Frequency of benign and preinvasive breast diseases

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ABSTRACT

Objectives: The importance of benign proliferative and non-invasive breast lesions as a risk factor preceding the development of invasive mammary carcinoma is well established in the literature. The objective of this study is to estimate the magnitude of benign proliferative diseases as well as mammary intra-epithelial neoplasia in the Western region of the Kingdom of Saudi Arabia (KSA), in order to encourage nationwide breast cancer screening programs for early detection of the high risk proliferative and pre-invasive breast lesions.

Methods: We reviewed histopathology records (reports and slides of selected cases) of 2129 breast cases including mastectomies and breast biopsies from January 1985 to December 2002 in King Abdul-Aziz University Hospital and King Khalid National Guard Hospital, Jeddah, KSA. All the cases and diagnosis are listed and reclassified using systematized nomenclature of medicine (SNOMED) coding system and then regrouped based on the associated risk factors of developing breast carcinoma.

Results: Two thousand one hundred and twenty-nine reports were reviewed and 2343 diagnosis were identified as some cases had more than one diagnosis. The total of benign diagnosis were 1504 after exclusion of malignant diagnosis (558), normal breast tissue, gynecomastia, and non-mammary tissue (281). All diagnosis (1504) were reclassified based on anatomical prognostic indicators into non-proliferative (1283/1504), proliferative (140/1504), atypical hyperplasia (AH) (8/1504), and carcinoma in situ (CIS) (73/1504). We compare our findings with the literature and we found that the percentage of benign non-proliferative diagnosis was 85.3% that is higher than the literature 69.7%. Proliferative diseases were 9.3% and atypical hyperplasia was 0.5%, which was lower than the literature 26.2% and 3.6%. On the other hand, CIS diagnosis was 4.9%, which is much higher than the reported literature 1.7%. The study findings could be explained on the basis of higher prevalence of benign breast lesions in our population, or it is related to the number of cases studied, or to the diagnostic criteria followed initially.

Conclusion: These findings should encourage us to refine our diagnostic criteria of proliferative diseases, AH and CIS (mammary intraepithelial neoplasia [MIN]). In addition, we strongly encourage a breast cancer screening program, nationwide.

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It is established in the literature that women who underwent breast biopsy for benign breast lesions were at an increased risk of developing breast cancer. The histological diagnosis of these lesions are of variable magnitude of risks, some have mild increased risk (1.5 - 2 folds over that of normal population), others have higher risk (10 x normal). The published reports of patients with proliferative breast disease estimate less than 10% of these patients will develop invasive carcinoma in the same breast after 17-21 years of follow up.[1,2] On the other hand, the risk of development of invasive

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carcinoma in the other breast is 0.7-4.9 %.[3] These data suggest that detection of proliferative breast lesions carry some increased risk of developing invasive carcinoma in one or both breast. Furthermore, proliferative breast lesion is a marker of mammary epithelial tissue disturbances of variable effect. The risk of bilaterality is more pronounced with mammary intraepithelial neoplasia (MIN) diagnosis. This fact should be considered in breast screening programs and the patient should be followed up for longer period for both breasts.[4] Numbers of local studies looked at the pattern of breast disease in different regions in the Kingdom of Saudi Arabia (KSA) and the majority of these studies had emphasized on breast carcinoma frequency, type, age of the patient and so forth.[5-8] No local study is directed to evaluate the frequency of benign breast disease (pre-cancerous indicators). This study is focused on evaluating the magnitude of benign breast diseases, especially lesions, which are known to carry certain risk of developing carcinoma or precede the development of invasive breast carcinoma. The criteria used to diagnose proliferative and non-proliferative breast disease and carcinoma in situ (CIS) is well documented in literature[9-11] and it was used to make the diagnosis reported in the study. Furthermore, due to difficulties, sometimes in differentiating between atypical hyperplasia (AH) and CIS which histologically based on architecture, morphology and extent of the disease. Rosai[12] suggested that both lesions to be amalgamated together in a single diagnostic category termed MIN.[12]

Methods. In retrospect, histopathology reports of breast biopsies and mastectomies from the archive of Pathology Department of King Abdul-Aziz University Hospital and King Khalid National Guard Hospital (KKNGH), Jeddah, KSA were reviewed for a total of 2129 breast cases from January 1985 to December 2002. These cases contained 2343 diagnosis as some of these cases had more than one diagnosis. All malignant diagnosis (558) (**Table 1**), normal breast and unrelated breast lesions are excluded from the study (839 diagnosis). The net diagnosis available for the study were 1504. Different diagnostic entities were classified into different categories using systematized nomenclature of medicine (SNOMED) coding system, these diagnosis were re-grouped based on associated increased risk of developing carcinoma. The following categories were created proliferative disease, non-proliferative disease (inflammatory and non-inflammatory), AH and CIS, (MIN).

Results. The total number of evaluated diagnosis were 1504. They were regrouped into proliferative disease (140), non-proliferative non-inflammatory (987), and non-proliferative inflammatory (296), MIN cases were 81 which include 5 atypical ductal hyperplasia (ADH) cases, 3 atypical lobular hyperplasia (ALH) cases and 73 CIS cases (**Table 2**). The higher percentage was benign non-proliferative diagnosis, which was 85.3%, followed by proliferative disease (9.3%), CIS (4.9%), and finally atypical ductal and lobular hyperplasia (0.5%).

Discussion. Histologically proven proliferative breast diseases, and some histological features of non proliferative diseases have been identified as a morphological markers of associated risks for subsequent development of invasive breast carcinoma.[1-4,13] It is documented in the literature[10-12] that invasive mammary carcinoma is preceded by certain proliferative breast diseases such as AH and preinvasive diseases such as CIS, early detection of these lesions will result in decrease of mortality rate of breast cancer. Introduction of breast cancer screening programs for early detection of breast cancer in developed countries increased the incidence of breast cancer and decreases the mortality rate among women enrolled in these screening programs.[13,14] The prevalence of benign breast lesions and preinvasive lesions associated with increased risk of breast cancer is not known in our region due to lack of studies addressing this issue. The national cancer registry of KSA in its 1998 issue ranked breast cancer as number one cancer in Saudi females, it's incidence is 19.8% with a median age of 46 years. The CIS diseases was detected in 3% of cases, while in 21% of cases the cancer was localized. Fifty percent of the cases showed regional lymph node extension and 15% had distant metastasis. In 11% of cases, the stage of the disease could not be determined.[15] Shapiro et al[14] report on breast cancer screening program (BCSP) showed marked increase in the incidence of invasive carcinoma, and steady decline in mortality rate by 30% in United States of America since 1985. Ontario, Canada cancer care report in 1998 showed improvement in the 5 years survival rate of breast cancer cases from 70% in 1970 to 75% in 1980 and this improvement is related to improvement in cancer research and treatment.[16] From these data, we may expect that if breast cancer screening program is introduced in the KSA, it would help in the detection of preinvasive lesions CIS, and other benign breast lesions associated with increased cancer risk. In addition, the mortality rate of this deadly disease will improve by improving the management. Some common risk factors are shared between benign breast lesions and breast carcinoma. It was showed that some of the risk factors of breast carcinoma increases the incidence of proliferative breast diseases, such as nulliparity, age of first child

birth and late menopause.[17,18] Dietary risk factors for breast cancer such as high intake of saturated fat in animal meat and caffeine are also associated with increase risk of benign breast disease.[19,20] Meat fat intake is associated with increase risk of MIN[19] and caffeine consumption augment the risk of atypical lobular hyperplasia, sclerosing adenosis and epithelial hyperplasia.[20] Cole et al[21] studied the relationship of positive family history of breast carcinoma and the presence proliferative breast changes in close relatives. They show no consistent family history association of breast carcinoma and proliferative breast disease. The significance and correlation between the molecular and genetic alteration in benign proliferative lesions is not fully established. Large number of molecular studies are applied currently on proliferative breast diseases trying to identify specific molecular changes. Kasami et al[22] studied the loss of heterozygosity (LOH) and Microsatellite instability (MSI) in proliferative breast disease. They sample 25 hyperplastic lesions and 8 micropapillomas found in 8 breast biopsies from 8 women. Genetic abnormalities were detected in different lesions in only 2 patients. In the first patient, they detected 5 loci with MSI and 2 loci with LOH, in one papilloma with florid hyperplasia and atypia, other 10 proliferative breast lesions(PBL) without atypia from the same patient were negative for genetic alteration (GA). The second patient had 3 loci with MSI detected in one PBL without atypia, whereas another lesion from this patient had minimal atypia but no GA. The first patient was alive for more than 25 years free of breast cancer. The other patient who had no GA, developed breast cancer 13 years after the biopsy. The authors concluded that correlation between histological and genetic changes is detected and the meaning of GA in premalignant breast lesion are not well correlated. Therefore, histological and molecular changes may not necessarily be precisely correlated, but additional investigation to study this association is required to established or deny this correlation. The role of mammographic appearance of benign breast proliferative lesion and CIS was studied by Boyd et al[23] and Urbanski et al[24] They found significant association between the mammographic appearance and the histopathological findings. In Boyd et al study, they follow up cases detected by mammography as greatest mammographic density. They found 9.7 fold increase risk of CIS or AH in patient with greatest mammographic density compared to women without density, in addition there is also 12.2 fold increase risk of hyperplasia without atypia. On the other hand, Moskowitz et al[25] found no association between mammographic pattern and histopathological findings. The role of mammography is highly stressed as mammograms detected ductul carcinoma in situ (DCIS) is seen in 10-15% of women receiving mammograms screening. This resulted in early management to prevent progression to invasive carcinoma, which was seen in 30% of cases where DCIS was left without treatment within 15 years.[26] In addition, mammographically discovered invasive breast carcinoma detected in breast cancer screening programs are defined as small size tumor of one cm in diameter or smaller. The prognosis of these tumors are excellent in comparison to the symptomatic tumors. It was found that the

Table 1 - Total number of invasive malignant cases

Diagnosis	n of cases	(%)
Carcinoma		
NOS	28	(5)
Infiltrating duct	440	(79)
Lobular infiltrating	25	(4.5)
Apocrine	1	(0.2)
Medullary	15	(2.7)
Mucinous	3	(0.5)
Papillary, NOS, adenoca	4	(0.7)
Scirrhous	5	(0.9)
Tubular	5	(0.9)
		(3.2)
Cystosarcoma, phyllodes, malignant	18	
Paget's disease, mammary	7	(1.3)
Paget's disease and	3	(0.5)
infiltrating duct CA of breast	1	(0.2)
Clear cell CA	1	(0.2)
Malignant lymphoma	1	(0.2)
Leukemic infiltrate		
Sarcoma	1	(0.2)
Total	**558**	**(100)**

NOS - not otherwise specified, CA - cancer

Table 2 - Frequency of benign proliferative, non-proliferaive, non-invasive diagnosis (N=1504).

Category	Total	(%)
Benign proliferative	**140**	(9.3)
Benign non-proliferative, inflammatory and non-inflammatory	**1283**	(85.3)
Total N of in situ	**73**	**(4.9)**
Total N of benign with atypical ductal and lobular	**8**	**(0.5)**

histological variant were tubular, cribriform and mucinous carcinomas which are low grade cancer and are more common seen in screened population than in symptomatic population.[27,28] Lymph node metastasis in carcinoma detected by screening is uncommon to rare and such finding suggest the omitting of lymph node dissection in small size tumors.[29] All this data are encouraging to start breast cancer screening program for our nation especially cases with benign proliferative breast disease or those with positive family history in order to detect them at an earlier stage when they carry excellent prognosis and good survival rate. In comparing the finding of this study in terms of frequency of breast diseases to one of the largest international studies with long follow up, we found that we have higher prevalence of non-proliferative breast disease 85.3% compare to 69.7%.[30] Furthermore, proliferative breast disease (9.3%) and atypical hyperplasia of 0.5% are much lower than what was reported in the literature as 26.2% and 3.6%. In addition, CIS prevalence is 4.9% which is much higher than the literature 1.7%. Our current findings is consistent with our previous publication of small scale study performed at KKNGH in 1997.[31] The differences in the prevalence of breast diseases in this study compared with the international study could be related to regional differences which is related to population susceptibility to develop benign breast diseases or carcinoma (related risk), which include environmental and racial factors, or it could be related to variable diagnostic experiences, especially in differentiating AH from CIS and some cases of AH were over called CIS. The latter factor could be eliminated if an expert study group is formed to implement a unified diagnostic criteria for diagnosis of CIS, AH and proliferative breast diseases in all of the detectable cases. Furthermore, presence of breast screening programs with screening mammograms in females above the age of forty or with positive family history of breast carcinoma in first degree relatives will help in detecting DCIS or small carcinoma.

In conclusion, proliferative breast diseases and MIN represent a measurable risk factor for breast cancer risk. Early detection by developing screening program will help in the final outcome of breast cancer. Establishment of breast pathology study groups from different health sectors who are involved in diagnosing large number of breast diseases will help in improving and unifying the diagnostic criteria used in breast lesion and it will give the real incidence and prevalence of proliferative breast disease and MIN as well as breast cancer.

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