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**PJBS**

ISSN 1028-8880

**Pakistan  
Journal of Biological Sciences**

**ANSI***net*

Asian Network for Scientific Information  
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

## Is Macromastia a Risk Factor for Breast Cancer? A Study on 198 Patients

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**Abstract:** Macromastia, or breast hypertrophy, is a very common finding and a frequent cause of reduction mammoplasty all over the world. This study aims to examine the breast tissue specimens obtained by reduction mammoplasty in patients with macromastia in terms of the frequency of histopathological abnormalities (malignant and non-malignant lesions). In this cross-sectional, retrospective study, paraffin-embedded specimens of breast tissue after reduction mammoplasty were histopathologically reviewed in Tabriz Imam Reza Teaching Hospital in three years (2010-2013). All the specimens were sectioned, stained and examined by an adroit pathologist. One hundred ninety eight out of 271 primary specimens were eligible for this study. The mean age of the patients was  $37.09 \pm 8.98$  (range: 20-59) years, with mean body mass index of  $27.44 \pm 3.85$  (range: 21-35)  $\text{kg m}^{-2}$ . Based on the findings of microscopic examination, normal tissue was present in 98 cases (49.5%), all with increased content of fat. Fibrocystic change was the prominent benign entity, which was reported in 47.5% of the cases. Intraductal papilloma was detected 2 cases (1%). There were 4 cases with malignant lesions (2%), including 2 cases (1%) with invasive ductal carcinoma (age: 22 and 31 years old) and 2 cases (1%) with lobular carcinoma *in situ* (age: 21 and 35 years old). Considering the intraductal papilloma as a premalignant condition, the total rate of non-benign lesions reached to 3%. Based on the results of the present study, macromastia may be considered as a risk factor of breast malignancy. Thorough histopathological examination of the breast specimens after reduction mammoplasty, as well as strict screening of the women with nonsurgical macromastia is highly recommended.

**Key words:** Macromastia, breast cancer, reduction surgery, premalignant breast lesions

### INTRODUCTION

Historically, large breasts have been always considered an emblem of femininity and ability to feed. In the present modern era, however, breast hypertrophy, or macromastia, is considered as a source of discomfort, both physically and psychosocially by many women (Ayhan *et al.*, 2002).

This is where the cutting-edge medicine, reduction mammoplasty, comes in handy. This very popular surgery may be employed to improve symptoms associated with the weighty breasts or for aesthetic proposes only (Muir *et al.*, 2010). This is very much efficacious operation has a high patient satisfaction rate, which has led to its spreading and growth (Roberts *et al.*, 2011).

One of the most frequent malignancies in females is breast cancer, with no specific geographical distribution. It is estimated that annually over a million women are diagnosed and 370,000 expire due to this malignancy (Khorshid, 2011; El-Refaei and El-Naa, 2011; Madkor *et al.*, 2012).

Bringing this high incidence of breast cancer along with the frequency of breast reduction operation, it is not surprising that abnormal histopathological

findings-benign, malignant or premalignant- are frequently found during examination of the left over specimens (Campbell *et al.*, 2010).

The rate of malignancy in these cases varies between 0.6 to 1.4% in different settings (Clark *et al.*, 2009).

According to available data in the literature, the histopathological examination of the breast remnant after reduction surgery (mammoplasty) has been highly advocated (Cook and Fuller, 2004), because they believe that reduction surgery provides an ample breast specimen for scrutinizing the tissue by pathologists (Ishag *et al.*, 2003).

The objective of the present study is to microscopically examine the breast tissue specimens after reduction surgery only in females without any risk of breast cancer, who have been candidates just because of macromastia. This concept that the macromastia itself can raise the risk of breast cancer in an independent manner has not been examined previously.

### MATERIALS AND METHODS

In this retrospective study, 271 breast specimens acquired from 271 consecutive breast reduction

operations were examined histopathologically in Tabriz Imam Reza Teaching Hospital from February 2010 through February 2013. The inclusion criteria were: age between 18 and 60 years, macromastia as the sole indication of surgery and no risk of breast cancer. As all the patients had been routinely undergone preoperative mammography and breast ultrasound before surgery and considering the inclusion criteria, these cases were excluded: candidates of breast reduction surgery due to etiologies other than benign macromastia (such as asymmetry, etc.,  $n = 39$ ), an abnormal finding during previous/preoperative screening of the breast ( $n = 15$ ), positive history of family breast cancer ( $n = 10$ ), any previous breast disease/operation ( $n = 6$ ) and the patients out of the considered age ( $n = 3$ ). Accordingly, 198 specimens from 198 patients were included in the present study (all bilateral cases). This study was approved by the Ethics Committee of Tabriz University of Medical Sciences.

All the specimens were fixed in 10% buffered formal for a day immediately after reduction surgery. A skilled pathologist sectioned all the specimens commensurate with the size of specimen, as well as considering the presence/absence of abnormal finding(s) during microscopic examination ( $n = 3-10$  sections, 0.5 mm each). The larger was the primary specimen, or in the case of encountering any abnormality during examination, a higher number of sections were provided.

After being stained with hematoxylin and eosin, the sections were evaluated under light microscopy with appropriate magnification.

**Statistical analysis:** Data were shown as Mean±Standard Deviation (age, body mass index) or number and percentage (histopathological subgroups).

## RESULTS

Breast specimens extracted from 198 female subjects with a mean age of  $37.09 \pm 8.98$  (range: 20-59) years were examined. Frequency of the age of participants is shown in Fig. 1. As shown in this figure, patients aged 30-40 years comprised the most common age-group in this series.

The mean body mass index of the participants was  $27.44 \pm 3.85$  (range: 21-35)  $\text{kg m}^{-2}$ . Frequency of the body mass index of the participants is shown in Fig. 2. Based on this figure, most of the patients lie between 25 and 30  $\text{kg m}^{-2}$ .

All the patients (100%) had undergone bilateral elective breast reduction due to macromastia. The weight of the specimens varied between 380-1430 g.

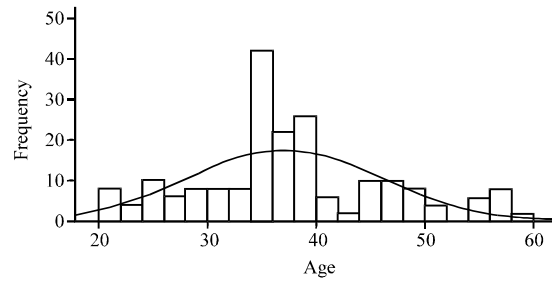


Fig. 1: Age distribution of the studied female candidates for breast reduction surgery

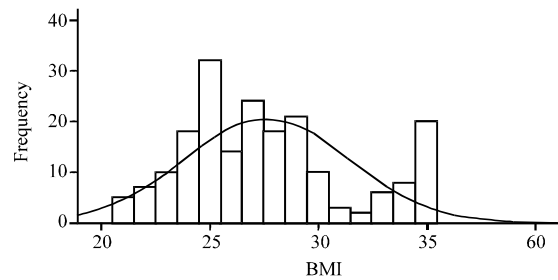


Fig. 2: Body mass index distribution of the studied female candidates for breast reduction surgery

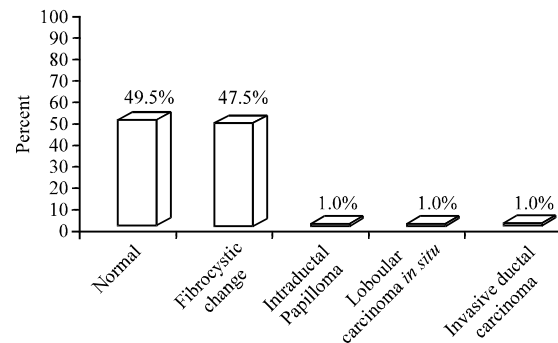


Fig. 3: Distribution of histopathologic diagnoses of the specimens extracted during breast reduction surgery

Various histopathologic subtypes are summarized in Fig. 3. Based on the findings of microscopic examination, normal tissue was present in 98 cases (49.5%). All these 98 cases had increased content of fat tissue.

The most common abnormality was fibrocystic change which was reported in 94 cases (47.5%). The microscopic histopathologic view of a specimen with fibrocystic change is depicted in Fig. 4a.

Another detected benign abnormality was intraductal papilloma in 2 cases (1%) who were aged 29 and 35 years old. Considering lobular carcinoma *in situ* as a malignant condition, there were 4 cases with cancerous lesions (2%)

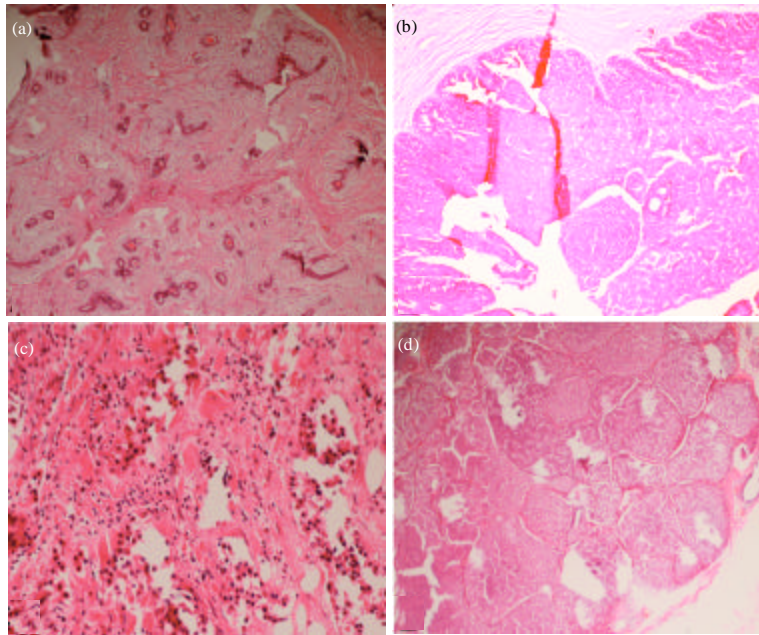


Fig. 4(a-d): The microscopic histopathologic views of the specimen with, (a) Fibrocystic change, (b) Intraductal papilloma, (c) Invasive ductal carcinoma and (d) Lobular carcinoma *in situ* (Hematoxylen and eosin staining, Original magnification: 10X, 10X, 40X and 10X, respectively)

in this series; including 2 cases (1%) with invasive ductal carcinoma (age: 22 and 31 years old) and 2 cases (1%) with lobular carcinoma *in situ* (age: 21 and 35 years old). The microscopic histopathologic views of the specimen with intraductal papilloma, invasive ductal carcinoma and lobular carcinoma *in situ* are depicted in Fig. 4b, c and d, respectively.

Adding up all nonmalignant conditions, the rate of these lesions was 48.5% of all the cases, while malignant conditions consisted 2%. Supposing the intraductal papilloma as a premalignant condition, the total rate of non-benign lesions reached up to 3% of the cases.

All the mentioned benign and malignant lesions (except for the fibrocystic change) were observed unilaterally.

## DISCUSSION

Breast reduction surgery has been nominated as an auxiliary method for detecting malignancy. However, this method is not liberally available for all suspects. In the patients who undergo breast reduction surgery, the techniques provides with ample amount of the tissue for thorough histopathologic examination and exact screening for possible atypical entities (Brown *et al.*, 1999).

In the present study, the results of histopathologic examination of the breast specimens obtained from the patients who had undergone elective breast reduction surgery due to macromastia are reported. Although this is neither the first nor the only survey in the literature, it bears two important fortes: first this is the first study which has been carried out in the Middle East (consider the role of ethnicity and genetics in this cancer) and second, this series encompasses those who were not in an increased risk of breast cancer.

Based on the findings over half of the patients had abnormal diagnoses, including non malignant (48.5%) and malignant (2%) conditions.

Ayhan *et al.* (2002) evaluated 149 Turkish patients who had undergone reduction mammoplasty. In 61% of these cases there was an abnormality in their histologic diagnoses. Fibrocystic change was documented in 47.1%, while intraductal carcinoma was present in 0.7%.

The rate of abnormality in their report is similar to that in ours. We also found fibrocystic change as the most prevalent benign alteration in the breast tissue (47.5%) and the rate of intraductal carcinoma was very similar (1%).

The Cancer Committee of the College of American Pathologists (Tavassoli, 1999) recommends that the fibrocystic change is only an exaggerated physiological

entity rather than a cancer or even an abnormality. According to this committee, the incidence for fibrocystic changes after a breast biopsy was 34%.

Taking this proposed incidence into account, it seems logical to propose that due to high prevalence of fibrocystic changes after mammoplasty comparing with normal corresponding women, there may be a strong association between this condition and breast macromastia. However, this hypothesis needs to be confirmed in future, well-controlled studies.

In another study in Turkey, Ishag *et al.* (2003) evaluated 540 patients and reported abnormality in 60.4%. Carcinoma was present in 0.7% overall, 2% in the patients with previous carcinoma and 0.6% in the patients with a negative history. They finally proposed that all these patients should be go thorough histopathological examinations, especially those with previous history of malignancy, as well as the patients 40 years or older.

Although, the rate of abnormality in this report is somewhat near to that in the present work, the rate of malignancy is apparently higher in our patients, because we excluded those cases with previous malignancy and this would have declined the rate of cancer in our series. Another interesting incongruity between the two reports is as to the age of patients. Unlike Ishag's conclusion, all the four patients with malignant lesions were under 35 years in our series.

Our results are also against this notion that the majority of breast cancers are ductal carcinoma (>90%) (Viana *et al.*, 2005), because both ductal and lobular carcinomas were equally encountered in our case (each in 1%)

So, one may deduce from the figures documented in the present work that unlike the general concept regarding breast cancer, macromastia may leave a woman susceptible to a cancer which may occur earlier than expected in her lifetime and/or contribute to less common forms routinely emerge in normal counterparts.

In a study by Viana *et al.* (2005) in Brazil, a total of 274 women who had undergone reduction mammoplasty were reviewed retrospectively. The frequency of carcinoma was 1.1%, including ductal carcinoma in 0.6%. According to their classification, intraductal papilloma could be regarded as a non-benign entity.

Papilloma of the breast is frequently a solitary Finding and comprises proliferation of intraductal epithelium, with or without variable degree of atypia. Although some authors consider it as a normal malignant lesion, others classify it under the category of potentially malignant abnormality (Viana *et al.*, 2005).

The relative risk of malignancy in the cases with intraductal papilloma is estimated to be 1.3-1.9, which is

considered moderate potential of cancer (Guray and Sahin, 2006).

If we had considered the cases with intraductal papilloma with malignant condition, the rate of malignancy would have increased to more than 2%, a rate around 3% of the examined specimens.

In Western studies, the rate of malignancy among the breast specimens obtained from patients after reduction surgery varies between 0.3 and 4 percent (Brown *et al.*, 1999; Blansfield *et al.*, 2004; Cook and Fuller, 2004; Ambaye *et al.*, 2009; Samdanci *et al.*, 2011).

Although, the rate of malignancy in our series lies between this range, it should be born in mind that, as mentioned earlier, this is the first study in the literature which examines the cases without apparent risk factors of breast cancer, who are candidates for surgery only due to macromastia. These criteria were expected to decline the rate of malignancy in comparison with available data in the literature.

For example, Colwell *et al.* (2004) examined the specimens obtained from 800 cases underwent reduction mammoplasties. Cancer was reported in 0.8% of the cases, including invasive (0.4%) and *in situ* (0.4%) ductal carcinoma. They reported that the rate of cancer was significantly higher in the patients who sought reconstructive vs. mere reconstruction surgery (1.2 vs. 0.7 percent).

We should remind that no case of reconstructive surgery were allowed in the present survey, because at least a portion of these cases might have suffered from previous operation, abnormalities in their breast, etc.

According to the results of a previous study by Abbasalizadeh *et al.* (2002) in our region, the rate of breast cancer among females over 30 years old is expected to be 0.24%. Comparing with the rate of malignancy in the present work (2-3%), it is apparent that the risk of breast cancer is considerably higher in the cases with macromastia. According to the results of the present work, it merits recommending that firstly, all the breast specimens acquired from the patients who undergo breast reduction must go under scrupulous histopathological examination with further necessary and appropriate decision-making (Clark *et al.*, 2009) and secondly, the screening program should be more stringent in the cases with macromastia than that in normal individuals.

## CONCLUSION

This study, for the first time, proposed that macromastia is possibly a significant risk factor for female breast cancer. According to this finding, all the women with macromastia should be screened thoroughly for

possible presence of premalignant/malignant conditions in their breast. Furthermore, full examination of the remained tissue after reduction surgery of the breasts due to macromastia is highly recommended.

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