OBESITY IN WOMEN TREATED FOR BREAST CANCER - CONTROVERSIAL OBSERVATIONS ASSOCIATED WITH MENOPAUSAL STATUS AT DIAGNOSIS

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OBESITY IN WOMEN TREATED FOR BREAST CANCER - CONTROVERSIAL OBSERVATIONS ASSOCIATED WITH MENOPAUSAL STATUS AT DIAGNOSIS (Abstract): Breast cancer is a polymorphic disease, obesity being an important risk factor. The aim of the study is to assess different clinical, imagistic, biological determinants of fat mass and of gonadotropic axis in breast cancer treated patients according to their menopausal status at diagnosis. **Material and methods**: Seventy-eight breast cancer female patients were recruited cross-sectionally. All women were at menopause (physiologic or therapeutically induced). Fat mass was assessed by dual-energy X-ray absorptiometry, and immunoassays were used to determine serum hormones levels. **Results**: Post-menopausal diagnosed women showed statistically significant higher BMI (t=-3.159, p=0.002), abdominal (t=-2.305, p=0.036) and hip circumference (t=-2.683, p=0.009), but not hip/abdominal ratio (t=-0.647, p=0.520); also, they had significantly higher body fat mass (either total, subtotal or trunk fat; $p<0.05$). No statistically significant differences were observed in fasting glucose (t=-0.800, p=0.426), cholesterol (t=-0.566, p=0.573) nor triglycerides (t=0.969, p=0.336). Insulin levels, however, were significantly increased in post-menopausal group (t=-2.420, p=0.018), and subsequently HOMA-IR index assessing insulin-resistance was significantly increased (t=-2.305, p=0.024). Regarding sex hormones, no statistically significant differences were observed in circulating estrogens (estradiol and estrone) nor androgens (total testosterone and calculated free androgen index). However, for both pre-menopause and post-menopause groups, no statistically significant differences were observed in sex hormones according to weight status (obese *vs* non-obese). **Conclusions**: There is significant difference between weight status and risk of breast cancer regarding menopausal status, many reports showing that obesity is a risk factor in post-menopause patients and a protective factor in pre-menopause women, underlying the polymorphism of breast cancer disease. **Keywords**: BREAST CANCER, OBESITY, MENOPAUSE.

Obesity is a disease characterized by excess amount and/or unhealthy distribution of body fat (1). According to the World Health Organization (WHO), excess

weight in adults is characterized by a body mass index (BMI, calculated as weight measured in kilograms divided by height measured in meters squared) ≥ 25.0 kg/m^2, including obesity with a BMI ≥ 30.0 kg/m^2 and overweight status with a BMI between 25 - 29.9 kg/m^2 (1). Excess weight is thus divided into two categories: overweight and obesity.

Compared to people with normal weight, overweight or obese patients have an increased risk of developing multiple diseases, the most common being diabetes, cardiovascular diseases, and cancer (at least 13 types of cancer are being associated with obesity including breast cancer, colorectal cancer, renal cancer, liver cancer, ovarian cancer, multiple myeloma, meningioma) (2-8).

Breast cancer is by far the most common neoplasm among women, with approximately 2.26 million new cases diagnosed in 2020 (24.5% of cancer cases). It is also the most common cause of cancer death in women (15.5%, 684,996 deaths), ranking fifth place globally after the cause of death by cancer (following lung, colorectal, liver, and gastric cancers) (9). Of these, 23.7% of breast cancer cases and 20.7% of deaths were reported in Europe, although Europe has only 10% of the world's female population. In Central and Eastern European regions, 158,708 new cases and 51,988 deaths from breast cancer were reported, representing 29.9% of newly diagnosed cases but 36.3% of deaths caused by this type of tumor (9).

In Romania, 12,085 new cases of breast cancer and 3,918 deaths were reported in 2020, accounting for 2.27% of new cases and 2.4% of deaths attributed to breast cancer in Europe, and 8.5% of newly diagnosed cases but 7.6% of reported deaths for the central and eastern European region (9). A study (10) that analyzed differences in breast cancer mortality in Romania compared to the European Union (EU) over a period of 10 years (from entering EU, 2007-2016) showed a greater increase in the number of deaths caused by breast cancer in Romania, a trend of increasing mortality (opposite to that in the EU) and a reduction in life expectancy that gradually increased from 0.45 years in 2007 to 0.48 years in 2016 (Romania already having one of the lowest life expectancies in the EU, at 76.8 years, 5.4 years lower than the European average) (10).

WHO European Regional Report on Obesity in 2022 estimated that only in Europe, obesity is directly responsible for at least 200,000 new cases of cancer annually and this value is projected to increase in the coming decades (6). In 2012, globally, 33% of breast cancer cases (in postmenopausal women) were attributed to excess weight and obesity totaling 110,000 cases of which 28,000 could have been prevented if average BMI values in general population remained constant since 1982 (11).

Breast cancer is a polymorphic disease, and the current investigation has the objective to assess the differences of different clinical, imagistic, biological determinants of fat mass and of gonadotropic axis in breast cancer treated patients according to their menopausal status at diagnosis of the disease.

MATERIAL AND METHODS

Seventy-eight breast cancer female patients were recruited cross-sectionally. All women were at menopause, either physiologic or therapeutically induced (in function of when the cancer was diagnosed: pre-menopause or post-menopause). Fat

mass was assessed using dual-energy X-ray absorptiometry (DEXA); data recorded included total fat mass, subtotal fat mass (without head region) and trunk fat mass measured in grams (g) or as percentage (%) of total body mass. Immunoassays were used to determine serum hormone levels of insulin, FSH (follicle stimulating hormone), estradiol, estrone, total testosterone. Fasting glucose, total cholesterol and triglycerides were also measured. Insulin-resistance was calculated by HOMA-IR index, and the free testosterone was assessed by determining FAI (free androgen index).

All statistical analyses were performed using *SPSS Version 24.0* software (IBM Corp., Armonk, NY, USA). Associations between continuous variables were analyzed using Spearman correlation coefficients. The level of statistical significance was established at $p<0.05$.

Ethical approval was obtained from the Ethics Committee of "Grigore T. Popa" University of Medicine and Pharmacy Iasi (no. 1642/25.01.2017). The research protocol was approved by the institutional ethics committees of "Sf. Spiridon" County Clinical Emergency Hospital Iasi (no. 78/21.12.2016) and "Grigore T. Popa" University of Medicine and Pharmacy Iasi.

RESULTS

Seventy-eight female patients evaluated at the Endocrinology Department for metabolic or endocrine disease associated to breast cancer treatment were included in the current analysis. Patients had a mean age of 53.3 ± 11.6 years (age between 35-78), among which 45 were diagnosed with breast cancer before menopause, and 33 patients after the menopause. However, all patients were at menopause (physiological or induced) at the moment of assessment.

The group of women diagnosed pre-menopause had a mean age at assessment of 47.5 ± 9.5 years old, being diagnosed at a mean age of 41.6 ± 7.8 years, with mean years of disease of 5.9 ± 5.6 years. They had a mean duration of fertile years (between menarche and induced menopause) of 28.8 ± 7.7.

Women diagnosed after menopause had a mean age at assessment of 61.2 ± 9.3 years old, being diagnosed at a mean age of 57.9 ± 9.3 years, with mean years of disease of 3.4 ± 3.6 years. They had a mean duration of fertile years (between menarche and physiological menopause) of 33.6 ± 4.6.

Morphometric parameters analysis showed that patients did not have a significant difference between height ($t = -0.436$, $p = 0.664$), however the weight was higher in post-menopausal diagnosed patients ($t = -2.8$, $p = 0.006$), determining subsequent variations in BMI ($t = -3.159$, $p= 0.002$). According to the WHO classification of weight status by BMI, in the group of women diagnosed pre-menopause: 57.8% had normal weight (n=26), 28.9% were overweight (n=13) and 13.3% obese (n=6). Post-menopausal group comprised of 36.4% patients with normal weight (n=12), 27.2% overweight (n=9) and 36.4% with obesity (n=12) (fig. 1).

Abdominal circumference ($t = -2.305$, $p = 0.036$) and, also, hip circumference ($t = -2.683$, $p = 0.009$) varied significantly in the two groups, however not the hip/abdominal ratio ($t = -0.647$, $p = 0.520$). The same thing was valid also for fat mass, either total, subtotal or trunk fat mass ($p<0.05$).

Regarding biological parameters, no statistically significant levels were observed in fasting glucose ($t = -0.800$, $p = 0.426$), total cholesterol ($t = -0.566$, $p = 0.573$) and triglycerides ($t = 0.969$, $p = 0.336$) levels between the groups.

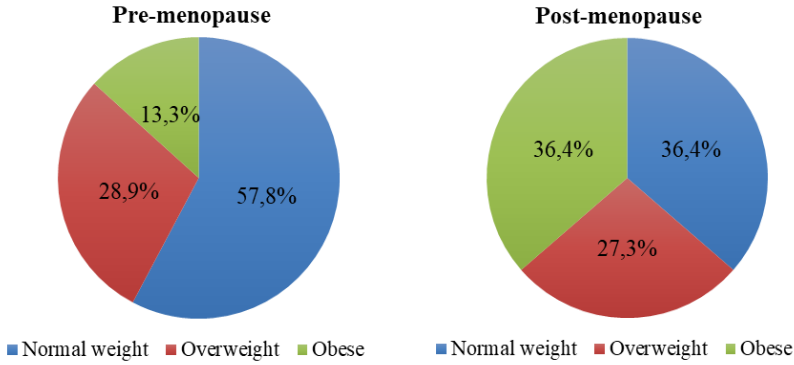

Fig. 1. Distribution of breast cancer cases in pre-menopause (right) *vs.* post-menopause (left) patients according to weight status

However, when analyzed, insulin levels were significantly different (t = -2.420, p = 0.018) in the two groups, pre-menopausal diagnosed women had a lower mean insulin level (9 ± 5.9 µUI/mL), than post-menopausal diagnosed cases (14 ± 11.8 µUI/mL), and subsequently the HOMA-IR assessing insulin-resistance (normal insulin-sensitivity when HOMA-IR below 2) was significantly different (t = -2.305, p = 0.024): in the pre-menopausal group HOMA-IR was lower (mean of 1.8) than in post-menopausal group (mean of 3.2).

Regarding ovarian function, even if all patients were at menopause at the moment of assessment, a difference was observed in FSH levels, as pre-menopausal diagnosed women had a lower mean FSH levels (33.1 mUI/mL), than post-menopausal diagnosed cases (53.4 mUI/mL), statistically significant (t = -2.899, p = 0.005). Estradiol levels measured in these groups showed slightly elevated values for what is normally considered in menopause (normally below 30 pg/mL): pre-menopausal diagnosed group had mean estradiol levels of 53.38 pg/mL, and post-menopausal group of 50.6 pg/mL, however not statistically significant different (t = 0.233, p = 0.817). Similarly, estrone levels also varied between the groups, but not reaching the statistical significance of $p<0.05$ (t = 1.870, p = 0.065): pre-menopausal group had a slightly higher mean value (84.9 ± 39.9 pg/mL) that the post-menopausal group (70.3 ± 25.3 pg/mL). Testosterone levels assessed by total testosterone (t = -2.899, p = 0.005) or as calculated free androgen index (t = -2.899, p = 0.005), were not significantly different between the two groups.

However, for both pre-menopause and post-menopause groups, when checked for differences in sex hormones according to weight status (obese *vs.* non-obese) no statistically significant differences were observed.

DISCUSSION

The major confirmation was that post-menopausal diagnosed women had significant higher fat mass indicators (BMI, abdominal and hip circumference, and quantity of body fat mass in all regions, assessed by DEXA). Even if the number of subjects included in the current analysis was small,

the data is concordat with global results.

Worldwide, the incidence of obesity has almost tripled since 1975 reaching pandemic levels (12). In Romania, available epidemiological data from 2007-2008 (13, 14) estimated a prevalence of overweight of 30-36% of the adult population and obesity of 20-25% (13, 14), with similar values reported in 2015 (15). WHO European Regional Report on Obesity 2022 placed Romania among countries with over 55% of the adult population being overweight and where more than 20% of the population is obese (6). Excess weight has a higher prevalence in men compared to women. In Romania excess weight has a lower prevalence of 51.1% in women compared to 64.3% in men (average prevalence in both sexes of 57.7%); on the other hand, obesity has a higher prevalence in women, of 23.4%, compared to 21.6% in men (average prevalence of obesity in both sexes of 22.5% in Romania, assessed by BMI) (6)We reported the differences between weight and gonadotropic axis in a cross-sectional analysis of female patients treated with breast cancer.

The association between excess weight (overweight/obesity) and breast cancer risk was reported to vary depending on menopausal status, with multiple studies showing a negative correlation between obesity and this risk in premenopausal women (16-18). Van den Brandt *et al.* (19) conducted an analysis of 7 prospective studies totaling a cohort of 337,829 women, of whom 4,385 were diagnosed with invasive breast cancer, finding that in pre-menopause women with a BMI over 31 kg/m^2 have a relative risk (RR) of 0.54 [95% confidence interval (CI 95%): 0.34-0.85] of developing breast cancer compared to those with a BMI below 21 kg/m2 (19). In 2001 Bergström *et al.* (20) conducted another meta-analysis including 9 studies also demonstrating an inverse correlation between obesity and increased BMI regarding breast cancer risk in premenopausal women (RR: 0.98; CI 95%: 0.97-0.99) (20). Renehan *et al.* (19) presented similar results in a meta-analysis consisting of 34 studies (totaling over 2.5 million women) that investigated breast cancer risk in relation to BMI (21). In total breast cancer was reported in 7,930 premenopausal women and 23,909 postmenopausal women. Breast cancer risk was reduced by approximately 8% per 5 kg/m^2 increase in BMI in premenopausal women (RR: 0.92; CI 95%: 0.88-0.97; p=0.001); on the other hand, in postmenopausal women breast cancer risk was increased (RR 1.12; CI 95%: 1.08-1.16; p<0.0001) (21).

The largest and most recent study investigating the association between obesity and breast cancer was conducted by the Premenopausal Breast Cancer Collaborative Group in 2018 (22). This multicenter study included 758,592 premenopausal women aged 18-54 years. They were followed for a median period of 9.3 years, during which 13,082 cases were diagnosed with breast cancer. The analysis showed that underweight women have a 4.2 times higher risk of developing breast cancer than obese women under the age of 24 and a 1.9 to 2.5 times higher risk in women over this age. Taking these results into account, the authors determined an estimated reduction of 12% to 23% in premenopausal breast cancer risk with a 5 kg/m^2 increase in BMI depending on age. Breast cancer positive for estrogen (ER) and/or progesterone receptors (PR) was associated with BMI in all age groups while hormone receptor-negative breast cancer was associated with BMI only in women aged 18-24

years. In this younger age group, the strength of the association between ER and/or PR positive breast cancer and BMI (HR: 0.75; CI 95%: 0.70-0.81) was much stronger than that for hormone receptor-negative breast cancer (HR: 0.85; CI 95%, 0.76-0.95) (22). The lack of association of triple-negative breast cancer with BMI in women over 25 years was contrary to previous reports (23). The authors considered that the discrepancy possibly reflects differences in study design (case-control versus prospective study), the former being more susceptible to potential selection bias (22).

Unlike women of reproductive age, several large studies and meta-analyses have demonstrated a direct and consistent association between obesity and breast cancer risk in postmenopausal women. The Million Women Study (24) followed 1.2 million women in the UK (including 45,037 cases with breast cancer) aged 50-64 years for a median period of 5.4 years. The study identified a risk about 30% higher for breast cancer in obese women compared to non-obese women (RR: 1.29; CI 95%: 1.22-1.36) in the postmenopausal period (24). These findings are comparable to those of Renehan *et al.* (21), previously described (breast cancer risk in postmenopausal women was positively associated with each 5 kg/m^2 increase in their BMI: RR: 1.12; $p < 0.001$) (21).

Local and systemic changes are hypothesized to support the relationship between obesity and breast cancer, including increased circulating levels of insulin and glucose as well as adipose tissue-derived estrogens, adipokines and inflammatory mediators (25).

Subsequent to increased fat mass, insulin levels and HOMA-IR (insulin-resistance) were significantly increased in post-menopause diagnosed women, and not pre-menopause breast cancer cases. No changes were observed with fasting glucose, total cholesterol, or triglycerides between the groups.

Also, no statistically significant differences were observed between circulating sex hormones levels in the two groups. All cases were at menopause and the only difference was in FSH levels; even if it was increased (considered inhibiting for the ovarian function), it was still lower in patients diagnosed with breast cancer in pre-menopause than in women with breast cancer after menopause, possibly in accordance with the number of years since the menopause occurred.

Given the impact of obesity on the development and progression of breast neoplasm, the recommendation is for overweight women to avoid weight gain during treatment and for obese women to lose weight immediately after treatment (26, 27). In the meta-analysis conducted by Chan *et al*. (28), which analyzed 23,182 deaths from 213,075 breast cancer survivors confirmed that the current indication for breast cancer patients is to remain as much as possible within the normal weight range (28).

CONCLUSIONS

Obesity and breast cancer are often associated; however, there is a significant difference between weight status and the risk of breast cancer regarding menopausal status, many reports showing that obesity is a risk factor in post-menopause patients and a protective factor for breast cancer in pre-menopause women. Our result show that post-menopause breast cancer patients present increased fat mass parameters,

insulin levels and insulin-resistance, compared to women diagnosed in premenopause, underlying the polymorphism of breast cancer disease.

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CONFLICT OF INTEREST AND FUNDING

There are no conflicts of interest to disclose.

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