

High Body Mass Index and Young Age Are not Associated with Post-Mastectomy Pain Syndrome in Breast Cancer Survivors: A Case-Control Study

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Abstract

Background: Surgery is usually the first treatment for breast cancer which is followed by some complications such as chronic pain. Post mastectomy pain syndrome (PMPS) is a common complication among breast cancer survivors and is considered as a chronic neuropathic pain in the side of surgery which persists more than three months. The exact mechanisms and related risk factors of the chronic pain after breast surgery are unknown. The aim of this study was to investigate the association of body mass index (BMI) and age with PMPS.

Methods: In this case-control study, a total of 122 women were assessed; of these, 61 women were diagnosed with PMPS and selected as cases and 61 pain-free patients were selected as controls. The demographic and clinical characteristics of participants were collected through questionnaires and medical record of patients. Logistic regression model was used to determine the association of BMI and age with PMPS, adjusted for demographic and clinical characteristics.

Results: No significant differences were found in means of weight (68.02 ± 8.80 vs. 68.67 ± 11.82 , $p=0.726$), BMI (26.38 ± 3.28 vs. 27.10 ± 6.03 , $p=0.410$), and age (46.34 ± 11.67 vs. 48.54 ± 12.57 , $p=0.319$) between those with PMPS and those not reporting PMPS. A non-significant slight increase in odds ratio of PMPS was observed in obese category compared to normal weight category [OR=1.152 (95% CI 0.405-3.275), $p=0.908$], but after adjusting the confounding factors, the risk of pain development was attenuated in obese subjects [OR=0.748 (95% CI 0.228-2.459), $p=0.633$]. Also, non-significant decrease in odds ratios of PMPS was found in 20-39 y, 40-49 y, and 50-59 y ages categories compared to oldest age category [adjusted OR=0.781 (95% CI 0.213-2.866), $p=0.576$; adjusted OR=0.485 (95% CI 0.152-1.554), $p=0.183$; adjusted OR=0.735 (95% CI 0.206-2.627), $p=0.628$; respectively].

Conclusion: In contrast with some observational studies, present study showed that high BMI and younger age might not be associated with increased risk of PMPS development. Further research is necessary to determine the main risk factors and directionality and causal mechanisms for associations of these risk factors with chronic pain after mastectomy.

Keywords: Breast cancer; Post-mastectomy pain syndrome; BMI; Age; Risk factors

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Introduction

Breast cancer is the most common cancer among women worldwide with more than a million

new cases each year [1, 2]. Breast cancer treatments, including breast surgery, radiation, chemotherapy, and hormone therapy are often followed by various

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side effects, such as chronic pain [3]. Post-mastectomy pain syndrome (PMPS) is a considerable side effect following breast surgery [4-5]. Persistent pain after mastectomy is considered as a chronic pain in the thoracic wall, axilla, and/or upper half of the arm which begins after mastectomy and continues more than three months after the surgical procedure [6]. It usually describes as feeling of burning, stabbing, and pulling around the treatment side [5]. The prevalence of this syndrome is fairly high, and has been reported to develop in 20–68% of women [5-7, 8]. In women who survived after mastectomy, chronic pain can cause difficulty at daily activity, and inversely affects the quality of life [6].

Although the exact mechanism of PMPS development is not thoroughly discovered, it is regarded as a neuropathic pain condition that might be generated due to the damage to nervous system in the axilla or the chest wall, because of surgical treatment of breast cancer [4, 5, 8]. Several non-modifiable and modifiable risk factors might be related to the PMPS occurrence [3]. Age appear to be a strong non-modifiable factor for PMPS development. Several observational studies indicate that younger age patients are more vulnerable to affect by chronic pain after breast surgery [3, 5, 9-15]. Also, it has been demonstrated that pre or post-operative adjuvant therapies like chemotherapy and radiotherapy can develop acute and chronic pain after breast cancer surgery [3, 10, 16]. In addition, some studies have shown that high body mass index (BMI) is linked to the pain development among general population [17-19]. Furthermore, the correlation between elevated BMI and chronic neuropathic pain after different surgeries such as cardiac surgery and herniorrhaphy has been reported [20, 21]. Although, some research has not found any association between BMI and PMPS [4, 10], there are some evidence that suggest the obesity and high BMI as the modifiable risk factors for this syndrome [6, 7, 14].

Therefore, the aim of this study was to investigate the association of BMI and age with PMPS, and to determine some probable factors that might be related to its occurrence. Based on our knowledge, the present study is the first case-control study worldwide which assays the association of BMI and age with PMPS in breast cancer survivors.

Materials and Methods

Study design and subjects

Present study is a case-control study and the participants in this study were women, client of cancer research center (Shahid Beheshti University of medical sciences, Tehran, Iran), who had undergone mastectomy surgery in Shohada Hospital, Tajrish, Tehran, Iran, between 2011 and 2013.

Post mastectomy pain syndrome definition

In order to reduce misselection of patients with PMPS, a definition for the PMPS was considered according to previous studies [4, 5]. It was determined based on three criteria including pain character, pain location, and pain duration. Therefore, pain was described as numbness, pins and needles, pulling, stabbing, or burning in the axilla, arm, shoulder, or chest wall at the treatment side which continues more than three months.

Study procedures

In this study, a total of 122 women were surveyed; of these, 61 women were diagnosed with PMPS and selected as case group and 61 pain-free patients were selected as control group.

Post mastectomy pain syndrome questionnaire (designed by cancer research center, Shohada Hospital, Tajrish, Tehran, Iran) was applied to identify patients with PMPS. This questionnaire included questions about the tumor location, presence or absence, location, characters, duration, and the intensity of pain based on numerical rating scale. In this case-control study some anthropometric measures, including weight, height, and BMI were measured. Body weight (kilograms) and height (centimeters) were measured when participants wore light clothes and without shoes by trained research staff. BMI was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). Normal body weight, overweight or obesity was defined as $18.5 < \text{BMI} \leq 24.9 \text{ kg}/\text{m}^2$, $25.0 < \text{BMI} \leq 29.9 \text{ kg}/\text{m}^2$ or $\text{BMI} \geq 30.0 \text{ kg}/\text{m}^2$, respectively.

A general information questionnaire was used to get information about demographic features of participants. The demographic information was on age at the surgery time, education, employment, and marital status. Clinical characteristics of subjects, including type of breast cancer, type of breast surgery, stage of cancer at the time of surgery, number of nodes excised, complication after surgery (infection, lymphedema, hematoma, seroma), other therapies after mastectomy (chemotherapy,

radiotherapy, and hormone therapy), and experience of pain before surgery were obtained from medical record of patients.

Statistical Analysis

Data were analyzed using SPSS (version 21.0). Distributions of all data were determined by Kolmogorov-Smirnov (K-S) test. The chi squared test for trend was used for comparing the distribution of categorical variable between cases and controls. Independent-samples t test was used for comparing the means of quantitative variables between case and control groups. Logistic regression model was applied to determine the association of BMI and age with pain in two groups and adjusted odds ratios (ORs), adjusted for some clinical and demographic confounding factors, and 95% confidence intervals (CIs) were calculated. P value < 0.05 was accepted as being statistically significant.

Results

Table 1 demonstrates the demographic characteristics of study participants. As shown in table 1, there were no significant differences in distribution of demographic features between case and control groups, except education (p=0.002). The age of those reporting PMPS ranged from 23 to 81 years with a mean of 46.34±11.67 years, and the age of non-reporters ranged from 28-91 with a mean of

48.54±12.57 years. Among patients with PMPS, most frequency of PMPS was observed in the 40-49 years age group (n=25, 41%). A total of 51 (83.6%) of the pain reporters were married and 10 (16.4%) remaining were single or divorced, 38 women (59.4%) of PMPS group were in employment and 33 (54.1%) of them had higher education.

Table 2 shows the clinical features of patients. The distributions of clinical parameters were not statically different between two groups, except infection (P=0.022). Of patients reporting pain, 22 (36.1%) were normal weight, 29 (45.5%) were overweight, and 10 (16.4%) were obese. Invasive Ductal Carcinoma (IDC) was the most type of cancer among cases and controls (90.3% and 78.7%, respectively). More than half patients reporting pain 35 (57.4%) reporting pain (57.4%) had stage II breast cancer, and about 42 (70%) of them had no experience of pain before breast surgery. Breast conserving surgery was the most common type of surgery among PMPS positive and PMPS negative group (80.3% vs. 73.8%). Most patients in both groups received adjuvant therapy (88.5% and 93.4%, respectively in cases and controls).

Differences between means of age and some anthropometric measures of those with PMPS and those without PMPS have been shown in table 3. There was no significant difference in means of age between the PMPS reporters and non-reporters

Table 1. It shows demographic characteristics of participants.

Characteristics	PMPS positive (n=61) N (%)	PMPS negative (n=61) N (%)	Total (n=122) N (%)	p value
Age groups				
- 20-39				
- 40-49	13 (21.3)	14 (23)	27 (22.2)	0.552
- 50-59	25 (41)	18 (29.5)	43 (35.2)	
- ≥60	15 (24.5)	17 (27.8)	32 (26.2)	
	8 (13.1)	12 (19.7)	20 (16.4)	
Employment status				
- Employed	28 (45.9)	35 (57.4)	63 (51.6)	0.277
- Unemployed	33 (54.1)	26 (42.6)	59 (48.4)	
Marital status				
- Single	6 (9.8)	7 (11.4)	13 (10.6)	0.958
- Married	51 (83.6)	50 (82)	101 (82.8)	
- Divorced	4 (6.6)	4 (6.6)	8 (6.6)	
Education				
- Less than high school diploma	10 (16.4)	18 (29.5)	28 (23)	0.002
- High school diploma	18 (29.5)	29 (47.5)	47 (38.5)	
- Higher education	33 (54.1)	14 (23)	47 (38.5)	

Table 2. It shows clinical characteristics of participants.

Characteristics	PMPS positive (n=61) N (%)	PMPS negative (n=61) N (%)	Total (n=122) N (%)	p value
BMI groups				
- 18.5-24.9	22 (36.1)	21 (34.5)	43 (35.2)	0.778
- 25-29.9	29 (47.5)	29 (47.5)	58 (47.5)	
- ≥30	10 (16.4)	11 (18)	21 (17.3)	
Breast cancer type*				
- DCIS	1 (1.6)	3 (4.9)	4 (3.3)	0.345
- IDC	55 (90.3)	48 (78.7)	103 (84.1)	
- ILC	1(1.6)	5 (8.2)	6 (4.9)	
- IDC+DCIS	3 (4.9)	2 (3.3)	6 (4.4)	
- IDC+ILC	1 (1.6)	3 (4.9)	4 (3.3)	
Stage of cancer				
- Stage I	15 (24.6)	12 (19.7)	27 (22.1)	0.222
- Stage II	35 (57.4)	28 (45.9)	63 (51.6)	
- Stage III	10 (16.4)	18 (29.5)	28 (23)	
- Stage IV	1 (1.6)	3 (4.9)	4 (3.3)	
Surgery type				
- Breast conserving surgery	49 (80.3)	45 (73.8)	94 (77.0)	0.519
- Modified radical mastectomy	12 (19.7)	16 (26.2)	28 (23.0)	
Comorbidity				
- Yes	22 (36.1)	18 (29.5)	40 (32.8)	0.563
- No	39 (63.9)	43 (70.5)	82 (67.2)	
Pain before surgery				
- Yes	17 (27.9)	9 (14.8)	26 (21.3)	0.16
- No	42 (68.8)	46 (75.4)	88 (72.1)	
- Not recorded	2 (3.3)	6 (9.8)	8 (6.6)	
Number of nods excised				
- 1-9	37 (60.7)	38 (62.3)	75 (61.4)	0.803
- 10-20	23 (37.7)	21 (34.4)	44 (36.1)	
- 21-30	1 (1.6)	2 (3.3)	3 (2.5)	
Infection				
- Yes	5 (8.2)	0 (0)	5 (4.1)	0.022
- No	56 (91.8%)	61 (100)	117 (95.9)	
Lymphedema				
- Yes	3 (4.9)	1 (1.6%)	4 (3.3)	0.328
- No	52 (85.3%)	57 (93.5%)	109 (89.3)	
- Not recorded	6 (9.8)	3 (4.9%)	9 (7.4)	
Adjuvant therapy				
- Hormone/chemo/radio-therapy	33 (54.1)	34 (55.6)	67 (54.9)	0.542
- Hormone/chemo-therapy	4 (6.6)	9 (14.8)	13 (10.7)	
- Hormone/radio-therapy	6 (9.8)	4 (6.6)	10 (8.2)	
- Chemo/radio-therapy	11 (18)	10 (16.4)	21 (17.2)	
- None	7 (11.5)	4 (6.6)	11 (9)	

* DCIS, Ductal Carcinoma in Situ; IDC, Invasive Ductal Carcinoma; ILC, Invasive Lobular Carcinoma; IDC+DCIS, Invasive Ductal Carcinoma and Ductal Carcinoma In Situ; IDC+ILC, Invasive Ductal Carcinoma and Invasive Lobular Carcinoma

Table 3. It shows comparison of mean (S.D) of some anthropometric measures and age between cases and controls.

Characteristics	PMPS positive N=61 Mean±SD	PMPS negative N=61 Mean±SD	p value
Age	46.34±11.67	48.54±12.57	0.319
Weight (kg)	68.02±8.80	68.67±11.82	0.729
Height (cm)	160.62±5.98	159.97±9.52	0.650
Body mass index	26.38±3.28	27.10±6.03	0.410

($p=0.319$). Also, no significant differences were found in means of weight, height, and BMI between those with PMPS and those not reporting PMPS ($p=0.729$, $p=0.650$, and $p=0.410$, respectively).

Adjusted logistic regression model was performed to determine the relationship of BMI and age with pain development (adjusted for education, drug intake, infection, pain before surgery, type of breast cancer, stage of cancer, type of surgery, and adjuvant therapy). As shown in table 4, there was not a significant association between BMI and reporting pain. The risk of pain occurrence was slightly higher in obese subjects compared to normal weight subject [OR=1.152 (95% CI 0.405-3.275), $p=0.908$] but after adjusting for confounding factors, a non-significant reduced risk of pain occurrence was observed in overweight patients [adjusted OR=0.740, (95% CI 0.298-1.836), $p=0.516$] and obese patients [adjusted OR=0.748 (95% CI 0.228-2.459), $p=0.633$] compared to normal weight patients.

In addition, there was not a significant association between age and pain occurrence. Younger age categories were non-significantly associated with lower risk of reporting pain compared to oldest age category (≥ 60 years) and the lowest risk was reported among patients aged 40-49 years [OR=0.480 (95% CI 0.163-1.414), $p=0.183$; adjusted OR= 0.485 (95% CI 0.152-1.554), $p=0.224$] (Table 4).

Discussion

Persistent pain in the surgical side after breast cancer surgery is an important complication in breast cancer survivors [22]. Some evidence shows young age [22] and high BMI (obesity) [6] are two possible risk factors for chronic pain development after mastectomy. Our results, demonstrated that young age and obesity are not associated with PMPS.

Unlike some studies, the findings of present study showed, younger age groups (20-39, 40-49, 50-59 years) are non-significantly associated with decreased risk of PMPS development compared to oldest age category as reference group (22%, 52%, 27%, respectively).

The evidence related to the effect of age on pain after breast surgeries is inconclusive. Some evidence suggests young age is strongly implicated in the development of pain after breast cancer surgeries, including mastectomy [5, 9]. However, some findings have reported no correlation between these two variables. For instance, Montgomery and Bovbjerg (2004) did not report any association between age and acute pain in women who underwent operation for breast cancer treatment [23].

Some evidence suggests that the higher pain reporting among young women, might cause due to the more aggressive feature of disease in this age group and applying more invasive surgical and adjuvant treatments for young women [8]. While in our study, there were not significant differences in cancer type, stage of cancer at the time of surgery, type of surgery and adjuvant therapy among different age groups (Data not shown) which may partly explain inconsistent results between our study and most other studies.

Furthermore, in this case-control study, we found that obesity might slightly (15%) increase the risk of pain development compared to normal weight, while after controlling the effects of some demographic/clinical characteristics, 24% reduction in the risk of pain development was observed in both overweight and obese subjects compared to normal weight subjects as reference group, but the results were not statistically significant.

Several cohort and epidemiologic studies have identified a link between increased BMI and chronic pain after breast surgery [4, 7, 8]. It seems high BMI can make it difficult to recognize the nerves in the

Table 4. Associations of BMI and age with PMPS in breast cancer survivors.

Variable	Odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	P-value
BMI				
Normal weight (18.5-24.9)	1 (Reference)	-	1 (Reference)	-
Over weight (25-29.9)	1.048 (0.476-2.306)	0.965	0.740 (0.298-1.836)	0.516
Obese (≥ 30)	1.152 (0.405-3.275)	0.908	0.748 (0.228-2.459)	0.633
Age				
20-39 y	0.718 (0.223- 2.315)	0.579	0.781 (0.213-2.866)	0.710
40-49 y	0.480 (0.163- 1.414)	0.183	0.485 (0.152-1.554)	0.224
50-59 y	0.756 (0.243-2.345)	0.628	0.735 (0.206-2.627)	0.636
≥ 60 y	1 (Reference)	-	1 (Reference)	-

surgical area and therefore increase the possibility of nerves damage [3]. However, some research did not observed associations between BMI and pain among breast cancer survivors, perhaps because of a focus on the presence versus absence of pain, on average pain severity, and lack of a strong case definition for pain [7]. For instance, in a retrospective study, Meijuan and coworkers (2013) found no significant association between BMI and PMPS [24].

The different result which was observed in our study might be due to different assessment of pain and its consequences, classification of the type of pain in some studies (acute and chronic pain) [25], different types of surgery and treatment modalities, and the type of study.

In addition, there are no specific questionnaires for assessing pain after surgical procedure in breast cancer patients [9], and the questionnaires provided for evaluating neuropathic pain could not satisfy the aims of our study. Therefore, we applied a questionnaire specifically for the present study and we do not have any evidence to confirm its validity which to some extent, this might be responsible for different finding among our study and other studies.

Besides the applied questionnaire in this study, another limitation of our study is that, it was a case-control study which did not follow breast cancer survivors who had undergone mastectomy, over time so it does not provide information on how the pain will develop with time after surgery. Also this type of study does not provide a cause-effect association. Furthermore, the low sample size of the study was another limitation of it.

Conclusion

Our study did not confirm the observational data which consider young age and obesity as main risk factors for pain development after mastectomy. In spite of some advances in breast cancer treatment, PMPS has remained as an unpleasant side effect among patients. So because of a considerable risk for developing PMPS in breast cancer survivors, identifying and management of its risk factors is critical for prevention and treatment of this syndrome and improving the quality of life of breast cancer survivors.

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Conflict of Interest

The authors have no conflict of interest in this article.

Authors' Contribution

This article has written in collaboration between all authors. Dr Sayed Hossein Davoodi and Dr Mohammad Esmaeil Akbari have designed and revised the study. Roghayeh Shahbazi has contributed to carry out the study, writing-up process, data analysis, and overall correction of the

manuscript. Dr Morteza Hashemian has helped in study design and carrying out. Mehrnaz Abbaci and Saba Jalali have helped in writing-up process and data analysis. Dr Reza Homayounfar has helped in statistical analysis. All authors have read and approved it finally.

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