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Original article

The association between body mass index and immunohistochemical subtypes in breast cancer

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ABSTRACT

Background: Body mass index (BMI) is defined as a poor prognostic factor in patients with breast cancer (BC). However, there are controversial results regarding the various effects of BMI on BC, hence the exact pathophysiology of the relation between obesity and BC is still under debate, and remains unclear. This paper aims to investigate the association between BMI at presentation and BC subtypes defined according to the immunohistochemical classification in both premenopausal and postmenopausal patients with BC.
Patients and methods: This study is a retrospective and explorative analysis of the 3767 female BC patients from a single center. All patients' BMI at the time of initial diagnosis and tumor demographics were recorded. BMI was stratified into 3 groups as normal-weighted (BMI <25 kg/m^2), over-weighted (BMI = 25–29.9 kg/m^2), and obese (BMI ≥30 kg/m^2). Immunohistochemical classification of the tumors was categorized into 4 groups as follows; luminal-like, HER2/luminal-like, HER2-like, and triple-negative according to the ER/PR and HER2 status. Distribution of Immunohistochemical subtypes, tumor characteristics, and overall survival (OS) analysis were evaluated according to the BMI groups in both premenopausal and postmenopausal patients.
Results: Median BMI of premenopausal and postmenopausal patients was 25.5 (kg/m^2) and 28.8 (kg/m^2), respectively ($P < 0.001$). In parallel with the increasing age, patients were more obese at diagnosis in both premenopausal ($P < 0.001$) and postmenopausal period ($P < 0.001$). Triple-negative subtype was significantly more frequent in premenopausal patients with BMI ≥30 kg/m^2 compared to BMI <30 kg/m^2 ($P = 0.007$). Additionally, premenopausal patients with BMI ≥30 kg/m^2 had less common luminal-like subtype ($P = 0.033$) and more frequently presented with higher tumor stage ($P = 0.012$) and tumor grade ($P = 0.004$) compared to patients with BMI <25 kg/m^2. On the other hand, premenopausal patients with BMI <25 kg/m^2 had significantly more ER-positive tumors ($P < 0.001$) and lower stages of disease ($P = 0.01$) compared to their counterparts with BMI ≥25 kg/m^2. Premenopausal obese patients with triple-negative ($P = 0.001$) and luminal-like subtype ($P = 0.002$) had significantly shorter OS duration compared to overweight counterparts. HER2/luminal-like subtype was found to be significantly greater in postmenopausal overweight patients ($P = 0.005$). However, BMI had no any other significant effect on survival and immunohistochemical subtypes in postmenopausal patients. Multivariate analysis revealed that triple-negative subtype, grade III tumor, BMI ≥30 kg/m^2, T3–4 ($P < 0.001$), nodal involvement, metastatic disease, and lymphovascular involvement were significantly associated with poorer OS.
Conclusion: Our data indicated that BMI was an independent factor in patients with BC, with an association indicating a decreased incidence for luminal-like subtype and increased incidence for triple-negative subtype among premenopausal patients. However, this significance was not found in postmenopausal patients. Accordingly, a plausible etiological heterogeneity in BC might play a role among immunohistochemical subtypes in every life stage of women.

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1. Introduction

Obesity has been a major health problem worldwide since its prevalence is increasing rapidly after 1980s [1] and it is a well-recognized risk factor for metabolic syndrome, cardiovascular disease, diabetes mellitus and various cancers including breast cancer (BC) [2]. The role of Body Mass Index (BMI) and its effect on the prognosis in patients with BC has been evaluated with a great interest for many years. Despite controversial results of some studies, obesity has been regarded as a poor prognostic factor in BC [3]. A recent analysis of the Women's Health Initiative randomized study has revealed that women who were overweight and obese were associated with an increased risk of BC compared to those with normal weight [4]. Most of the previous epidemiological studies have shown a positive association between obesity and postmenopausal BC risk and an inverse relation between obesity and premenopausal BC risk [5]. This low risk in premenopausal period may be due to some endogenous hormonal factors and higher number of anovulatory menstrual cycles in obese premenopausal women [6]. By contrast, the high risk in postmenopausal period might be explained by increased concentrations of circulating estrogens since the adipose tissue is the main source of estrogens in postmenopausal period. Additionally, endogenous hormones such as estrogen and progesterone were reported to have mitogenic and morphogenic effects on mammalian epithelial cells by paracrine effect [7]. However, the main pathophysiology of this complex association between BMI and BC risk in women's life periods has not yet been clarified.

BC is a heterogeneous disease with different clinical presentations and classified into several histological subtypes according to the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status [8]. The effect of obesity on BC prognosis changes in compliance with the clinical and histopathological characteristics of disease, such as menopausal status and tumor subtypes [3].

Today, possible effects of obesity on immunohistochemical subtypes of BC (luminal-like, HER2/luminal-like, HER2-like, triple-negative) are still unclear in pre and postmenopausal patients [9]. Herein we aimed to determine the association between BMI and immunohistochemical subtypes of BC whether the obesity has any manipulating role in the incidence of developing different BC subtypes in pre and postmenopausal patients.

2. Materials and methods

2.1. Data collection and enrollment

In this retrospective and explorative analysis, we reached to medical records of 4413 Turkish female BC patients being followed between 1994 and 2015 in Hacettepe University Institute of Oncology. Of the 4413 patients, 646 were excluded due to unknown BMI data (n = 296), missing receptor status (n = 203) or ductal carcinoma in situ histology (n = 147). Remaining 3767 patients were enrolled in this study (Fig. 1). Tumor demographics including, tumor stage, tumor grade, lymphovascular invasion (LVI), perineural invasion (PNI), ER, PR, and HER2 status, and nodal involvement were found from original histopathology reports. BMI and other clinical information of all patients were carefully recorded during the follow up period. Final status of the patients was found by using the hospital death records notification system.

2.2. Definition of tumor subtypes and BMI

HER2 status was determined by immunohistochemical (IHC) staining. Tumors having score of 3 were considered as HER2-positive. Tumors scoring 2 (+) for HER2 expression were subsequently analyzed by fluorescence in situ hybridization (FISH) test and were considered as HER2-positive if HER2 amplification was present in FISH test. ER and PR nuclear staining ≥1% were accepted as ER and/or PR-positive by IHC evaluation according to the ASCO/CAP - guidelines [10]. Immunohistochemical subtypes were categorized into 4 groups as luminal-like (ER and/or PR-positive and HER2-negative), HER2/luminal-like (ER and/or PR-positive and HER2-positive), HER2-like (ER and PR-negative and HER2-positive) and triple-negative (ER, PR and HER2-negative) according to the ER/PR and HER2 status [11]. BMI was calculated by the formula of weight (kg)/height^2 (m^2) and then stratified into 3 groups as normal-weighted (BMI <25 kg/m^2), over-weighted (BMI = 25–29.9 kg/m^2) and obese (BMI ≥30 kg/m^2), according to World Health Organization Classification – 2012. As the number of patients with BMI <18.5 kg/m^2 (n = 29) was too small, we have not constituted a separate group for underweight patients and this group of patients were combined with the normal-weighted group.

Distribution of clinical features, immunohistochemical and histological subtypes, age, grade, LVI, PNI, nodal status, tumor stage, clinical stage and cumulative overall survival (OS) probability were analyzed according to BMI stratification.

2.3. Statistical analysis

All statistical analysis was performed by using the computer program of 'Statistical Package for The Social Sciences' version 18.0 for Windows (SPSS, Inc., Chicago, IL, USA). P-value equal or less than 0.05 was accepted as statistically significant in all analysis. For descriptive analysis, categorical variables were defined as frequency and distributions with percentages and quantitative variables were presented as median, minimum, and maximum values. Categorical variables were analyzed by using Chi-square or Fisher exact test. Kruskal-Wallis and a following Mann-Whitney U test were used if data were not normally distributed. The differences among the groups were evaluated by post hoc analysis. Survival analysis was performed according to the Kaplan-Meier Method. Log-rank statistics was used to compare the subgroup analysis. OS was defined as the period from the diagnosis until the date of death or the date of last visit. Factors identified by univariate analysis were subsequently evaluated in Cox-regression analysis for the purpose of determining the independent predictors of survival.

3. Results

3.1. Patient characteristics

Of the 3767 patients, 1834 were premenopausal (48.7%), 1666 (% 44.2) were postmenopausal and 267 (7.1%) were perimenopausal. All women aged greater than 60 years, women who had bilateral ovariectomy operation and women aged younger than 60 years with an intact uterus not receiving hormone replacement therapy and being amenorrheic for at least one year before the BC diagnosis were defined as postmenopausal according to the National Comprehensive Cancer Network-guidelines version 1.2016 [12]. The number of normal-weighted, overweight and obese patients in premenopausal group was 954 (45.4%), 710 (33.8%) and 437 (20.8%), respectively and in postmenopausal group this was 347 (20.8%), 638 (38.3%) and 681 (40.9%), respectively. Median age of all patients was 48.6 years (range: 18.1–92.1). According to the menopausal status, median age of premenopausal and postmenopausal patients was 42.5 (range: 18.1–58.8) and 58.1 years (range: 31.1–92.1), respectively. In parallel with the aging, patients were more obese at diagnosis in both premenopausal and postmenopausal period (P < 0.001 vs. P < 0.001, respectively). Median

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