ASSOCIATION OF MARITAL STATUS, EARLY MARRIAGE AND PARITY WITH FIBROADENOMA

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ABSTRACT

Objective: To evaluate the association of marital status, early marriage and parity with fibroadenoma patients at a tertiary care hospital of Pakistan.

Study Design: Case control study.

Place and Duration of Study: Pak Emirates Military Hospital, Rawalpindi Pakistan, from Jul 2015 to Jan 2016.

Methodology: A total of 156 cases were included which were diagnosed histologically for fibroadenoma. Similarly 152 controls were inducted which were matched for age and body mass index. The case and control groups were interviewed about exposure of risk factors.

Results: All the patients were females. The mean age of case group was 23.71 ± 3.81 and mean age of control group was 23.99 ± 3.95 (*p*-value=0.544). There was no significant difference in body mass index of two groups (*p*-value=0.756). Marital status (OR=1.807 95% CI 1.074-3.039) and nulliparous status (OR=2.372 95% CI 1.398-4.024) were associated with development of fibroadenoma. However early marriage did not have any significant relation with fibroadenoma (OR=0.928 CI 95% 0.511-1.683).

Conclusions: Fibroadenoma is more likely to develop in unmarried and nulliparous women however early marriage may not be related to its development.

Keywords: Fibroadenoma, Female hormones, Risk factors.

INTRODUCTION

Every year 200,000 breast diseases are diagnosed worldwide with benign breast disease presentation in 90% of cases[1,2]. Among benign diseases fibroadenoma accounts for 50% of all the breast lumps especially in young women[3]. The growing awareness in public has exponentially increased its importance. In Pakistan, benign breast disease is most commonly diagnosed and fibroadenoma is the most common lesion[2]. Due to our cultural background, breast diseases usually report late. This fact may impart this disease as ice berg phenomenon and prevalence reported might be much less.

Risk factors for benign breast diseases have been studied to a limited extent[3,4]. One study in Iran showed that history of full term pregnancy and live child birth could reduce the risk of fibroadenoma. In fact 50% of fibroadenoma were in nulliparous women whereas the same situation was 11% in control group. Similarly fibroadenoma was more prevalent in single women that mean 8% of normal women were single whereas 36% of cases were single. At the same time early marriage (<21 years) were considered as another possible risk factor of fibroadenoma in married women that means 60% of married women with fibroadenoma got married before 21 years whereas only 36.9% of control group had early marriage in their reproductive history[5]. In Pakistan most studies are done either on malignancies or whole spectrum of breast diseases[2]. Unfortunately limited work is available in Pakistan on demographic factors of benign breast diseases in general and fibroadenoma in particular.

Purpose of this study is to look for association of demographic factors as marital status, early marriage and parity with fibroadenoma. Such study has not been conducted in Pakistan till date. Early marriage and multiparity is quite common in Pakistan and results in changes in hormonal balance of female. As fibroadenoma has association with exposure of female hormones

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especially estrogen so early marriage and number of child births might well be associated with fibroadenoma[5,6]. These factors are modifiable and hence awareness can be created if they are significantly related to fibroadenoma.

METHODOLOGY

After ethical approval from concerned ethics review committee and written consent from all potential participants this observational study was planned from July 2015 to January 2016 at Pak Emirates Military Hospital Rawalpindi. All subjects were females. Patients were selected on consecutive basis. Female patients reporting in OPD between ages 18-35 years with histopathological diagnosis of fibroadenoma were included as cases whereas healthy females reporting with other problems than breast ailments with no prior family history of any breast disease were included as controls. Non-consenting patients or those having any malignancy, pregnancy or family history of any breast diseases were excluded from study. Post-menopausal women were also not included. After the application of inclusion and exclusion criteria, 308 subjects were included in the analyses. The sample size was calculated using open-epi calculator for case control study[5].

The consenting subjects were provided with a detailed description of the study. Subjects were inquired about previous breast ailments and detailed history was taken. Demographic factors including age, BMI, marital status, age of marriage, smoking, parity, breast feeding and menopausal status was recorded and entered on research profroma. All data was collected in presence of attendant/chaperon. Control groups were also selected keeping in view the inclusion and exclusion criteria. The controls were healthy females reporting in OPD with some other condition matched on age and BMI bases with cases.

Data obtained was entered and analyzed using Statistical Package for Social Sciences (SPSS) version 16. Mean ± SD for age was calculated. Frequency and percentage for marital status, early marriage and parity for cases and controls was evaluated.Chi-square was applied to compare frequency and percentage for marital status, early marriage and parity between the two groups.

Odds ratio was calculated to determine the relationship between age at marriage and parity with fibroadenoma in both case and control keeping confidence interval of 95% and taking *p*-value of <0.05 as significant. Stratification of the data to minimize confounding by controlling age of menarche, breast feeding and use of contraceptive pills was done. Post stratification chi-square was again applied to compare frequency and percentage for marital status, early marriage and parity between the two groups.

RESULTS

In this case-control study, a total of 308 patients were included, out of them 156 (50.6%) were cases of fibroadenoma who were diagnosed on histopathology and 152 (49.4%) were controls who presented in OPD with other problems. All the patients were female.

The age distribution in cases and controls is shown in table-I. The minimum age in both groups was 18 years and maximum age in both groups was 35 years. The mode and median of both groups was same that is 22 years and 23 years respectively. There was no significant difference between the means of the two groups as depicted by student t-test (*p*-value = 0.544).

Minimum BMI in both groups was 18 whereas maximum was 35.5 in case and 35 in control group. Median and mode of both groups was 24. Mean BMI of case group was 23.628 ± 2.776 and mean BMI of control group was 23.642 ± 2.751. The analysis shows that there was no significant (*p*-value = 0.756) difference in both groups on the basis of BMI.

In case group, 79 (50.6%) patients were unmarried and 77 (49.4%) were married whereas in control group 53 (34.9%) were unmarried and 99 (65.1%) were married. Chi-square test was used for analysis and it showed significant relationship as shown in table-II (*p*-value=0.005). Odds ratio was calculated and it also confirmed a

significant relationship between marital status and case group (OR=1.919, 95% CI, 1.212-3.030).

Analysis showed that in case group, out of 77 patients who were married, 38 (49.4%) had age <21 years at time of their marriage and 39 (51.6%) patients had age >21 years, whereas in control group out of 99 patients who were married, 47 (47.5%) were <21 years old at time of their marriage and 52 (52.5%) women were more than 21 years old at time of marriage. Chi-square test

Table-I: Descriptive statistics for age between case and control group.

Groups	n	Minimum	Maximum	Mean	Std. Deviation	*p*-value
Case	156	18	35	23.72	3.813	
Control	152	18	35	23.99	3.959	0.544

851, 95% CI, 1.025 to 3.342 (p-value = 0.041).

Table-II: Association of marital status, early marriage and parity between cases and controls.

Parameters	Cases	Controls	*p*-value	Odds ratio	95% CI
Marital Status					
Unmarried	79 (50.6%)	53 (34.9%)	0.005	1.919	1.212-3.030
Married	77 (49.4%)	99 (65.1%)			
Early Marriage					
Yes	38 (49.4%)	47 (47.5%)	0.805	0.928	0.511-1.683
No	39 (50.6%)	52 (52.5%)			
Parity					
Nulliparous	107 (68.6%)	69 (45.4%)	<0.001	2.627	1.650-4.182
Parous	49 (31.4%)	83 (54.6%)			

Confounding Variables		Case	Control	*p*-value	Odds ratio
Breast Feeding	**Early Marriage**				
Yes	Yes	2	10	0.360	0.46
	No	10	23		
No	Yes	36	37	0.938	0.973
	No	29	29		
	Parity				
Yes	Nulliparous	-	2	0.383	1.292
	Parous	12	31		
No	Nulliparous	107	67	<0.001	2.244
	Parous	37	52		
Early Menarche	**Marital status**				
Yes	Unmarried	12	5	0.786	1.200
	Married	18	9		
No	Unmarried	67	48	0.003	2.129
	Married	59	90		
	Parity				
Yes	Nulliparous	18	5	0.133	2.700
	Parous	12	9		
No	Nulliparous	89	64	<0.001	2.781
	Parous	37	74		
	Early Marriage				
Yes	Yes	6	3	1.000	1.00
	No	12	6		
No	Yes	32	44	0.523	1.239
	No	27	46		

was used for analysis and result showed significant relationship as shown in table-II, (*p*-value= 0.805). The odds ratio did not show statistically significant relation between early marriage and development of fibroadenoma (OR=0.928, 95% CI, 0.511 to 1.683).

Analysis for parity showed that case group had 107 (68.6%) nulliparous patients and 49 (31.4%) patients had children. In control group 69 (45.4%) women were nulliparous and 83 (54.6%) had children. Chi-square test was used for analysis and it showed significant relationship as shown in table-II (*p*-value <0.001). Odds ratio was calculated and it also confirmed a significant relationship between nulliparous women and case group (OR = 2.627, 95 % CI, 1.650 to 4.182).

To minimize the effect of confounding factors of use of oral contraceptive use, early menarche and breast feeding binary logistic regression was used keeping confidence interval of 95% and is given in table-III. The odds ratio adjusted for oral contraceptive use, menarche and breast feeding of marital status is significant (OR=1.807, 95% CI, 1.074 to 3.039, *p*-value=0.026).

Similarly parity was adjusted for oral contraceptive use, menarche and breast feeding using binary logistic regression shown in table-III. The odds ratio adjusted after stratification of confounding factors was significant (OR=2.372, 95% CI, 1.398 to 4.024 *p*-value = 0.001).

Data stratification was done using multinomial regression for age at marriage and after adjusting for oral contraceptive use, menarche and breast feeding shown in table-III, the corrected odds ratio for early marriage and case group is significant (OR=1).

Table-III: Stratification of confounding factors for marital status, early marriage and parity.

Oral Contraceptive Pills Exposure	Marital status				
No	Unmarried Married	78 61	53 87	0.002	2.099
Yes	Unmarried Married	1 16	- 12	0.393	0.750
	Early Marriage				
Yes	Yes No	8 8	7 5	0.662	0.714
No	Yes No	30 31	40 47	0.701	1.137
	Parity				
Yes	Nulliparous Parous	8 9	5 7	0.774	1.244
No	Nulliparous Parous	99 40	64 76	<0.001	2.939

DISCUSSION

The increasing awareness about breast diseases and easy access to information has resulted in frequent visits to clinics and is depicted in form of increased incidence of breast diseases over last decade. Spectrum of breast diseases range from inflammatory and benign diseases to malignant ailments. Benign lumps are more common than malignant cancers accounting for 75% of all breast biopsies in Pakistan[7]. Among benign breast diseases fibroadenoma is present in 66% of cases[2]. This is the first study being conducted in Pakistan evaluating relationship of marital status, early marriage and parity with fibroadenoma.

As fibroadenoma is more common between second and third[8] decade of life so our study population ranged between 18-35 years, both the groups were matched on basis of age and there was no significant difference (*p*-value=0.544). Similarly both groups were also matched on the

basis of BMI to nullify its effect on overall result (*p*-value = 0.756)[9].

In this study it was concluded that there is a statistically significant association between unmarried women and development of fibroadenoma (*p*-value=0.005). In other words unmarried women had approximately two times more risk of developing fibroadenoma as compared to controls of same age and BMI. Our findings were consistent with study carried out by Bidgoli *et al*, which showed that only 8% of controls were unmarried whereas 36% of cases were married (OR = 6.64)[5]. However in a similar study Arjitha *et al*, showed that fibroadenoma was prevalent in 62% of married women[10]. Similarly a study conducted by Amruthavalli *et al*, showed that married women were more likely to develop benign breast diseases[11].

In fibroadenoma cases, 38 patients got married before the age of 21 years and in control group 47 women had married before the age of 21 years. There appears to be no significant relationship between early marriage and fibroadenoma (*p*-value=0.805). On the contrary, study conducted in Iran showed that 60% of married women who had fibroadenoma got married before 21 years whereas in control group only 36.9% were married before 21 years[5].

It was inferred from our study that nulliparous women had statistically significant relationship with fibroadenoma (*p*-value=0.000). It means that nulliparous women had approximately 2.6 times greater odds of developing fibroadenoma than control group. A study conducted by Nelson *et al*, in China, showed that with increasing number of births the chances of fibroadenoma decrease exponentially[12]. Similarly, Bridgoli *et al* showed that nulliparous women had 8 times more chance of getting fibroadenoma[5]. A studied conducted in Kurnool also showed that nulliparous young female have more chances of developing fibroadenoma[21]. A Cohort study conducted in Shanghai identified a decreasing risk of fibroadenoma with increasing number of live child births[13]. Previous studies did not show any significant association between parity and fibroadenoma[14].

Reproductive background of female is related to the development of fibroadenoma and it is primarily due to endogenous female hormonal exposure[15]. Estrogen being a steroid hormone exerts its effects by synthesizing proteins and inducing proliferation of cells. In benign breast diseases the cell differentiation and apoptosis is averted probably by steroid hormones[5]. The function of estrogen and the cellular response are thought to be impaired due to unknown causes hence resulting in breast lumps of benign diseases as fibroadenoma[16]. It is possible early pregnancy induce cellular proliferation and differentiation of mammary epithelium which in turn act to prevent development of fibroadenoma.

Various confounding factors were also studied which included age at menarche[17], use of oral contraceptive pills[18], breast feeding and smoking[19]. The studied factors were stratified using logistic regression model and multinominal regression model. The major confounder in our study was early age at menarche (OR = 2.5), rest of the confounding factors did not have any statistically significant effect. One study in China showed that cases of fibroadenoma had early menarche as compared to controls[3,20]. Similarly a study conducted in India showed that women with early menarche had more fibrocystic changes in their breasts[21]. On the contrary various studies did not find any significant relation between early menarche and benign breast diseases[21]. The use of contraceptive pills did not have any significant relationship with development if benign lumps in various studies although previously they were thought to have protective function[5]. Similarly breast feeding once attributed to have a protective effect did not show any relationship with development of fibroadenoma[21]. Smoking had inverse relation with fibroadenoma in studies[9].

The major limitation in our study was the recall bias as patient had to recall about exposure of associated factors. The case selection was

based on consecutive convenient sampling and was not randomized. Since the study was carried out in a tertiary care hospital so generalization to the whole population may be done cautiously. There is a problem with diagnosis in studies of fibroadenomas, because some fibroadenomas go undetected and may regress with time and hence may be included in control group instead which could have affected the whole result introducing observation bias.

CONCLUSION

Fibroadenoma is the most common breast lump present in Pakistani female population in pre-menopausal age. Unmarried women are more likely to develop fibroadenoma as compared to married females of same age and BMI. Similarly nulliparous women have more odds of developing benign lumps as compared to females who had one or more full term pregnancies. However, women who got married in their early age (<21years) did not show any increased risk of developing fibroadenoma.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Okoth C, Galukande M, Jombwe J, Wamala D. Benign proliferative breast diseases among female patients at a sub Saharan Africa tertiary hospital: a cross sectional study. BMC Surg 2013; 13(1): 9-12.
2. Aslam HM, Saleem S, Shaikh HA, Shahid N, Mughal A, Umah R. Clinico-pathological profile of patients with breast diseases. Diagn Pathol 2013; 8(2): 77-79.
3. Dijkstra SC, Johanna WL, Ray RM, Brown R, Chunyuan WU, Wenjin LI, et al. Biomarkers of dietary exposure are associated with lower risk of breast fibroadenomas in Chinese women. J Nutr 2010; 140(7): 1302-10.
4. O'brien S, Kowdley GC. Benign breast diseases and body mass index: is there a correlation?. Am Surg 2014; 80(5): 461-65.
5. Bidgoli SA, Eftekhari T. Role of exogenous and endogenous sources of estrogen onthe incidence of breast fibroadenoma: case-controlstudy in Iran. Asian Pac J Cancer Prev 2011; 12(5): 1289-93.
6. Bernardi S1, Londero AP, Bertozzi S, Driul L, Marchesoni D, Petri R. Breast-feeding and benign breast disease. J Obstet Gynaecol 2012; 32(1): 58-61.
7. Malik N, Salahuddin O, Irshad H, Azhar S, Salahuddin M, Dilawar A, et al. Breast Diseases; Spectrum In Wah Cantt; Pof Hospital Experience. Professional Med J 2010; 17(3): 366-72.
8. Bewtra C. Fibroadenoma in women in Ghana. Pan African Med J 2009; 2(1): 11-14.
9. Berkey CS, Willett WC, Frazier AL, Rosner B, Tamimi RM, Colditz GA, et al. Prospective study of growth and development in older girlsand risk of benign breast disease in young women. Cancer 2011; 117(8): 1612-20.
10. Ajitha MB, Srinivasan N, Shivaswamy BS. A Systematic Study On Fibroadenoma Of The Breast. IJBAR 2012; 3(12): 302-07.
11. Amruthavalli BV, Srihari V. Clinical Study of Benign Breast Diseases. J Dental Med Sci 2015; 14(2): 34-40.
12. Nelson ZC, Ray RM, Wu C, Stalsberg H, Porter P, Lampe JW, et al. Fruit and vegetable intakes are associated with lower risk of breast fibroadenomas in chinese women. The J Nutr 2010; 140(7): 1294-01.
13. Nelson ZC, Ray RM, Gao DL. Risk Factors for fibroadenoma in a cohort of female textile workers in Shanghai, China. Am J Epidemiol 2002; 156(7): 599–05.
14. Pengelly S, Lambert AW, Khan M, Groome J. Breast lumps in service women. J R Nav Med Serv 2014; 100(2): 174-78.
15. Manjiri S, Padmalatha SK, Jeevak S. A Prospective observational study of breast lumps in adolescent girls: tertiary care south indian teaching hospital experience. Ind J Surg Oncol 2018; 9(3): 402-06.
16. Pasqualini JR, Cortes-Prieto J, Chetrite G. Concentrations of estrone, estradiol and their sulfates, and evaluation of sulfatase and aromatase activities in patients with breast fibroadenoma. Int J Cancer 2007; 70(6): 639–43.
17. Krings G, Bean GR, Chen YY. Fibroepithelial lesions; The WHO spectrum. Semin Diagn Pathol 2017; 34(5): 438-52.
18. Friedenreich CM, Bryant HE, Alexande F, J Hugh, J Danyluk, DL Page, et al. Risk Factors for benign proliferative breast disease. Int J Epid 2000; 29(4): 637-44.
19. Ezer SS, Oguzkurt P, Ince E, Temiz A, Bolat FA, Hicsonmez A. Surgical treatment of the solid breast masses in female adolescents. J Pediatr Adolesc Gynecol 2013; 26(1): 31-35.
20. Tan BY, Tan PH. A Diagnostic Approach to Fibroepithelial Breast Lesions. Surg Pathol Clin 2018; 11(1): 17-42.
21. Giri D. Recurrent challenges in the evaluation of fibroepithelial lesions. Arch Pathol Lab Med 2009; 133(5): 713-21.