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BODY MASS INDEX AND SURVIVAL RATE OF NONMETASTATIC BREAST CANCER WOMEN

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INTRODUCTION

Breast cancer is a global health problem and most common type of cancer among women that's make up 25.1% of all new cancer diagnoses in women according to global cancer project.[1] In 2011, World Health Organization estimated around 508,000 death cases among women worldwide due to breast cancer.[2] Around 252,710 new cases of invasive breast cancer and 40,610 breast cancer deaths were expected to die in United State in 2017, with increased incidence rate ranged from. 3% to 1.7% according to ethnic groups.[3] In Jordan, breast cancer is considered to be among top five cancers: breast cancer 1008 (20.1%), followed by colorectal 567 (11.3%), lung 371(7.4%), lymphoma 327 (6.5%), and urinary bladder 246 (4.9%) according to Jordan Cancer Registry (2012).[4]

The survival rate is an important concept to measure cancer care. Furthermore, it is a helpful tool to make comparison between countries. In general, Survival rates varied worldwide but are improving overall due to early diagnosis and advanced treatment. Early detection of breast cancer through organized mammography screening program showed an improvement in survival rate.[5] Nationwide study conducted in Netherlands between 1999 and 2012 among 173797 patients revealed that five year survival rate 2006 to 2012 was 96% improved compared to 1999 to 2005 in all tumor and nodal stage and conclude that early tumor stage detection remain vital in survival rate.[6] Mammography screening program has proven to be effective in finding cancers at earlier stages and resulted in an improvement of systemic therapy which decrease mortality rate among patients.[7] American Cancer Society recommended annual mammography for those above age of 40 years with average risk of breast cancer.[8]

Obesity is a chronic metabolic disorder resulted from interaction between environmental factors, lifestyle factors, and endogenous factors. Obesity is a risk factor for many diseases such as diabetes type 2, cardiovascular disease, metabolic syndrome and breast cancer.[9] Relationship between body mass index and breast cancer has been widely studied in literature.[10-12] Risk of developing breast cancer was higher among obese women than normal body weight women, especially among women who gained weight since menopause.[13] Moreover, it has been verified that obese women with breast cancer have poor prognosis with regard to menstrual cycle, and effectiveness of systemic medication in comparison to normal body weight women.[9] In breast cancer histopathology study, high BMI was associated with large size tumor for premenopausal and postmenopausal women, and more metastatic auxiliary lymph nodes, and presence of vascular invasion in premenopausal women compared to underweight/normal body weight women.[14] In contrast, obese women showed more advanced stage at time of diagnosis, but the obesity was not an independent factor for worse prognosis.[14,15]

In meta-analysis that reviewed 82 studies about breast cancer survivors and its relation with body mass index (BMI) before and after diagnosis. The study reported that relative risk of total mortality for obese (BMI >30.0 kg/m^2), overweight (BMI 25.0–<30.0 kg/m^2), and underweight (BMI <18.5 kg/m^2) women were 1.41, 1.07, and 1.10 respectively. Furthermore, obese women had worsened course and outcomes than women who have BMI less than 30 kg/ m^2.[16] Neuhouser et al (2015) reported that the greatest risk for invasive breast cancer was among obese women with grade II and III (BMI>35.0 kg/m^2). Furthermore, strong association found between BMI>35.0 kg/m^{2}and risk for positive estrogen receptors (ER+)/ positive progesterone receptors (PR+) breast cancers.[17] Similarly, the relative risk for ER+ breast cancers among normal body weight women versus obese women in pre-menopause was 1.15, while in post menopause was 1.53.[18]

The prevalence of obesity in the world has reached epidemic proportion with at least 300 million are clinically obese[19], while in Jordan the prevalence of overweight was 30% and obesity was 38.8% among Jordanian women aged 15–49 years.[20]

The physiological impact of obesity on breast cancer development and progression is not understood yet. Several hypotheses attempted to explain the link between obesity and breast cancer. One hypothesis is that obesity is associated with elevated leptin, insulin and inflammatory mediators such as TNF-alpha, prostaglandin E2 (PGE2) and interleukin 1 beta (Il-1β) in post menopausal women. These factors influence breast cancer growth and prognosis independently of estrogens by interacting with estrogen signaling at a cellular level and in turn raising the risk of endocrine-receptive positive (ER-positive) breast cancer in post-menopausal women.[21] Second hypothesis is elevation of circulating estrogens from peripheral aromatization of androgens in adipose tissue in obese postmenopausal women compared with normal body weight postmenopausal women.[22] Third hypothesis focused on autocrine, paracrine, and endocrine functions of adipocytes. Dizdar & Alyamac, 2004 claimed that obesity should be considered as endocrine tumor.[23] The paracrine and endocrine panel of stromal adipocyte-derived secretory products adipokines, which may act largely not only to promote tumor cell invasion, but also to enhance tumor growth indirectly by stimulating angiogenesis.[24,25] The current study aimed to determine the impact of BMI on survival rate for patients with breast cancer in Jordan.

METHODOLOGY

Study design: Retrospective cohort design was used.

Sample and setting: Eligible patients were women treated at Royal Medical Services as a case of breast cancers between years of 2008 and 2013. Data were collected through electronic medical records. Eligibility criteria included all female with nonmetastatic breast cancers, above age of 18, and Stage I-III breast cancer. Collected data included age, marital status, body mass index (BMI), type of breast cancer, tumor size, hormonal receptors, type of chemotherapy, stage of cancer at time of diagnosis, and menopausal status. Exclusion criteria determined as all women with metastatic breast cancer and previous history of invasive cancer other than breast.

Body mass index (BMI) categorized into four groups according to the Centers for Disease Control and Prevention (CDC): underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2).[26]

Menopausal status determined by 1 year of amenorrhea, and follicle-stimulating hormone (FSH) higher than 40 IU/L.[27, 28]

Researchers adopted breast cancer subtyping classifications described by Sharma et al (2010): Ductal carcinoma in situ (DCIS), Infiltrating lobular carcinoma (ILC), Infiltrating ductal carcinoma (IDC), and others (mixed type, mucinous, tubular, phyllodes).[29] Regarding breast cancer staging process, researchers adopted staging system of the American Joint Committee on Cancer (AJCC) which is called TNM system. TNM system classified the stage based on 7 keys: tumor size (T), spread to lymph node (N), metastasis (M), estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (Her2) status and grade of the cancer (G).[30]

Ethical consideration: All data about patients were handled under conditions of strict confidentiality and data were analyzed anonymously by patient ID number. No contacts were made with patients or their relatives. This study was approved by the Ethics Review Board at Royal Medical Services.

Data analysis: Descriptive statistics were run using SPSS software for Windows version 22 and level of significance was set as $p<.05$. Normal distribution of variables was tested with Kolmogorov– Smirnov procedure. Mean, standard deviation, and proportion were applied to summarize sample characteristics. t test was run to compare mean of continuous variables, while chi square test was run to test association between categorical variables. The Kaplan-Meier method was used to estimate survival rate of breast cancer patient, and the log-rank test was used to assess the possible differences between subgroups of body mass index. In order to study the adjusted BMI effect, multivariate survival analysis adjusting for confounders was also carry out using the Cox model. Particularly, the multivariate model included BMI, age, marital status, type of breast cancer, tumor size, hormonal receptors, type of chemotherapy, stage of cancer at time of diagnosis, and menopausal status.

RESULT

Demographic Characteristics

The present study consisted of 312 female patient diagnosed with breast cancer and treated between 2008 and 2013 at Royal Medical Services. Two hundred eighty seven patient's still under follow up (92%), while 10 patients were died (3%) and 15 patients were lost their follow up (5%) during the study period. Two hundred and eighty patients (89.7%) were classified at age groups above 40 years and majority of them (78.5%) were married. Postmenopausal patients comprised 71.8 % and premenopausal patients comprised 28.2% of the study sample. Most of patients were obese (46.8%). Finally, there was no statistically significant difference between BMI groups in relation to age, marital status and menopausal status (p=.063, .858, and .432 respectively). Table (1) shows descriptive statistics for the sample characteristics and its relation to BMI groups.

Clinical profile of the study sample

Infiltrating ductal carcinoma (IDC) was the most common type of breast cancer (83.3%), followed by infiltrating lobular carcinoma (ILC) (6.8%), and ductal carcinoma in situ (DCIS) (1.9%). Furthermore, other types of breast cancers comprised of 8% of total types. Distribution of breast cancer types significantly differed between underweight, normal weight, overweight, and obese patients (p=.001). Regarding hormonal status, majority of the study sample was ER +ve (96.5%) and PR +ve (84.9%) whereas, HER2 +ve comprised of 4.5% of the study sample. None of the distribution of hormonal receptors differed significantly between BMI groups (p>.05). Patients who received chemotherapy comprised 289 (92.6%) of the study sample, while 23 (7.4%) of patients were not received chemotherapy. Moreover, 147 (47.1%) patients had stage II of breast cancer, followed by 117 (37.5%) patients had stage III, 42 patients (13.5%) had stage I of breast cancer and the rest of patients (1.9%) had stage 0. Distribution of breast cancer stages significantly differed between BMI groups (p=.023). Table (2) shows clinical profile of breast cancer and its relation to BMI groups.

Breast cancer survival rate

Overall, Kaplan Meier 5 year of survival showed that survival rate of the study sample was estimated to be 72.9%. Median of survival for underweight patient was 65 month, but this result can't be generalize because there was only one patients had this category of BMI. Patients with normal body weight carried the highest median of survival (59.7 month) according to Kaplan-Meier survival, while obese patient carried the lowest median of survival (44.8 month). Moreover, log rank-test of survival for those obese or overweight was differed significantly from those with normal BMI (p=.014). Table (3) and figure (1) shows median of survival with regard to BMI.

Factors that influence breast cancer survival

Risk of death for underweight patients with breast cancer was 1.69 times greater than those with normal body weight (p=.000) whereas, for obese patients was 1.37 times (p=.001), and for overweight patient it was 1.23 times greater than those with normal body weight (p=.043). Age groups were significantly affected survival rate among breast cancer patients (p<.05) except for those less than 30 years old (p>.05). Survival rate was significantly better in patient aged >30-≤40 years (HR. 890; CI: 556-1.82; P=.012) and >40-≤50 years (HR.572; CI: .425-1.06; P=.001) than those in another age groups. In contrast, risk of death for patients aged >50-≤60 years and >60 years were greater than other age groups (HR 1.73 and 1.94; P=.001 and .042 respectively). Regarding stage of breast cancer, patients with stage II (HR 1.27; CI: .732-1.78; P=.019) and III (HR 1.82; CI: .525-2.74; P=.028) were at a greatest risk for death than patients with stage 0. Moreover, marital status, menopausal status, types of breast cancer, chemotherapy and hormonal status were not associated with increased risk of death among patients with breast cancer (p>.05). Table (4) shows multivariate survival analysis of variables that influence survival of breast cancer.

Table 1: Descriptive statistics for the sample characteristics and its relation to BMI groups.

Variable	Frequency (%)	Underweight	Normal weight	Overweight	Obese	P-value
BMI						
Underweight	1 (.3%)					
Normal	62 (19.9%)					
Overweight	103 (33%)					
Obese	146 (46.8%)					
Age						
≤ 30	3 (1%)	0	2	0	1	
>30-≤40	29 (9.3%)	0	9	9	11	
>40-≤50	92 (29.5%)	0	22	27	43	.063
>50-≤60	96 (30.7%)	1	14	35	46	
>60	92 (29.5%)	0	15	32	45	
Marital status						
Single	39 (12.5%)	1	23	5	10	
Married	245 (78.5%)	0	34	84	127	.858
Divorced	5 (1.6%)	0	1	1	3	
Widow	23 (7.4%)	0	4	13	6	
Menopause status						
Premenopausal	88 (28.2%)	0	22	25	41	.432
Postmenopausal	224 (71.8%)	1	40	78	105	

Table 2: Breast cancer characteristics and its relation to BMI groups.

Variable	Frequency (%)	Underweight	Normal weight	Overweight	Obese	P-value
Breast cancer type						
DCIS	6 (1.9%)	0	3	1	2	
IDC	260 (83.3%)	1	50	90	119	.001
ILC	21 (6.8%)	0	5	4	12	
Others	25 (8%)	0	4	8	13	
Hormonal status						
ER						
+ ve	301 (96.5%)	1	59	100	141	.926
- ve	11 (3.5%)	0	3	3	5	
PR						
+ve	265 (84.9%)	1	51	87	126	.860
- ve	47 (15.1%)	0	11	16	20	
HER2						
+ve	14 (4.5%)	0	2	5	7	.954
-ve	11 (3.5%)	0	3	2	6	
Unknown	287 (92%)	1	57	96	133	
Chemotherapy						
Yes	289 (92.6%)	1	54	97	137	.724
No	23 (7.4%)	0	8	6	9	
Stage						
0	6 (1.9%)	0	3	2	1	
I	42 (13.5%)	0	9	17	16	.023
II	147 (47.1%)	1	28	45	73	
III	117 (37.5%)	0	22	39	56	

Table 3: Median time of survival time with regard to BMI.

BMI categories	Median	95% confidence interval
Underweight	65	65-65
Normal weight	59.7	51.7-67.8
Overweight	45.3	40.1-59.5
Obese	44.8	45.5-56.8
Overall	47. 9	44.8-51.2

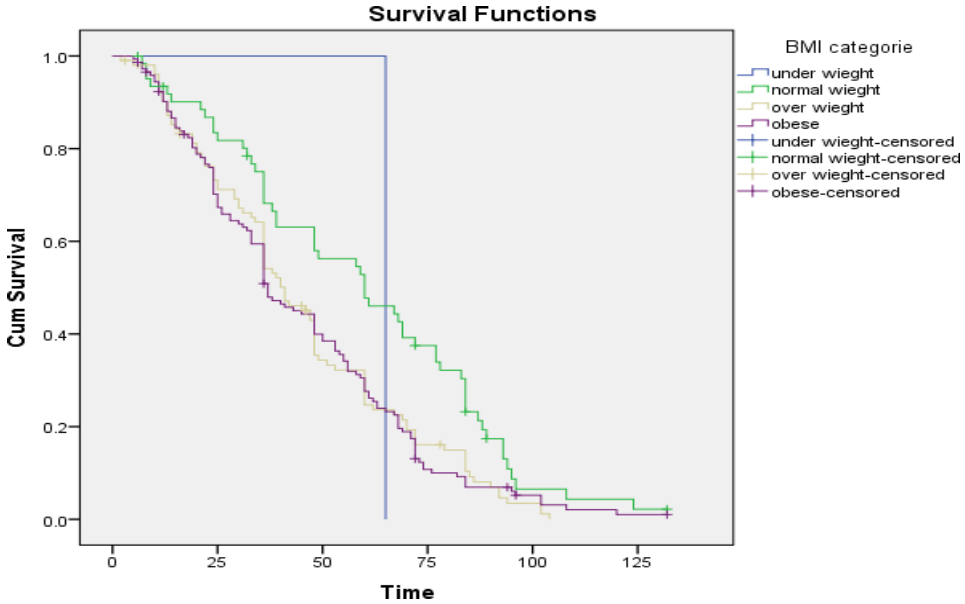

Figure 1.

Table 4: Multivariate survival analysis of variables that influence survival of breast cancer patients.

Variable	Hazard ratio	95% confidence interval	P value
BMI (vs. Normal BMI)			
Underweight	1.69	1.23-1.76	.000
Overweight	1.23	1.05-1.43	.043
Obese	1.37	1.17-1.60	.001
Age			
≤ 30	1.21	.819-2.81	.069
>30-≤40	.891	.556-1.82	.012
>40-≤50	.572	.425-1.06	.001
>50-≤60	1.73	1.23-2.64	.042
>60	1.94	1.73-3.72	.028
Marital status (vs. married)	.431	.611-1.86	.981
Menopausal status (vs. premenopausal)	.694	.454-1.06	.092
Type of breast cancer			
DCIS	.780	.564-6.23	.582
IDC	2.79	.831-8.11	.062
ILC	.723	.427-1.62	.421
Others	.845	.438-2.23	.646
Hormonal status			
ER (vs ER –ve)	.835	.527-1.63	.084
PR (vs PR –ve)	.923	.734-2.52	.071
HER2 (vs HER2 –ve)	.628	.372-2.51	.116
Chemotherapy (vs no chemotherapy)	.832	.659-5.31	.069
Stage (vs stage 0)			
Stage I	.764	.831-1.67	.072
Stage II	1.27	.732-1.78	.019
Stage III	1.82	.525-2.74	.028

DISCUSSION

In this retrospective cohort study, we provide considerable data about survival rate of women diagnosed with breast cancer in Jordan in 2008-2013. Moreover its present information about factors that affect survival such as age, menopausal status, stage, hormonal status, breast cancer subtypes, and body mass index. The present study demonstrated that survival rate of women with breast cancer as 72.9% according to Kaplan Meier 5 year survival, which was greater than survival obtained from previous study in Jordan.[31] This study suggests that being overweight or obese is a strong predictive factor for survival of female with breast cancer. Median time of survival for overweight and obese female patients was 45.3 and 44.8 month compared to 59.7 month for female patients with normal body mass index. This result is consistent with the previous meta-analysis that confirmed increased relative risk of mortality for overweight and obsess patient compared to normal BMI (RRs were 1.07 and 1.41 respectively).[16] Previous studies in Jordan focused on life style as a risk factor for breast cancer conclude that physical activity and control of body weight were inversely associated with the risk of breast cancer[32] and postmenopausal obesity was a significant risk factor for breast cancer among Jordanian females.[33]

Regarding age at time of diagnosis, literature revealed contradictory data whether its affects survival rate or not. In the present study, age more than 30 years was a significant factor that influence survival rate for breast cancer women (p<.05). In contrast, Vostakolaei et al found that women above age of 50 years presented more advanced and poorly differentiated breast tumors (*p*=.001), but after adjusting confounding variables, age wasn't significantly different across age groups with regard to survival and risk of death.[34] Similarlly, another population based studies conclude that middle aged 40-49 years women exhibited better survival rate compared to older and younger age groups.[35- 37]

Marital status effects on survival rate among patients with cancer has been widely studied and there is a growing body of evidence support that being unmarried women has an adverse effects on mortality compared to married women.[38- 40] Data specific to breast cancer also confirmed marital differences in field of survival and risk of death among unmarried women which were greater than married women.[41-43] Our research showed no effect of marital status on risk of mortality among breast cancer women (HR .431, 95% CI .611-1.86, p value=.981).

In term of menopause status, menopausal status considered as a risk factor for breast cancer[44-45], recurrence of breast cancer[46] and its affects pathological feature of tumor[47], but in term of survival menopausal status was strongly associated with obesity in premenopausal women as it in postmenopausal women.[48-49] In our study, menopausal status wasn't associated with increased risk of death (HR .694, 95% CI .454-1.06, *p* value=.092). Our results also consistent with

Guerra et al study.[50]

In our study, infiltrating ductal carcinoma (IDC) was the most common type of breast cancer (83.3%), followed by infiltrating lobular carcinoma (ILC) (6.8%). ER +ve and PR +ve accounted for 96.5% and 84.9% respectively of the study sample, whereas HER2 +ve comprised of 4.5% of the study sample. Neither breast cancer types nor hormonal status found to have an effect on survival rate among breast cancer women according to Cox model multivariate analysis.

The result was consistent with Rakha et al study.[51] In contrast, several studies found that survival was the highest for ER+ and/or PR+/ HER2- type followed by ER- and PR-/HER2+ and lowest survival for ER- and PR-/HER2- type.[52- 54]

The present study demonstrated the influence of stage at time of diagnosis on survival and found that survival varied significantly between stages. Furthermore, hazard ratio for stage II and stage III was 1.17 and 1.57 respectively (p value =.014 and .022 respectively). Our sample showed higher proportion for stage II (47.8%) and stage III (38.4%) which may affect the survival rate of our sample. Zue et al (2017) investigated the survival rate in term of breast cancer stage and the result showed the 5-year overall survival rates for patients with stage I, II, III, and IV diseases as 96.5%, 91.6%, 74.8%, and 40.7%, respectively.[53]

In multivariate analysis, chemotherapy didn't has a significant influence on survival among breast cancer women (p =.069). In large prospective cohort study included 32,502 women treated for invasive breast cancer without metastasis, the overall survival at 5 years follow up was 87.6% (95% CI 86.7–88.6) for group without chemotherapy versus 92.1% (95% CI 91.3–92.9) for chemotherapy group.[55]

Our study has a few limitations; the study design is retrospective in nature that may affect the accuracy of data gained. Weight status was measured by BMI which is accepted by World Health Organization (WHO) for classification of body weight, but on the other hand BMI may possibly ignore the relationships with body composition, adiposity, and adipose distribution. Furthermore, underweight group was underestimated in our study because the number of patients who represent this category was only one patient. However, strength of our study was the ability to investigate the influence of demographic, BMI, type of breast cancer, stage, hormonal receptors, and chemotherapy treatments variables on survival rate of breast cancer. Statistical analysis analyze the impact of four groups of BMI on survival but in literature, many studies only assessed up to two groups only.[11,56] The current study used Multivariate Cox model analysis, so we were able to investigate the impact of BMI on survival without the effects of confounding variables.

CONCLUSION

In the present study, BMI was a significant predictive factor for survival rate of female with breast cancer. Patients with normal body weight exhibited better survival rate than overweight and obese female. Statistical analysis also demonstrated other significant predictive factors for survival such as breast cancer stage and age above 30 years. Further prospective studies with large sample size are needed to confirm and replicate our result. Moreover, other risk factors need to be including in future research such as age of menarche, pregnancy history and use of oral contraceptives.

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