# BREAST CANCER RESEARCHES
## IN SAUDI ARABIA

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# contents

# EDITORIAL

Dear colleagues,

Breast cancer is the most common cancer among Saudi males and females according to the Cancer Incidence report from the National Cancer Registry of the kingdom of Saudi Arabia. Despite the low Cancer Incidence in the Kingdom of Saudi Arabia, because of the high percentage of young population, we must be ready to face the expected increase in cancer burden attributed to growth, aging of population and awareness of our society which will lead to tremendous increase in detecting breast cancer early and hence, significant reduction in mortality. Research promotion in general is one of the important steps in identifying breast cancer epidemiology, causation, the need for breast cancer screening and health care planning.

This publication is one step to promote awareness and education among physicians, nurses and health care providers in the KSA and hence more research in breast cancer. In this occasion, and on behalf of Faculty of Medicine, King Abdulaziz University, I would like to thank Dr. Samia Al-Amoudi – CEO of Sheikh Mohammed Hussien Al-Amoudi Center of Excellence in Breast Cancer, for her great effort at national and international levels, leading the society towards a new era in women's health and especially in breast cancer.

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# ASSESSMENT OF THE QUALITY OF BREAST CANCER CARE: A SINGLE INSTITUTIONAL STUDY FROM SAUDI ARABIA*

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ABSTRACT

Objective: To evaluate the quality of operable breast cancer care in a tertiary care institution.

Design: A retrospective analysis of all breast cancer patients seen in our institution between 1995 and 2000. Data were abstracted from the charts of these patients. Indicators were based on an international consensus conference and other publications.

Setting: A tertiary care health care institution.

Main measures: We evaluated the charts and calculated the percentage for which the internationally accepted quality care indicators were followed during the continuum of care. We also reviewed the histopathological reports to evaluate conformation with the accepted indicators.

Results: Charts of 75 patients (four exclusions, three metastatic, and one male), diagnosed to have breast cancer during the study period were reviewed. Only 28 (37%) patients had triple assessment before a definitive surgical procedure. Pre-operative staging including a CT and bone scan was performed in 58 (77.3%). Among the 50 patients who had definite surgical intervention, the majority had mastectomy (44/50, 88%) whereas axillary dissection was performed in 46 (46/50, 92%). Estrogen and progesterone receptor status was reported in only four (4/50, 8%) and the exact tumor size in 24 (24/50, 48%) of the histopatho-

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logical reports. Adjuvant chemotherapy was used in accordance with the international standards but radiotherapy was under-utilized.

Conclusion: Our study demonstrated that the quality of breast cancer care in this institution was below the accepted international standards. This study may be used to make interventions for improvement of quality in similar institutions all over the kingdom.

Keywords: assessment of care, breast cancer, care quality, health care quality, quality assessment

Defined as 'the degree to which health services for individuals and populations increase the likelihood of the desired outcomes and are consistent with current professional knowledge'; quality of care is a matter of concern both for the care providers and the health care recipients [1–3]. Process quality, which refers to what health care workers do, and how well they do it, both technically as well as interpersonally, is commonly used to assess the quality of care. Particularly the quality of the technical process is measured, which refers to whether the right choices are made in diagnosing and treating the patient and whether care is provided in an effective and skillful manner. Obviously the best process measures are those for which there is evidence from research that a better process leads to an improved outcome [4]. Breast cancer is the most common cancer diagnosed in the world among women. During all phases of continuum of breast cancer care, an association between the process and outcome is supported by extensive scientific literature including many randomized trials, meta-analyses, and international guidelines [5–8]. It therefore provides an excellent opportunity to assess the quality of care among this group of oncological patients. For this reason, even though the age-standardized rate for breast cancer is quite low (4.73/100 000) in the Al-Qassim region of Saudi Arabia [9], we conducted a retrospective study to assess the quality of care offered to these patients at the King Fahd Specialist Hospital and its Prince Faisal Oncology Center.

## PATIENTS AND METHODS

According to the 1999 census, the population of

**Table 1:** Indicators used for the assessment of quality of care in breast cancer patients 1995-2000

| Parameter | Expert target (%) | Reference |
|---|---|---|
| Diagnosis<br>Pre-operative mammography | ~100 | [21] |
| Pre-operative biopsy[1] | >95 | [11] |
| Non-diagnostic fine needle biopsy | <10 | [13] |
| Triple assessment | ~100 | [16,22] |
| Pre-operative staging | >94 | [12] |
| Surgical treatment<br>Breast-conserving treatment | ~50 | [11] |
| Axillary dissection | >90 | [11] |
| Histopathological reporting<br>Tumor size | >99 | [17,18,23,29] |
| Grade | >99 | [19,23] |
| ER/PR status | >99 | [17–19,23] |
| Number of nodes | >99 | [17,18,23] |
| Adjuvant chemotherapy<br>Pre-menopausal | >90 | [11] |
| Post-menopausal | ~50 | [11] |

ER/PR, estrogen receptor/progesterone receptor.

[1]Biopsy could be aspiration cytology, core biopsy, or excisional biopsy.

the Al-Qassim region was 933 146, of which 427 507 were females [10]. The King Fahd Specialist Hospital, run by the Ministry of Health, is the main referral hospital of the region. To streamline the management of cancer patients the Prince Faisal Oncology Center was commissioned within this institution in 1998. The King Fahd Specialist Hospital and its Prince Faisal Oncology Center at Buraidah receive the majority of patients suspected or diagnosed to have malignant disease, from all over Al-Qassim region. The latter also maintains a hospital-based cancer registry for the region. We identified breast cancer patients from our medical record indexing system and the database of Prince Faisal Oncology Center. Data abstracted from the charts of 78 breast cancer patients, seen in our institution between 1995 and 2000, were copied into a blank proforma.

To study the quality of care in this group of patients, indicators proposed by the National Cancer Policy Board [4] and Hillner et al.[11] were used. In addition, standards of practice outlined in various guidelines and reviews were utilized to assess other parameters of breast cancer care *(Table 1)* [8,12–15].

The quality of fine needle aspiration cytology was assessed by dividing our patients into two groups: those whose diagnosis was established by this procedure and others who needed a subsequent core or excision biopsy before a definitive surgical procedure due to non-diagnostic aspiration cytology.

The accuracy of clinical examination, mammography, and fine needle aspiration cytology increases when they are used together; a procedure called triple assessment or triple diagnosis.

When the results of all the components of triple assessment indicate a benign lesion, cancer will be found in less than 0.5% of cases. On the other hand if all three indicate cancer the diagnosis is likely to be confirmed in more than 99% of cases [14,18]. The size of the tumor was abstracted from the pathological, surgical, or clinical record of the patient, whichever was available. When all three were documented pathological size took precedence.

Pre-operative staging was considered complete if the patient had a chest X-ray, liver function tests, abdominal ultrasound, computerized tomography scan, and a bone scan.

Clinical and pathological staging information was additively utilized to identify the stage of disease according to the American Joint Committee for Staging (AJCC) classification [23].

We reviewed the histopathological reports of all the biopsies as well as post-operative specimens of those patients who had a definitive surgical procedure. *Table 1* shows the criteria used to evaluate the quality of histopathological reporting.

**Table 2:** Characteristics of breast cancer patients 1995-2000

| Parameter | No. (%) |
|---|---|
| Age at diagnosis (years) Mean (range) | 46 ± 14.7 (23–100) |
| ≤40 | 32/75 (42.7) |
| 41–50 | 24/75 (32) |
| >51 | 19/75 (25.3) |
| Pre-menopausal | 55/75 (73.3) |
| Post-menopausal | 20/75 (26.7) |
| Symptoms at presentation Lump | 74/75 (98.7) |
| Nipple discharge | 1/75 (1.3) |
| Tumor size distribution[1] T1 (<2 cm) | 3/75 (4) |
| T2 (2–5 cm) | 25/75 (33.3) |
| T3 (>5 cm) | 23/75 (30.7) |
| T4[2] | 17/75 (22.7) |
| Tx (unknown) | 7/75 (9.3) |
| Stage distribution II | 30/75 (40) |
| III | 22/75 (29.3) |
| Unknown | 23/75 (30.7) |

Stage II, T0N1M0, T1N1M0, T2N0M0, T2N1M0, T3N0M0; stage III, any TN2M0, T3N1M0 (N, lymph node involvement; M0, no distant metastasis).
[1]Based on clinical, operative, or final pathological evaluation.
[2]T4, any T with direct extension to chest wall and/or skin.

## RESULTS

During the 5-year period from 1995, 78 female breast cancer patients were seen in our institution. A lone male was excluded. As shown in *Table 2* the mean age at diagnosis of our patients was 46 ± 14.7 years (range 23–110 years). Three of these patients were detected to have metastatic disease at presentation and were excluded from further analysis.

Pre-operative bilateral mammogram was performed in 39 (39/75,52%) and fine needle aspiration cytology in 46 patients (46/75, 61.3%) *(Table 3)*. Only 28 patients (28/75,37.3%) had triple assessment before a definitive surgical procedure.

A core biopsy (27/75, 36%) or excisional biopsy

(24/75,32%), was performed in 51 (51/75, 68%) patients and 22 patients (22/46, 47.8%) had this procedure after a non-diagnostic aspiration biopsy. Exact tumor size, either clinically, peri-operatively, or pathologically, had been documented in 68 patients (68/75, 90.6%). The majority of these patients had large tumors (T3 + T4 = 40/68, 58.8%). Fifty-two of the 58 patients (58/75, 77.3%) who had complete pre-operative staging, had adequate data available for staging according to the AJCC. The majority had advanced stage disease *(Table 2)*.

Fifty (50/75, 66.6%) patients underwent a definitive surgical procedure in our institution, 44 (44/75, 58.7%) had mastectomy and the others (6/75, 8%) had only lumpectomy. The remainder (25/75, 33.3%) either refused surgery here or demanded referral elsewhere. No follow-up records were available for these patients. *Table 3* also shows the indicators as recorded in the histopathological reports of these patients.

Adjuvant hormone therapy was used in 24 pre-menopausal (24/38, 63.2%) and 11 post-menopausal (11/12, 91.6%) patients. Rational use of hormone therapy could not be assessed because estrogen and progesterone receptor status was not available in the majority of these patients. Twenty-five patients (20/38, 52.6% pre-menopausal; 5/12, 41.6% post-menopausal) received adjuvant radiotherapy.

## DISCUSSION

The large number of studies that have been conducted to assess the process of breast cancer care in different settings, makes this extensive literature difficult to summarize. Our study, a single institutional study, assessed the quality of care during a period of time using the data abstracted from the medical records of these patients. Like a recently published series, this study albeit small, confirms the feasibility of assessing the quality of cancer care by abstracting the data from the medical records of patients [3]. Similarly, the American Society of Clinical Oncology-sponsored National Initiative for Cancer Care Quality is currently evaluating the feasibility of getting information from the medical records of patients to assess the quality of care on a large scale [24].

This study highlights some of the unique epidemiological features of breast cancer seen in this region; younger age, large tumor size, and advanced stage at presentation. In contrast to data from the West, where more than half of breast cancer patients are above 50 years of age, the majority of our patients were younger than that *(Table 2)*. This age distribution has been reported previously from this area [25]. Racial difference in stage at presentation and aggressive disease in younger patients have been described in the literature [26,27].

A younger age at presentation may be one of the reasons for the advanced stage of disease seen in our patients. However, lack of awareness regarding breast cancer and delay in seeking medical advice may be additional factors contributing to this late presentation [28].

Ideally, every breast cancer patient should have a bilateral mammogram before the definitive surgical procedure for primary disease [16]. Similarly, triple assessment is an important part of the evaluation of any breast lump [17]. Both mammography and as a result, the triple assessment, were under-utilized in our patients. Among other factors, temporary non-availability of mammography in our institution, at the time of referral of some of these patients, could have contributed to the low rate of pre-operative bilateral mammography seen in our patients.

Although an operator-dependent procedure, the diagnostic value of fine needle aspiration cytology is reported to be ~90% with a false-negative rate ranging between 0.4 and 35% [4,13].
As most of the clinicians would themselves carry out this procedure in this institution, the high rate of non-diagnostic fine needle biopsy seen by us may indicate an initial learning curve.

In order to plan adequate treatment, especially breast-conserving surgery, every breast cancer patient needs evaluation by a team consisting of a surgeon, medical oncologist, radiation oncologist, pathologist, and a radiologist. Non-availability of radiotherapy and barriers to patient follow-up may possibly explain why only a small proportion of patients undergoing surgery in our institution had lumpectomies. Nevertheless, patient preference and physician's choice are two of the other factors that may override the medical criteria and affect the rate of breast-conserving surgery in an institution [29].

In conformity with international standards, all but four patients undergoing definitive surgery here had axillary dissection.

The pathological report is a critical link between pathologist and clinician. Deficits in pathological reports have, therefore, been the target of many quality improvement projects.

In our study the histopathological reporting did not meet the expected international standards. Although a low rate of reporting of estrogen and progesterone receptor status could be due to non-availability of such marker studies until 1999 in our

institution, other aspects of histopathological reporting were also below the acceptable standard *(Table 3)*. The number of incomplete breast cancer pathology reports was recently reduced as reported by Hammond and Flinner [22] from 57/356 (16%) to 2/190 (1.1%) by instituting a template for reporting.

The rate of utilization of adjuvant chemotherapy both in pre-menopausal and post-menopausal patients met the expected target [11]. Because chemotherapy can be made easily available there is a high rate of concordance. Adjuvant radiotherapy is an integral part of the management of breast cancer, particularly in patients with large tumors and many positive nodes [30]. Most of our patients had large primary tumors with axillary lymph node involvement and were, therefore, candidates for local adjuvant radiotherapy. Again, perhaps due to non-availability of radiotherapy on site, it was under-utilized in this patient population.

## CONCLUSION

This small retrospective analysis shows that quality of breast caner care in this institution falls well below the accepted international standards, possibly due to non-availability of some of the facilities on site and the absence of local guidelines. Additionally, a low volume of breast cancer patients in this institution may have contributed. Since the compilation of this report a clinic for fine needle aspiration cytology has been established and local guidelines have been formulated including a template for histopathological reporting. Collaboration with an institution for radiotherapy facilities has been established.

It would be interesting to review the status of practice in future and compare that with the present study.

**Table 3:** Compliance with the guidelines as observed in breast cancer patients 1995-2000

| Parameter | No. having the procedure (%) |
|---|---|
| Diagnosis<br>Pre-operative mammography | 39/75 (52) |
| Pre-operative biopsy<br>Fine needle biopsy | 46/75 (61.3) |
| Core biopsy | 27/75 (36) |
| Excisional biopsy | 24/75 (32) |
| Non-diagnostic fine needle biopsy | 22/46 (47.8) |
| Triple assessment | 28/75 (37.3) |
| Pre-operative staging | 58/75 (77.3) |
| Surgical treatment<br>Breast-conserving surgery | 2/22 (9.1) |
| Axillary dissection | 46/50 (92) |
| Histopathological reporting<br>Tumor size | 24/50 (48) |
| Grade | 36/50 (72) |
| ER/PR status | 4/50 (8) |
| Total number of nodes removed | 39/50 (78) |
| Adjuvant chemotherapy<br>Pre-menopausal | 34/38 (89.5) |
| Post-menopausal (58.3) | 7/12 |

FNAC, fine needle aspiration cytology; ER/PR, estrogen receptor/ progesterone receptor.

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# KNOWLEDGE OF BREAST CANCER AND ITS RISK AND PROTECTIVE FACTORS AMONG WOMEN IN RIYADH*

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ABSTRACT

Background: We conducted this study to assess knowledge of breast cancer and sources of information about breast cancer among women in Riyadh. We also analyzed whether associations existed between demographic variables, knowledge of breast cancer, and the practice of breast self-examination and use of mammography screening.

Methods: Women interested in participating in this community-based descriptive study provided data by completing a pre-tested structured questionnaire.

Results: Of 864 participating women, 84% were Saudi, 45% were married and 67.8% had a university level education. Eighty percent were between the ages of 20 to 50 years. Knowledge of breast self examination (BSE) was high; 82% (95% confidence intervals [CI], 79.2%-84.4%) knew about BSE, while 61% (95% CI: 57.9%-64.5%) knew about mammography, but only 41.2% (95% CI, 37.9%-44.5%) had performed BSE and 18.2% (95%CI, 15.5%-20.8%) had had mammography screening. Knowledge of breast cancer, risk factors and protective factors for breast cancer was moderate. There was a statistically significant association between the demographic characteristics (marital status, educational status and family history of breast cancer) and knowledge and practice of BSE and mammography.

Conclusion: Though it has limitations, this study revealed an imbalance between the knowledge and practice

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of BSE among women. It also showed that there is only moderate knowledge of risk and protective factors for breast cancer and that knowledge and practice of BSE and mammograms vary according to marital and educational status. Hence, frequent community-based awareness programs are needed so that all women can know and practice BSE, which in turn helps to prevent breast cancer.

Breast cancer continues to be a major cause of morbidity and mortality throughout the world. With 1 million new cases in the world each year, breast cancer is the commonest cancer in women, comprising 18% of all female cancers. Of every 1000 women 50 years of age, two will have recently had breast cancer diagnosed and about 15 will have had a diagnosis made before the age of 50 years, giving a prevalence of breast cancer of nearly 2%.[1] The incidence of breast cancer increases up to the age of 80 years, plateaus between the ages of 80 to 85 years, and then declines. However, the measured decline after the age of 85 years is difficult to interpret and may reflect the inadequacy of the epidemiologic data. The prevalence of breast cancer in recent years has prompted women to seek medical advice randomly with minimal breast symptoms, but only a small number of women are aware of the the society, with childbearing extending practically over the entire reproductive period of life. Due to the conservative nature of the society, many females will refrain from seeking medical advice out of shyness until their disease becomes far advanced, particularly in cases of carcinoma of the breast. Often Breast cancer engenders an exceptional level of fear among women, most probably because of its external location on the body, with all of the obvious cosmetic and psychosocial implications, coupled with proper methods of conducting breast self examination (BSE) or are aware of the importance of radiological screening for breast cancer.[2] Breast cancer is known to be the most common malignancy among women internationally and the Kingdom of Saudi Arabia is no exception.[3] Certain social factors and demographic findings contribute to the pattern of disease of the breast encountered in Saudi Arabia.[4] Saudi Arab females tend to marry at a young age, according to the traditional conservative values of they fear the treatment more than the disease itself.[4] the major concern with all types of cancer, namely loss of life. This places an even greater burden upon the healthcare system to convince such patients to undergo screening for not only will earlier disease be more curable, it will more likely be treatable without loss of the breast. Paramount to early detection in an organized screening program is physician examination, at appropriate intervals, coupled with patient self-examination where this is acceptable,[5] and the efforts of the nursing staff in various clinics to encourage females to seek medical help if they feel a breast lump. However, such efforts are more successful among younger females who are using the available facilities, such as the breast clinic and most importantly, mammography.[4] In the United States, factors considered statistically “protective” against breast cancer include early child bearing, multiparity and breastfeeding. All of these factors are commonly present among Saudi women, yet not only do they get breast cancer anyway, but frequently at an age more than a decade younger than their American counterparts.[5]

In the Cancer Incidence Report for Saudi Arabia, published in May 1999, breast cancer accounted for 19.1% of cancers among females whose mean age at diagnosis was 48.3 years. Diagnosis of in situ carcinoma was almost nil, while infiltrating ductal carcinoma was diagnosed in 76.1 %.[6] In a study of 130 women with invasive breast cancer in Saudi Arabia, 82% were under 50 years of age and 16% were under 30 years of age. This suggests that the lower age limit for breast cancer screening, when un-dertaken in Saudi Arabia, should be younger than the European recommendation, which states that breast screening could start at age 40, but the most beneficial age is 50 years and older.[7] El-Harith et al concluded that BRCA1 and BRCA2 mutations are likely to contribute to the pathogenesis of familial breast cancer in female patients from Saudi Arabia.[8] Breast and lung cancer share the second position as leading causes of death from cancer among Saudi females, with each being responsible for 10% of the total deaths from cancer.[3] Delays in diagnosis and management are associated with advancing disease and consequently poorer results with any appropriate treatment.[9] The incidence of breast carcinoma is increasing in the Kingdom. According to the 2001 Tumor Registry Annual Report published by King Faisal Specialist Hospital and Research Center, 348 cases were seen in 2001 compared with 131 cases seen in 1985.[10] The incidence rate of cancer in Saudi Arabia is predicted to continue rising, partly due to rapid changes in lifestyle, the increasing consumption of cigarettes, the high caloric and fatty diet intake observed during the last decade, and partly due to the natural aging of this young Saudi population in the years to come.[11]

For mammography to be useful, it must be available to the population of women at risk. There must

be sufficient numbers of well-trained, experienced mammographers to interpret the films, and there must be methodology available to define and diagnose mammographically detected lesions. Physicians must also emphasize the critical application of screening mammography to the early detection and treatment of breast cancer. Therefore, the care of patients should be enhanced as should the education of those in training in this area. It provides a richer professional environment for all involved in the care of breast cancer patients, and provides a fertile ground for exchange of ideas for research. Ongoing research projects are enhanced by this exchange, and ideas for new projects have been spawned.[5]

Generally, classical medical care for patients with breast and ovarian cancers is easily accessible in most of the major medical centers of Saudi Arabia. The diagnostic facilities available in this country are quite adequate and they include, other than mammography, routine medical examination, fine needle aspiration and other advanced histopathological techniques. However, genetic testing for assessment of predisposing to breast cancer is presently not offered.[3] The spectrum of treatment services offered includes lumpectomy, mastectomy with or without breast reconstitution, chemotherapy and/or radiotherapy.

The greatest advantage to the women of the Kingdom will be the development of more widespread screening and educational programs. Currently, lectures in a major hospital in Riyadh that foster public awareness of breast cancer are given every two months and certified nurses provide workshops on breast-examination.[11] Breast cancer awareness programs (BCAP) are meant to help in the prevention and early detection of breast cancer. This study was carried out with the objectives of (i) assessing the knowledge of breast cancer and its associated factors (risk and protective) among the women of Riyadh city, (ii) assessing the source of knowledge of breast cancer, (iii) observing any association between family history of breast cancer, marital status and educational level of study participants versus their knowledge and practice of breast self examination and mammography.

## MATERIALS AND METHODS

A community-based descriptive study was conducted on a sample of 864 adult women during a health education campaign held in October 2003 in the Ladies Kingdom Mall in Riyadh. Women willing to participate, regardless of their age or educational level were included in the study.

A questionnaire was distributed to participants that asked about sociodemographic factors such as age, nationality, occupation, marital status, and level of education. It also included questions about the changes that occur in relation to breast cancer, risk factors that increase susceptibility, management practices for breast cancer, protective factors against breast cancer and sources of knowledge. The data was analyzed using SPSS-PC statistical software. For descriptive statistics, 95% confidence intervals were used to show the precision of the estimates. The chi-square test was used to test for association.

## RESULTS

The sample consisted of 864 women of different ages, with 80% between the ages of 20 to 50 years. Details of the age structure of participants and other sociodemographic characteristics are shown in *Table 1*. Saudi nationals represented 724 (83.8%), while 129 (14.9%) were non-Saudi. Of the total participants, only 21.5% (95% CI, 18.8-24.2) had a family history of breast cancer.

Breast self examination was known to 697 (81.8%) participants whereas only 518 (61.2%) of the study subjects had knowledge of mammography. All participants had moderate knowledge of the changes that occur in breast cancer, but only 49.5% knew about the size changes, 49% were aware of heaviness under the armpit, 47% knew about touch, 45.4% had knowledge of discharge from the nipple and only 40.9% of the sample knew about the change in the shape of the nipple.

The level of knowledge of risk factors that increase susceptibility and knowledge of protective factors is shown in *Table 2*. The main sources of knowledge were television (59.4%), the internet (26.4%), magazines (55%), books (29.1%), relatives (16.3%), friends (19.2%) and the doctor (24.5%). Some of the participants had more than one source of information. Breast self examination had been performed by 41.2% (95% CI, 37.9-44.5) of the participants and 18.2% (95% CI, 15.5-20.8) had undergone mammography.

The univariate analysis showed that there was a highly statistically significant association between marital status, educational status and family history of breast cancer of the participants and knowledge of BSE, mammography and the practice of BSE and use of mammography. Married women had significantly greater knowledge and practiced BSE and mammography more than single and other women. Women with a university level education had significantly greater knowledge and practice of BSE and

**Table 1:** sociodemographic characteristics of study sample (n=847)

| Characteristics | | |
|---|---|---|
| Age | | |
| Below 20 | 131 | 15.2 |
| 20-24 | 260 | 30.1 |
| 25-29 | 134 | 15.5 |
| 30-34 | 113 | 13.1 |
| 35-39 | 74 | 8.6 |
| 40-44 | 61 | 7.1 |
| 45-49 | 49 | 5.7 |
| 50+ | 30 | 3.5 |
| Unknown | 12 | 1.4 |
| Marital status | | |
| Single | 433 | 50.3 |
| Married | 391 | 45.4 |
| Divorced | 26 | 3.0 |
| Widow | 11 | 1.3 |
| Educational level | | |
| Illiterate | 10 | 1.2 |
| Primary-secondary | 268 | 31.0 |
| University | 586 | 67.8 |
| Occupation* | | |
| Students | 206 | 29.3 |
| Housewifes | 195 | 27.7 |
| Health workers | 71 | 10.1 |
| Educational workers | 115 | 16.3 |
| others | 117 | 16.6 |

*n=704

mammography than the women of other levels of educational status. Women with a family history of breast cancer had significantly greater knowledge and practice of BSE and mammography *Table 3* and *Table 4*.

## DISCUSSION

The etiology of breast cancer is still uncertain and as a result adequate primary prevention is difficult. Hence, early detection remains the first priority for national health promotion programs. These measures include breast self-examination, which is a unique procedure in many ways because it is in-

**Table 2:** participants knowledge about breast cancer and its associated risk and protective factors.

| | count (%) | 95% Confidence intervals |
|---|---|---|
| Knowledge of breast cancer | | |
| Knowledge of BSE (n=852) | 697 (81.8) | 79.2-84.4 |
| Knowledge of mammography (n=847) | 518 (61.2) | 57.9-64.5 |
| Heard of BSE (n=695) | 569 (81.9) | 79.0-84.8 |
| Heard of mammography (n=687) | 434 (63.2) | 59.6-66.8 |
| Changes that occur in relation to breast cancer (n-864): | | |
| Size Changes | 428 (49.5) | 46.2-52.8 |
| Heaviness under armpit | 423 (49) | 45.7-52.3 |
| Touch | 406 (47) | 43.7-50.3 |
| Discharge from nipple | 392 (45.4) | 42.1-48.7 |
| Shape of nipple | 353 (40.9) | 37.6-44.2 |
| Knowledge of risk factors (n=864): | | |
| Contraceptive pills | 261 (30.0) | 27.1-32.9 |
| HRT | 411 (47.6) | 44.3-50.9 |
| Exposure to excess radiation | 410 (47.5) | 44.2-50.8 |
| Smoking | 472 (54.6) | 51.3-57.9 |
| Hereditary | 338 (39.1) | 35.9-42.3 |
| Age | 119 (13.8) | 11.5-16.1 |
| Nutrition | 353 (40.9) | 37.6-44.2 |
| Lack of physical exercise | 137 (15.9) | 13.5-18.3 |
| Irregular cycles | 54 (6.3) | 4.7-7.9 |
| Race | 45 (5.2) | 3.7-6.7 |
| Infertility | 140 (16.2) | 13.7-18.6 |
| Knowledge of protective factors (n=864): | | |
| Breast feeding | 597 (69.1) | 66-72.1 |
| Nutrition | 536 (62.0) | 58.8-65.2 |
| Exercise | 322 (37.3) | 34.1-40.5 |
| Regularity of menstrual cycle | 256 (29.6) | 26.6-32.6 |
| Pregnancy earlier than 40 years | 217 (25.1) | 22.2-28.0 |
| Early marriage | 103 (11.9) | 9.8-14.0 |

**Table 3:** Association between characteristics of sample with their Knowledge and practice of breast self examination.

| Characteristics of sample | Know BSE count (%) | | Practice BSE count (%) | |
|---|---|---|---|---|
| | Yes | No | Yes | No |
| Marital status<br>married | 374 (53.8) | 53 (34.2) | 223 (63.7) | 202 (40.5) |
| Single | 294 (42.3) | 94 (60.6) | 110 (31.4) | 278 (55.7) |
| Others | 27 (3.9) | 8 (5.2) | 17 (4.8) | 19 (3.8) |
| Educational level<br>Primary | 6 (0.9) | 2 (1.4) | 2 (0.6) | 5 (1.0) |
| Intermediate | 29 (4.2) | 7 (4.9) | 12 (3.4) | 34 (6.8) |
| High school | 153 (22.0) | 53 (36.8) | 64 (18.3) | 145 (28.9) |
| University | 474 (68.3) | 77 (53.5) | 254(72.8) | 298 (59.5) |
| Others | 32 (4.6) | 5 (3.5) | 17 (4.9) | 19 (3.8) |
| Family history<br>Yes | 153 (22.5) | 31 (20.3) | 95 (27.7) | 89 (18.2) |
| No | 527 (77.5) | 122 (79.7) | 248 (72.3) | 401 (81.8) |

† Marital status, $\chi^2$= 19.5, P<0.0001; Educational level, $\chi^2$= 25.9, P<0.0001; $\chi^2$= 0.245, P= 0.62

* Marital status, $\chi^2$= 49.3, P<0.0001; Educational level, $\chi^2$= 19.8, P<0.0001;Family history, $\chi^2$= 10.1, P<0.0001

**Table 4:** Association between characteristics of sample with their Knowledge and practice of mammography.

| Characteristics of sample | Know of mammography count (%) † | | Had mammogram count (%) * | |
|---|---|---|---|---|
| | Yes | No | Yes | No |
| Marital status<br>married | 289 (56.0) | 134 (40.8) | 117 (75.9) | 303 (44.7) |
| Single | 203 (39.3) | 183 (55.8) | 26 (16.9) | 352 (52.0) |
| Others | 24 (4.6) | 11 (3.3) | 11 (7.1) | 22 (3.2) |
| Educational level<br>Primary | 4 (0.8) | 2 (0.6) | 2 (1.3) | 6 (0.9) |
| Intermediate | 15 (2.9) | 32 (9.7) | (3.9) | 36 (5.3) |
| High school | 106 (20.6) | 103 (31.2) | 36 (23.5) | 167 (24.5) |
| University | 362 (70.4) | 185 (56.1) | 100(65.3) | 443 (65.1) |
| Others | 27 (5.2) | 8 (2.4) | 9 (5.9) | 28 (4.1) |
| Family history<br>Yes | 136 (26.7) | 49 (15.3) | 44 (29.5) | 137 (20.5) |
| No | 374 (73.3) | 271 (84.7) | 105 (70.5) | 532 (79.5) |

† Marital status, $\chi^2$= 21.9, P<0.0001; Educational level, $\chi^2$= 25.9, P<0.0001; Family history, $\chi^2$= 13.9, P<0.0001

* Marital status, $\chi^2$= 62.9, P<0.0001; Educational level, $\chi^2$= 1.4, P=0.70;Family history, $\chi^2$= 5.28, P=0.02

expensive, non-invasive, involves little time and physical energy, is simple and does not depend on professional help. Knowledge of breast cancer risk factors and protective factors are also very important in the health of women. Regardless of family history, women still need to be “breast aware” and to accurately identify breast symptoms in order to receive treatment as quickly as possible.

In the present study, it was found that knowledge of breast self-examination was high when compared with knowledge of mammography. In contrast, the practice of BSE was low and a high rate for having had a mammogram was observed only in women who had a family history of breast cancer. Maha and Hadi[12] showed that 78% of 300 women had previously performed BSE, but only 42.7% had agreed to a mammography screening. This is in contrast to our finding, where it was found that 41.2% women had performed BSE and only 18.2% had mammography screening. Hadi`s study also rated the level of knowledge of methods to detect breast cancer as low and found that 3.3% of 300 of those who had a positive family history had performed BSE while 6.7% had a mammography screening. In this study, 51.6% of 184 of those who had a positive family history had performed BSE while only 24.3% had a mammography screening. The results imply that even women with a previous family history of breast cancer were not performing BSE and mammography testing.

While we expected that more women who performed BSE would have a previous family history, our results showed the opposite, which might be either the result of lack of knowledge of BSE or poor technique or it may be due to the larger sample of those participants without a previous family history. The marital status of women was useful in acquiring knowledge of BSE and its practice, which leads in knowing about mammogram also to perform mammogram.

It is generally interesting to know how education reflects on the knowledge and practice of BSE and if higher education would make women more aware of the disease. Our results revealed that women who reached a primary-secondary educational level had less knowledge and practiced BSE poorly, while women who had at least a bachelors degree had better knowledge and practice. Knowledge of breast changes that occur when disease develops was below 50% for all the symptoms.

Knowledge of risk factors is the essence of prevention. The results of our study show a low-to-moderate level of knowledge, regardless of the women’s educational status, marital status and their family history of breast cancer. The same pattern was observed in relation to the knowledge and practice of mammography. The sources of knowledge among these women was diverse, coming from more than one resource.

In spite of the limitations encountered while conducting this study, the results suggest that knowledge of breast cancer and its associated factors was not that high, and differed in relation to the character-istics of the women. But there is a need to improve knowledge and practice of women regarding issues related to breast cancer prevention, early detection and intervention through continuous awareness programs. And these educative programs will help in preventing the disease and also help women at higher risk for developing breast cancer.

As the total sample were taken from the Ladies Kingdom Mall, a luxurious mall in the north of Riyadh city and since most of the women are from a high social class, therefore this sample cannot be generalized to the total population of Saudi Arabia. Selection bias is unavoidable in any study comparing women with high educational levels to those of lower educational levels. Highly educated women, particularly those with a family history of breast cancer, are more likely to be referred for early screening mammography and to receive a breast examination, therefore allowing their breast cancers to be diagnosed at an earlier stage than others. As a consequence, breast cancer survival in highly educated women with a previous family history should be improved due to the detection of the breast cancer at an earlier stage of the disease.

## RECOMMENDATIONS

The results have shown that most women are familiar with BSE, but few perform BSE. Even those considered educated were either not aware of how to perform BSE or were simply not doing it. It is therefore of utmost importance to launch educational programs to increase public awareness of the prevalence of breast cancer, its risk factors and the importance of educating woman. Awareness should be enhanced by all available means. Important tools include news media, schools, social gatherings, hospital waiting areas, and distribution of pamphlets. The Ministry Of Health and educational facilities should play a leading role in increasing awareness. Physicians and surgeons need to make people aware of the increasing incidence of breast cancer during routine patient visits. They should use their influence to promote public education. Mobile units should provide services to people

living in remote areas. Health professionals should be required to provide mammography and genetic counseling for those who are at high risk. Pre-marital medical examination and counseling, which has been made mandatory recently in the Kingdom, is a step in the right direction. It is hoped that women will become more aware of their health responsibility. Routine check-ups should be encouraged at the primary health care level.

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# THE KNOWLEDGE OF BREAST CANCER AMONG YOUNG SAUDI FEMALES*

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ABSTRACT

الأهداف: تقييم مستوى المعلومات التي تمتلكها طالبات المدارس السعوديات حول سرطان الثدي.

الطريقة: أُجريت هذه الدراسة الاستفتائية في مستشفى جامعة الملك عبدالعزيز، جدة، المملكة العربية السعودية وذلك خلال الفترة من أبريل إلى يونيو 2009م. شارك في هذه الدراسة 500 طالبة من مختلف المدارس الثانوية بجدة. لقد قمنا بتحديد مواقع المدارس في مختلف أنحاء مدينة جدة باستخدام الخريطة، ومن ثم قمنا بتوزيع الاستفتاء الذي يحتوي على مجموعة من الأسئلة التفصيلية حول سرطان الثدي وذلك بعد أخذ الترخيص من وزارة التربية والتعليم. وقد تدرب مجموعة من المتطوعين على كيفية توزيع أوراق الاستبيان وجمعها، وبعد ذلك تم تحليل نتائج الاستبيان إحصائياً. لقد تم استخدام نتائج الاستفتاء من أجل بناء قاعدة للبرنامج التثقيفي حول هذا المرض.

النتائج: أظهرت نتائج التحليل لما يعادل 337 من أوراق الاستبيان بأن مستوى المعلومات التي تمتلكها طالبات المدارس والجامعات محدودة وغير كافية. إلا أنه تم ملاحظة اهتمام الطالبات وحماسهم نحو معرفة المزيد عن سرطان الثدي وكيفية الوقاية منه.

خاتمة: أشارت الدراسة إلى أن تدني مستوى المعلومات التي يمتلكها الجيل الجديد قد يكون عائقاً أمام برامج الفحص والتشخيص المبكر لسرطان الثدي، ولهذا فنحن بحاجة إلى زيادة الوعي حول هذا المرض وذلك من خلال المحاضرات، والحلقات الدراسية، وورشات العمل، وبرامج التدريب.

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Objectives: To assess the breast cancer knowledge level of Saudi female school students.

Methods: A detailed questionnaire on cancer breast was designed with all the needed information. Using a map of the Jeddah area of Saudi Arabia, schools were identified in each area and permission was sought from the Ministry of Education to distribute the questionnaire to the students. A team of volunteers was instructed on how to distribute and collect the questionnaires. The collected questionnaires were then statistically analyzed. This Pilot study of 500 students was performed in King Abdul-Aziz University Hospital using high schools from the city of Jeddah between April and June 2009. The results were used to build up a base for designing a community educational program.

Results: Analysis of the data from 337 questionnaires from high school and college students showed that the level of knowledge of young females on breast cancer is limited. However, it also indicated that the students are very enthusiastic to learn about cancer breast, and its prevention.

Conclusion: The limited knowledge level of breast cancer in the younger generation might be an obstacle to screening programs and early diagnosis. Awareness programs should be developed including lectures, seminars workshops, and on hands training.

Breast cancer remains the most commonly diagnosed cancer in women, and it is the second leading cause of cancer related death.[1] Worldwide, more than a million women are diagnosed with breast cancer every year.[2] Breast cancer incidence rates vary considerably, and have shown a marked geographical variation, with the highest rates in western countries, and lowest in Asian and African countries.[3] The breast cancer incidence is increasing in most regions; the changes are greatest in areas where rates were previously low.[4] Environmental factors might be the cause for the global variations. It was found that women from Japan that emigrate to the USA ultimately lose the advantage of low risk, and within one to two generations they develop the same risk profile as USA residents.[4] For primary prevention of breast cancer, women need to be adequately informed of risk factors and risk reduction strategies for breast cancer.[5] Low cancer awareness contributes to delay in presentation for cancer symptoms, and may lead to a delay in cancer diagnosis.[6] Breast selfexamination detects new breast cancers in high-risk women undergoing screening mammogram, clinical breast examination, and yearly breast MRI.[7] The aim of this research is to assess the breast cancer knowledge level of Saudi female school students, which will help in designing breast cancer awareness education programs for the younger generations.

## METHODS

This pilot study was carried out at King

Abdulaziz University Hospital, Jeddah, Saudi Arabia between April and June 2009, and the research proposal was approved by the Research Ethical Committee of the institute. A map of Jeddah was used to locate the schools in each area, and permission was sought from the Ministry of Education to distribute the questionnaires to the students. A team of 4 volunteers' and 2 physicians were instructed on how to distribute and collect the questionnaire. Verbal informed consent was taken from all the students prior to participating and completing the questionnaire.

The detailed questionnaire on breast cancer included 9 questions in the first section: name, age, age of menarche, level of education, social status, family history, what is a mammogram, if there are any symptoms of breast disease, and if there any surgical procedures in the breast. The second part of the questionnaire comprised 6 questions on the risk factors of breast cancer, including knowledge of oral contraceptive pills, radiation, smoking, fatty foods, family history of ovarian and colonic cancer. This was followed by 3 questions on self-breast examination, like how and when to carry out a self-examination, and if they would like to receive training on how to carry this out. Finally, there were 5 general questions including relationship of breast-feeding, breast brassiere, if there is any treatment for breast cancer, does it cause death, and should the diagnosis be secret.

The questionnaires were collected and the data were entered and analyzed using the Statistical Package for Social Sciences version 15 (SPSS Inc, Chicago, IL, USA). Percentages of the different variables were calculated, risk factors and knowledge about cancer breast was analyzed, and the results were used to build up a base for designing a community educational program.

## RESULTS

Out of 500 students, only 337 answered. On analysis of 337 questionnaires, 21% were college students, and 79% were high school level, 99% were single and only 1% were married. Age ranged from

12-18 years with a mean of 16.2±1.5, and the age of menarche between 9-16 years with a mean of 12.6±1.2 years. Of the 337 students, 9.8% admitted that they have a family history of breast cancer, 83.9% answered that they have no family history of breast cancer, and 8.3% did not know. On direct questioning on mammograms, only 30% knew what this was, and 70% did not know. Only 18.4% had complaints regarding their breasts, such as mastalgia, pain, lumps, or their breasts were getting bigger, and only 1.8% reported previous surgery, mainly aspiration, or biopsy. *Table 1* summarizes the results of exploring the level of knowledge of certain risk factors, namely, oral contraceptive pills (OCP), radiation, smoking, and fatty food. On direct question regarding carrying out self-breast examination, 61.1% answered yes and 39.9% answered no. Surprisingly approximately 55% answer that it has to be carried out after the monthly period and not before as recommended, and 72.1% of the students were very enthusiastic about receiving a training course to learn how to perform self-breast examination. Only 2% of students reported a family history of ovarian or colonic cancer. *Table 2* summarizes the results of questions regarding knowledge of breast cancer prevention and treatment.

**Table 1:** Results of the questions related to knowledge of breast cancer risk factors.

| Risk factor | Yes | No | Don't Know | Missing** |
|---|---|---|---|---|
| OCP | 32.6 | 26.7 | 39.2 | 1.5 |
| Radiation | 60.8 | 13.6 | 24.0 | 1.5 |
| Smoking | 65.0 | 15.1 | 19.3 | 0.3 |
| Fatty food | 48.4 | 14.2 | 35.6 | 1.8 |

**missing means did not answer, OCP - oral contraceptive pill

**Table 2:** Results of the questions related to knowledge of breast cancer prevention and treatment.

| Variable | Yes | No | Don't Know | Missing** |
|---|---|---|---|---|
| Breast feeding | 68.8 | 6.2 | 22.3 | 2.7 |
| Breast brassiere | 44.2 | 19.9 | 31.5 | 4.5 |
| Any treatment | 77.7 | 2.4 | 16.0 | 3.9 |
| Can cause death | 0.6 | 32.6 | 63.2 | 3.6 |
| Should you talk about breast cancer | 3.0 | 85.5 | 5.6 | 5.9 |

**missing means did not answer.

## DISCUSSION

It seems that the younger Saudi generation has limited information and knowledge of cancer breast, and it is well known that low cancer awareness contributes to delays in presentation of cancer symptoms, and subsequent diagnosis.[6] Approximately 40% of the study population reported a lack of knowledge regarding breast self examination. Although, breast self examination has not been proven to be effective in early detection or in lowering mortality from breast cancer,[7] it is a good way to raise awareness regarding the appropriate age to start screening, namely, periodic clinical breast examination and mammographic screening. Screening mammography is the only modality proven by randomized clinical trials to allow early detection resulting in overall lower mortality.[8] In our study, only 30% of our students knew of the mammogram. It is also known that mammographic screening is effective not only in women aged 50 years or more, but also in those aged less than 50 years.[8] The risk factors for breast cancer are well known, such as female gender, older age, and the older the age the greater the risk of breast cancer, a positive family history of breast cancer, being exposed to large amounts of radiation, such as very frequent spinal x-rays for scoliosis or treatment for Hodgkin's disease at a young age, a personal history of breast or ovarian cancer, being overweight after menopause, or gaining weight as an adult and current or recent use of birth control pills.[9-17] A recent meta-analysis of 54 studies relating OCP use to breast cancer found that women who are currently using combined OCP or have used them in the past 10 years are at a slightly increased risk (relative risk 1.07-1.24) compared with never users.[14]

A similar study carried out by Millat in 2000,[18] concluded that female secondary-school students in Jeddah had very little knowledge of the presentation of breast cancer and its risk factors. Students were also not familiar with breast self-examination. The study indicated the necessity for a health education program on risk factors, early signs, and methods of diagnosis of breast cancer for this group of easily targeted young women.[18]

In conclusion, our results indicate the limited information about cancer breast in the younger generation, which might be an obstacle to screening programs and early diagnosis. However, we also

found that the younger generation was very enthusiastic to learn more about breast cancer. An awareness program has to be developed including lectures, seminars, workshops, and hands on training. To improve the medical knowledge of young women seeking education, this information could be introduced in the basic curriculum in high school.

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# 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.

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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%

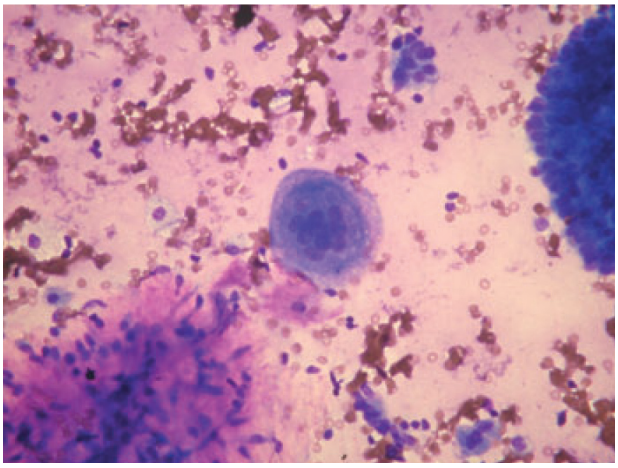

**Figure 1:** A smear from a fibroadenoma showing a multinucleated giant cell with clear cytoplasm lying beside a fragment of fibromyxoid stroma and clusters of ductal epithelial cells. Note the large number of bipolar naked nuclei in the background (May-Grünwald-Giemsa ×400).

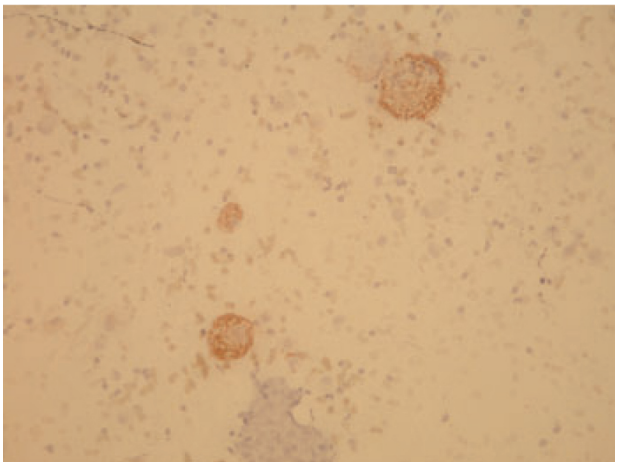

**Figure 2:** Multinucleated giant cells with positive cytoplasmic immunreaction to CD 68 (×200).

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)*.

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.

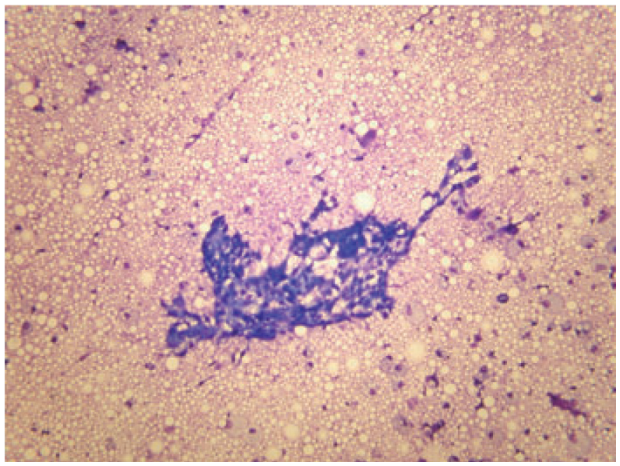

**Figure 3:** A smear from a fibroadenoma with lactational changes. A monolayered sheet of ductal epithelial cells against a lipidaemic background with foamy macrophages (May-Grünwald-Giemsa×200).

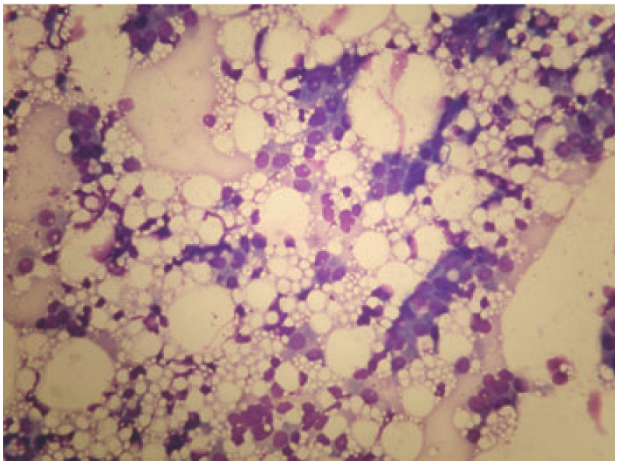

**Figure 4:** Fibroadenoma with markedly dissociated epithelial cells with intact cytoplasm against a lipidaemic background (May-Grünwald-Giemsa ×400).

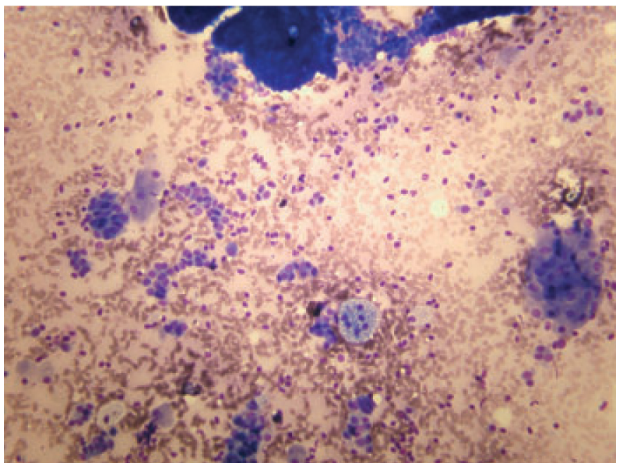

**Figure 5:** Fibroadenoma showing a bland mixture of apocrine cells, ductal epithelial cells, foamy multinucleated giant cells and numerous bipolar naked nuclei (May-Grünwald-Giemsa ×200).

**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 المصَحّحة 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 المصحّحة 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,

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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 ($\alpha$=0.05, 1–$\beta$=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.