

ROUTINE BIOPSY OF SONOGRAPHICALLY BENIGN
BREAST LESIONS GREATER THAN 3CM IS
NECESSARY FOR THE DIAGNOSIS OF
MALIGNANCY IN WOMEN LESS THAN 40 YEARS
OF AGE

Dr Marnie Laura Kemp

A research report submitted to the Faculty of Health Sciences, University of the
Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the
degree of Master of Medicine in Diagnostic Radiology

Johannesburg, 2013

Declaration

I, Dr Marnie Laura Kemp, declare that this research report is my own work. It is being submitted for the degree of MMed (RadD) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

DR ML KEMP

On this 13th day of February 2013.

To my brother John, for paving the way.

Publications and presentations

This work has never been published or presented.

Abstract

Palpable solid breast masses that are circumscribed and not calcified on mammogram or ultrasound are probably benign. There is controversy therefore, whether these deserve tissue diagnosis. More data is required to determine whether short term follow up can replace the need for biopsy.

Benign appearing lesions greater than 3cm in diameter on ultrasound continue to undergo biopsy due to fear that a malignancy or phyllodes tumour might be missed. Published research reflects patients from Europe and North America, and no relevant data from Africa exists.

AIM: This study aims to determine the histological spectrum of sonographically benign lesions greater than 3cm, which were biopsied, in our local population (majority of black patients) and to determine whether biopsy is indicated based on the local cancer risk. The study also aims to characterise the results by age and population group as well as correlate the histological result with the size of the lesion on ultrasound, the HIV status, family history and the seniority of the examining radiologists.

MATERIALS AND METHODS: A retrospective descriptive study of biopsy results of sonographically benign breast masses was undertaken using biopsy procedural recording sheets. .

The size of the lesions (continuous variables) mean with standard deviations was determined. The prevalence of lesions was expressed as a percentage. Other categorical variables were summarized as frequency and percentage. The

histological spectrum of the lesions was determined. The HIV status and family history of the patients as well as the seniority of the reviewing radiologist was assessed. A Kruskal Wallis test and separate logistic regression analysis was used.

RESULTS: A total of 68 patients (below 40 years of age) were included from a total of 13112 patients (of all ages) seen between 2007 and the end of 2010. 73 lesions were identified (65 benign and 8 malignant). The prevalence of benign lesions was 89.7%. The prevalence of malignant lesions was 10.29%. There was little evidence to support lesion size for predicting histology (p value = 0.22) or benignity. There was little evidence that the family history and HIV status were significant.

CONCLUSION: There was a high prevalence (10.29%) of malignancies in lesions classified by ultrasound as benign. The size of the lesion did not correlate with histological subtype or whether the lesion was benign or malignant.

Training of sonographers, standardization of technique for established users and double reading, may produce a different result, as both junior and senior radiologists mistook malignant lesions for benign ones on ultrasound. Repeating this research using double reading after training may demonstrate whether there is a true higher prevalence of malignancy in ultrasonically benign breast lesions in our community. Until then, routine biopsy of these lesions is recommended.

Acknowledgements

To Savvas Andronikou, for helping me to make this happen.

To Su Lucas, for the final polishing and preparation.

The Mammography Unit, Helen Jospeh Hospital especially Ms Naome Modiba.

Table of Contents

Declaration	ii
Publications and presentations.....	iv
Abstract	v
Acknowledgements	vii
Table of Contents.....	viii
List of Figures.....	xi
List of Tables	xii
1. Introduction.....	1
1.1. Sonomammography.....	3
1.1.1 Margins	3
1.1.2 Size	3
1.1.3 Shape.....	3
1.1.4 Density	3
1.1.5 Location.....	4
1.1.6 Multiplicity.....	4
1.2. Sonographically benign lesions	4
1.3. Prevalence of Breast Cancer in Relation to Other Malignancies	6
1.4. Histological Spectrum of Ultrasonographically Benign Lesions	6
1.4.1 Fibroadenomas	7
1.4.2 Phyllodes tumour.....	7
1.4.3 Fibrocystic disease.....	8
1.4.4 Lipomas.....	8

1.4.5 Benign mesenchymal tumours of the breast	8
1.4.6 Diabetic fibrous mastopathy	9
1.4.7 Primary lymphoma	9
1.4.8 Hamartomas.....	10
1.4.9 Special variations of fibroadenomas.....	11
1.5 Aim.....	11
1.6. Study Objectives.....	12
2. Materials and Methods	13
2.1. Inclusion criteria.....	14
2.2. Exclusion criteria.....	14
3. Results	16
3.1. Study population	16
3.2 Histological results.....	16
3. 3 Demographics of the patients with biopsy proven malignancies.....	19
3.4 The seniority of the reviewing radiologists.	20
3.5 Statistics	20
4. Discussion	21
4.1 Demographics of our study population.....	22
4.2 Operator factors.....	25
4.3 Limitations:.....	27
4.4. Future projects.....	27
4.5. The way forward	28
5. Conclusion.....	29
Appendix A: Data collection sheet.....	30

Appendix B: Ethics Clearance Certificate	31
Appendix C: The BIRADS Ultrasound Lexicon.....	32
6. References	34

List of Figures

Fig 1.1 Examples of 4 patients with breast fibroadenomas demonstrating ultrasound features of benignity.	5
--	---

List of Tables

Table 1.1: The BIRADS mammography imaging lexicon	2
Table 3.1: Histological results and their percentages	17
Table 3.2: The distribution of lesions according to patient age.....	18
Table 3.3: The distribution of lesions according to race	19
Table C.1 The BIRADS Ultrasound Lexicon.....	32

1. Introduction

Breast masses are classified as benign or malignant on imaging and reported according to the Breast Imaging Reporting and Data system (BIRADS) (1). This is summarised in Table 1.1. The BIRADS classification has been developed for both ultrasound and mammogram (2). Lesions classified as BIRADS 3 and 4 require 6 month follow up and core biopsy respectively (1) providing histological confirmation and a definitive diagnosis in the latter. For all palpable solid masses that are circumscribed and not calcified, a tissue diagnosis is recommended by some authors even when the features indicate the mass is probably benign.(3) This point is controversial, however, and more data is required to determine whether short term follow up will replace the need for biopsy in these patients (3).

Patients, in our breast-imaging unit, with benign appearing lesions greater than 3cm in diameter on ultrasound, are currently undergoing biopsy due to a growing fear that a malignancy or phyllodes tumour might be missed. A biopsy is a painful, expensive and invasive procedure, which is currently being performed without adequate data on the true prevalence and spectrum of disease in our specific population. To the best of our knowledge, all research on BIRADS lesions have been performed on Western patients from Europe and North America. The aim of this study is to determine the spectrum of disease of sonographically benign lesions greater than 3cm in our local population including a majority of black patients. This is in order to determine whether biopsy is indicated because of a true risk of cancer in patients with sonographically benign lesions or if patients can be followed up over six months as recommended by the BIRADS system.

Table 1.1: The BIRADS mammography imaging lexicon

BIRADS Category	Description
0	Needs additional mammographic / sonographic information and/or prior mammogram for comparison. This should only be used when such a comparison is needed to make the diagnosis
1	Negative. Breasts are normal. Plan : annual follow up
2	Benign finding e.g. typical nodes, calcified fibroadenomas and scattered microcalcifications. Plan : annual follow up
3	Probably benign finding with < 2% chance of malignancy. These include non palpable non calcified circumscribed solid masses, focal asymmetry and a cluster of round / punctuate calcifications. Plan: 6 month follow up.
4	Suspicious abnormality. Plan: biopsy. 4a findings needing intervention, low suspicion of malignancy. 4b: lesions with intermediate suspicion for malignancy. 4c: lesions with moderate concern not classic for malignancy.
5	>95% chance of malignancy including spiculate lesions. Plan: biopsy or excision
6	Known biopsy proven malignancy but patient hasn't yet undergone definitive treatment.

1.1. Sonomammography

Sonomammographically, masses are assessed according the following criteria: (1)

1.1.1 Margins

Indistinct margins indicate tumours that are rapidly growing. This is not limited to malignancy. Microlobulations are more suggestive of malignancy. Margins obscured by surrounding breast tissue are neither a sign of benignity or malignancy. Circumscribed margins, that are well defined, are rare in malignant lesions, only occurring in 2 % of these.

1.1.2 Size

The size of all masses does not correlate with the prevalence of malignancy. However malignant masses larger than 1cm are twice as likely to have spread to the axillary nodes.

1.1.3 Shape

The shape of lesions can be round, oval lobular and irregular. The more irregular the mass, the greater the likelihood of malignancy.

1.1.4 Density

Masses can be very dense, isodense, hypodense or fat-containing. Malignancies are usually very dense for their size, while hypodense or fat-containing masses are usually benign.

1.1.5 Location

1.1.6 Multiplicity

Depending on age, multiple well circumscribed lesions are either benign fibroadenomas (<35years old) or cysts (>35 years old). In older patients, breast metastases should be excluded.

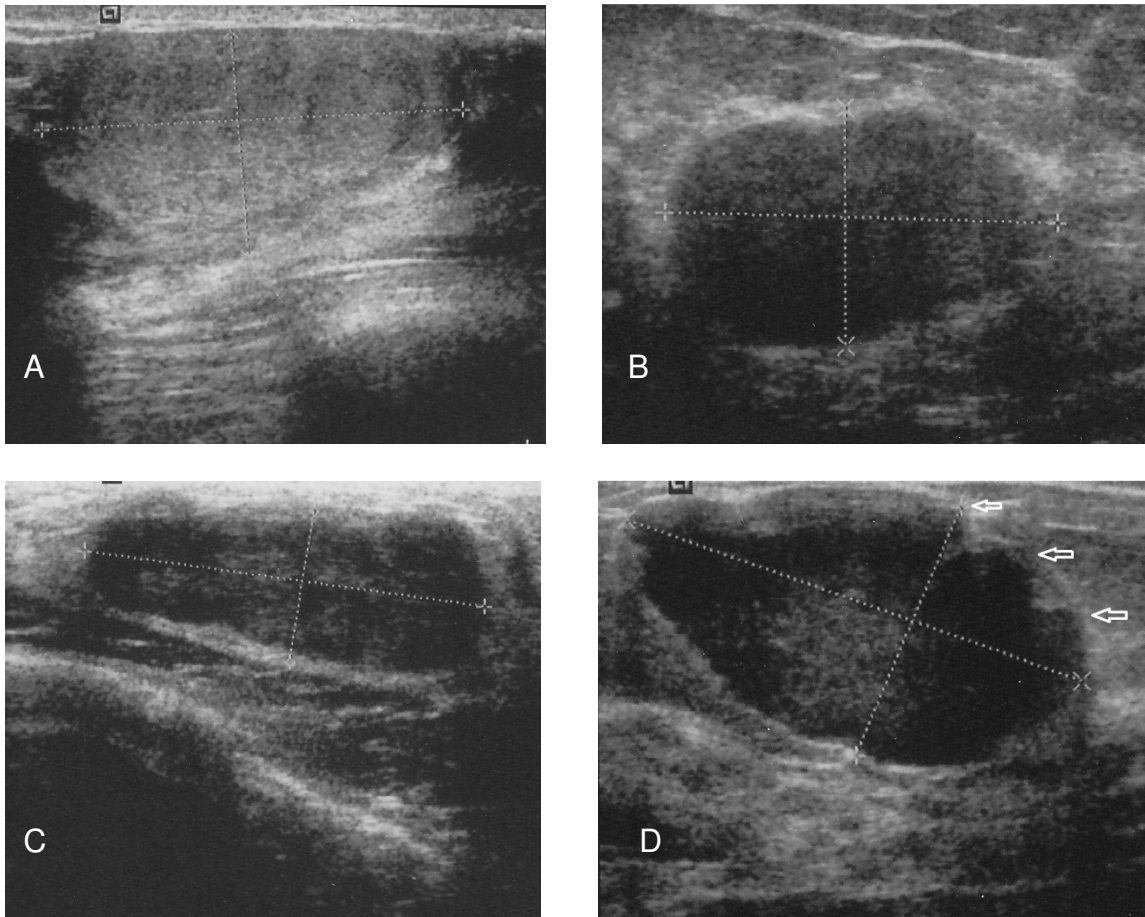
1.2. Sonographically benign lesions

Sonographically benign lesions show features that include the following:

- Well circumscribed oval, round or macrolobulated mass (4)
- Hypoechoic mass (4)
- 3 or less circumscribed lobulations (4)
- Horizontal length greater than vertical length (4)
- Homogeneous hyperechogenicity relative to breast fat (5)

Lesions that fit these criteria would fall into the BIRADS 3 Ultrasound Category as set out in Appendix C.

Some examples of these sonographic features are demonstrated in Figure 1.1.



- A. A well circumscribed mass that demonstrates homogeneous hyperechogenicity relative to breast fat.
- B. A well circumscribed mass that is hypoechoic.
- C. A well circumscribed hypoechoic mass demonstrating that the horizontal length is greater than the vertical length.
- D. A well circumscribed hypoechoic mass demonstrating 3 lobulations (open white arrows).

Fig 1.1 Examples of 4 patients with breast fibroadenomas demonstrating ultrasound features of benignity.

1.3. Prevalence of Breast Cancer in Relation to Other Malignancies

From 1993 to 1995, statistics showed that breast cancer had become the most common cancer in South African women (6). The age standardised incident rate in 2003 was 28.84 per 100 000 (7). The total percentage of breast cancer in 2003 was 20.32% which was the highest percentage of all cancers (7). The percentage of breast cancer was highest in asian (35.51%) and coloured females (24.46%) (7). In white patients, the percentage of breast cancer (20.37%) was secondary only to that of basal cell carcinoma (32.29%) (7). In black patients the percentage of breast cancer (18.09%) was less than that of cervical carcinoma (32.15%) (7).

1.4. Histological Spectrum of Ultrasonographically Benign Lesions

Of all malignant breast tumours, 99% are adenocarcinomas (1). Primary breast cancer in patients less than 25 years of age is exceedingly rare (4). In radiologically benign appearing lesions of the breast, the overall cancer prevalence is similar in palpable (0.3%) and non palpable lesions (1.6%) (8).

Lesions that have a benign appearance on Ultrasound include:

- Fibroadenoma
- Phyllodes tumour (9)
- Fibrocystic disease
- Lipoma (10)
- Benign mesenchymal tumours (focal fibrosis, pseudoangiomatous stromal hyperplasia and desmoid tumours) (11)
- Diabetic fibrous mastopathy (11)
- Lymphoma (12)
- Hamartoma (12)

- Adenomas (tubular adenoma, lactational adenoma, apocrine adenoma, pleiomorphic and ductal adenoma) (12)
- Breast carcinoma (1) (8)
- Metastases

1.4.1 Fibroadenomas

Fibroadenomas are the most frequently occurring benign lesions in patients under 40 years of age (1). They arise from the terminal ductal lobular unit by localised hypertrophy (13). Fibroadenomas occasionally grow into very large masses which are known as giant fibroadenomas (11). Multiple fibroadenomas are present in 15 % of patients (11). The average size is 1.6cm (9). Fibroadenomas typically display sonographically benign characteristics. Occasionally they have irregular borders or heterogeneous internal echoes and in these situations biopsy is needed to distinguish them from malignant lesions (13).

1.4.2 Phyllodes tumour

Phyllodes tumours are rare and account for 0.3 to 1.0 % of all breast neoplasms (14). These typically occur in women between 40 and 50 years of age except in Asian countries where they occur in younger women between the ages of 25 to 30 years (15). The average size is 3.2cm (9) but they can measure up to 5cm at the time of detection (13). They may be malignant and metastasize but are more commonly benign (13). There are no distinguishing features to differentiate malignant and benign phyllodes tumour on imaging (13). Phyllodes tumours are important when considering sonographically benign lesions of the breast as they

are often mistaken for fibroadenomas or circumscribed malignancy on ultrasound (13).

Core biopsies taken in our unit for any sonographically benign lesions measuring more than 3 cm in longest axis are primarily aimed at excluding phyllodes tumour (9).

1.4.3 Fibrocystic disease

Fibrocystic disease is very common, affecting approximately 50% of all women (10). It is due to an exaggerated cyclical proliferation and involution of normal breast tissue (10) resulting in the formation of cysts, fibrosis and adenosis (10).

1.4.4 Lipomas

Lipomas are well circumscribed benign masses that appear in older females (10). They typically present with a palpable soft mass (13). Lipomas never calcify and ultrasound demonstrates a well circumscribed oval or round mass containing fat(13).

1.4.5 Benign mesenchymal tumours of the breast

Benign mesenchymal tumours of the breast include:

- Pseudoangiomatous Stromal Hyperplasia (PASH) (12). When nodular, this tumour may mimic a fibroadenoma (12). It is most commonly seen in young females although nodular PASH accounts only for 0.4% of biopsy results (12) .It is more common in premenopausal women or women receiving hormone replacement therapy (13). Occasionally it grows rapidly prompting

biopsy (13). Because core biopsy can be inconclusive, excisional biopsy is recommended when these lesions are suspected. (13)

- Breast desmoid tumours are rare extra abdominal tumours (1). They are usually in close proximity to the pectoralis muscle and may have spiculated margins mimicking malignancy (1) but they never form microcalcifications (1).

1.4.6 Diabetic fibrous mastopathy

Diabetic fibrous mastopathy often occurs in patients with Type 1 Diabetes Mellitus after 20 years from onset (11). The patients present with firm non tender masses (11) which may be recurrent or bilateral (13). This is due to the accumulation of abnormal matrix proteins from an autoimmune reaction to hyperglycaemia which causes fibrosis in the breast (13). The masses are of a hard consistency making needle biopsy insufficient and often requiring that patients undergo surgical excision biopsy (13). This can lead to exacerbation of the disease with masses redeveloping in the same area (13).

1.4.7 Primary lymphoma

Primary lymphoma of the breast is rare and accounts for only 0.04%–0.5% of all breast neoplasms (16). The diagnostic criteria for primary breast lymphoma include:

- Breast as the primary clinical site of presentation
- Absence of previous lymphoma or widespread disease at time of diagnosis

- Close association of breast tissue with lymphoma in histological specimens
- Involvement of ipsilateral lymph nodes if they develop at the same time as the primary breast lesion (16).

The Wiseman and Liao criteria include only tumours that are:

- Lymphoma limited to the breast – Stage I
- Lymphoma limited to breast and axillary lymph nodes – Stage 2 (16).

Primary breast lymphoma occurs more commonly in the right breast (17).

Secondary involvement of the breast by lymphoma is more common than primary involvement albeit rare (16). This manifests with multiple breast lesions, simultaneous lesions in the breast and other organs and a known history of the disease (17).

On ultrasound primary or secondary lymphomas appear as hypoechoic masses and often the diagnosis of primary breast lymphoma is unsuspected until histological results become available (13). Lymphoma often causes axillary lymphadenopathy which appears on ultrasound as hypoechoic oval masses without a fatty hilum (13).

1.4.8 Hamartomas

Hamartomas are also known as fibroadenolipomas and are rare lesions composed of fat, fibrous and glandular tissue (10). They usually vary from 3 to 5cm in size (1). If they contain mainly fat and glandular tissue they may not be palpable on clinical examination (13). Because hamartomas contain breast elements and ducts, malignancy can develop within them (13). Biopsy should be performed on

any new mass or when suspicious microcalcifications appear within a known hamartoma (13). On ultrasound, hamartomas appear well circumscribed, solid and oval (18). There is no intra-tumoral microcalcification and the internal echotexture is either mixed or hyperechoic (18).

1.4.9 Special variations of fibroadenomas

Special variations of fibroadenomas include the fibroadenoma with lactational adenoma and tubular adenoma (11). Lactational adenomas occur in the second or third trimester and can enlarge rapidly (13). Patients with these lesions often present with palpable firm painless masses that can regress rapidly in size once the patient is post partum (13). Possible aetiologies for lactational adenomas include hormonal changes in a fibroadenoma or tubular adenoma (13). Tubular adenomas are rare and are benign, consisting of tubular structures on histology (1). They appear well circumscribed, elliptic and either hypo or isoechoic (11) which is consistent with a benign ultrasound appearance.

1.5 Aim

This study aims to determine the histological spectrum of sonographically benign lesions greater than 3cm, which were biopsied, in our local population (majority of black patients) and to determine whether biopsy is indicated based on the local cancer risk. The study also aims to characterise the results by age and population group as well as compare the histological result to the size of the lesion on ultrasound, the HIV status, family history and the seniority of the examining radiologists.

1.6. Study Objectives

To:

- determine the prevalence of malignancy in sonographically benign lesions which were biopsied in South African women under 40 years of age
- characterise the results by age and population group
- determine the histological spectrum and prevalence of each lesion
- correlate the histological result with the size of the lesion on ultrasound.
- determine the HIV status and family history of the patients diagnosed with a malignancy in this population.
- determine whether the level of seniority of the reviewing radiologist had an effect on the results.

2. Materials and Methods

This is a retrospective descriptive study of the biopsy results of sonographically benign breast masses at the Helen Joseph Mammography Unit from the beginning of 2007 to the end of 2010. For the detection of malignancy with a reported prevalence of 5 % for a power of 80%, the sample size was calculated (using Statistica 10.0) at 204. However, our sample size was restricted by the database which was estimated according to a previous limited audit to yield between 50 to 80 patients with sonographically benign lesions.

Breast masses are usually diagnosed by the patient or referring health care worker and then sent for mammographic and / or ultrasound assessment depending on patient age. In our unit patients below 35 years of age first undergo an ultrasound examination and then depending on the findings may undergo 2 medial lateral oblique mammograms. For females from 36 to 40 years a baseline mammogram is done. For females from 41 to 45 years of age, annual mammographic screening is performed for 2 years. For patients presenting older than 45 years, a mammogram is performed every 18 months.

Patients with BIRADS 3, 4 and 5 masses on ultrasound and mammogram undergo ultrasound guided core biopsy of the mass as routine practice in our department since 2007 (limiting the study period). Our data was collected from the biopsy procedural recording sheets. The folders of the patients diagnosed with malignancy were used to obtain the HIV status and the family history.

2.1. Inclusion criteria

Female patients less than 40 years old with available breast ultrasound and histological results of a biopsied breast mass were considered for inclusion.

Data was collected on sonographically benign lesions that were defined as:

- Well circumscribed oval, round or macrolobulated mass
- Hypoechoic mass
- 3 or less circumscribed lobulations
- Horizontal length greater than vertical length
- Homogeneous hyperechogenicity compared to breast fat.

2.2. Exclusion criteria

- Unavailable histological results
- Equivocal histological results
- Illegible and incomplete biopsy recording forms

The data was collected using a data collection sheet (Appendix A) and entered into an Excel spread sheet.

The size of the lesion (continuous variables) and means with standard deviations (calculated from the maximum measurable diameter) was determined. The prevalence of the lesions was expressed as a percentage. Other categorical variables were summarised as frequency and percentages.

The Statistica 10.0 software package was used to correlate the size of the lesion to the histology of the lesion using the Kruskal Wallis test as the variables were not normally distributed. A logistic regression analysis test and Pearson goodness of fit test were also used to assess whether there was a correlation between lesion size and whether the lesion was benign or malignant.

3. Results

3.1. Study population

A total of 68 patients were included from a total of 13112 patients seen between 2007 to the end of 2010.

The age ranged from 14 to 40 years with a mean age of 25.9 years.

The cultural background distribution included:

- 62 (91%) black patients,
- 4 (6%) white patients,
- 2 (3%) coloured patients and
- (0%) asian patients

All but one (67 patients, 99%) patients had palpable lesions.

The lesions ranged in size from 3cm to over 20 cm in diameter.

The mean size was 5.2 cm.

Of the 68 patients, 5 had more than one lesion with a total of 73 lesions. One of these 5 patients had breast carcinoma and DCIS (ductal carcinoma in situ) and 4 had bilateral fibroadenomas.

3.2 Histological results

Out of the 73 lesions, 65 were benign and 8 were malignant. Table 3.1, 3.2 and 3.3 summarise the histological spectrum of lesions and lists them according to age and race.

Table 3.1: Histological results and their percentages

Histological diagnosis	Prevalence (Percentage)
Fibroadenoma	44 (60%)
Phyllodes	1 (1%)
PASH	4 (6%)
Diabetic Fibrous mastopathy	1 (1%)
Breast cancer	5 (7%)
Lymphoma	1 (1%)
Hamartoma	2 (3%)
Lipoma	0 (0%)
Lactational adenoma	3 (4%)
Tubular adenoma	1 (1%)
Inflammation	2 (3%)
Fibroadenosis	3 (4%)
Benign proliferative disease	1 (1%)
Malignant spindle cell carcinoma	1 (1%)
Tuberculosis	1 (1%)
Galactocoele	1(1%)
Usual ductal hyperplasia	1 (1%)
Epidermal inclusion cyst	1 (1%)
DCIS	1 (1%)

Table 3.2: The distribution of lesions according to patient age

Age in years	Lesion type (histological)
14	1 Phyllodes
15	1 Fibroadenoma
16	6 Fibroadenomas
17	2 Fibroadenomas
18	4 Fibroadenomas
19	1 PASH 2 Fibroadenomas
20	4 Fibroadenomas
21	1 Galactocoele 6 Fibroadenomas
22	3 Fibroadenomas 1 Benign proliferative breast disease
23	2 Lactational adenomas 1 Fibroadenoma
24	2 Fibroadenomas
25	2 Fibroadenomas 1 Fibroadenosis/fibrocystic disease
26	1 Tubular adenoma 1 Diabetic fibromastopathy
27	1 Lymphoma
28	1 Breast Cancer
29	1 Usual ductal hyperplasia 1 Inflammation
30	2 Fibroadenomas
31	1 Fibroadenosis/fibrocystic disease 1 Tuberculosis 1 Lactational adenoma
32	2 Breast cancer 1 Hamartoma
33	1 Breast cancer 1 DCIS
34	No lesions
35	1 PASH 1 Fibroadenosis/fibrocystic disease 1 Breast cancer
36	1 PASH 1 Fibroadenoma
37	2 Fibroadenomas
38	3 Fibroadenomas 1 Inclusion cyst
39	1 Fibroadenoma
40	1 PASH 1 Malignant spindle cell carcinoma 1 Hamartoma

Table 3.3: The distribution of lesions according to race

Black	43 Fibroadenomas 1 Tubular adenoma 2 PASH 1 Phyllodes 1 Diabetic Fibromastopathy 2 Lactational adenomas 1 Benign proliferative breast disease 5 Breast cancers 2 Fibroadenosis/ Fibrocystic disease 1 Malignant spindle cell carcinoma 1 TB 1 Usual ductal hyperplasia 1 Inflammation 1 Lymphoma 1 Hamartoma 1 Galactocoele 1 DCIS 1 Inclusion cyst
Coloured	1 PASH 1 Lactational adenoma
White	1 Hamartoma 1 Fibroadenoma 1 PASH 1 Fibroadenosis/ Fibrocystic disease
Asian	No lesions.

3. 3 Demographics of the patients with biopsy proven malignancies

Of 8 patients with a biopsy proven malignancy, one folder was lost so the HIV status and family history could not be obtained. Out of the remaining seven, 4 had never had an HIV test. Of the three patients with HIV testing, 2 were HIV positive. Of the 2 HIV positive patients one was proven have Burkitt's lymphoma while the other had DCIS and invasive ductal carcinoma in each breast respectively.

Only one patient diagnosed with breast cancer had a positive family history. The rest all had negative family histories.

The patient with a positive family history was HIV negative. The HIV positive patients had no family history of breast cancer.

3.4 The seniority of the reviewing radiologists.

Four of the malignant lesions were diagnosed as benign by junior radiologists with less than five years of experience and 4 by senior radiologists with more than ten years of experience (including the patient with bilateral DCIS and breast cancer).

3.5 Statistics

The prevalence of benign lesions was 89.7%

The prevalence of malignant lesions was 10.29%

The Kruskal Wallis (KW) test showed there is little evidence of lesion size being useful to predict the histological result (p value = 0.22).

A logistic regression analysis performed independently and separate from the KW test showed that there is very little evidence that lesion size can be used to predict a distinction of a malignant or benign lesion.

The Pearson goodness-of-fit test was used to test the validity of the logistic regression test. The p-value of 0.7111 for the goodness-of-fit test suggests that the model fits reasonably well.

4. Discussion

Although the sample size was small, the range of biopsy results was wide indicating that the population sample was adequate and that there was a good representation of disease. There was a high proportion of malignancy with the prevalence of malignant lesions being 10.29%. This is in contrast to the overall cancer prevalence in the literature of 0.3% for palpable and 1.6% for non-palpable lesions with benign imaging features (8).

This has marked significance as ultrasound features of benignity are accepted as sufficient criteria for ensuring that malignant lesions are excluded. The current literature (3) (8) (19) recommends that short term follow up is a reasonable alternative to biopsy of palpable breast lesions with ultrasonographically benign imaging features. This should be associated with a subsequent malignancy rate of less than 2% (19).

When ultrasound is used, the decision to perform a biopsy in a solid mass is often swayed by whether the mass is palpable or not (19). This is regardless of recognised benign imaging features (19). Some published reports cite benign histology results as high as 100% in palpable lumps with benign mammographic and ultrasound findings (20) (21). The costs of this large number of negative biopsies has impacted on the already challenged health care system of the United States of America (22) as it incurs both psychological and financial costs (19).

Ways to limit unnecessary biopsies include surgical triage, periodic physical examination and mammographic surveillance of probably benign lesions (23).

However, breast biopsy is considered the gold standard for establishing the true nature of a breast lesion identified palpably or radiologically (24). Before the early

1990s the recommended evaluation of a suspicious breast lesion either on clinical examination or mammography involved a surgical breast biopsy (24).

Subsequently less invasive alternatives to open breast biopsy have been evaluated (24). Ultrasound core needle biopsies have been shown to have a high degree of diagnostic accuracy (24). Other advantages include patient convenience, decreased cost and less invasiveness than excisional breast biopsy with comparable accuracy (24). This has reduced the need for surgical intervention and reduced biopsy costs by more than 50 percent (24). The advent of less invasive techniques may have contributed to an increased utilisation of biopsies (24). Ghosh et al, have shown that the overall malignancy rate and the benign – malignant ratio suggests that the introduction of a new diagnostic breast biopsy technique was not associated with unnecessary biopsies (24).

Possible reasons for the high proportion of malignancies in this study include the following:

1. Demographics of our study population
2. Operator factors
 - Errors in obtaining the images
 - Errors in interpreting the images

4.1 Demographics of our study population

Racial predilection:

Breast carcinoma is the most common cancer in South African women (6) at 20.32% of all cancers (7). The percentage of breast cancer is reported to be highest in asian (35.51%) and coloured females (24.46%) (7) followed by white

patients and black patients(18.09%)(7). The incidence per 100 000 people of breast cancer in black South Africans under 40 years of age ranges from 0.223 to 19.237 (7) Our patient population was composed of 91% black patients with only 3% coloured and 6% white patients. In the census of 2010 the total percentage of blacks in South Africa was 79.4% (25). This is lower than the percentage of black patients in our study but this may be due to the small sample size of only 8 malignancies. To the best of our knowledge there is no existing literature exploring the racial influences on the likelihood of malignancy in breast lesions that appear benign on ultrasound. Our prevalence of breast cancer was up to 10% more than reported in the literature and the malignant lesions were exclusively in the black population. Although this may be due to the small sample size, this may in itself suggest a higher prevalence of malignancy in the black population of South Africa than previously thought and must be investigated further for all breast malignancies and not only those with a benign ultrasound appearance. This particular study relating to ultrasound has included a younger population group who undergo ultrasound in preference to mammography and thus may have uncovered a higher prevalence than expected for this particular age group.

Family History:

Most breast cancers are sporadic, developing as a cause of cumulative effects of genetic susceptibility and environmental risk factors (26). Approximately 20% of breast cancers are associated with a clear family history (27).The association between a positive family history, presentation and outcome is uncertain as the results of multiple studies are conflicting (26).One of our patients had a positive family history of breast cancer.

Age:

Several large population based studies have demonstrated that breast cancer in younger women has unfavourable characteristics and a poorer prognosis which is partially due to a lower response rate to systematic adjuvant therapy (28) (29)

HIV Infection:

One of our HIV positive patients was diagnosed with Burkitt's lymphoma. This is a subtype of non-Hodgkins lymphoma that is more prevalent in HIV and is known to be associated with extranodal lymphoma as in our patient (30). Only a few papers have reported an association between HIV and primary breast lymphoma (31) (32) (33). Primary breast lymphomas account for less than 0.7% of all non-Hodgkins lymphomas (31) (34). This is due to the relative paucity of intramammary nodes (31). The majority of AIDS related non-Hodgkins lymphomas demonstrate rapid clinical progression (35).

The second HIV positive patient had DCIS and breast cancer in each respective breast. The patient was 33 years old. The mean age for HIV positive patients presenting with breast cancer is 37 years old (35). Consistent with the findings in our patient, HIV infected patients with breast cancer have an earlier age of presentation and increased bilaterality of disease with a poorer outcome due to early metastatic spread (35) (36) (37). There is also an accelerated aggressive clinical course and early relapse (35). Metastatic spread may involve unusual sites such as the meninges (35) (36). The incidence of breast carcinoma in HIV positive patients is significantly increased in both African (38) and developed countries (35). This statement is controversial as a study done by Amir et al in Tanzania

during the AIDS epidemic demonstrated a statistically significant decrease in the incidence of breast cancer (39). Patel et al also demonstrated that a lower risk of breast cancer was associated with the use of antiretroviral therapy (40). This is once again controversial as other studies have found no association between antiretroviral therapy and a decreased incidence of breast cancer (41) (42)

4.2 Operator factors

Ultrasound, including breast ultrasound is very operator dependant. It is not only dependent on the technique of the operator but also on the operator's interpretation of the images obtained.

In our study there were a total of 8 biopsy proven malignancies of which 4 were diagnosed as benign by junior radiologists with less than 5 years experience. The remaining four were diagnosed as benign by senior radiologists with more than ten years experience. This may or may not indicate faulty technique. Further assessment of this finding such as reviewing of images by other radiologists was not a component of the approved research and remains out of the scope of this study. It should form part of future research. The ultrasound features of benignity in these histologically malignant lesions needs to be evaluated by a panel of experienced radiologists who have acquired a level of standardisation within their practice and this should form part of future research.

Breast Ultrasound lesion characterisation, BIRADS categorisation and management recommendations have only been in use for a short time (19). The Ultrasound lexicon is only in its first edition and guidelines for the management of

ultrasound detected lesions are less widely validated than those used in mammography (19). Raza et al found that interpretation and use of the BIRADS category 3 recommendations vary (19). This is possibly due to the operator dependant nature of ultrasound (19). The recommendations vary perhaps more than that reported for mammography (43).

Raza et al reported that the BIRADS 3 category was correctly used in 86% of cases (19) while in the remaining 14%, the recommendations for biopsy were contradictory and ultimately led to an interventional procedure (19). Training in BIRADS specifically has been shown to improve agreement in final mammogram assessments (44) and may also be a solution for ultrasound.

The ultrasound criteria for benignity are subjective. One objective and repeatable measure that can be easily performed on ultrasound is a lesion size measurement. However we demonstrated a lack of correlation between lesion size and whether the lesion is benign or malignant in keeping with current literature (45).

There is also a lack of correlation between lesion size and the histopathological diagnosis of the breast lesion. To the best of our knowledge, there is limited literature on this topic.

Although double reading by a second radiologist and computer aided detection are widely used in the interpretation of mammograms, there is to the best of our knowledge no available literature discussing breast ultrasound and double reading. Double reading of ultrasound images is not done in our department.

4.3 Limitations:

Limitations of the study include the facts that it was a retrospective review of patient records and that ultrasound which is known to be operator dependant was the imaging modality in our population group. Ultrasound is also a real time form of imaging. Unlike computer tomographic images, the images taken by the attending radiologist could not be accurately reviewed making a retrospective review thereof difficult. A possible solution to this is double or triple reading with an expert panel who would judge the actual images which would be obtained in a systematic manner.

We did not test each consultant and registrar radiologist against the final diagnosis to try and identify if there was an interpretation fault as this was outside the scope of this study.

4.4. Future projects

We plan to introduce the BIRADS Ultrasound Lexicon (46)- see Appendix C- as an image-based wall chart in the examination room to assist operators in using the standardised terminology and to try reduce operator interpretation error. This study could be repeated as a prospective study after the intervention to assess the impact this wall chart will have on the malignancy rate in this group of patients.

We plan to do a study reviewing all the images of the patients of this study to ascertain whether these eight carcinomas might have been incorrectly classified as benign.

4.5. The way forward

The way forward includes repeating the study prospectively and to put a chart of the BIRADS ultrasound lexicon in the radiologists' reviewing room. Ultrasound elastography which is a relatively new technique (47) is the subject of active research in breast imaging (48) and should be included in any future research we perform. Compression elastography may have a role in differentiating benign from malignant breast lesions (48) therefore reducing the biopsy rate. Although there was no correlation between lesion size and whether the lesion was benign or malignant in our study using conventional ultrasound images, elastogram size is one of the most important characteristics in ultrasound elastography (48). Due to the desmoplastic reaction of many malignant breast neoplasms (49), a malignancy will appear larger on the elastogram than on a conventional ultrasound image (48). The converse is true of benign breast lesions (48). Although it is not established for routine clinical use yet, ultrasound elastography is a promising adjunct modality in the conventional ultrasound assessment of focal breast lesions (48).

5. Conclusion

We demonstrated a high prevalence (10.29%) of malignancies in lesions classified by ultrasound as benign.

The only available objective measure – the size of the lesion – did not correlate with histological subtype and whether the lesion is benign or malignant so it cannot be used as a discriminating factor.

Therefore, the use of ultrasound in its current form is not acceptable as a screening tool to separate benign from malignant lesions in our department and possibly our population, because a screening tool must be able to detect all true positive cases even if there is a high false positive detection rate.

Possible solutions include review of training of sonographers in using the BIRADS ultrasound lexicon, standardisation of technique with assistance of established users and possibly double reading for a period. Once this has been done, a repeat of this evaluation will be able to demonstrate whether there is a true higher prevalence of malignancy in our black community who present with breast lesions that have ultrasound features of benignity. Ultrasound elastography, once approved for clinical use, may obviate the need for depending solely on the structural features of benignity during ultrasound of breast lesions. Until then routine biopsies of these lesions is recommended.

Appendix A: Data collection sheet

Patient Code	Age	Population Group				Size	Histological result										
		W	B	C	A		Fibro-adenoma	Carcinoma	Phyllodes	Lipoma	Fibrocystic disease	Benign mesenchymal tumours	Diabetic fibrous mastopathy	Lymphoma	Hamartoma	Special variations	Other

Appendix B: Ethics Clearance Certificate

M110426

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

R14/49 Dr ML Kemp

CLEARANCE CERTIFICATE

M110426

PROJECT

Is Biopsy of Sonographically Benign Lesions
Greater than 3cm in women Under 40 Years of Age
Warranted?

INVESTIGATORS

Dr ML Kemp.

DEPARTMENT

Department of Diagnostic Radiology

DATE CONSIDERED

06/05/2011

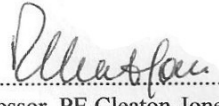
DECISION OF THE COMMITTEE*

Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 06/05/2011

CHAIRPERSON


(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr G Rubin

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix C: The BIRADS Ultrasound Lexicon

The use of the BIRADS system has a threefold aim:

- To standardise the reports
- To facilitate the comparison of follow up examinations from the same or different sources
- To allow a collection of data for treatment on an individual scale and to follow the results of detection on a larger scale

Table C.1 The BIRADS Ultrasound Lexicon

BIRADS Category	Description
0	Incomplete evaluation. Further imaging is required.
1	Negative examination: Normal Ultrasound
2	Benign findings. There is no need to continue examinations and the risk of cancer is negligible This includes simple cysts, typical intramammary nodes, implants and stable or biopsy proven fibroadenomas
3	Probably benign lesions (>98%)- short term follow up is recommended. No change is expected during the interval period. In the case of change during the interval period a biopsy is done. It seems possible to include solid masses with circumscribed margins, an oval or gently lobulated shape and a parallel orientation as the risk for malignancy in these lesions is less than 2%.

4	Suspicious abnormality- a biopsy should be considered. These lesions do not have all the typical imaging features of a malignancy but there is a higher probability thereof (3 to 94%). Therefore histological assessment is necessary. This also includes growth more than 20%.
5	Highly suggestive of a malignancy- an appropriate action is needed. This includes masses that are irregular, have angular or indistinct margins and those that demonstrate posterior acoustic shadowing.
6	Proven malignancy – an appropriate action needs to be undertaken. This is the pre therapeutic assessment of biopsy proven malignancies.

6. References

1. Weissleder R WJ, Harisinghani MG, Chen JW. Primer of Diagnostic Imaging. 4th Edition ed: Mosby Elsevier; 2007.
2. Nothacker M DV, Hahn M, Warm M, Degenhardt F, Madjar H, Weinbrenner S, Albert U. Early detection of breast cancer: benefits and risks of supplemental breast ultrasound in asymptomatic women with mammographically dense breast tissue: a systematic review. *BMC Cancer*. 2009;9:335.
3. Graf O, Helbich TH, Fuchsjaeger MH, Hopf G, Morgun M, Graf C, et al. Follow –up of Palpable Circumscribed Noncalcified Solid Breast Masses at Mammography and US ; Can Biopsy Be Averted? *Radiology* 2004;233:850 – 6.
4. Weinstein SP, Conant EF, Orel SG, Zuckerman JA, Bellah R. Spectrum of US findings in pediatric and adolescent patients with palpable breast masses. *Radiographics*. 2000 Nov-Dec;20(6):1613-21.
5. Stavros AT, Thickman D, Rapp CL, Dennis MA, Parker SH, GA S. Solid breast nodules: use of sonography to distinguish between benign and malignant lesions. *Radiology* 1995;Jul: 196(1):123 – 34.
6. Vorobiof DA, Sitas F, Vorobiof G. Breast cancer incidence in South Africa. *J Clin Oncol*. 2001 Sep 15;19(18 Suppl):125S-7S.
7. The National Cancer Registry, Service TNHL.
http://www.nioh.ac.za/?page=cancer_statistics&id=163.
8. Harvey JA, Nicholson BT, Lorusso AP, Cohen MA, Bovbjerg VE. Short-term follow-up of palpable breast lesions with benign imaging features: evaluation of 375 lesions in 320 women. *AJR Am J Roentgenol*. 2009 Dec;193(6):1723-30.
9. Bode MK RT, Apaja-Sarkkinen M. Ultrasonography and core needle biopsy in the differential diagnosis of fibroadenoma and tumour phyllodes. *Acta Radiol* 2007 September; 48(7): :708 -13.
10. Marsteller LP, Shaw de Paredes E. Well defined masses in the breast. *Radiographics*. 1989 Jan;9(1):13-37.
11. Goel NB, Knight TE, Pandey S, Riddick-Young M, de Paredes ES, Trivedi A. Fibrous lesions of the breast: imaging-pathologic correlation. *Radiographics*. 2005 Nov-Dec;25(6):1547-59.
12. Irshad A, Ackerman SJ, Pope TL, Moses CK, Rumboldt T, Panzegrau B. Rare breast lesions: correlation of imaging and histologic features with WHO classification. *Radiographics*. 2008 Sep-Oct;28(5):1399-414.
13. Ikeda D. Breast Imaging: The Requisites: Elsevier Mosby; 2004.
14. Buchberger W SK, Heim K, Muller E, Schrocksnadel H. Phylloides Tumour: Findings on Mammography, Sonography and Aspiration Cytology in 10 cases. *AJR Am J Roentgenol*. 1991 157:715 – 9.
15. Chua CL, Thomas A, Ng BK. Cystosarcoma Phyllodes - Asian Variations. *Australian and New Zealand Journal of Surgery*. 1998;58(4):301 - 5.
16. Yi JI, Chae BJ, Bae JS, Kang BJ, Lee A, Song BJ, et al. Bilateral primary breast lymphoma. *Chin Med J (Engl)*. 2010 Jun;123(11):1482-4.
17. Yang WT, Lane DL, Le-Petross HT, Abruzzo LV, Macapinlac HA. Breast lymphoma: imaging findings of 32 tumors in 27 patients. *Radiology*. 2007 Dec;245(3):692-702.

18. Chao TC, Chao HH, Chen MF. Sonographic features of breast hamartomas. *J Ultrasound Med*. 2007 Apr;26(4):447-52; quiz 53.
19. Raza S, Chikarmane SA, Neilsen SS, Zorn LM, Birdwell RL. BI-RADS 3, 4, and 5 lesions: value of US in management--follow-up and outcome. *Radiology*. 2008 Sep;248(3):773-81.
20. Graf O, Helbich TH, Fuchsjaeger MH, Hopf G, Morgun M, Graf C, et al. Follow-up of palpable circumscribed noncalcified solid breast masses at mammography and US: can biopsy be averted? *Radiology*. 2004 Dec;233(3):850-6.
21. Mainiero MB, Goldkamp A, Lazarus E, Livingston L, Koelliker SL, Schepps B, et al. Characterization of breast masses with sonography: can biopsy of some solid masses be deferred? *J Ultrasound Med*. 2005 Feb;24(2):161-7.
22. Lindfors KK, Rosenquist CJ. Needle core biopsy guided with mammography: a study of cost-effectiveness. *Radiology*. 1994 Jan;190(1):217-22.
23. Dennis MA, Parker SH, Klaus AJ, Stavros AT, Kaske TI, Clark SB. Breast biopsy avoidance: the value of normal mammograms and normal sonograms in the setting of a palpable lump. *Radiology*. 2001 Apr;219(1):186-91.
24. Ghosh K, Melton LJ, 3rd, Suman VJ, Grant CS, Sterioff S, Brandt KR, et al. Breast biopsy utilization: a population-based study. *Arch Intern Med*. 2005 Jul 25;165(14):1593-8.
25. Statistics, South, Africa. Statistical release PO302 Mid-year population estimates 2010. <http://www.statssa.gov.za/publications/P0302/P03022010pdf>. 2010.
26. Cao AY, He M, Di GH, Wu J, Lu JS, Liu GY, et al. Influence of a family history of breast and/or ovarian cancer on breast cancer outcomes. *Exp Ther Med*. 2011 Sep;2(5):917-23.
27. Easton DF. Familial risks of breast cancer. *Breast Cancer Res*. 2002;4(5):179-81.
28. Anders CK, Hsu DS, Broadwater G, Acharya CR, Foekens JA, Zhang Y, et al. Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. *J Clin Oncol*. 2008 Jul 10;26(20):3324-30.
29. Livi L, Meattini I, Saieva C, Borghesi S, Scotti V, Petrucci A, et al. The impact of young age on breast cancer outcome. *Eur J Surg Oncol*. 2010 Jun 5.
30. Vaishnav K, Shah S, Pandhi S, Rath Y. Multifocal bilateral breast masses in HIV-positive status. *Indian J Cancer*. 2011 Apr-Jun;48(2):253-5.
31. Akinwande OK, Paley R. Primary breast lymphoma: a consideration in an HIV patient when a mass is discovered by screening mammography: a case report. *Cases J*. 2008;1(1):387.
32. Chanan-Khan A, Holkova B, Goldenberg AS, Pavlick A, Demopoulos R, Takeshita K. Non-Hodgkin's lymphoma presenting as a breast mass in patients with HIV infection: a report of three cases. *Leuk Lymphoma*. 2005 Aug;46(8):1189-93.
33. Georgountzos V, Ioannidou-Mouzaka L, Soldatos T, Apessou D, Karatasiou A, Tsouroulas M, et al. Secondary involvement of breast with non-Hodgkin's lymphoma in a patient with HIV infection -- case report. *Eur J Gynaecol Oncol*. 2008;29(2):196-7.
34. Topalovski M, Crisan D, Mattson JC. Lymphoma of the breast. A clinicopathologic study of primary and secondary cases. *Arch Pathol Lab Med*. 1999 Dec;123(12):1208-18.

35. Pantanowitz L, Connolly JL. Pathology of the breast associated with HIV/AIDS. *Breast J.* 2002 Jul-Aug;8(4):234-43.
36. Mayer AP, Greenberg ML. FNB diagnosis of breast carcinoma associated with HIV infection: a case report and review of HIV associated malignancy. *Pathology.* 1996 Jan;28(1):90-5.
37. Cuvier C, Espie M, Extra JM, Marty M. Breast cancer and HIV infection: two case reports. *Eur J Cancer.* 1997 Mar;33(3):507-8.
38. Patil P, Elem B, Zumla A. Pattern of adult malignancies in Zambia (1980-1989) in light of the human immunodeficiency virus type 1 epidemic. *J Trop Med Hyg.* 1995 Aug;98(4):281-4.
39. Amir H, Kaaya EE, Kwesigabo G, Kiitinya JN. Breast cancer before and during the AIDS epidemic in women and men: a study of Tanzanian Cancer Registry Data 1968 to 1996. *J Natl Med Assoc.* 2000 Jun;92(6):301-5.
40. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. *Ann Intern Med.* 2008 May 20;148(10):728-36.
41. Hessol NA, Pipkin S, Schwarcz S, Cress RD, Bacchetti P, Scheer S. The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS. *Am J Epidemiol.* 2007 May 15;165(10):1143-53.
42. Serraino D, Piselli P, Busnach G, Burra P, Citterio F, Arbustini E, et al. Risk of cancer following immunosuppression in organ transplant recipients and in HIV-positive individuals in southern Europe. *Eur J Cancer.* 2007 Sep;43(14):2117-23.
43. Rosen EL, Baker JA, Soo MS. Malignant lesions initially subjected to short-term mammographic follow-up. *Radiology.* 2002 Apr;223(1):221-8.
44. Bowles EJ, Sickles EA, Miglioretti DL, Carney PA, Elmore JG. Recommendation for short-interval follow-up examinations after a probably benign assessment: is clinical practice consistent with BI-RADS guidance? *AJR Am J Roentgenol.* 2010 Apr;194(4):1152-9.
45. Sickles EA. Nonpalpable, circumscribed, noncalcified solid breast masses: likelihood of malignancy based on lesion size and age of patient. *Radiology.* 1994 Aug;192(2):439-42.
46. Levy L, Suissa M, Chiche JF, Teman G, Martin B. BIRADS ultrasonography. *Eur J Radiol.* 2007 Feb;61(2):202-11.
47. Krouskop TA, Dougherty DR, Vinson FS. A pulsed Doppler ultrasonic system for making noninvasive measurements of the mechanical properties of soft tissue. *J Rehabil Res Dev.* 1987 Spring;24(2):1-8.
48. Ginat DT, Destounis SV, Barr RG, Castaneda B, Strang JG, Rubens DJ. US elastography of breast and prostate lesions. *Radiographics.* 2009 Nov;29(7):2007-16.
49. Insana MF, Pellot-Barakat C, Sridhar M, Lindfors KK. Viscoelastic imaging of breast tumor microenvironment with ultrasound. *J Mammary Gland Biol Neoplasia.* 2004 Oct;9(4):393-404.