Original Article

Impact of Body Mass Index on Breast Cancer Subtypes in Iranian Women

Hamid Ahmadi[1], Bita Eslami[1], Sadaf Alipour[1,2], Adel Yazdankhahkenary[3], Ramesh Omranipour[1,4]

[1]Breast Disease Research Center (BDRC), Tehran University of Medical Sciences, [2]Department of Surgery, Arash Women's Hospital, Tehran University of Medical Sciences, [3]Trauma and Surgery Research Center, Sina Hospital, Tehran University of Medical Sciences, [4]Department of Surgical Oncology, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Background: The incidence of obesity as one of the risk factors of breast cancer (BC) is increasing dramatically. Our objective was to evaluate the association between body mass index (BMI) and three subtypes of BC in Iranian women. **Materials and Methods:** In this retrospective study, BC patients' information was recorded by referring to their medical records in the Cancer Institute of Imam Khomeini Hospital, Iran, from 2015 to 2017. The data of 374 patients were entered into the study, and tumor data were classified into three groups by molecular markers (human epidermal growth factor receptor 2 [HER2] enriched, triple negative, and luminal). **Results:** Luminal subtype comprised the majority (71.1%) of all diagnosed BC patients. The proportion of obese women was higher in triple-negative group (35.3%), although the differences between three subtypes of BC were not statistically significant (P = 0.30). Multivariate logistic among cases only, considering luminal as the comparison group, indicated a positive association between age of menarche and HER2-enriched subtype (odds ratio [OR] = 1.18, 95% confidence interval [CI]: 0.99–1.41, P = 0.07) and also suggested a reverse association between age at time of diagnosis and triple-negative subtype (OR = 0.97, 95% CI: 0.95–1, P = 0.09) with borderline significance. **Conclusion:** We did not find any statistically significant differences in BMI between three subtypes of BC. It seems that there is a correlation between triple-negative subtypes of BC in Iranian population and obesity. However, further studies with larger sample size are needed.

Keywords: *Body mass index, breast cancer, molecular subtype*

Introduction

Breast cancer (BC) is the most common malignancy leading to death among women, and the incidence is increasing by 3.1% annually in the world.[1] As well, BC is the most common cancer in Iranian women, and according to the latest national database in 2018, the age-standardized rate for BC was 33.21/100,000.[2] Obesity is one of the risk factors of BC, and the incidence has increased dramatically.[3] A result of a nationwide survey has shown that 56.9% of Iranian women aged 15–65 years had excess body weight and body mass index (BMI) ≥25.[4] Evidence supported that obesity is associated with increased risk of invasive BC in women who are in postmenopausal status.[5] A case–control study in postmenopausal Iranian women showed that the women who are in the obese range had a 3-fold increased risk of BC.[6] Meanwhile, overweight is associated with an increased risk of BC recurrence, death, and worse survival outcomes.[7] A recent study in Mexico showed that obesity is associated with more advanced stages of BC.[8]

BC is subtyped by molecular markers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2); those are useful in planning treatment and developing new therapies.[9]

Obesity and probably waist-hip ratio can affect the risk of BC by altering concentrations of sex hormones.[10] The positive or negative relationship between obesity and hormone receptor subtypes (ER and PR) of BC is well established in some studies.[11-18] However, some evidence did not find any statistically significant correlation between BC hormone receptors subtypes and BMI both in pre- and postmenopausal women.[19] Govind Babu *et al*. study reported that BMI was higher in patients with luminal subtype (hormone receptors positive) followed by triple negative and lowest for HER2 at the time of diagnosis.[20]

A systematic review and meta-analysis revealed that obese women are at increased

How to cite this article: Ahmadi H, Eslami B, Alipour S, Yazdankhahkenary A, Omranipour R. Impact of body mass index on breast cancer subtypes in Iranian women. Clin Cancer Investig J 2019;8:52-6.

Address for correspondence:
Dr. Ramesh Omranipour, Breast Disease Research Center, Sadaf Building, Imam Khomeini Hospital, Keshavrz Blvd., Tehran, Iran.
E-mail: omranipour@tums.ac.ir

Access this article online

Website: www.ccij-online.org

DOI: 10.4103/ccij.ccij_8_19

Quick Response Code:

risk of presenting with triple-negative (ER, PR, and HER2 negative) subtype than nonobese women.[21] The results of the more recent studies are consistent with this study and report the high prevalence of obesity in patients who are triple-negative subtype.[22-24] However, a number of epidemiological studies did not confirm the association between obesity and triple-negative subtype.[14,15,18] Hansra *et al*. study in 2018 showed that BC survivors with triple-negative BC will present with obesity and gain weight after chemotherapy and intensive weight loss intervention in this subtype of BC are necessary.[25] A few epidemiological studies reported that BMI is associated with an increased risk of both triple-negative and luminal subtypes of BC.[12,17,26]

Although many types of research have been performed on this subject, it remains uncertain whether any association occurs between BC subtypes and obesity. Since full comprehension of the subtypes of BC may clarify mechanism affecting the etiology of disease, further studies in different populations are needed. Based on our knowledge, there is no evidence about the obesity in subtypes of BC in Iranian population. Because obesity is common among Iranian women and BC is increasing in young people, finding prevention strategies for subtypes of this malignancy are needed.

Therefore, the objective of this study was to evaluate the association between BMI and distribution of BC subtypes in Iranian women.

Materials and Methods

Patients and design

This retrospective study was approved by the Ethics Committee of Tehran University of Medical Sciences. BC patients' information was extracted from medical records in the Cancer Institute of Imam Khomeini Hospital, Iran, from 2015 to 2017. Of 430 patients, 56 were excluded due to unknown BMI (n = 20) and missing tumor data (n = 36), and 374 patients were enrolled in this study. Tumor data were classified into three groups: HER2 enriched (ER−/PR−/HER2+), triple negative (ER−/PR−/HER2-), and luminal (ER+/PR+). Data about BC subtypes and individual characteristics (age at diagnosis, weight, height, reproductive factors, family history of BC, menopausal status, and breastfeeding) were extracted from patient's medical records by the main investigator. BMI was calculated by the formula of weight divided by height squared (kg/m^2) and categorized based on the WHO classification (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m^2). Because only four patients belong to the BMI category of <18.5 kg/m^2, we have not established a separate group for this category as underweight and it was combined with the normal weighted group. Therefore, BMI <25 was considered as normal weight, 25–29.9 overweight, and ≥30 kg/m^2 as obese.

Statistical analysis

Statistical analysis was performed using SPSS software (version 18, Chicago, IL, USA). Categorical and continuous variables were summarized as N (%) and mean ± standard deviation, respectively. For categorical variables, Chi-square test was used. Continuous variables were compared with ANOVA test. The case-only odds ratio (OR) and 95% confidence intervals (CIs) were estimated using logistic regression as a measure of association. The ORs were calculated among case only using luminal (the most common type) as the comparison group. $P < 0.05$ was considered to be statistically significant.

Results

Final analysis in 374 women with BC showed that luminal subtype comprised the majority (71.1%) of all diagnosed BC patients. Triple negative represented 18.2%, and HER2 enriched 10.7% of all BCs. Of the total patients, 241 (64.4%) were premenopause and 133 (35.6%) were postmenopausal women.

Table 1 shows the distribution of the patient's characteristics. Only the age of menarche was statistically higher in HER2-enriched group. There was not any significant difference between BMI in pre- and postmenopausal (27.42 ± 5.20 vs. 27.57 ± 5, P = 0.78) cases (data not shown in table). Table 2 compares BMI between the three subtypes by considering menopausal status of patients. The analysis considering BMI categories showed that the prevalence of obese patients is higher (≥30) in the triple negative than other groups, and the difference is pronounced compared to patients with luminal-type tumors [Table 3]. However, this difference was not statistically significant. Furthermore, we also evaluated the difference between BMI categories and three subtypes of BC considering the menopausal status, and no differences were observed (data not shown in table).

Case-only crude ORs comparing each subtype to luminal type are presented in Table 4. We evaluated ORs of some demographic variables (age at the time of diagnosis, age of menarche, parity, menopause, breastfeeding, and BMI). Our findings indicated a positive association between age of menarche and HER2-enriched subtype (OR = 1.18, 95% CI: 0.99–1.41, P = 0.07) and also suggested a reverse association between age at the time of diagnosis and triple-negative subtype (OR = 0.97, 95% CI: 0.95–1, P = 0.09) with borderline significance.

Discussion

Due to the increasing prevalence of obesity and its relationship with BC risk and worse prognosis of the disease in obese women,[27] it is interesting to understand the association of obese or overweight state with specific subtype of BC. In the present study, we evaluated the association between BMI at the time of diagnosis and

Table 1: Basal characteristics of the study population

Variable	Total (*n*=374)	Luminal (*n*=266)	HER2 enriched (*n*=40)	Triple negative (*n*=68)	*P*
Age (years)	47±10.31	47.64±10.14	46.60±11.72	44.76±9.91	0.12
BMI (kg/m^2)	27.74±5.12	27.42±5.08	27.41±5.21	27.73±5.31	0.61
Age of menarche (years)	13.62±1.66	13.57±1.44	14.23±2.95	13.46±1.33	0.04*
Age at the first pregnancy (years)	22.84±5.58	22.69±5.56	23.65±6.32	23.07±5.28	0.63
Parity (*n*)	2.41±1.70	2.49±1.69	2.05±1.69	2.31±1.71	0.28
Age of menopause (years)	48.14±4.90	48.19±5.17	47±3.74	48.61±4	0.66
Menopause					
Yes	133 (35.6)	103 (38.7)	12 (30)	18 (26.5)	0.13
No	241 (64.4)	163 (61.3)	28 (70)	50 (73.5)	
Breastfeeding					
Yes	326 (87.2)	238 (89.5)	31 (77.5)	57 (83.8)	0.75
No	48 (12.8)	28 (10.5)	9 (22.5)	11 (16.2)	
Positive FH	180 (48.1)	122 (45.9)	21 (52.5)	37 (54.4)	0.38

*Significant at 0.05 level. Data are expressed as mean±SD and number with percentages in parenthesis. *P* value refers to ANOVA test and Chi-squared test, when appropriate. BMI: Body mass index, FH: Family history, SD: Standard deviation

Table 2: Comparison of BMI between three groups considering menopause status

Menopause	*n*	Mean±SD	*P**
Premenopause			
Luminal	163	27.39±5.13	0.91
HER2 enriched	28	27.14±5.74	
Triple negative	50	27.65±5.20	
Total	241	27.42±5.20	
Postmenopause			
Luminal	103	27.45±5.02	0.88
HER2 enriched	12	28.03±3.86	
Triple negative	18	27.94±5.74	
Total	133	27.57±5	

**P* value refers to ANOVA test between three subtypes of BC. SD: Standard deviation

Table 3: Comparison of categorical body mass index in three subtyped of breast cancer

BMI category	Luminal (*n*=266)	HER2 enriched (*n*=40)	Triple negative (*n*=68)	*P**
Normal	95 (35.7)	14 (35)	26 (38.2)	0.92
Overweight	102 (38.3)	14 (35)	18 (26.5)	0.19
Obese	69 (25.9)	12 (30)	24 (35.3)	0.30

**P* value refers to Chi-squared test. BMI: Body mass index

three subtypes of BC in Iranian women. We could not find any statistically significant differences between BMI (continuous or categorical) and subtypes of BC in this population. We found that the proportion of obese women was higher in triple-negative subtype of BC. However, none of the associations was statistically significant.

There are several studies which demonstrated that being overweight or obese increased the risk of triple-negative type, and their findings are consistent with the present study.[21-24] However, two studies reported that higher BMI and obesity increased the incidence of triple-negative subtype particularly among premenopausal patients,[22,23] and other studies showed the same results in BC patients without considering menopausal status.[21,24] However, we did not detect differences in BMI considering menopausal status or significant among the three subtypes [Table 2]. Since the sample size in the present work was very low in comparison with other studies, and grouping them based on menopausal status results in a very low number of cases in each category, the results may become significant if larger sample size is considered. There are some studies with contradictory results which did not find any relation between triple-negative subtype and BMI.[14,15,18] A multicenter study by Song *et al*. in seven regions of China reported that triple-negative BC had a lower BMI in contrast to luminal A subtype and that obesity decreased the risk of triple-negative subtype BC.[28]

Turkoz *et al*. study detected that obesity is associated with ER- and PR-negative tumors and poor overall survival in premenopausal women with BC[11] because obese or overweight patients are more likely to present with lymph node involvement and advanced clinical stage at the time of diagnosis. Another study showed that increasing BMI was positively associated with the risk of ER- and PR-negative tumors among postmenopausal women who never used hormone replacement therapy (HRT), and HRT users were at increased risk of both hormone receptor-negative and positive BC, although this association was stronger for receptor-positive tumors.[29]

The relation between body weight and ER + PR + subtype BC was revealed in a meta-analysis study,[16] and they suggested that weight control may be an effective strategy for preventing ER + PR + tumor after menopause. On the other hand, Ma *et al*. showed that high BMI near the end of adolescence (18 years) decreases the risk of ER-, PR-, and HER2-positive premenopausal BC.[30] A prospective study in the Japan Public Health Center showed that high recent BMI and subsequent BMI gain from age 20 were associated with increased risk of

Table 4: Case-only odds ratios and 95% confidence intervals from logistic regression models of association between breast cancer subtypes and patient's characteristics

Patients demographic	Univariate model			Multivariate model		
	OR	95% CI	*P*	OR	95% CI	*P*
HER2 enriched (*n*=40)						
Age at menarche	1.19	1.01-1.42	0.046*	1.18	0.99-1.41	0.07
Triple negative (*n*=68)						
Age at diagnosis	0.97	0.95-0.99	0.04*	0.97	0.95-1.00	0.09

*Significant at 0.05 level. Multivariate analysis was performed by considering age the time of diagnosis, age of menarche, parity, breastfeeding, BMI, and menopausal status. ORs were calculated among case using luminal as the comparison group. OR: Odds ratio, CI: Confidence interval, BMI: Body mass index

postmenopausal ER- and PR-positive tumors.[31] Therefore, it seems that more investigation about the relationship between weight at the time of adolescence and developing subtypes of BC in the future life is necessary.

In a recent meta-analysis by Li *et al*., they observed that overweight status appears to increase the risk of both luminal and triple-negative tumors in East-Asian women, and these associations were not impacted by menopausal status.[15] They also evaluated reproductive factors such as age of menarche, age at first pregnancy, and breastfeeding. They reported that late menarche and absence of breastfeeding appear to increase the risk of both luminal and ER − PR − tumors, and these associations were not impacted by menopausal status. Another study results suggested that low parity and short or no duration of breastfeeding have a correlation with the occurrence of luminal-like BC subtypes.[32] In the present study, we confirmed the positive association between age of menarche and HER2+ (ER−, PR−, and HER2+) tumors with borderline significance ($P = 0.07$). However, our study did not confirm the same result in breastfeeding or parity.

Due to the controversial results of studies, this issue needs to be further studied. Different results among studies may have arisen due to differences in sample sizes, study populations, laboratory methodologies, and different classifications for BC subtypes or menopausal status.

This study had some limitations. One of the limitations of our study included the retrospective design and reliance on BMI to assess obesity. We cannot exclude the possibility that some women may have misreported their weight or height, which could result in the misclassification of BMI. Since BMI is an incomplete measurement of obesity and it is unable to discriminate between different body compositions, specifically in patients with increased central adiposity, it is better to evaluate the association of waist/hip ratio in BC subtypes. Certainly, we had no access to the information of waist and hip measurement of the patients. Another limitation of our study was the low sample size, we think that by increasing the sample size, some results may become statistically significant. Based on our knowledge, the present study is the first description of this subject in Iranian women, which is the strength of our study.

Conclusion

We did not find any statistically significant correlation between BC subtypes and BMI both in pre- and postmenopausal women. However, BMI was higher in premenopausal patients with triple-negative tumors [Table 2], and obesity was more prevalent [Table 3] in this subtype of BC. It seems that there is a correlation between triple-negative subtypes of BC in Iranian population and BMI. Further studies with more sample size are needed in this regard. Since obesity is associated with poor overall survival in triple-negative subtype specifically in premenopausal women,[11] body weight control will be an effective strategy for preventing triple-negative subtype of BC in pre- and postmenopausal women.

Financial support and sponsorship

This study was financially supported by a grant (no# 36638) of the Vice-Chancellor of Research of Tehran University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, *et al.* Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.
2. Nafissi N, Khayamzadeh M, Zeinali Z, Pazooki D, Hosseini M, Akbari ME. Epidemiology and histopathology of breast cancer in Iran versus other Middle Eastern countries. Middle East J Cancer 2018;9:243-51.
3. Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. Lancet 2011;378:815-25.
4. Janghorbani M, Amini M, Willett WC, Mehdi Gouya M, Delavari A, Alikhani S, *et al.* First nationwide survey of prevalence of overweight, underweight, and abdominal obesity in Iranian adults. Obesity (Silver Spring) 2007;15:2797-808.
5. Neuhouser ML, Aragaki AK, Prentice RL, Manson JE, Chlebowski R, Carty CL, *et al.* Overweight, obesity, and postmenopausal invasive breast cancer risk: A secondary analysis of the women's health initiative randomized clinical trials. JAMA Oncol 2015;1:611-21.
6. Montazeri A, Sadighi J, Farzadi F, Maftoon F, Vahdaninia M, Ansari M, *et al.* Weight, height, body mass index and risk of breast cancer in postmenopausal women: A case-control study. BMC Cancer 2008;8:278.
7. Jiralerspong S, Goodwin PJ. Obesity and breast cancer prognosis: Evidence, challenges, and opportunities. J Clin

Oncol 2016;34:4203-16.
8. Alarcón Rojas CA, Alvarez-Bañuelos MT, Morales-Romero J, Suárez-Díaz H, Hernández-Fonseca JC, Contreras-Alarcón G. Breast cancer: Metastasis, molecular subtypes, and overweight and obesity in Veracruz, Mexico. Clin Breast Cancer 2019;19:e166-71.
9. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, *et al.* Molecular portraits of human breast tumours. Nature 2000;406:747-52.
10. Verkasalo PK, Thomas HV, Appleby PN, Davey GK, Key TJ. Circulating levels of sex hormones and their relation to risk factors for breast cancer: A cross-sectional study in 1092 pre- and postmenopausal women (United Kingdom). Cancer Causes Control 2001;12:47-59.
11. Turkoz FP, Solak M, Petekkaya I, Keskin O, Kertmen N, Sarici F, *et al.* The prognostic impact of obesity on molecular subtypes of breast cancer in premenopausal women. J BUON 2013;18:335-41.
12. Kawai M, Malone KE, Tang MT, Li CI. Height, body mass index (BMI), BMI change, and the risk of estrogen receptor-positive, HER2-positive, and triple-negative breast cancer among women ages 20 to 44 years. Cancer 2014;120:1548-56.
13. Bandera EV, Chandran U, Hong CC, Troester MA, Bethea TN, Adams-Campbell LL, *et al.* Obesity, body fat distribution, and risk of breast cancer subtypes in African American women participating in the AMBER consortium. Breast Cancer Res Treat 2015;150:655-66.
14. Horn J, Alsaker MD, Opdahl S, Engstrøm MJ, Tretli S, Haugen OA, *et al.* Anthropometric factors and risk of molecular breast cancer subtypes among postmenopausal Norwegian women. Int J Cancer 2014;135:2678-86.
15. Li H, Sun X, Miller E, Wang Q, Tao P, Liu L, *et al.* BMI, reproductive factors, and breast cancer molecular subtypes: A case-control study and meta-analysis. J Epidemiol 2017;27:143-51.
16. Suzuki R, Orsini N, Saji S, Key TJ, Wolk A. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status – A meta-analysis. Int J Cancer 2009;124:698-712.
17. Gaudet MM, Press MF, Haile RW, Lynch CF, Glaser SL, Schildkraut J, *et al.* Risk factors by molecular subtypes of breast cancer across a population-based study of women 56 years or younger. Breast Cancer Res Treat 2011;130:587-97.
18. Crispo A, Montella M, Buono G, Grimaldi M, D'Aiuto M, Capasso I, *et al.* Body weight and risk of molecular breast cancer subtypes among postmenopausal mediterranean women. Curr Res Transl Med 2016;64:15-20.
19. Biglia N, Peano E, Sgandurra P, Moggio G, Pecchio S, Maggiorotto F, *et al.* Body mass index (BMI) and breast cancer: Impact on tumor histopathologic features, cancer subtypes and recurrence rate in pre and postmenopausal women. Gynecol Endocrinol 2013;29:263-7.
20. Govind Babu K, Anand A, Lakshmaiah KC, Lokanatha D, Jacob LA, Suresh Babu MC, *et al.* Correlation of BMI with breast cancer subtype and tumour size. Ecancermedicalscience 2018;12:845.
21. 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.
22. Sahin S, Erdem GU, Karatas F, Aytekin A, Sever AR, Ozisik Y, *et al.* The association between body mass index and immunohistochemical subtypes in breast cancer. Breast 2017;32:227-36.
23. Turkoz FP, Solak M, Petekkaya I, Keskin O, Kertmen N, Sarici F, *et al.* Association between common risk factors and molecular subtypes in breast cancer patients. Breast 2013;22:344-50.
24. Gershuni V, Li YR, Williams AD, So A, Steel L, Carrigan E, *et al.* Breast cancer subtype distribution is different in normal weight, overweight, and obese women. Breast Cancer Res Treat 2017;163:375-81.
25. Hansra DM, Rollins R, Rados K, Johnson A, Ramey J, Pannell R, *et al.* Analysis of weight trends over time in female survivors with triple negative breast cancer. Clin Oncol 2018;36 Suppl 7:28.
26. Sueta A, Ito H, Islam T, Hosono S, Watanabe M, Hirose K, *et al.* Differential impact of body mass index and its change on the risk of breast cancer by molecular subtype: A case-control study in Japanese women. Springerplus 2012;1:39.
27. Carmichael AR. Obesity and prognosis of breast cancer. Obes Rev 2006;7:333-40.
28. Song Q, Huang R, Li J, Fan J, Zheng S, Zhang B, *et al.* The diverse distribution of risk factors between breast cancer subtypes of ER, PR and HER2: A 10-year retrospective multi-center study in China. PLoS One 2013;8:e72175.
29. Ritte R, Lukanova A, Berrino F, Dossus L, Tjønneland A, Olsen A, *et al.* Adiposity, hormone replacement therapy use and breast cancer risk by age and hormone receptor status: A large prospective cohort study. Breast Cancer Res 2012;14:R76.
30. Ma H, Ursin G, Xu X, Lee E, Togawa K, Malone KE, *et al.* Body mass index at age 18 years and recent body mass index in relation to risk of breast cancer overall and ER/PR/HER2-defined subtypes in white women and African-American women: A pooled analysis. Breast Cancer Res 2018;20:5.
31. Suzuki R, Iwasaki M, Inoue M, Sasazuki S, Sawada N, Yamaji T, *et al.* Body weight at age 20 years, subsequent weight change and breast cancer risk defined by estrogen and progesterone receptor status – The Japan public health center-based prospective study. Int J Cancer 2011;129:1214-24.
32. von Au A, Klotzbuecher M, Uhlmann L, Boudewijns M, Michel L, Wallwiener M, *et al.* Impact of reproductive factors on breast cancer subtypes in postmenopausal women: A retrospective single-center study. Arch Gynecol Obstet 2017;295:971-8.