FNA OF BREAST FIBROADENOMA: OBSERVER VARIABILITY AND REVIEW OF CYTOMORPHOLOGY WITH CYTOHISTOLOGICAL CORRELATION*

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ABSTRACT

Objective: To determine the observer variability in reporting fibroadenoma of the breast by fine needle aspiration (FNA) and to review the cytomorphological features of the lesion with cytohistological correlation.

Methods: Retrospective analysis of FNA smears from 110 cases diagnosed as fibroadenoma of which surgical pathology follow-up was available in 33. Two pathologists were asked to categorize smears from 67 cases of breast lesions while blinded to the clinical finding as fibroadenoma, epithelial hyperplasia (usual and atypical) and malignant. All fibroadenoma (33) and cancer (15) cases were biopsy-proven. The same set of slides was re-circulated to one of the pathologists, and his first and second round results were compared.

Results: Pre-review cytohistological correlation was attained in 32 of 33 cases of fibroadenoma (97%). The overall agreement between the two observers was 87% [Kappa ¼ 0.74, 95% confidence interval (CI) 0.72–0.76]. Cytohistological correlation was achieved in 26 of 33 (79%) cases. Intra-observer agreement was 91% (Kappa ¼ 0.82, 95% CI 0.89–0.93) with cytohistological correlation in 29 of 33 (87%) cases. Causes of diagnostic errors included marked dissociation, pleomorphism, poorly cellular smears from hyalinized fibrodenoma, lacational changes and apocrine metaplasia with cystic changes. Multinucleated giant cells were frequently encountered in FNA smears from fibroadenoma (31.8%), but in none of the lumpectomy specimens. Their histiocytic nature was suggested by immunohistochemistry.

* Cytopathology. 2006 Oct, 17 (5):239-44

Conclusion: FNA was a highly sensitive method for the diagnosis of fibroadenoma. Current cytological criteria were reliable and gave high inter- and intra-observer reproducibility.

Keywords: fine needle aspiration, fibroadenoma, cytology, reliability, reproducibility.

INTRODUCTION

Fine needle aspiration cytology (FNAC) has become an important preoperative and screening test for breast masses. The sensitivity and specificity of the procedure are extremely high when combined with clinical examination and imaging.[1] The main objective of breast FNAC is to separate malignant lesions that require prompt surgical excision from benign ones. Fibroadenoma is one of the benign conditions in which a specific cytological diagnosis can be offered confidently, when the cytological findings of staghorn clusters of ductal cells, fibromyxoid stroma and numerous bare nuclei are combined with the clinical finding of a well circumscribed and freely mobile mass in a young woman. Nevertheless, fibroadenoma is the most common cause of false positives and false negatives in breast FNA.[2] This is because the cytomorphological features of fibroadenoma overlap with other benign lesions, proliferative and non-proliferative, and carcinoma. As a conservative approach to management and follow-up by ultrasonography and FNA has recently been adopted,[3] reliability and reproducibility of the procedure have to be assured. The aim of this study was to review the most commonly encountered cytomorphological features of fibroadenomas and to know how far fibroadenomas can be diagnosed reliably by cytology. The inter-observer and intra-observer reproducibility in the cytodiagnosis of fibroadenomas is also determined. The causes of diagnostic pitfalls and the significance of combining clinical examination with FNAC findings in the diagnostic accuracy of fibroadenomas are elucidated.

METHODS

At our hospital, the initial diagnostic workup of all breast masses includes FNAC. The procedure is always performed by the pathologist using 22G needles and the smears are air-dried and stained with May-Grünwald–Giemsa. All the smears of fibroadenomas diagnosed over a 10-year period (1994–2004) were retrieved from the files of the cyto/histo department and reviewed. The detailed cytomorphological features, namely cellularity, epithelial cell arrangement, nuclear pleomorphism, cell dissociation, presence of single bare nuclei, fibromyxoid stromal fragments, myoepithelial cells, apocrine metaplasia, myxoid background and miscellaneous cells, e.g. multinucleated cells, macrophages were studied. The aspirates were regarded as adequate for evaluation if six clusters of at least 5–10 well preserved epithelial cells were present on all slides.[4] Four smears from three cases of biopsy-proven fibroadenoma with abundance of multinucleated giant cells were washed in methanol for 1 hour after demounting and each slide was stained simultaneously for CD 68, cytokeratin and vimentin. Immunostaining was performed by the enzyme-labelled avidin-biotin method.[5] All reagents were purchased from DakoCytomation (DK-2600, Glostrup, Denmark). Sections from tonsils and appendix served as positive controls.

At our hospital, fibroadenoma cases are managed either conservatively or operated on at the patients request. The smears from histologically confirmed cases of fibroadenomas (33 cases) were mixed with smears reported as epithelial hyperplasia (usual and atypical) (19 cases) and 15 cases of histologically proven carcinomas.

None of the 19 cases reported as epithelial hyperplasia turned out to be malignant during the review period. A panel of two pathologists were asked to read the smears while blinded to the clinical findings and categorize them as fibroadenoma, epithelial hyperplasia (usual and atypical) and malignant. This also mimics the situation where the smears are performed by the clinicians. The inter-observer reproducibility in the categorization of these breast lesions was measured. The intra-observer reproducibility was studied by recirculating the same set of slides to one of the pathologist. His first and second round results were compared. Kappa statistics with 95% confidence interval (CI) were performed.6 The FNA diagnosis in fibroadenoma cases correlated with histopathogy in different settings. Discrepant cases were analysed and possible causes of errors were determined.

RESULTS

The total number of cases diagnosed cytologically as fibroadenomas was 110. All were female patients aged 13–49 years (median 21 years). The smears from all cases of fibroadenoma were adequate for cytological evaluation (100%). The commonly encountered cytological features of fibroadenomas are shown in *Table 1*. The main features of staghorn clusters, fragments of fibromyxoid stroma and numerous single bare nuclei are seen in 73.6%, 92.7% and 73.6% of cases respectively. Cellular

Table 1: Common cytomorphological features of fibroadenoma

Cytomorphological features	Frequency (%)
Moderate to high cellularity	85
Clusters of ductal epithelial cells admixed with myoepithelial cells	100
Staghorn clusters	73.6
Monolayered sheets	96.4
Tubular clusters	70
Papillary clusters	90
Cell dissociation	47.3
Nuclear pleomorphism	40
Moderate to large number of bare nuclei	73.6
Fibromyxoid stroma	92.7
Apocrine metaplasia	17.3
Myxoid background	50
Macrophages	52.7
Multinucleated giant cells	31.8

dissociation and mild nuclear pleomorphism were observed in nearly half of the cases. Multinucleated giant cells with 4–15 bland-looking nuclei, small but clearly visible nucleoli, and foamy or clear cytoplasm were observed in 31.8% of cases *(Figure 1)*. Weak to moderate expression of CD 68 was detected in all multinucleated giant cells in all examined smears *(Figure 2)*. Cytokeratin (CK) and vimentin were not expressed by any of the multinucleated giant cells.

All biopsied fibroadenomas (33 cases) correlated with the FNA diagnosis except one, giving a sensitivity of 97% which was compared with sensitivities repor ted by other authors *(Table 2)*. Marked cellular dissociation and pleomorphism were the causes of overcalling the case of atypical epithelial hyperplasia.

The two reviewers rendered the same cytological diagnosis in 29 of 33 cases (87%) of fibroadenoma with a Kappa score of 0.74 and a 95% CI between 0.72 and 0.76. Cytohistological correlation was achieved in 26 of 33 cases (79%). The other cases (7/33) were misread by one or both of the pathologists as epithelial hyperplasia in five cases, fat necrosis in one case and carcinoma in one case. The first and second round results agreed in 30 of 33 cases (91%) with a kappa score of 0.82, and a 95% CI between 0.89 and 0.93. Cytohistological correlation was achieved in 29 of 33 cases (87%). The causes of pitfalls in the cyto-diagnosis of fibroadenomas are enumerated in *Table 3*. The absence of one or more of the cytological triad (staghorn pattern, fibromyxoid stroma and bare nuclei) and low cellularity were the leading causes of error. This was followed by lipidaemic background, lactational changes *(Figure 3)*, cellular dissociation *(Figure 4)* and prominent apocrine metaplasia *(Figure 5)*.

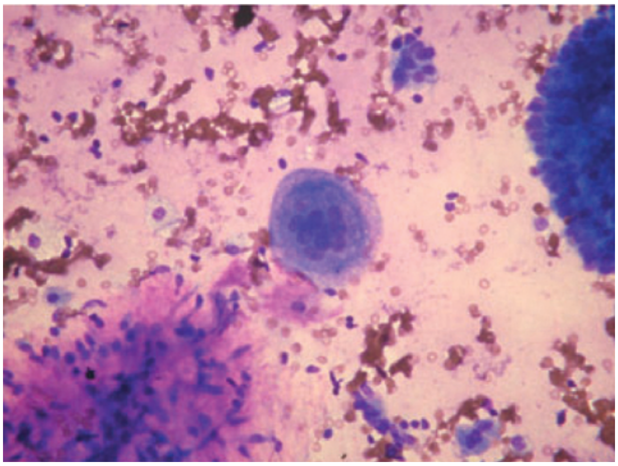

Figure 1: A smear from a fibroadenoma showing a multinucleated giant cell with clear cytoplasm lying beside a fragment of fibromyxoid stroma and clusters of ductal epithelial cells. Note the large number of bipolar naked nuclei in the background (May-Grünwald-Giemsa ×400).

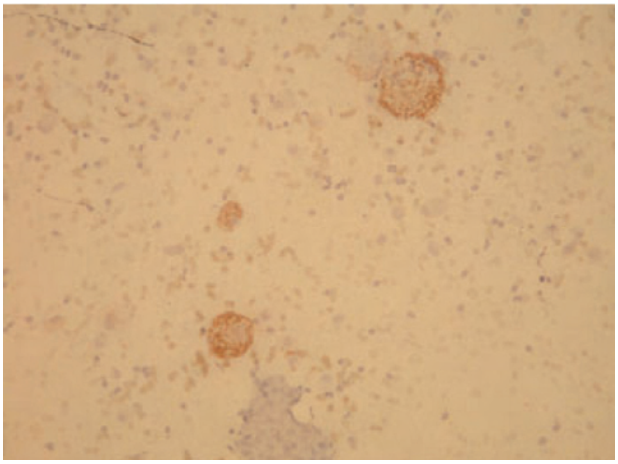

Figure 2: Multinucleated giant cells with positive cytoplasmic immunreaction to CD 68 (×200).

Finally cyto/histological correlation was done for the presence of giant cells and poorly cellular smears. Poor cellularity smears correlated with hyalinized fibroadenomas in all three cases. There was no correlation between the presence of giant cells in smears and the respective histological sections. Giant cells were not identified in any of the biopsied fibroadenoma.

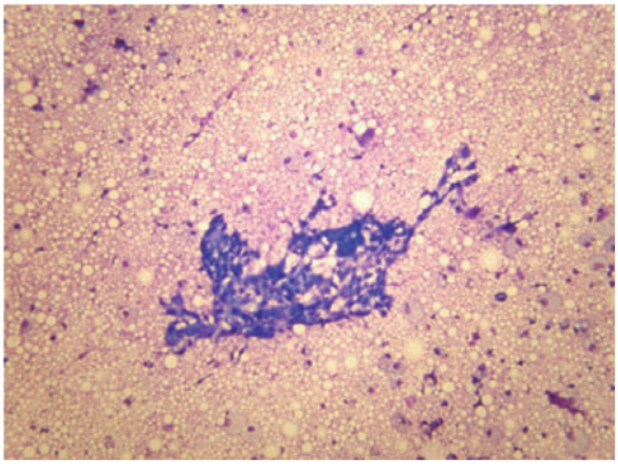

Figure 3: A smear from a fibroadenoma with lactational changes. A monolayered sheet of ductal epithelial cells against a lipidaemic background with foamy macrophages (May-Grünwald-Giemsa×200).

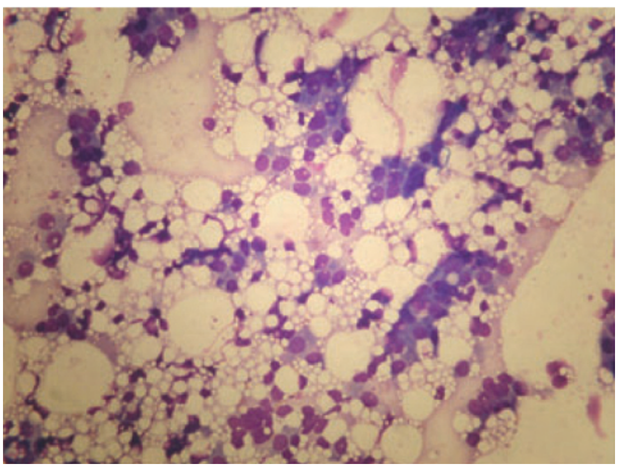

Figure 4: Fibroadenoma with markedly dissociated epithelial cells with intact cytoplasm against a lipidaemic background (May-Grünwald-Giemsa ×400).

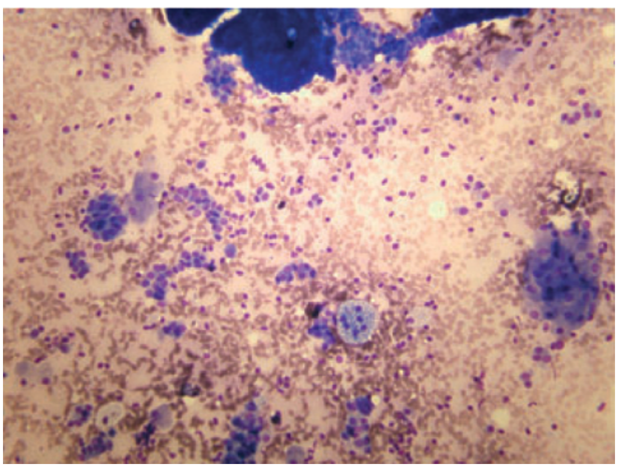

Figure 5: Fibroadenoma showing a bland mixture of apocrine cells, ductal epithelial cells, foamy multinucleated giant cells and numerous bipolar naked nuclei (May-Grünwald-Giemsa ×200).

Table 2: Sensitivity of FNA in the diagnosis of fibroadenoma

Reference	Sensitivity (%)
Benoit et al.[2]	93
Lopez-Ferrer et al.[7]	86
Carty et al.[18]	84
Walters et al.[22]	68
Present study	97

Table 3: Causes of errors

Reference	
Absence or minimal presence of fibro-myxoid stroma	7/7
Absence of staghorn pattern	6/7
Small number of bare nuclei	6/7
Low cellularity	4/7
Lipidaemic background	3/7
Cellular dissociation	1/7
Prominent apocrine metaplasia	1/7
Lactational changes	1/7

DISCUSSION

Fibroadenoma is a commonly encountered benign breast tumour of young age groups. Fibroadenomas have a characteristic cytological appearance, nevertheless, it is the single most common cause of falsepositive and false-negative results in breast FNAC.[2] The cytodiagnosis of fibroadenoma is easy and straightforward in most of the cases, especially when staghorn clusters of ductal epithelial cells, numerous single bare nuclei and fragments of fibromyxoid stroma coexist in one smear. However, at times the picture is complicated by the presence of one or more features that skew the diagnosis towards malignancy, e.g. cell dissociation and nuclear pleomorphism, or towards fibrocystic disease when the smears are hypocellular, showing apocrine metaplasia and cystic changes. In this study the common cytomorphological features encountered in the diagnosis of fibroadenoma were not much different from those described earlier.[7] The finding of fibromyxoid stroma (92.7%), staghorn clusters of ductal epithelial cells (73.6%) and the presence of a moderate to large number of bare bipolar nuclei (73.6) remained the key diagnostic triad. Of interest and quite different from other reports was the high rate of occurrence in our material of benign looking multinucleated giant cells (31.8%). Multinucleated giant cells were described as being rarely present or absent in fine needle aspirates[8,9] or histological sections from fibroadenomas.[10,11] A stromal origin was suggested.[8,10] Their diagnostic significance lies in their strong association with phyllodes tumour and other malignant stromal tumours.[9,11,12] Our experience with multinucleated giant cells in fine needle aspirates from fibroadenomas was quite different. First, multinucleated giant cells were frequently encountered in our aspirates. Second, their immunocytochemical profile suggested a histiocytic origin and third, their finding in smears did not correlate with the respective surgical pathology. In fact they were not seen in any of our biopsied fibroadenomas. We felt that the presence of such benign looking multinucleated giant cells in a florid epithelial lesions could be assuring. The discrepancy between their frequent presence in fine needle aspirates and their absence in histological sections, as well as their histiocytic nature, suggested to us an extra-tumoral reactive process in the surrounding breast tissue, i.e. a sort of palpation granuloma or fat necrosis. Most of our operated fibroadenomas were simply enucleated with no, or a very narrow, rim of normal breast tissue, which made the assessment for the presence of fat necrosis or granuloma on histological sections not rewarding. The development of cancer in fibroadenomas is quite rare (2.0–2.9%), usually of in situ or lobular type and this does not occur before the age of 40 years.[13,14] Furthermore, fibroadenoma is associated with a slight increased risk of breast cancer (2.17), close to that of other benign proliferative lesions without atypical hyperplasia (1.9).[15,16] The risk increases with a family history of breast cancer. Because fibroadenomas have negligible premalignant potential and tend to resolve, reduce in size or remain static with time, conservative non-surgical management has been advocated.[3,17–19] Monitoring by regular ultrasonography and FNAC is advised. Surgical excision can be reserved for women above the age of 40 years, those with a family history of breast cancer or breast tumours that rapidly

increase in size. The success of the conservative approach depends on a reliable and reproducible pre-operative test. In our hands FNA proved to be highly sensitive and reproducible. A sensitivity of 97%, inter- and intraobserver reproducibility of 87% and 91% were, respectively, achieved. This indicates that the cytological criteria used were adequate and reliable. To our knowledge, data on observer variability in reporting fibroadenoma by FNA have not been previously published. However, FNA of the breast was reported to be of limited value in classifying benign breast diseases[20] and in distinguishing between proliferative and non-proliferative benign breast changes.[21] From our experience, reliable and reproducible cytological differences to separate at least fibroadenoma from other benign lesions do exist, as was reflected in the high observer agreement. The 97% sensitivity acheived in this study was higher than that reported earlier[2,7,18,22] *(Table 3)*. This could be partly due to the small number of aspirators involved[2,3] with a 100% adequacy rate. Errors in the cytodiagnosis of fibroadenoma *(Table 3)* can be minimized by triple assessment of clinical examination, cytology and imaging. The triple approach has been shown to boost the sensitivity to 100%.[1] Our results emphasize the importance of the pathologist taking the aspirates. Our sensitivity in such a set-up was 97%. This came down to 79% when the pathologist was blinded to the clinical details in a situation similar to a remote cytology service, where surgeons aspirate. In conclusion, the cytological criteria for the diagnosis of fibroadenoma by FNA are quite reliable and when used in an appropriate setting (triple approach) give high sensitivity and good reproducibility.

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DIETARY FAT AND BREAST CANCER IN SAUDI ARABIA: A CASE–CONTROL STUDY*

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الدهن الغذائي وسرطان الثدي في المملكة العربية السعودية : دراسة للحالات والشواهد

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الخلاصة: يستعرض الباحثون دراسة للحالات والشواهد واستقصاء الترابط بين الدهن الغذائي وسرطان الثدي لدى نساء المملكة العربية السعودية، اللاتي يراجعن المستشفيات التخصصية في الرياض. وقد شملت الدراسة 499 من النساء المصابات بسرطان الثدي، اللواتي شُخِّصَت إصاباتهن منذ وقت قريب في الفترة 1996-2002، إلى جانب 498 من النساء اللواتي تم اختيارهن بشكل عشوائي، من المريضات اللواتي يراجعن المستشفيات لأسباب أخرى ومن قريباتهن. وقد استكملن استبيانات حول تواتر الأكل، ثم أجري قياس مستويات الكوليسترول الكلي وثلاثي الغليسيريد في المصل، ووجد ترابط إيجابي هام بين خطر الإصابة بسرطان الثدي وبين دخل الدهنيات والبروتينات والكالوريات، وقد بلغت نسب الأرجحية المصحَّحة لأعلى شريحة ربعية من الدخل الغذائي مقارنة بأخفض شريحة ربعية من الدخل الغذائي: 2.43 من الدهنيات المشبعة، و 2.25 من البروتين الحيواني، و 2.12 من الدهنيات المتعددة اللاتشبع، و 1.88 من الكوليسترول، و 2.69 من مجمل الطاقة المتناولة من الطعام. وقد بلغت نسبة الأرجحية المصحِّحة لثلاثي الغليسريد في المصل 2.16 من أعلى شريحة ربعية.

ABSTRACT

A case-control study investigated the association between dietary fat and breast cancer in Saudi Arabian women attending a specialist hospital in Riyadh. Women with breast carcinoma (n=499) newly diagnosed between 1996-2002, and control women (n=498) randomly selected from patients' attendants and relatives, completed a food frequency questionnaire. Serum levels of triglycerides and total cholesterol were measured. A significant positive association was found between risk of breast cancer and intake of fats,

* Eastern Mediterranean Health Journal, Vol. 10, No. 6, 2004

protein and calories. Adjusted odds ratios for the highest quartile of intake versus the lowest were 2.43 for saturated fat, 2.25 for animal protein, 2.12 for polyunsaturated fat, 1.88 for cholesterol and 2.69 for total energy from dietary intake. For serum triglycerides the adjusted odds ratio was 2.16 for the highest quartile.

INTRODUCTION

A large body of evidence has accumulated concerning the association between diet and breast cancer. Much of this has focused on the possible causative role of dietary fat. These studies have provided somewhat inconsistent support for an association between fat intake and breast cancer [1]. Conclusions from some case–control studies have suggested a positive association between breast cancer and saturated fat intake [2], whereas others demonstrated a reduced risk due to total and polyunsaturated fat intake [3]. A prominent Harvard cohort study of nearly 90 000 American nurses compared nurses who ate low-fat diets with nurses who consumed higher fat diets and concluded that no relationship existed between the risk of breast cancer and the amount of fat consumed [4]. Willett's review of epidemiological studies of the relationship between diet and breast and colon cancers suggested there was a null or weak association between dietary fat and breast cancer [5].

In Saudi Arabia, breast cancer is becoming a major health risk and is the most common female malignancy in the country [6–8]. Several studies have shown an upward trend in the incidence of breast cancer in Saudi Arabia [9–13]. Breast malignancy had the highest relative frequency in the eastern region of Saudi Arabia during 1981–83 in relation to previous studies [9]. This shows an upward trend in that region as it rose from the third most common cancer during 1952–60 to the second most common in 1962–73 [10]. However, it is the sixth most common malignancy in the southern region [11], and for females it is the most common cancer [12]. The number of breast cancer cases registered at King Khalid University Hospital, Riyadh were 47, 48 and 107 during the periods 1985–87, 1988–90 and 1990–93 respectively and breast cancer was the second most common malignancy among females in that hospital [13]. Data suggests that breast cancer in Saudi Arabia occurs in a relatively younger age group compared with industrialized countries. The mean age of Saudi women with breast cancer is 47 years as compared with 54 years in Western Europe and America [9].

With increasing prosperity and commercial exposure of the population of Saudi Arabia, there has been an influx of western affluence foods over the last 3 decades. The increased consumption of new types of food, which are rich in fat, meat and refined carbohydrates, may be a contributory factor for the increase in breast cancer incidence in Saudi Arabia. The national nutrition survey of the population of Saudi Arabia showed that per capita energy intake in Saudi Arabia rose from 1801 kcal in 1971 to 3082 kcal in 1992 [14,15]. Percent of energy from carbohydrates decreased from 75% to 43% and from fat increased from 10% to 42% during the same period. Protein intake increased from 49 g/day in 1971 to 114 g/day in 1992, with 60% of protein intake from animal sources, while fat intake increased from 34 g to 144 g during the same period.

Despite concerns about changing dietary habits and the incidence of breast cancer in Saudi Arabia, no study has investigated the association between diet and breast cancer among Saudi females. Therefore, this case–control study at a specialist hospital in Riyadh was conducted to investigate if there is an association between breast cancer and dietary risk factors, including high protein, fat and calorie intake, high body mass index (BMI) and raised serum cholesterol and trigycerides levels.

METHODS

Sample

This was a case–control study of women attending the breast cancer clinic at King Faisal Specialist Hospital and Research Centre in Riyadh. Patients attending the hospital are referred from all areas of the country.

The sample size was estimated by assuming the proportion with high fat intake among controls is 9% and among cases 15% to give an odds ratio of 1.78 as an indication of a significant association between fat intake and breast cancer (α=0.05, 1–β=0.80). Using Epi-Info, version 6, the number of cases required was 500 and controls 500.

The cases were recruited prospectively in the order in which they came to the clinic and were women with newly diagnosed, histopathologically confirmed breast cancer. Control women were selected from the patients' attendants and relatives, frequency matched for age, parity, breastfeeding practice and age at marriage. Data collection took place from September 1996 to April 2002.

The women were enrolled after giving informed consent. Approval for the study was obtained from the Ethics Committee of the Research Centre of King Faisal Specialist Hospital.

Dietary study

An existing food frequency questionnaire, used in the National Nutrition Survey for Saudi Arabia [14], was modified to accommodate the food habits of Saudis. To help record the usual intake of food items accurately we used food models. The 40 food items listed in the questionnaire were: beef, lamb, poultry, fish, camel meat, goat meat, eggs, corn oil, olive oil, sunflower oil, ghee/samnah, butter, shaham, ghusdah, tahinah, other fats and oils, salt, pepper, sauces, vegetables, fruits, cow's milk, laban milk, yoghurt, cheese, powdered milk, camel's milk, goat's milk, concentrated milk, sweetened condensed milk, milk with other flavours, tea with milk, coffee with milk, coffee without milk, bran flakes, corn, bread, rice, cakes, pie, pudding, ice cream, crème caramel. The food frequency questionnaire was administered by interview using well-trained nutritionists. Intake frequencies were expressed as number of times each item was consumed per week. The food frequency data were crosschecked with a 3-day food record.

A risk factors questionnaire collected demographic, anthropometric and reproductive information from cases and controls. It included questions on nationality, residence, age, age at menarche, menopausal status, breastfeeding, number of pregnancies, number of abortions, history of oral contraceptive use, family history of breast cancer, weight and height (for calculation of body mass index).

Serum levels of total cholesterol and triglycerides were obtained for patients and controls. For patients, the data was extracted from the laboratory records. For controls, a blood sample was taken and analysed at the hospital laboratory.

Diet analysis software (NSL Diet Analyzer and WinDiet version 5) and Saudi food tables [14] were used to indirectly calculate nutrients from reported intakes of individual foods. We calculated the daily intake of: total energy (kcal), total fat (g), saturated fat (g), polyunsaturated fat (g), protein (g) and cholesterol (mg) from the self-reported food consumption and validated against the 3-day food record. One case and 2 controls were excluded from the analysis because of unacceptably low or high nutrient values. Thus data from 499 cases and 498 controls were analysed.

Statistical analysis

Means and standard deviations (SD) were compared using the t-test and frequencies using the chi-squared test. Odds ratios were estimated and 95% confidence intervals (CI) from multiple logistic regression, adjusting for the following potential confounding factors: age, nationality, province and menopausal status. We modelled nutrients across quartiles using the first quartile as the reference group. A P-value less than 0.05 was considered significant.

RESULTS

Table 1 shows the demographic and reproductive characteristics of the study sample. Breast cancer cases relative to controls in this study group were older ($P<0.001$), less heavy ($P<0.01$) and shorter ($P<0.0001$) with similar BMI, had more pregnancies ($P<0.0001$), had a higher age at menarche ($P<0.05$) and were less likely to have ever-used oral contraceptives ($P<0.01$).

Table 2 shows the relationship between breast cancer and serum triglycerides level, cholesterol level and BMI for the case and control samples analysed at the 25th, 50th and 75th percentiles. Univariate analyses showed that cases and controls had no significant association between serum cholesterol level and BMI and breast cancer. However, the cases had significantly higher serum triglycerides levels than the control women. The multivariate odds ratio for raised trigycerides level, adjusted for age, nationality, province and menopause, was 2.16 (95% CI: 1.21–3.88) at the highest quartile ($P<0.05$).

Table 3 shows the association between breast cancer and daily intake of different nutrients for the cases and controls analysed at the 25th, 50th and 75th percentiles of the recommended daily allowance. Crude and adjusted odds ratios of these nutritional factors in relation to breast cancer are also given. Univariate analysis showed that cases and controls were similar in intake of total protein, but cases had significantly lower intake of energy and of all the components of fat (total fat, saturated and polysaturated fats) relative to controls ($P<0.05$). When adjusted for age and province, none of the nutrition variables showed an association with breast cancer.

Table 3 also presents the odds ratios for the intake of various nutrients to breast cancer after adjustment for age, nationality, province, menopause and triglycerides levels. This analysis showed that the intake of protein was significantly related to breast cancer risk after adjustment for other possible confounding factors. Multivariate adjustment reversed the associations noted earlier between breast cancer and the various dietary components. The adjusted odds ratios for the highest quartile of intake versus the lowest were 2.43 (95% CI: 1.36–4.34) for saturated fat, 2.25 (95% CI:1.27–3.99) for

Table 1: Demographic and reproductive characteristics of breast cancer cases and control women.

Characteristics	Mean (SD) values		P-value
	Cases (n=499)	Controls (n=498)	
Age (years)	44.8 (11.5)	36.8 (12.8)	0.0001
Age at menarche (years)	13.2 (1.5)	13.0 (1.6)	0.037
Age at menopause (years)	48.2 (7.6)	47.9 (8.1)	0.759
Age at first delivery (years)	20.6 (4.9)	20.7 (4.5)	0.759
Age at marriage (years)	20.6(4.8)	20.7(12.1)	0.174
Number of pregnancies	6.6 (3.8)	5.3 (3.8)	0.0001
Number of abortions	1.0 (1.4)	1.0 (1.4)	0.968
Weight at diagnosis (kg)	70.0 (15.3)	72.4 (14.9)	0.014
Height at diagnosis (cm)	154.1 (6.7)	157.1 (6.5)	0.0001
Body mass index (kg/m2)	29.5 (6.2)	29.4 (6.2)	0.818
% ever-used oral contraceptives	54.1	62.5	0.013
% breastfeeding	89.7	85.9	0.094
% family history of breast cancer	15.0	12.1	0.174

n = number of women.
SD = standard deviation.

Table 2: Relation between breast cancer and serum lipid levels and body mass index for case and control women analysed by quartiles.

Variables (quartiles)	No. of Cases/ Controls	Crude odds ratio (95% CI)	Age/province adjusted odds ratio (95% CI)	Multivariate adjusted odds ratio[a] (95% CI)
Triglycerides (mM/L)				
< 0.9	47/95	1 (reference)	1 (reference)	1 (reference)
0.9–1.3	54/80	1.36 (0.84–2.23)	1.03 (0.60–1.74)	0.73 (0.40–1.32)
> 1.3–2.0	75/68	2.23 (1.38–3.60)**	1.75 (1.04–2.94)*	1.67 (0.96–2.93)
> 2.0	77/53	2.90 (1.79–4.81)***	2.21 (1.29–3.79)**	2.16 (1.21–3.88)*
Cholesterol (mM/L)				
< 4.3	122/140	1 (reference)	1 (reference)	1 (reference)
4.3–5.0	117/115	1.67 (0.82–1.67)	0.95 (0.64–1.41)	0.80 (0.51–1.25)
> 5.0–5.7	140/131	1.23 (0.87–1.72)	1.05 (0.72–1.54)	0.92 (0.59–1.43)
> 5.7	120/112	1.23 (0.86–1.75)	1.13 (0.76–1.68)	0.96 (0.63–1.55)
Body mass index (kg/m2)				
< 24.9	113/135	1 (reference)	1 (reference)	1 (reference)
24.9–28.9	131/118	1.33 (0.93–1.89)	0.91 (0.61–1.36)	0.80 (0.51–1.25)
> 28.9–33.5	125/124	1.20 (0.85–1.71)	0.69 (0.46–1.03)	0.92 (0.59–1.43)
> 33.5	128/120	1.27 (0.89–1.81)	0.66 (0.44–0.99)	0.99 (0.63–1.55)

[a] Adjusted for age, nationality, province and menopause.
* P< 0.05; **P< 0.01; ***P< 0.001.
CI = confidence interval.

Table 3: Relationship between breast cancer and self-reported daily intake of dietary nutrients for case and control women analysed by quartiles.

Daily intake of nutrient (quartiles)	No. of Cases/ Controls	Crude odds ratio (95% CI)	Age/province adjusted odds ratio (95% CI)	Multivariate adjusted odds ratio[a] (95% CI)
Total energy from fat (kcal)				
< 1084.1	131/118	1 (reference)	1 (reference)	1 (reference)
1084.1 < 1426.2	130/119	0.98 (0.69–1.40)	1.24 (0.84–1.83)	2.65 (1.44–4.86)**
1426.2 < 1872.9	132/118	1.00 (0.71–1.43)	1.27 (0.85–1.88)	3.19 (1.74–5.83)***
> 1872.9	106/143	0.67 (0.47–0.95)*	0.84 (0.56–1.24)	2.69 (1.51–4.81)**
Total protein (g)				
< 52.2	127/122	1 (reference)	1 (reference)	1 (reference)
52.2 < 68.9	130/119	1.05 (0.74–1.49)	1.14 (0.77–1.68)	2.65 (1.41–4.98)**
68.9 < 88.1	135/115	1.13 (0.79–1.60)	1.16 (0.78–1.72)	3.12 (1.71–5.70)***
> 88.1	107/142	0.72 (0.51–1.03)	0.74 (0.50–1.09)	2.25 (1.27–3.99)**
Total fat (g)				
< 35.4	134/115	1 (reference)	1 (reference)	1 (reference)
35.4 < 51.1	128/121	0.91 (0.64–1.29)	1.08 (0.73–1.60)	1.65 (0.90–3.02)
51.1 < 70.9	138/112	1.06 (0.74–1.50)	1.34 (0.91–1.99)	2.67 (1.47–4.83)**
> 70.9	99/150	0.57 (0.40–0.81)**	0.73 (0.49–1.09)	1.64 (0.92–2.95)
Polyunsaturated fat (g)				
< 19.9	138/111	1 (reference)	1 (reference)	1 (reference)
19.9 < 30.4	127/122	0.84 (0.59–1.19)	0.96 (0.65–1.41)	2.15 (1.17–3.92)*
30.4 < 41.3	126/124	0.82 (0.58–1.16)	1.12 (0.76–1.67)	2.43 (1.30–4.53)**
> 41.3	108/141	0.62 (0.43–0.88)**	0.78 (0.53–1.16)	2.43 (1.36–4.34)**
Polyunsaturated fat (g)				
< 15.6	131/118	1 (reference)	1 (reference)	1 (reference)
15.6 < 21.3	144/105	1.23 (0.87–1.76)	1.56 (1.05–2.31)	2.19 (1.18–4.07)*
21.3 < 29.2	124/126	0.89 (0.62–1.26)	1.15 (0.78–1.70)	2.73 (1.53–4.87)**
> 29.2	100/149	0.61 (0.42–0.86)**	0.78 (0.52–1.15)	2.12 (1.17–3.83)*
Cholesterol (mg)				
< 169.6	135/114	1 (reference)	1 (reference)	1 (reference)
169.6 < 266.4	128/121	0.89 (0.63–1.27)	1.00 (0.68–1.48)	1.64 (0.90–2.98)
266.4 < 400.7	125/125	0.84 (0.59–1.20)	0.99 (0.67–1.46)	2.11 (1.16–3.84)*
> 400.7	111/138	0.68 (0.48–0.97)*	0.81 (0.55–1.20)	1.88 (1.03–3.44)*

[a] Adjusted for age, nationality, province, menopause and triglycerides.
*P< 0.05; **P< 0.01; ***P< 0.001.
CI = confidence interval.

animal protein, 2.12 (95% CI: 1.17–3.83) for polyunsaturated fat, 1.88 (95% CI: 1.03–3.44) for cholesterol, 2.69 (95% CI: 1.51–4.81) for total energy obtained from fat, and 2.16 (95% CI: 1.21–3.88) for triglycerides. It is worth noting that the association between triglycerides and the risk of breast cancer remained significantly positive irrespective of all other variables investigated *(Table 2)*.

DISCUSSION

Breast cancer is the most common cancer among women in Saudi Arabia. The number of reported cases of breast cancer in Saudi Arabia in 1999–2000 was 1157 (out of a female population of 7 788 754) [8]. There is no available data showing the number of deaths that can be attributed to breast cancer in Saudi Arabia. The descriptive epidemiology of breast cancer has demonstrated a rapid increase in the incidence rates in developing countries [16,17]. Identification of the contributing factors for the increasing rate would contribute substantially to our understanding of the epidemiology of breast cancer [16]. Environmental factors rather than genetic factors have been considered as the reason for variation in breast cancer rates among countries [17].

Socioeconomic development is normally associated with increasing wealth, changing lifestyle, disease pattern and increasing life expectancy. This association of changes, known as epidemiologic transition, is seen in many parts of the world and is very well demonstrated in Saudi Arabia, which has experienced rapid socioeconomic changes during the last 3 decades. As food habits mimic changes in lifestyle, there has been a dramatic shift from traditional foods which are based on whole wheat flour, milk and dates towards an affluent diet which is rich in total calories, meat, fat and refined carbohydrates. This change in dietary habit may be related to the increase in the number of breast cancer cases in Saudi Arabia [6–8].

Dietary fat has been proposed as one of the etiologic factors for breast cancer [2,4,5]. However, the relationship between fat intake and the risk of breast cancer has been examined in a number of case–control and cohort studies. The findings reported in the literature are not conclusive enough to establish a pattern for the real cause of the disease [4,5].

Our data suggest that, among women living in Saudi Arabia, a diet that is high in fat predisposes to breast cancer development. In terms of nutrients, this high-risk dietary profile translates to a modest, positive association with total fat intake, saturated fat, and cholesterol. This is in contrast to an earlier study, which has cast doubt on a positive association between dietary fat and breast cancer [4]. However, our findings agree with those of Toniolo et al. [18] and Zaridze et al. [19] who showed a positive association between high dietary fat intake and breast cancer. Also high animal protein intake was significantly associated with breast cancer in our study, which supports the findings of De Stefeni et al. [20] and Levi et al. [21] who showed a positive relationship between high dietary meat consumption and breast cancer. Boyd et al. in their quantitative summary of all papers published up to July 2003 on dietary fat and the risk of breast cancer found intake of saturated fat and meat consumption is associated with an increased risk of breast cancer [22].

High consumption of sugar-rich foods, meat and other animal products rich in saturated fats has been recorded in Saudi Arabia [Khan MA, unpublished report, 1996]. Despite the inconclusive evidence about diet and disease, it is important to educate the population about the possibility of a link between dietary habits and cancer and to encourage them to adopt a diet that is low in calories, saturated fat and meat intake.

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PATTERN OF CANCER IN SAUDI ARABS REFERRED TO KING FAISAL SPECIALIST HOSPITAL*

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A total of 7251 histologically confirmed new cases of cancer (4117 males and 3134 females) were seen in the 6-year period 1979 to 1984 at the King Faisal Specialist Hospital and Research Centre in Riyadh, Saudi Arabia. The crude relative frequencies of cancer at various primary sites have been determined with reference to sex, age, geographic origin, and year of diagnosis. The most common cancer sites among males were non-Hodgkin's lymphomas, esophagus, lung, liver, stomach, and nasopharynx. Breast cancer was the most common tumor among the females, followed by non-Hodgkin's lymphomas and cancers of the thyroid, esophagus, cervix, and ovary. The most marked deviations were found in the Southern Region for cancers of the oral cavity (2.4 times higher), bladder (1.8 times higher), and lung (4.3 times lower).

Known etiologic factors, such as local chewing, smoking habits, and schistosomiasis are likely to be responsible for these differences. Upward trends in cancers of lung, breast, colon and rectum, and the downward trend in esophageal cancer may reflect the rapid pace of modernization. Cuncer 58:1172-1178,1986.

Saudi Arabia has been undergoing unprecedented economic development since the early 1970s. This is having a profound impact on air and water quality, diet and consumption patterns, lifestyle, and occupational conditions. These changes are likely to have altered the patterns of exposure to environmental cancer risk factors.

Simultaneously, the widespread availability of modern medical facilities and increasing public awareness of cancer has made possible the detection and reliable diagnosis of cancer in most regions of the country.[1] This provides a unique opportunity to study the trends in frequency of different types of cancer over time that may be expected to accompany rapid economic and social transformation.

* Cancer. 1986 Sep 1, 58(5):1172-8

Being a vast country of some 2,240,000 square kilometers with regions of varying climatic, topographic, and cultural backgrounds, the frequency of different types of cancers may vary significantly from one place to another.[2]

This study investigates the geographic and temporal patterns of cancer occurrence in Saudi Arabs. Most previous studies[2-6] have been limited with respect to the geographic area from which the patient population was drawn, time interval covered, or total number of cancer patients seen. The current study draws from 725 1 patients referred from all parts of the country over a 6-year period to King Faisal Specialist Hospital and Research Centre, which is situated in Riyadh, the central region of Saudi Arabia.

MATERIALS AND METHODS

The King Faisal Specialist Hospital and Research Centre, established in Riyadh in 1975, is a national referral hospital and the principal center for cancer therapy in Saudi Arabia. It has been operating a fully computerized cancer registry since April 1982. New patients first seen before this date were entered into the registry retrospectively from medical records. Operating on a PDP 11/70 computer (Digital Equipment Co., Maynard, MA), the cancer registry consists of detailed patient records that include personal background, diagnosis, treatment, and follow-up information.

During the period 1979 to 1984, the years for which complete computerized cancer registration are currently available, 725 1 new patients with histologically confirmed neoplasms were admitted. There were 41 17 males and 3134 females. The vast majority were Saudi nationals coming from virtually every region of the country, though a somewhat disproportionate number arrived from the Central Region *(Table 1)*. The mean age was 44.6 years.

Patients were generally accepted for treatment only after the diagnosis of cancer had been histologically proven. Pathological diagnoses made elsewhere were not considered final until the slides had been reviewed by our pathology staff. Neoplasms were classified by both anatomic site and morphology according to the coding schemes of the International Classification of Diseases (9th Revision).[7] For the purpose of studying geographic variations in the crude relative frequency (CRF) of cancer, the country was divided into seven major geographic regions *(Table1)*. These divisions often correspond to administrative boundaries, but some, such as the line between Regions 2 and 3 are primarily topographic and are intended to provide more even distribution of population among the regions *(Figure 1)*. Less than 0.5% of patients were referred from outside the country. Time trends were estimated by ity, and central nervous system (CNS). The commonest calculating CRF for individual years.

RESULTS

cancers among females were breast cancer, non-Hodghn's lymphomas, cancers of the thy-

Table 1: Different Regions of Saudi Arabia and Their Percentage of Case Referrals

Region	No.	Main cities & areas	% referred cases	Population (100,000)*
Central	1	Riyadh, Qasim, Kharj	36.6	17.13
Western	2	Jeddah	11.8	32.17
Western	3	Makkah, Medina, Taif	19.2	
Eastern	4	Dhahran, Dammam, Al-Khobar, Al-Ahsa, Qatif	11.7	8.59
Northern	5	Tabuk, Hail, Al-Jawf	5.7	6.05
Southern	6	Asir, Jizan, Najran	12.3	8.32
Al-Rub Al-Khali (Empty Quarter)	7		0.2	-
Abroad			0.5	-
Nonsoecified			2.0	-

* Population estimated from 1974 census adjusted for subsequent years by correction for births and deaths per region.

roid, esophagus, cervix, ovary, oral cavity, myeloid leukemia, cancers of the uterus and CNS. Unlike most Western countries, cancers of the The CRF of the most common cancers are given in *Table 2* for males and females. The commonest cancers in males were non-Hodgkin's lymphomas, cancers of the esophagus, lung, liver, stomach, and nasopharynx, Hodgkin's disease, lymphoid leukemia, cancers of the oral cavskin as well as of the colon and rectum were comparatively uncommon *(Tables 2 and 4)*. The overall male to female ratio was 1.3. The largest ma1e:female ratios in non-sex organs were found in cancers of the larynx (7.2), bladder (4.4), liver (4.4), pancreas (3.4), lung (3.3), Hodg-

Figure 1: Map of Saudi Arabia showing the seven geographic regions for the purpose of cancer registration.

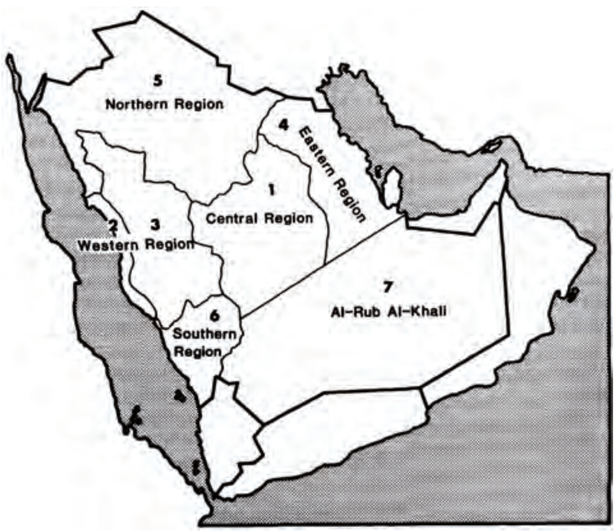

Figure 2: Age and sex distribution of all cancer patients seen at the King Faisal Specialist Hospital between 19791984-.

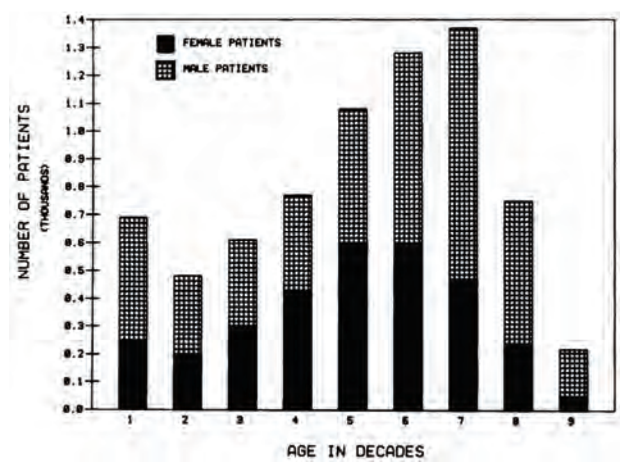

Table 2: Crude Relative Frequency and Rank Order of Most Common Cancers

	Both sexes		Males		Females	
RO	DescriDtion	CRF %	Description	CRF %	Description	CRF %
1	NH lymphoma	10.3	NH lymphoma	12	Breast	17.2
2	Breast	7.6	Esophagus	6	NH lymphoma	1.9
3	Esophagus	5.6	Lung	5.8	Thyroid	5.6
4	Lung	4.3	Liver	5	Esophagus	4.9
5	Oral cavity	4.3	Stomach	4.8	Cervix	4.6
6	Lymphoid leukemia	3.8	Nasopharynx	4.7	Ovary	4.5
7	Stomach	3.8	Hodgkin's	4.6	Oral cavity	4.4
8	Thyroid	3.7	Lymphoid leukemia	4.5	Myeloid leukemia	3.1
9	Nasopharynx	3.6	Oral cavity	4.1	Uterus	3
10	Hodgkins	3.6	CNS	3.9	CNS	2.9
11	Liver	3.5	Skin, non-melanoma	3.8	Lymphoid leukemia	2.9
12	Myeloid leukemia	3.5	Bladder	3.7	Stomach	2.7
13	CNS	3.5	Myeloid leukemia	3.3	Skin, non-melanoma	2.5
14	Skin, non-melanoma	3.2	Bone sarcoma	2.6	Nasopharynx	2.3

RO: relative frequency; CRF: crude relative frequency; NH: non-Hodgkm's; CNS: central nervous system.

kin's dis ease (2.7), cancer ofthe nasopharynx (2.6), skin melanoma (2.4), and cancer of the stomach (2.3). Only thyroid cancer exhibited a markedly low ma1e:female ration of 0.54. The largest number of cancers was seen in the 6th and 7th decades in males and in the 5th and 6th decades in females.

A secondary peak in the first decade of life was seen in both sexes *(Figure 2)*.

Over one third of all cancer patients came from the

Central Region-1 (Nejd). The rest were well distributed among the other populated areas. The CRF of specific types of cancers are compared among these regions in *Table 3*. The most dramatic deviations from national norms were seen in patients referred from the Southern Region-6. For example, the CRF of oral cavity cancer in females (12.9%) was three times the rate in the country as a whole (4.4%), and in males it was twice as high (8.2% versus 4.1%). The CRF of bladder cancer in this region was roughly double that of the rest of the country (6.0% versus 3.7% in males, and 2.4% versus 1.1% in females).

On the other hand, lung cancer was much less frequent (1.2% versus 5.8% for males, and 0.6% versus 2.3% for females). Jeddah and the developed coastal strip comprising the Western Region-2 had the highest CRF of lung cancer (9.7% in males) and the lowest CRF of stomach cancer (2.8% in males). This region also had the highest CRF of breast cancer in females (24.3%). The Northern Region-5 had the highest CRF of female thyroid cancer (11.3%), twice the national average (5.6%). CRF of esophageal cancer was the highest in the Central Region-1 (Nejd) 6.5%, in both males (7.5%) and females (5.1%). The lowest CRF of esophageal cancer in males was found in the Eastern Region-4 (4.6%) and the Southern Region-6 (3.8%).

In females, this difference in CRF was not well demonstrated.

Non-Hodgkin's lymphomas and nasopharyngeal carcinomas were common in all regions compared to other countries.[8,9] The number of new cancer cases seen each year has shown a steady rise from 911 to 1979 to 15 11 in 1984 and the male to female ratio has steadily declined from 1.5 to 1.3. The CRF by primary site and year of diagnosis for males and females is given in *Table 4*. During this period the CRF of esophageal carcinoma has steadily declined (from 8.1% to 4.7% in males, and from 6.7% to 5.6% in females). Colorectal cancers appear to be on the rise (from 2.9% to 4.8% in males and from 1.9% to 2.7% in females.) Following the worldwide trend, lung cancer is steadily increasing from 5.2% to 6.5% in males and from

Table 3: Trends of Crude Relative Frequency and Rank Order of Some Cancers by Geographic Region

	Region											
	1		2		3		4		5		6	
	CRF%	RO	CRF%	RO	CRF%	RO	CRF%	RO	CRF%	RO	CRF%	RO
Males												
Oral cavity	2.9	10	4.0	5	4.4	7	4.9	6	2.6	10	8.2	2
Esophagus	7.5	2	6.6	3	7.4	3	4.6	7	6.2	4	3.8	7
Stomach	5.8	3	2.8	10	3.5	10	3.3	11	7.0	3	5.0	3
Lung	4.2	6	9.7	2	7.9	2	7.9	2	4.0	8	1.2	16
Bladder	3.2	9	3.3	8	3.7	9	3.5	10	3.1	9	6.0	4
Females												
Oral cavity	2.7	11	3.0	8	3.6	5	5.4	5	4.4	5	12.9	2
Esophagus	5.1	3	3.8	6	6.2	4	5.4	5	3.8	6	4.0	6
Bladder	0.7	21	0.3	18	1.9	14	0.6	16	0.6	11	2.4	10
Breast	17.6	1	24.3	1	18.1	1	17.0	1	17.0	1	13.5	1
Thyroid	4.9	4	3.9	6	7.2	3	5.7	4	11.3	2	4.9	4
Lung	1.8	15	4.4	4	2.1	10	3.3	9	1.9	9	0.6	15

CRF: crude relative frequency; RO rank order.

Table 4: Trends of Crude Relative Frequency and Rank Order of Some Cancers by Year

	Year											
	1979		1980		1981		1982		1983		I984	
	CRF%	RO	CRF%	RO	CRF%	RO	CRF%	RO	CRF%	RO	CRF%	RO
Males												
Esophagus	8.1	2	7.8	2	6.7	2	4.9	6	6.0	3	4.7	6
Colon	1.3	16	2.1	14	0.5	19	1.5	16	0.8	19	1.8	18
Rectum	I .6	14	1.4	15	2.8	11	1.5	16	1.4	15	3.0	13
Lung	5.2	4	4.6	6	4.7	6	6.4	2	6.4	2	6.5	2
Thyroid	1.4	15	2.1	14	2.8	11	2.2	14	2.6	12	2.4	14
Females												
Esophagus	6.7	2	6.5	3	2.9	9	4.8	5	3.8	6	5.6	4
Colon	0.8	16	0.3	18	1.9	14	1 .0	19	0.8	17	1.2	18
Rectum	1.1	15	3.1	8	2. I	13	1.2	18	2.3	10	1.5	16
Lung	1.9	12	2.3	11	1.3	17	2.0	13	2.9	8	2.8	9
Thyroid	3.3	8	4.9	5	6.5	3	5.8	4	5.7	3	6.5	3
Lung	14.5	1	12.9	1	19.8	1	16.9	1	16.0	1	20.6	1

CRF crude relative frequency; RO: rank order.

1.9 to 2.8% in females. Thyroid malignancies also appear to be rising in both males (from 1.4% to 2.4%) and females (from 3.3% to 6.5%). In women, breast cancer is increasing (from 14.5% to 20.6%). No clear trend is currently discernable in stomach cancer.

DISCUSSION

Since the incidence of specific cancers varies considerably in different age groups, comparison of CRF between countries is likely to be very skewed if these countries have very different population age distributions. Thus, cancers which are more common in childhood will have an exaggerated CRF in young populations. More accurate comparisons can only be made with age standardized data.

With available non age standardized data, comparison with other countries will be limited to cancers whose CRF differs by unmistakably large ratios. Interpretation of data from a single referral hospital has clear limitations. First, the referral procedure itself is a selective process that biases the composition of patients admitted. Second, the number of cancer cases cannot be viewed with reference to a well-defined population base.

Although population incidence (i.e., new cancer cases per year per 100,000 population) is not currently available, a number of significant comparisons can still be made.

The most striking feature is the unusually high CRF of non-Hodgkin's lymphoma, which is the most common type of cancer seen in males and the second most common in females. Overall, 744 cases were confirmed, accounting for 10.3% of all neoplasms. This is over 4 to 6 times the CRF in most other parts of the world [8,9] (over view in *Table 5*). In one series of childhood non-Hodgkm's lymphomas, 79% presented with the unique abdominal form.[10] In adults, gut lymphomas constituted 19.8% of all non-Hodgkin's lymphomas.[11] There was no increase in inci dence of enteric (2%) or parasitic (3%) infections among those patients compared to the general population. In the current survey, non-Hodgkin's lymphomas appear to be very common in all regions of Saudi Arabia. This is consistent with their elevated frequency throughout the Middle East [12-16] suggesting etiologic factors affecting the Middle Eastern populations in general.

The CRF of lymphoid and myeloid leukemias in Saudis is generally 3 to 4 times higher than in other parts of the world (e.g., 3.2 times higher than Denmark, 4.1 times higher than the USA, and 2.8 times higher than Bombay, India).[8-9] The most dramatic CRF ratios are seen in nasopharyngeal carcinoma

Table 5: Crude Relative Frequencies of Non-Hodgkin's Lymphomas in Saudi Arabia and Several Other Countries.

Location and period		Crude relative frequency (%)	Ref.
Saudi Arabia (KFSH)	1979-1984	10.3	-
Saudi Arabia (KFSH)	1975-1978	11.5	2
Saudi Arabia (West)	1974-1977	12.8	4
Saudi Arabia (East)	1950-1961	15.2	3
Lebanon	1953-1960	11.7	11
Iraq (Mosul)	1971-1975	13.5	14
Iran (Fars Prov.)	1963-1968	7.6*	15
PDR Yemen (Aden)	1958-1962	3.8	12
India (Bombay)	1973- 1975	2.3	8
Brazil (Sao Paulo)	1973	1.9	8
USA (est.)	1973- 1977	1.9	9
Denmark	1968- 1976	1.6	8

* Malignancies of lymph nodes, spleen, thymus, and tonsils including metastases of unknown primary.
KFSH: King Faisal Specialist Hospital.

(e.g., 33.3 with respect to Denmark, over 20 with respect to the USA, and 8.0 with respect to Bombay, India). Certain lymphoproliferative malignancies and nasopharyngeal carcinomas may have in common a potential link with Epstein-Barr virus,[17] although its precise etiologic role is neither established nor understood.

The incidence of esophageal carcinoma is markedly more frequent in Saudi Arabia than in Western countries (ie., 6.7 times higher than Denmark and 7.9 times higher than the USA). The average age is 62 years for males and 58 years for females. The M to F ratio is 1.65. This is appreciably lower than in the USA (M:F=2.4), which may suggest an equal exposure of both sexes to an environmental factor. Many patients with cancer of the esophagus reported consumption of very "thermally" hot food, and came from one particular area, Qasim, in the northern part of Region 1.[18] No difference was found in their age or sex distribution compared to the rest of the country. High CRF ratios are also found for cancer of the oral cavity (5.9 with respect to Denmark, 3.6 for USA).

The observed frequency of oral cavity cancer in the Southern region equals the unusually high rate in Bombay, India. The CRF ratio between the Southern region and the USA is 8.5. The chewing of several tobacco-like substances such as shamma and qat, prevalent mainly in the Southern region particularly the Jizan area and neighbouring Yemen, may contribute to the high frequency of oral cancer. [19]

In this study, the frequency of lung cancer is much lower than in Western countries (e.g., CRF ratios of 0.37 with respect to Denmark, 0.39 for USA), most likely reflecting the much lower levels of smoking and industrial air pollution. However, the apparent rise in CRF of lung cancer within the short span of 6 years is both alarming and consistent with increasing smoking habits, particularly among the younger population. Colorectal cancer is markedly less common than in the West (e.g., CRF ratios of 0.23 and 0.30 with respect to Denmark and the USA respectively), for which dietary factors, particularly lower animal fat intake, may play a role. The CRF ratios for slun melanoma and non-melanoma are also very low with respect to Western populations (e.g., 0.37 for Denmark, 0.12 for the USA), but large compared to Bombay, India (CRF ratio 2.3). The low rate of skin cancers (despite bright sunlight) may be attributed to cultural habits of avoiding exposure to solar ultraviolet radiation and the wearing of headdresses (ghutrah, shmakh, and veil).[20] The observed rate of prostatic cancer in men is much lower than in the West (CRF ratio 0.2 1 with respect to Denmark, 0.16 for the USA), but close to the rate in Bombay, India (CRF ratio 0.8 1). The frequencies of breast and uterine cancers are very close to other developed countries. The greater CRF ratio of cervical (4.6) compared to uterine cancer (3) may be mainly due to more referrals of cervical cancer for radiation treatment available in our institution.

Western Region-2, including Jeddah, comprises an area that has historically been economically developed and open to outside influences. The pattern of cancer in this region reflects what is known about the impact of modernization: highest CRF of lung cancer in the country, lowest rate of stomach cancer, and highest rate of breast cancer in women. However, the frequency of colorectal cancer is not elevated compared with the rest of the country.

Consistent with the high level of education and urbanization in Western Region-2, its male to female ratio for cancer referrals is closest to unity. By contrast, the Northern and Southern Regions, being the least exposed to outside influences, exhibit the lowest apparent rates of lung cancer and among the highest rates of stomach cancer. They also have the highest male to female referral ratios in the country.

The differences between the Southern region, and the rest of Saudi Arabia are multifactorial. It is culturally more closely associated with Yemen. As a predominantly mountainous region, it has a generally cooler and less arid climate and has the most intense concentration of traditional agriculture. Within this region, Jizan, in particular, is known to have the highest levels of schistosomiasis infestation in its perennial surface water reservoirs.[21] Schistosomiasis in man is believed to be an etiologic agent in bladder cancer. [22,23] Because this region has the highest CRF of bladder cancer in the country, a causal or increased risk relationship must be considered. The association of elevated frequency of cancer of the oral cavity and the local habit of chewing shamma and gat, is supported by in vitro tests which have demonstrated the potential carcinogenicity of shamma.[24] The apparently low CRF of lung cancer in the Southern region may be associated with the local preference for smoking water pipes rather than unfiltered tobacco. It is conceivable that passing the smoke through water reduces levels of some carcinogenic components.

The trends in pattern of cancer over time are consistent with the consequences of modernization witnessed in virtually every part of the world. The rise in lung cancer is most readily attributable to the increased use of cigarettes in a population that has traditionally shunned smoking. The marked decline in esophageal cancer may be related to both rapidly changing eating habits as well as steadily improving nutrition. The rise in breast cancer follows worldwide trends, although a trend in reproductive habits is not readily discernible. The lack of a clear trend in stomach cancer may reflect a longer time scale of change or a longer lag period for lifestyle factors to become manifested in an altered cancer frequency. Trend interpretations must be accepted with caution, as referral patterns to a national cancer center are likely to change over time as local hospitals gradually acquire more capabilities to diagnose and treat cancer locally. Nevertheless, the fact that so many trends are apparent within a short 6-year span is remarkable testimony to the rapidity of economic development in Saudi Arabia.

CONCLUSION

As expected, Saudi Arabia, being a vast country with regions of varying climatic, topographic, and lifestyle characteristics, has considerable geographic variation in the frequency of different types of cancer. Rapid economic and social development and increasing availability of modern medical facilities all over the country have influenced the trends in frequency of certain types of cancer over time. Comparison with data from other countries has revealed a significantly different pattern of cancer in Saudi Arabia. A more precise comparison of such patterns within Saudi Arabia and with other countries requires the calculation of age standardized rates and the establishment of a population based cancer registry. This would aid in the development of active studies on cancer epidemiology and shed further light on the specific causes of cancer in the country. Such information will make possible the development of more specific programs for cancer prevention which incorporate studies on environmental, dietary, social, genetic, and other factors that may be responsbile for the current and future pattern of cancer in Saudi Arabia.

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PATTERN OF CANCER AT ASIR CENTRAL HOSPITAL, ABHA, SAUDI ARABIA*

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تمت على مدى ثلاث سنوات، ١٩٨٧م-١٩٨٩م معاينة ستمائة وسبع وتسعين حالة سرطان مؤكدة بالفحص النسيجي وذلك في مستشفى عسير المركزي في أبها بالمملكة العربية السعودية. وقد حددت بسبب تواتر السرطان (نسبية وتقريبية) في مواضع مختلفة من الجسم. وكانت أكثر المواضع تواراداً بين الذكور هي الجلد والكبد والنسيج اللمفاوي (أي الأورام اللمفية غير الهدجكينية) والمثانة، الدم (ابياضاضات الدم) والمعدة والقولون والمريء والجهاز العصبي المركزي والموثة. وكان سرطان الجلد أيضاً أكثر الأنواع تواراداً بين الإناث، يليه سرطان الثدي والنسيج اللمفاوي (الأورام الليمفاوية غير الهدجكينية) والدم (ابيضاضات الدم) والدرقية والمعدة والقولون وجوف الفم والمريء وعنق الرحم.

Six hundred ninety-seven histologically confirmed cases of cancer were seen in the three-year period, 1987 to 1989, at Asir Central Hospital in Abha, Saudi Arabia. Percentage (crude relative) frequencies of cancer at various sites were determined. The most common cancer sites among males were skin, liver, lymphoid tissue (i.e., non-Hodgkin's lymphomas), bladder, blood (leukemias), stomach, colon, esophagus, central nervous system, and prostate. Skin cancer was also the most common cancer among females, followed by the breast, lymphoid tissue (non-Hodgkin's lymphomas), blood (leukemias),thyroid, stomach,colon, oral-cavity, esophagus, and cervix.

* Annual of Saudi Medicine 1991 May, 11(3):285-8

There is currently no national cancer registry in Saudi Arabia [1]; therefore, the incidence and mortality statistics for cancer cannot be deter mined accurately. Reports regarding the incidence of cancer originating from the eastern [2], central [3-5], western [6], and Al-Baha [7] region of Saudi Arabia were derived from hospital statistics. No separate figures concerning the pattern of malignancies in the Asir region are currently available. Based on histologically confirmed diagnoses, our study attempts to delineate the pattern of malignancies for the Asir region.

The Asir region *(Figure 1)* has a high population density. About 75% of the inhabitants live in rural areas and are engaged in agriculture, trade, or government work. There is less involvement in fishing and animal husbandry [8]. Asir Central Hospital (ACH), in Abha, is a 576-bed, regional seferral facility for patients of the Asir region. The surgical pathology laboratory of ACH also furnishes routine services to other hospitals located in Khamis Mushait, Bisha, Zahran-al-Janoob, Sarat Abidah, Ahad Rufidah, Rijal Alma, and Muhayl.

MATERIAL AND METHODS

From January 1987 to Decemher 1989 the surgical pathology laboratory at ACH received 18,174 surgical and biopsy specimens. The histopathology reports of the specimens were reviewed and those containing a diagnosis of Inalignancy were collected. Only one pathology report per patient was included in our data, even though multiple specimens may nave been examined. Malignancies were then tabulated according to the organs or affected primary body sites. Uncommon tumors of sites such as lung, bone, nasopharynx, uterus, ovary, testis, salivary glands, adrenals, gallbladder, soft tissue, pancreas, thymus, paraganglia, and maxillary an-

Figure 1: Map of Saudi Arabia, showing the location of the Asir Province.

Table 1: Rank order and percentage frequencies of malignant neoplasms at Asir Central Hospital in 425 males.

Rank order	Siteol malignancy	No. (%)
1	Skin	62(14.6)
2	Liver	47(11.0)
3	Non. Hodgkin's lymphoma	41(9.6)
4	Bladder	40(9.4)
5	Leukemia	38(8.9)
6	Stomach	34(8.0)
7	Colon	20(4.7)
8	Esophagus	16(3.8)
9	Central nervous system	11(2.6)
10	Prostate	10(2.3)
11	Others*	106(24.9)

* This category constitutes uncommon tumors of sites such as the lung, bone, nasophiarynx, testis, salivary glands. adrenals, gallbladder, Soft tissue, pancreas, thymus, paraganglia, and maxillary antrum.

Table 2: Rank order and percentage frequencies of malignant neoplasms at Asir Central Hospital in 272 females.

Rank order	Siteol malignancy	No. (%)
1	Skin	62(14.6)
2	Breast	25(9.2)
3	Non. Hodgkin's lymphoma	23(4.8)
4	Leukemia	20(7.3)
5	Thyroid	17(6.3)
6	Stomach	13(4.8)
7	Colon	13(4.8)
8	Oral	11(4.0)
9	Esophagus	10(3.7)
10	Cervix	10(3.7)
11	Others*	96(35.2)

* See Table 1 for explanation of this category.

trum were designated as "others." The sex and nationality of patients in eatch category were also identified. The nationality for some patients was unknown. To facilitate a comparison of malignancies in each category with previously published data [2-7], percentage (crude relative) frequencies were determined.

During the three-year period, 1987 to 1989, 697