p* < 0.001). OB patients were not associated with ER negativity. Molecular subtypes were not different according to BMI categories (Table 2). NW, OW, and OB patients had a similar proportion of TNBC.

Obesity and pCR to NAC

Overall, the pCR rate was 9.6%. The pCR rate was not different among each group (9.7% in NW, 10.0% in OW, 5.3% in OB, *p* = 0.804 by chi-square test). On the univariate logistic regression model, there was no association between pCR and BMI as a continuous variable (odds ratio [OR], 0.993; 95% confidence interval [CI], 0.899-1.097; *p* = 0.892). BMI as a categorical variable did not show statistical significance with pCR (Table 3).

Table 3. Logistic regression model for pCR and Cox proportional hazard regression model for relapse-free survival and overall survival

	pCR		Relapse-free survival		Overall survival	
	OR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
BMI*	0.993 (0.899-1.097)	0.892	0.995 (0.938-1.056)	0.864	1.002 (0.918-1.095)	0.958
BMI†						
NW‡	1		1		1	
OW	1.032 (0.487-2.188)	0.934	1.151 (0.748-1.772)	0.523	1.234 (0.650-2.343)	0.520
OB	0.516 (0.067-3.999)	0.527	0.957 (0.350-2.613)	0.931	1.133 (0.272-4.719)	0.864

pCR = pathologic complete response; OR = odds ratio; CI = confidence interval; HR = hazard ratio; BMI = body mass index; NW = normal/underweight; OW = overweight; OB = obese.

*As continuous variable; †As categorical variable; ‡Reference group.

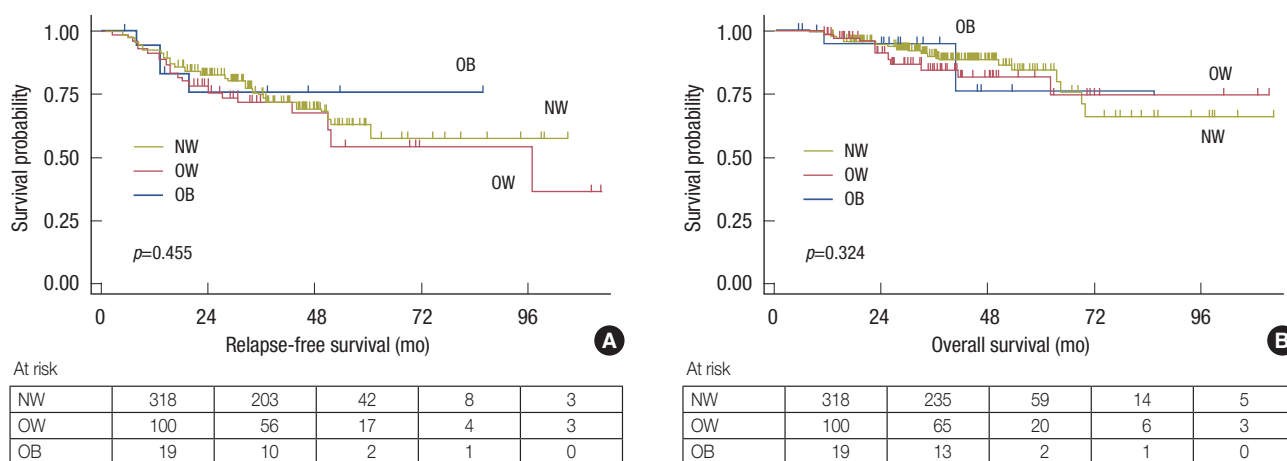


Figure 1. (A) Relapse-free survival by body mass index (BMI) categories, and (B) overall survival by BMI categories. NW = normal/underweight; OW = overweight; OB = obese.

Obesity and survival

With a median follow-up of 35.4 months, there were 112 (25.6%) recurrent patients, and 49 (11.2%) patients died. All of the deaths were from breast cancer progression, and there were no deaths from obesity related complications such as cardiovascular disease or diabetes. Kaplan-Meier survival curve indicated that RFS or OS was not different by BMI categories (log-rank $p=0.455$ and $p=0.324$, respectively) (Figure 1). In univariate Cox PHM, OB or OW patients did not show a difference in RFS compared to NW patients (hazard ratio [HR], 1.151; 95% CI, 0.748-1.772; $p=0.523$, and HR, 0.957; 95% CI, 0.350-2.613; $p=0.931$, respectively), and also no difference in OS (HR, 1.234; 95% CI, 0.650-2.343; $p=0.520$, and HR, 1.133; 95% CI, 0.272-4.719; $p=0.864$, respectively). Harrell's C-index of BMI was 0.506 in discriminating RFS, and 0.501 in discriminating OS, which means that BMI has no discriminatory ability for RFS or OS in these Cox PHMs. When analyzed separately by ER status, BMI remained non-significant in both ER positive and negative patients (data not shown). Multivariate analysis of clinical and pathological parameters using Cox proportional hazard model for OS is shown in Table 4. As interactions between age and BMI were suggested (Table 1), Table 4 shows the results of models that indicate interactions between age and BMI, and OS was not

Table 4. Multivariate analysis of clinical and pathological parameters using Cox proportional hazard model for overall survival

Parameter	Overall survival	
	HR (95% CI)	<i>p</i> -value
Age (≥ 35 yr)	0.489 (0.202-1.183)	0.112
T stage		0.047
1	1	
2	0.555 (0.144-2.139)	
3	1.095 (0.312-3.850)	
4	1.851 (0.518-6.621)	
N stage		0.010
0	1	
1	0.684 (0.083-5.630)	
2	1.248 (0.153-10.155)	
3	2.501 (0.304-20.570)	
ER positive	0.335 (0.131-0.861)	0.023
PR positive	0.217 (0.044-1.065)	0.060
HER2 positive	0.916 (0.475-1.766)	0.793
BMI		0.605
NW	1	
OW	0.343 (0.040-2.913)	
OB	0.810 (0.107-6.137)	
Interaction of age (≥ 35 yr) and BMI	4.835 (0.504-46.378)	0.172

pCR=pathologic complete response; HR=hazard ratio; CI=confidence interval; ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; BMI=body mass index; NW=normal/underweight; OW=overweight; OB=obese.

significantly different among BMI groups. Models with BMI and no interaction term gave consistent results (data not shown).

DISCUSSION

In the present study, neither obesity nor higher BMI was associated significantly with pCR and survival in Korean patients with breast cancer who received NAC. Obesity has been regarded as a poor prognostic factor, although several studies showed no association between obesity and clinical outcomes, like the present study [7]. Several meta-analyses have indicated that obesity adversely influences the clinical outcomes in breast cancer [20-22]. However, the majority of the studies were conducted in Western countries, except for in 2 Japanese reports [23,24], and data is limited in Asian patients. Hence, it seems that we may need to pay attention when adapting the prognostic value of obesity in studies acquired from Western countries to Asian patients.

In locally advanced breast cancer patients receiving NAC, 2 reports from M.D. Anderson Cancer Center [13,14] are available. Dawood et al. [13] analyzed 602 patients, and reported that OB or OW patients had a significantly worse recurrence-free survival and OS than NW patients ($p=0.001$ and $p=0.001$, respectively). However, the pCR rate of OB or OW patients were not different than that of NW (13.5% in NW, 10.3% in OW, 8.8% in OB, $p=0.38$) in the study. Litton et al. [14] reported that pCR was not associated with BMI in univariate logistic analysis but significant on multivariate logistic analysis.

Plausible explanations for the lack of association between obesity and clinical outcomes are: First, non-breast cancer related death could contribute, because OB or OW itself has a higher mortality than NW [25], mainly due to cardiovascular disease. Litton et al. [14] reported that OB or OW status was not associated with progression-free survival or breast cancer-specific survival, but significantly associated with OS when adjusting for other prognostic factors. Dignam et al. [7] found that OB patients had greater all-cause mortality due to causes unrelated to breast cancer in node negative, ER positive breast cancer. This suggested that non-cancer causes of death could contribute to the unfavorable outcomes of OB patients [26]. In contrast to the previous reports where non-cancer mortality could confound the data, all deaths were attributed to progression of breast cancer in the present study.

The second plausible explanation is ethnic differences. In 2 reports from M.D. Anderson Cancer Center, OB patients were more likely to have hormone receptor negativity [14], advanced stage [13,14], and high tumor grade [13]. On the contrary, this trend was not observed in the present study. This may be attributed to differences in epidemiology and

tumor biology of breast cancer between Asians and Westerns [11,27]. Korean patients have shown higher ER negative rates and a higher portion of young breast cancer patients than Western patients [10,11]. The ER negative rate in our study (52.1%) was higher than observed in Western populations (39.9%) [14]. The peak incidence age of breast cancer in Korean patients occurs in women aged 45 to 49 years, which is 10 years younger than the peak at which breast cancer occurs in Western women [11]. The median age of patients in our study was 45 years, which is comparable with Korean epidemiologic data. In Korea, young breast cancer patients demonstrate a higher ER negative rate [10], and tend to have lower BMI [12], also shown in the present study. However, in Western countries, African-American breast cancer patients have higher BMI [9] and higher proportion of TNBC [28], this could contribute to obesity being a poor prognosis. Western obese and overweight patients were more likely to present with TNBC [29], while our study population did not show this.

Third, the patterns of obesity in Korean population were different from those of Western populations. The patients in the present study were leaner than their Western counterparts. The prevalence of obesity in our study was 4.3% which is lower than 30% [14] or 34% [13] in Western populations. Because of the different proportion of BMI categories, a different cut-off for obesity in Asian has been proposed [30]. However, we found no significant differences in pCR or survival according to this criteria (data not shown). Moreover, we found no optimal cut-off for BMI in the ROC analysis for determining an optimal cut-off value of BMI to predict pCR. In addition, a meta-analysis have indicated that the adverse effect of obesity on breast cancer may be overestimated because of publication bias against negative studies [22].

The present study is the first in an Asian population that identifies the association between obesity and pCR. Furthermore, this is a report of homogenous patient population from a single center with a relatively large sample size (n = 438). On the other hand, retrospective single institution studies such as ours have limitations and should be further validated in a larger population.

In conclusion, obesity or higher BMI plays neither a predictive nor a prognostic role in association with breast cancer in our Korean patients who received NAC. Our results suggest that the prognostic impact of BMI in Asian breast cancer patients may be different from that of Western patients.

ACKNOWLEDGEMENTS

We thank BioMed Proofreading LLC for English editing.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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