World Cancer Research Journal WCRJ 2023; 10: e2553

THE CORRELATION BETWEEN INCREASING BODY MASS INDEX AND THE INCIDENCE OF LOCAL RECURRENCE AND DISTANT METASTASIS IN BREAST CANCER PATIENTS

R.F. MOHAMED[1], M.I. MELEK[2], S. EID[1], A. MORSY[1]

[1]Clinical Oncology Department, Faculty of Medicine, Assiut University Hospitals, Assuit, Egypt
[2]El-Mabarah Health Insurance Hospital, Assuit, Egypt

Abstract – *Objective:* *Patients with breast cancer (BC) who are obese or overweight at the time of diagnosis have a low survival rate and a high death rate. We aimed to investigate if having a higher body mass index (BMI) at diagnosis raised the risk of local recurrence (LR) and distant metastasis.*

Patients and Methods: *Patients were divided into three categories based on their BMI. The patient's BMI was determined by dividing his weight in kilograms by his height in square meters (kg/m^2). The WHO defines normal weight as 18.5 ≤ BMI < 25 kg/m^2, overweight as 25 ≤ BMI < 30 kg/m^2, and obesity as BMI ≥ 30 kg/m^2.*

Results: *The mean BMI was 30.27±6.06 kg/m2. Out of 250 patients, 60 (24.0%), 73 (29.2%) and 117 (46.8%) patients had normal, overweight and obese BMI respectively. No significant difference between BMI and estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER2) was found, but there was an association between tumor (T) stage and lymph vascular invasion (LVI) (p<0.05). Obese patients had poorer disease-free survival (DFS) and overall survival (OS) than normal and overweight categories (35.38 ±1.72* vs. *42.38 ± 2.79 and 37.82 ± 2.27 months) (39.65±1.65* vs. *45.70 ± 2.53 and 44.31 ± 2.04 months)* (p*<0.001). LR occurs more prevalent in over-weight and obese patients than normal* (p*<0.03) but there is no significant difference for distant metastasis.*

Conclusions: *There is a strong negative association between increased BMI and BC prognosis and patient survival; controlling of this phenomenon may improve the response to treatment and survival, therefore health awareness programs should be implemented.*

KEYWORDS: *BMI, Breast cancer, Distant metastasis, Local recurrence.*

INTRODUCTION

Overweight and Obesity are described as abnormal or excessive fat accumulation that may have a negative impact on health[1]. Obesity rates have risen dramatically around the globe in recent decades[2-4]. Between 1975 and 2016, the global incidence of obesity nearly tripled. More than 1.9 billion people were overweight in 2016. Over 650 millions of these people were obese. Body Mass Index (BMI) is a metric widely used to categorize adults aged 20 years and up. It is determined by dividing a person's weight in kilograms (Kg) by his height in meters (m^2); which is expressed as kg/m^2. According to the World Health Organization (WHO), overweight and obesity are defined as follows: 18.5 to 24.9 is considered normal or healthy weight, 25 to 29.9 is considered overweight, and 30 to 39.9 is considered obese and 40 or above means severely obese[5]. BMI is regarded

DOI: 10.32113/wcrj_20235_2553

Corresponding Author: Rehab Farouk Mohamed, Ph.D; e-mail: foroukrehab@aun.edu.eg

as the most useful measure because it is the same for both sexes and people of all ages. Diabetes, dyslipidemia, hypertension, stroke, cardiovascular diseases, musculoskeletal disorders, and at least 13 types of cancer including estrogen-positive breast cancer (BC) in post-menopause and triple-negative subtypes in pre-menopause are all associated with increased BMI.[6-12]. Obesity is well-established risk factors for breast cancer (BC) development and is associated with a 30% increased chance of recurrence or death [13]. The chance of developing BC in post-menopausal persons is 1.2–1.4 times higher in those who are obese or overweight compared to those who are not and 1.2 times higher for every 5-unit increase in BMI[14,15]. According to the International Agency for Research on Cancer (IARC) Working Group, people with obesity or overweight are 0.8 times more prone to develop cancer during menopause[15, 16].

PATIENTS AND METHODS

Study design and patient population

Patients with early BC who attended the Clinical Oncology Department at Assiut University Hospital between January 1st, 2012 and December 31st, 2016 and satisfied the inclusion criteria were included in our study.

Inclusion criteria

- Female patients aged 20 years and older with histologically confirmed invasive ductal carcinoma (IDC) and had early stages BC according to the staging system of the American Joint Committee of Cancer (AJCC) [17].
- Patients who underwent surgery followed by adjuvant treatment.
- The weight and height at the time of diagnosis have been recorded in the files.
- Patients have been followed up on for 5 years.

Exclusion criteria

- Male patients.
- No definitive surgery.

At the time of evaluation, there was no documentation of weight or height. There was no recorded follow-up. The following data were reviewed: multiple variables were examined and analyzed including age at diagnosis in years, weight in kg and height in meters, menopausal status (premenopausal or postmenopausal), tumor size (T), pathological types, grades (G), lymph vascular invasion (LVI), stage of the disease, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER2) status, surgery type: either modified radical mastectomy (MRM) or breast conservative surgery (BCS) and adjuvant treatment including chemotherapy and radiotherapy± hormonal therapy.

GROUP CLASSIFICATION

We calculated BMI by dividing the patient's weight in kg by his height in square meters; we divided our enrolled patients into three groups: normal weight $18.5 \leq BMI < 25$ kg/m^2, overweight $25 \leq BMI < 30$ kg/m^2., and obesity $BMI \geq 30$ kg/m^2.

Follow-up

Clinical examination and radiological investigation were performed every three months for the first two years then every six months for the third year and then annually for the next two years. Disease-free survival (DFS) was defined as the period from diagnosis to the appearance of first sighs of recurrence (distant metastasis or local-regional recurrence) or the date of last follow-up (31st December 2021). Overall survival (OS) was defined as the period between diagnosis and the last follow-up or death from breast cancer. DFS was defined as the period from diagnosis to the appearance of the first signs of recurrence (distant metastasis or local-regional recurrence) or the date of last follow-up. (31st December 2021). Overall survival (OS) was defined as the period between diagnosis and the last follow-up or death from BC.

Primary endpoint

The primary goal was to study the impact of increased BMI at diagnosis on the disease characteristics.

Secondary end point

Determine the DFS, which is described as the time between random assignment in a clinical trial and disease progression or death from any cause, as well as the OS, which is measured from the date of diagnosis to the date of death from any cause or date of last Follow-up.

Statistical analysis

The data was presented as a number, a percentage, and mean ± standard deviation (SD). The Chi-square test was used in the comparison. The Kaplan-Meier method was used to determine DFS and OS throughout a 5-year period. For significance, the log-rank test was used, and the *p*-value is considered statistically significant when $p<0.05$. The Statistical Package for Social Science version 22 (SPSS Inc. Armonk, NY, USA) was used for statistical analysis.

RESULTS

This retrospective study included 250 patients with early stages BC who presented to our department between the 1st of January 2012 and to 31st of December 2016.

Table 1 shows the demographic data of our enrolled patients. The mean age was 49.79±10.34 years (range 27-75 years). The mean weight and height were 74.72 ±15.80 kg and 1.57 ±0.06 m, respectively. As a result, the mean BMI was 30.27±6.06 kg/m^2 (range 18.7-53.3 kg/m^2). According to the WHO BMI classification, 60 (24.0%), 73 (29.2%), and 117 (46.8%) patients were normal, overweight, and obese, respectively; this indicates that approximately three fourth of our enrolled patients (no = 190, 76%) were either overweight or obese. There were 118 (47.2%) pre-menopausal patients with 91 (77.1%) being overweight or obese. There were 132 (52.8%) postmenopausal patients, with 99 (75%) being overweight or obese. IDC was the most prevalent pathology, affecting 236 (94.4%) of the patients. A total of 208 (83.2%) of the cases were with pathological G II. stage III was present in 117 (46.8%), and LVI in 83 (33.2%). Table 2 shows that nearly two-thirds of the overweight group (no = 73) were ER-positive 47 (64.38%), 37 (50.68%) were PR-positive, and the majority were HER2 negative 61 (83.56%). In obese cohort (no = 117), 81 (69.23%) patients were ER-positive, 77 (65.81%) patients were PR-positive, and 97 (82.90%) were HER2 negative. In the overweight and obese categories, 128 (67.3%) patients were ER-positive, 114 (60%) were PR-positive, and 158 (83.15%) were HER2 negative. There was no significant difference between molecular subtypes and BMI ($p=0.330$). T ≥2 cm was found in 146 (76.84%) of overweight and obese patients, LVI was found in 57 (30%). The Chi-square test revealed that there was no significant difference between BMI and ER, PR, and HER2 status but there was a significant difference between T stage and LVI ($p<0.05$). In regards to patient treatment, Table 3 shows the various treatment options. In regards to the surgery approach, MRM had been carried out in (82.0%) of the patients. Adjuvant chemotherapy was given to (98.0%) of patients. Adjuvant local radiation was administered to (85.2%) of patients. regarding adjuvant hormonal therapy, (36.4%), (20%), (5.2%) and (6.8%) of patients received tamoxifen, letrozole, anastrozole and tamoxifen followed by aromatase inhibitor (AI), respectively. Trastuzumab was given to (4.4%) of patients as showed in Table 4. Local recurrence occurs more frequent in over-weight and obese patients (no= 26, 13.68%) than normal (no= 1, 1.67%) ($p<0.03$) whereas distant metastasis occurred in 66 (34.7%) patients with overweight and obesity compared to14 (23.33%) patients with normal BMI ($p=0.254$). The mean DFS and OS were 37.77±1.25 and 43.40±1.15 months, respectively (95% CI; 35.52 - 40.22 and 41.40 - 45.66). Obese patients had poorer mean DFS and OS than normal and over-weight patients (35.38 ±1.72 *vs.* 42.38 ± 2.79 and 37.82 ± 2.27 months) (39.65±1.65 *vs.* 45.70 ± 2.53 and 44.31 ± 2.04 months) ($p<0.001$) as shown in Figures 1 and 2.

TABLE 1. Patients and tumor characteristics.

Variable	*Total (no=250)/%*
Age:	
Mean ± SD (Range)	49.79 ± 10.34 (27.0-75.0)
Weight:	
Mean±SD (Range)	74.72±15.80(42.0140.0)
Height:	
Mean ± SD (Range)	1.57 ± 0.06 (1.4-1.7)
BMI:	
Mean ± SD (kg/m^2) (Range)	30.27 ± 6.06 (18.7-53.3)
- Normal	- 60 (24.0%)
- Overweight	- 73 (29.2%)
- Obese	- 117 (46.8%)
Menopausal status:	
- Pre-menopausal	- 118 (47.2%)
- Post-menopausal	- 132 (52.8%)
Pathology:	
- IDC	- 236 (94.4%)
- others	- 14 (5.6%)
Pathological grade (G):	
- G I	- 5 (2.0%)
- G II	- 208 (83.2%)
- G III	- 37 (14.8%)
Stage:	
- 0	- 2 (0.8%)
- I	- 17 (6.8%)
- II	- 114 (45.6%)
- III	- 117 (46.8%)

Abbreviations - SD: Standard deviation, BMI: Body mass index, IDC: Invasive ductal carcinoma.

TABLE 2. The tumor characters according to BMI.

Item	BMI status			p-value
	Normal no (%) n=60	Overweight no (%) n=73	Obese no (%) n=117	
ER:				
Positive	39 (65.0%)	47 (64.38%)	81 (69.23%)	
Negative	21 (35.0%)	26 (35.62%)	36 (30.77%)	*p*= 0.744
PR:				
Positive	33 (55.0%)	37 (50.68%)	77 (65.81%)	
Negative	27 (45.0%)	36 (49.31%)	40 (34.18%)	*p*=0.098
HER2:				
Positive	6 (10.0%)	12 (16.43%)	20 (17.12%)	
Negative	54 (90.0%)	61 (83.56%)	97 (82.90%)	*p*=0.434
Luminal A	35 (58.3%)	43 (58.9%)	77 (65.8%)	
Luminal B	4 (6.7%)	6 (8.2%)	8 (6.8%)	
TNBC	19 (31.7%)	18 (24.7%)	20 (17.1%)	
Her2 enriched	2 (3.3%)	6 (8.2%)	12 (10.3%)	*p*=0.330
T stage:				
T: ≤ 2 cm	20 (33.33%)	23 (31.5%)	21 (17.94%)	
T: 2-5 cm	30 (50.0%)	37 (50.7%)	64 (54.7%)	
T: > 5 cm	10 (26.7%)	13 (17.8%)	32 (27.35%)	*p*<0.03*
LVI:				
Yes	26 (43.3%)	16 (21.9%)	41 (35.0%)	*p*<0.02*
No	34 (56.7%)	57 (78.1%)	76 (65.0%)	

Abbreviations - BMI: Body mass index, ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor, TNBC: Triple negative breast cancer, T: Tumor, LVI: Lymph vascular invasion.

TABLE 3. Lines of treatment in study group.

Item "n=250"	Descriptive
Type of surgery:	
• **MRM**	205 (82.0%)
• **BCS**	45 (18.0%)
Adjuvant chemotherapy:	
• **Yes:**	245 (98.0%)
- **Anthracycline based**	191 (76.4%)
- **Anthracycline and taxane based**	44 (17.6%)
- **Anthracycline then capecitabine**	5 (2.0%)
- **CMF**	3 (1.2%)
- **Anthracycline and taxane based then capecitabine**	1 (0.4%)
- **Capecitabine only**	1 (0.4%)
• **No**	5 (2.0%)
Adjuvant local radiotherapy:	
• **Yes**	213 (85.2%)
• **No**	37 (14.8%)
Adjuvant hormonal therapy:	
• **Tamoxifen**	91 (36.4%)
• **Letrozole**	50 (20%)
• **Anastrozole**	13 (5.2%)
• **Tamoxifen then AI**	17 (6.8%)
Trastuzumab:	
• **Yes**	11 (4.4%)
• **No**	239 (95.6%)

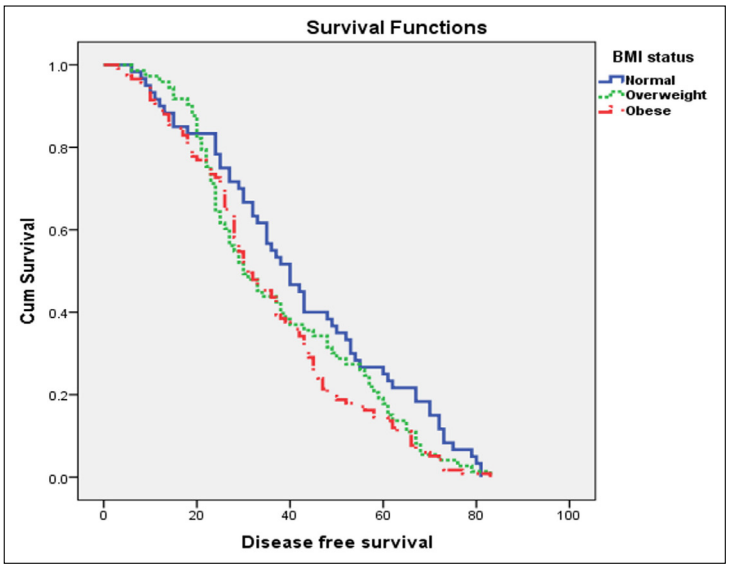
Abbreviations - MRM: modified radical mastectomy, BCS: breast conservative surgery, AI: aromatase inhibitor.

TABLE 4. The tumor characters according to BMI.

Item	*Total no (%)*	*BMI status*			*p-value*
		Normal "n=60"	*Overweight "n=73"*	*Obese "n=117"*	
LR:					
Yes	27 (10.8%)	1 (1.67%)	10 (13.69%)	16 (13.67%)	$p<0.03$*
No	223 (89.2%)	59 (98.3%)	63 (86.3%)	101 (86.3%)	
Metastasis:					
Yes	80 (32%)	14 (23.33%)	25 (34.24%)	41 (35.04%)	$p=0.254$
No	170 (68%)	46 (76.67%)	48 (65.75%)	76 (64.95%)	
DFS:					
Mean± SD	37.77±1.25	42.38 ± 2.79	37.82 ± 2.27	35.38 ± 1.72	$p<0.001$*
(95% CI)	(35.52-40.22)	(36.9 –47.86)	(33.36-42.28)	(32.00 – 38.76)	
OS:					
Mean± SD	43.40 ± 18.23	45.70 ± 2.53	44.31 ± 2.04	39.65 ± 1.65	$p<0.001$**
(95% CI)	(41.40 - 45.66)	40.74 – 50.65	(40.29-48.33)	(38.4-44.89)	

Abbreviations - BMI: Body mass index, LR: Local recurrence, DFS: Disease-free survival, CI: Confidence interval, OS: Overall survival.

Fig. 1. Disease-free survival of patients according to BMI.



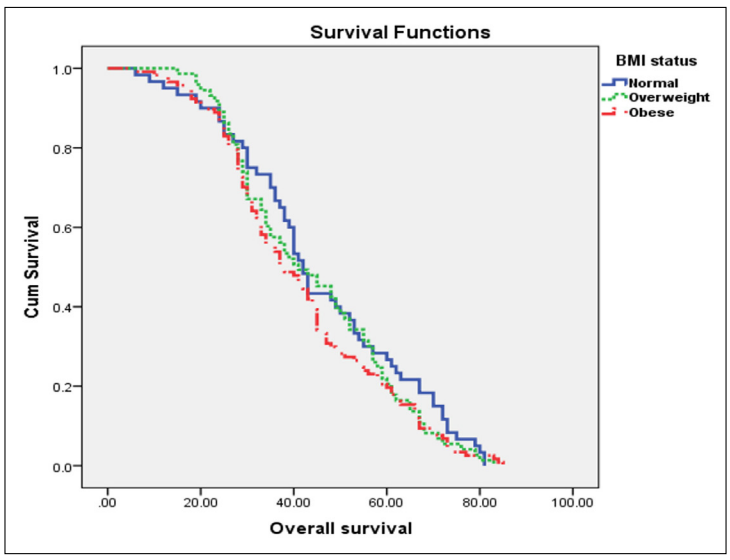


Fig. 2. Overall survival of patients according to BMI.

DISCUSSION

BC is the most prevalent malignancy in females and the second leading cause of cancer death in the United States. According to the American Cancer Society 290,560 Americans will be diagnosed with BC in 2022 with 43,780 dying from the disease [18]. Similarly, BC is the most prevalent malignancy in Egyptian women. In 2020, approximately 22,700 new cases are anticipated, accounting for 38.8% of all new cancer cases and approximately 46.000 cases are expected in 2050[19]. BC mortality in Egypt is around 11%, making it the second leading cause of cancer-related death after liver cancer[20].

Obesity is one of the risk factors for BC development, so there is a significant association. In our study we found that roughly three-quarters of the 190 cases (76%) were either overweight or obese; this high incidence is consistent with the findings of many other studies[13,21,22]. However, this association between BMI and BC risk varies depending on menopausal status. According to significant number of studies, as BMI increased, the risk of developing BC increased in post-menopause[23,24,26-29] and decrease in pre-menopause[23-28]. Iyengar et al[30] demonstrated that obesity in post-menopause is associated with an increased risk.

Liu et al[31] discovered that as BMI increased by about 5 kg/m^2 in post-menopause, the risk increased by about 2% whereas it had a protective effect in pre-menopause. However, our results challenge these studies because we found no significant difference in incidence between pre-menopause and post-menopause patients. Our results concluded that overweight and obesity are strongly associated with high T stages (p<0.03) which is consistent with previous studies[32-34]. Although approximately two-thirds of overweight and obese patients were ER and PR positive, no significant difference was observed. Several studies support these findings [35-37] but other disagree [38-40]. LR was found to be more prevalent in overweight and obese patients than in normal patients with a significant difference (p<0.03) which agrees with other results[41-43]. Other studies, however, found no change in LR between BMI categories[44,45].

In comparison, there was no significant difference in distant metastasis between overweight and obese patients and normal BMI patients (p=0.254). Ewertz et al [44] reported that patients with a BMI of 25 kg/m^2 or higher had a 42% to 46% higher risk of getting distant metastasis than patients with a BMI less than 25 kg/m^2. Blair et al[44] and Osman et al[46] found the same results, so our results didn't correspond to these studies[47]. In terms of DFS and OS, we found that obese patients had substantially lower DFS and OS than normal and over-weight (p<0.001). A significant number of studies' results agree with ours[13,48,49]; however, Carmichael et al[50] disagree with us as because they discovered no difference.

Recommendations

Based on our finding, there should be awareness programs to explain the dangers of being overweight or obese to reduce their prevalence and as a consequence the incidence of BC. Overweight or obese people should have a regular periodic breast examination through screening programs to detect the tumor in its early stages. weight management and lifestyle changes should be implemented after a diagnosis of breast cancer BC in overweight or obese patients to improve response to treatment and decrease the chance of recurrence. Breast cancer BC caused by being overweight or obese should be avoided through health education initiatives.

CONCLUSIONS

The purpose of this study is to assess BMI as a risk and prognostic factor in BC. We found that overweight and obesity at diagnosis can be considered independent risk factors independent of others as well as a prognostic factor as by increasing the BMI worsens the prognosis.

Ethics approval and Consent to participate:
The study is approved by the Ethical Committee of Faculty of Medicine, Assiut University. Registered in Clinical Trials.gov Identifier: NCT03429504.

Availability of data and materials:
All data generated or analyzed during this study are included in this published article.

Conflict of interests:
The authors declare that they have no competing interests.

Funding:
No funding is declared for this article.

Author contributions:
All authors contributed to the study conception and design. All authors read and approved the final manuscript.

REFERENCES

1. Garvey WT, Mechanick JI. Proposal for a scientifically correct and medically actionable disease classification system (ICD) for obesity. Obesity (Silver Spring) 2020; 28: 484-492
2. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C. Global, regional and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden0020of Disease Study 2013. Lancet 2014; 384: 766-781.
3. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, Marczak L, Mokdad AH. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017; 377: 13-27.
4. Roberto CA, Swinburn B, Hawkes C, Huang TT, Costa SA, Ashe M. Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. Lancet 2015; 385: 2400-2409.
5. Obesity and overweight. 2020; Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
6. Berrington de Gonzalez A, Hartge P, Cerhan JR. Body-mass index and mortality among 1.46 million white adults. New Engl J Med 2010; 363: 2211-2119.
7. Kitahara CM, Flint AJ, Berrington de Gonzalez A. Association between class III obesity (BMI of 40-59 kg/m2) and mortality: A pooled analysis of 20 prospective studies. PLoS Med 2014; 11: e1001673.
8. Adams KF, Schatzkin A, Harris TB. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. New Eng J Med 2006; 355: 763-778.
9. Cohen SS, Park Y, Signorello LB. A pooled analysis of body mass index and mortality among African Americans. PLoS One 2014; 9: e111980.
10. Wormser D, Kaptoge S, Angelantonio ED, Wood AM, Pennells L, Thompson A, Sarwar N. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet 2011; 377: 1085-1095.
11. Cleary MP, Grossmann ME. Obesity and breast cancer: the estrogen connection. Endocrinology 2009; 150: 2537-2542.
12. Pierobon M, Frankenfeld CL. Obesity as a risk factor for triple negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat 2013; 137: 307-14.
13. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. Breast Cancer Res Treat 2010; 123: 627-635.
14. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: A systematic review and meta-analysis of prospective observational studies. Lancet 2008; 371: 569-578.
15. Munsell MF, Sprague BL, Berry DA, Chisholm G, Trentham-Dietz A. Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status. Epidemiol Rev 2014; 36: 114-136.
16. Schoemaker MJ, Nichols HB: Association of body mass index and age with subsequent breast cancer risk in premenopausal women. JAMA Oncol 2022; 4: e181771.
17. Hortobagyi GN, Connolly JL, D'Orsi CJ, Edge SB, Mittendorf EA American Joint Committee on Cancer. AJCC cancer staging manual. 8th Ed. New York, NY: Springer 2017.
18. Siegel RL, Miller KD, Fuchs HE, Jemal ACancer statistics, 2022. Cancer J Clin 2022; 72: 7-33.
19. Ibrahim AS, Khaled HM, Mikhail NN. Cancer incidence in Egypt: Results of the national population-based cancer registry program. J Cancer Epidemiol 2014; 437971: 2014.
20. International Cancer Control Partnership: WHO Cancer Country Profiles 2020. Available at https://www.iccp-portal.org/news/who-cancer-country-profiles-2020.
21. Neuhouser ML, Aragaki AK, Prentice RL, Manson JE, Chlebowski R, Carty CL. Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk: A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials. JAMA Oncol 2015; 1: 611-621.
22. Suzuki R, Orsini N, Saji S. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status—a meta-analysis. Int J Cancer 2009; 124: 698-712.
23. Huang Z, Hankinson SE, Colditz GA: Dual effects of weight and weight gain on breast cancer risk. JAMA 1997; 278: 1407.
24. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ 2007; 335: 1134.
25. Schoemaker MJ, Nichols HB, Wright LB. for the Premenopausal Breast Cancer Collaborative Group. Association of body mass index and age with subsequent breast cancer risk in premenopausal women. JAMA Oncol 2018; 4: e181771.
26. Chan DSM, Abar L, Cariolou. World Cancer Research Fund International: Continuous Update Project-systematic literature review and meta-analysis of observational cohort studies on physical activity, sedentary behavior, adiposity, and weight change and breast cancer risk. Cancer Causes Control 2019; 30: 1183-1200.
27. Park JW, Han K, Shin DW. Obesity and breast cancer risk for pre- and postmenopausal women among over 6 million Korean women. Breast Cancer Res Treat 2021; 185: 495-506.
28. Van den Brandt PA, Ziegler RG, Wang M. Body size and weight change over adulthood and risk of breast cancer by menopausal and hormone receptor status: a pooled analysis of 20 prospective cohort studies. Eur J Epidemiol 2021; 36: 37-55.
29. Luo J, Chen X, Manson JE. Birth weight, weight over the adult life course and risk of breast cancer. Int J Cancer 2020; 147: 65-75.
30. Iyengar NM, Arthur R, Manson JE. Association of body fat and risk of breast cancer in postmenopausal women with normal body mass index: a secondary analysis of a randomized clinical trial and observational study. JAMA Oncol 2018; 5: 155-163.
31. Liu K, Zhang W, Dai Z. Association between body mass index and breast cancer risk: evidence based on a dose response meta-analysis. Cancer Manag Res 2018; 10: 143-151.
32. Kaviani A, Neishaboury M, Mohammadzadeh N. Effects of obesity on presentation of breast cancer, lymph node metastasis and patient survival: a retrospective review. Asian Pac J Cancer Prev 2013; 14: 2225-2229.

33. Daling JR, Malone KE, Doody DR. Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. Cancer 2001; 92: 720-729.
34. Chen HL, Ding A, Wang ML. Impact of central obesity on prognostic outcome of triple negative breast cancer in Chinese women. Springer Plus 2016; 5: 594.
35. Sparano JA, Wang M, Zhao F, Stearns V, Martino S, Ligibel JA. Obesity at diagnosis is associated with inferior outcomes in hormone receptor-positive operable breast cancer. Cancer 2012; 118: 5937-5946.
36. Berstad P, Coates R J, Bernstein L. A case-control study of body mass index and breast cancer risk in white and African-American women. doi: 10.1158/1055-9965. EPI-10-0025. Cancer Epidemiol Biomarkers Prev 2010; 19: 1532-1544.
37. Bandera EV, Chandran U, Zirpoli G. Body fatness and breast cancer risk in women of African ancestry. BMC Cancer 2013; 13: 475.
38. Nagrani R, Mhatre S, Rajaraman P. Central obesity increases risk of breast cancer irrespective of menopausal and hormonal receptor status in women of South Asian Ethnicity. Eur J Cancer 2016; 66: 153-161.
39. John EM, Sangaramoorthy M, Phipps AI. Adult body size, hormone receptor status, and premenopausal breast cancer risk in a multiethnic population: the San Francisco Bay Area breast cancer study. Am J Epidemiol 2011; 173: 201-216.
40. Wang F, Liu L, Cui S. Distinct Effects of Body Mass Index and Waist/Hip Ratio on Risk of Breast Cancer by Joint Estrogen and Progestogen Receptor Status: Results from a Case-Control Study in Northern and Eastern China and Implications for Chemoprevention. Oncologist 2017; 22: 1431-1443.
41. Sun L, Zhu Y, Qian Q. Body mass index and prognosis of breast cancer: An analysis by menstruation status when breast cancer diagnosis. Medicine (Baltimore) 2018; 97: e11220.
42. Marret H, Perrotin F, Bougnoux P, Descamps P, Hubert B, Lefranc T. Low body mass index is an independent predictive factor of local recurrence after conservative treatment for breast cancer. Breast Cancer Res Treat 2001; 66: 17-23.
43. Bergom C, Kelly T, Bedi M, Saeed H, Prior P, Rein LE. Association of Locoregional Control With High Body Mass Index in Women Undergoing Breast Conservation Therapy for Early-Stage Breast Cancer. Int J Radiat Oncol Biol Phys 2016; 96: 65-71.
44. Ewertz M, Jensen MB, Gunnarsdóttir KA, Højris I, Jakobsen EH, Nielsen D, Stenbygaard LE, Tange UB, Cold S. Effect of obesity on prognosis after early-stage BC. J Clin Oncol 2011; 29: 25-31.
45. Majed B, Moreau T, Senouci K, Salmon RJ, Fourquet A, Asselain B. Is obesity an independent prognosis factor in woman breast cancer? Breast Cancer Res Treat 2008; 111: 329-342.
46. Blair CK, Wiggins CL, Nibbe AM, Storlie CB, Prossnitz ER, Royce M. Obesity and survival among a cohort of breast cancer patients is partially mediated by tumor characteristics. Breast Cancer 2019; 5: 33.
47. Osman MA, Hennessy BT. Obesity Correlation with Metastases Development and Response to First-Line Metastatic Chemotherapy in Breast Cancer. Clin Med Insights Oncol 2015; 9: S32812.
48. Chan DSM, Vieira AR, Aune D, Bandera E V, Greenwood DC, McTiernan A Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. Ann Oncol Off J Eur Soc Med Oncol 2014; 25: 1901-1914.
49. Abrahamson PE, Gammon MD, Lund MJ, Flagg EW, Porter PL, Stevens J. General and abdominal obesity and survival among young womenwith breast cancer. Cancer Epidemiol biomarkers Prev a Publ Am Assoc Cancer Res cosponsored by Am Soc Prev Oncol 2006; 15: 1871-1877.
50. Carmichael AR, Bendall S, Lockerbie L, Prescott RJ, Bates T. Does obesity compromise survival in women with breast cancer? Breast 2004; 13: 93-96.