Overweight: Is It a Prognostic Factor in Women with Triple-Negative Breast Cancer?

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Abstract

Background: Obesity is associated with poor outcomes in patients with breast cancer expressing hormone receptors, but this association is not well established for triple-negative breast cancer. In this study, we investigated the influence of body mass index (BMI) in triple-negative breast cancer outcomes. Methods: This is a descriptive and analytical retrospective cohort study at the Regional Oncology Center Hassan II-Oujda. We identified 115 patients with triple-negative breast cancer, met the criteria for inclusion, treated between January 2009 and December 2011. The clinicopathological characteristics were collected to assess the association between BMI and overall survival and disease-free survival at 5 years, using the Kaplan-Meier and Cox model. Results: Data analysis focused on 115 patients, 34 patients (28.7%) were normal weight (BMI < 25) and 82 patients (71.3%) were overweight (BMI ≥ 25). The rates of overall mortality and progression at 5 years were 37.4% and 69.6% respectively. After adjusting for clinicopathological variables and menopausal status, overweight was associated with OS (HR: 2.903, 95% CI: 1.551-5.432, p = 0.001) and DFS (HR:1.899, 95% IC: 1.05 – 3.433, p=0.034) in all patients with triple-negative breast cancer. When stratified by menopausal status, overweight was associated with DFS and OS (HR : 3.242, 95% CI: 1.249 to 8.412, p = 0.016) and (HR : 2.752, 95% CI: 1.267 to 5.978, p = 0.011) respectively in pre-menopausal women. By cons, BMI was not associated with DFS or OS in postmenopausal women. Conclusions: Overweight is an independent prognostic factor for OS and DFS at 5 years in all patients with triple-negative breast cancer, and menopausal status may be a mitigating factor. Premenopausal women with overweight are at greater risk of death and progression than women with normal weight. Once validated, these results should be considered in the development of prevention programs.

Keywords: Body mass index- Triple-negative breast cancer- overweight- overall survival- disease free-survival
models. All P values were two-sided. Statistical analyses were performed using SPSS Statistics 21.0. P<0.05 was considered significant.

Results

Patients and follow up

The study included 115 women with TNBC, 34 (28.7%) of whom were a normal weight (BMI <25 kg/m²) and 82 (71.3%) of whom were overweight (BMI ≥25 kg/m²).

The normal weight group’s median age was 47.1 years (range: 29–65 years). The overweight group’s median age was 45.6 years (range: 26–87 years).

The overweight group had a significantly higher proportion of larger tumours (>3 cm; p=0.05) with vascular emboli (p=0.038) and included more premenopausal women (p<0.001). BMI was not associated with tumour grade, lymph node status and age (Table 1).

Mortality and disease progression

Rates of overall mortality and disease progression at 5 years were 37.4% and 69.6%, respectively.

The normal weight group’s rates of overall mortality and disease progression at 5 years were 41.9% and 61.3%, respectively. The overweight group’s rates of overall mortality and disease progression at 5 years were 66.7% and 81.6%, respectively.

After adjusting for clinico-pathological variables and menopausal status, overweight BMI was associated with a worse overall survival OS (p=0.002) and disease-free survival DFS (p=0.002) than underweight BMI in patients with TNBC (Figure 1).

In multivariable analysis, overweight was significantly with OS (hazard ratio [HR] for mortality 2.903, 95% CI: 1.551–5.432, p=0.001, Table 3) and DFS (HR for progression 1.899, 95% CI: 1.05–3.433, p=0.034, Table 2) after adjustment for clinico-pathologic risk factors.

In stratification analysis, overweight was an independent prognostic factor for DFS (HR: 3.242, 95% CI: 1.249–8.412, p=0.016, Table 2) and OS (HR: 2.752, 95% CI: 1.267–5.978, p=0.011, Table 3).

Among postmenopausal women, BMI did not predict for DFS (HR: 1.345, 95% CI: 0.375–4.831, P = 0.648, Table 2) or OS (HR: 1.305, 95% CI: 0.276–6.172, p = 0.736, Table 3).

Discussion

Patients with this breast cancer phenotype tend to have a worse clinical outcome partly as a result of lacking a...
therapeutic target. Consequently, establishing a relation between modifiable factors that may portend an adverse outcome potentially may be beneficial to these patients (Ademuyiwa et al., 2011).

A number of studies (Dal Maso et al., 2008; Kroenke et al., 2005; Loi et al., 2005; Nichols et al., 2009) have evaluated the adverse prognostic effect of general obesity before breast cancer diagnosis or at the time of or shortly after a diagnosis of breast cancer, but very few studies have focused on BMI’s prognostic role in specially TNBC, the results of which vary considerably (Tao et al., 2006; Majed et al., 2008; Dawood et al., 2008).

In the current study, we demonstrated that overweight has a negative influence on DFS and OS only in premenopausal patients with TNBC but not in postmenopausal ones. Our results agreed with several reports in the literature, which showed that increasing BMI is related to a poor outcomes and short survivorship.

In a large study that involved 8,872 women, Fontanella et al. demonstrated that mean DFS and OS were shorter in obese and very obese compared with normal weight patients in TNBC after a median follow-up of 42.7 months (Fontanella et al., 2015). In a single center study of 818 patients with TNBC, obesity was more frequent in patients who were overweight than patients with triple-negative cancers. Leptin implicates stimulatory effects on breast cancer cell proliferation and those with triple-negative cancers. Leptin receptor gene at codon 109 (LEPRO-109RR genotype) was more frequent in patients who were overweight and those with triple-negative cancers. Leptin receptor expression in breast cancer tissue was associated with distant metastases. And Liu et al. (2011) reported that serum leptin concentrations were higher in patients with high-grade tumors and that a polymorphism in the leptin receptor gene at codon 109 (LEPRO-109RR genotype) was more frequent in patients who were overweight and those with triple-negative cancers. Leptin implicates stimulatory effects on breast cancer cell proliferation and invasion, but also possesses angiogenic activity (Niu et al., 2013).

It seems to be the first study to examine the relationships between obesity and outcomes in patients with TNBC after controlling for clinically significant factors was found either by Tait et al. (2014) or Ademuyiwa et al (Ademuyiwa et al., 2011). This is possibly because TNBC patients tend to receive cytotoxic chemotherapy which may neutralize potential detrimental effects of a higher BMI (Hao et al., 2015).

There are several hypotheses on the mechanisms that link increasing BMI to TNBC prognosis (Rose et al., 2009; Verreault et al., 1989; Foluso et al., 2011). Such as obesity associated comorbidities that interfere with optimal treatment (Hao et al., 2015). Metabolic syndrome, presents increased levels of insulin and insulin-like growth factor, hormones with potent mitogenic activity toward epithelial cells (Nelson et al., 2013; Renehan et al., 2006; Yu et al., 2000). Also paracrine secretion of interleukin-6 and tumor necrosis factor-alpha and the establishment of a pro-inflammatory micro-environment can induce the development of malignant phenotypes that are independent of hormonal secretion (Howe et al., 2013). Alternatively, the detrimental effect of obesity on TNBC prognosis might be linked to sub-therapeutic treatment. Drug dosing has traditionally been based on a patient’s estimated body surface area (BSA) in adults (Chen et al., 2016). It’s suggested elsewhere that the adipokines, which include leptin and vascular endothelial growth factor and heparin-binding epidermal growth factor-like growth factor, hormones with potent mitogenic activity toward epithelial cells (Nelson et al., 2013; Renehan et al., 2006; Yu et al., 2000). Also paracrine secretion of interleukin-6 and tumor necrosis factor-alpha and the establishment of a pro-inflammatory micro-environment can induce the development of malignant phenotypes that are independent of hormonal secretion (Howe et al., 2013).

Alternatively, the detrimental effect of obesity on TNBC prognosis might be linked to sub-therapeutic treatment. Drug dosing has traditionally been based on a patient’s estimated body surface area (BSA) in adults (Chen et al., 2016). It’s suggested elsewhere that the adipokines, which include leptin and vascular endothelial growth factor and heparin-binding epidermal growth factor-like growth factor, exert a stimulatory effect on ER-negative breast cancers, where estrogen action is not a factor, by hormonal, paracrine, and autocrine mechanisms (Zheng et al., 2013). Ishikawa et al. (2004) found that high leptin and leptin receptor expression in breast cancer tissue was associated with distant metastases. And Liu et al. (2011) reported that serum leptin concentrations were higher in patients with high-grade tumors and that a polymorphism in the leptin receptor gene at codon 109 (LEPRO-109RR genotype) was more frequent in patients who were overweight and those with triple-negative cancers. Leptin implicates stimulatory effects on breast cancer cell proliferation and invasion, but also possesses angiogenic activity (Niu et al., 2013).

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study established a relationship between overweight and TNBC which is beneficial for this aggressive subtype of breast cancer. These results will be taken into account in the programs of prevention and also in the medical management by using intensified treatments in patients with overweight. However, there were some potential limitations in our study. Firstly, due to the relatively proportion of underweight and obese patients, classification was measured in a binary scale. This classification did not allow to clearly distinguish between women who were obese and those who were overweight. Secondly, the retrospective nature of the study design and its relatively small sample size.

In conclusion, this retrospective cohort analysis showed that overweight BMI was an independent prognostic factor for OS and DFS at 5 years in women with TNBC. Our analysis indicated that menopausal status may be a mitigating factor, with overweight premenopausal women at greater risk of death and progression than women with a normal weight. Clearly, the relationships between outcome and obesity in triple-negative breast cancer are an important topic for further study. Once validated, these results could be considered in the clinical management of breast cancer and in the development of targeted preventive programs.

List of abbreviations
BMI, Body Mass Index
OS, Overall Survival
HR, Hazard Ratio
CI, Confident Interval
DFS, Disease Free Survival
DNA, Deoxy-Ribonucleic Acid
ER, Oestrogen Receptor
PR, Progesteron Receptor
HER 2, Human Epidermal growth factor Receptor 2

Declarations section
Ethics approval and consent the study was performed according to the ethical principles and informed patient consent for using data was obtained.

Standards of reporting
Reporting guidelines “STIPOD”.

Consent of publication
The patients provided consent for publication.

Availability of Data and Materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
Al jarroudi performed data collection, analysis and interpretation and drafted the article. Seddik and Brahmi participated in the collection of data. Abdra participated in the statistical analysis and interpretation of results. Said Afqir contributed in the article’s drafting and performed a critical revision of the article. All authors read and approved the final manuscript.

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