Prevalence of breast cancer in patients undergoing microdochectomy for a pathological nipple discharge

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DECLARATION

I, Chiapo Lesetedi, declare that this research project is my own work. It is being submitted for the degree of Master of Medicine in Surgery at the University of the Witwatersrand, Johannesburg, South Africa. It is submitted by submissible paper format. It has not been submitted before for any degree or examination at this or any other University.

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18th July 2016

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Finally, I dedicate this project to my wife Tumisang, for her support and encouragement, and to my son Kago.

ABSTRACT

Introduction

Although a pathological nipple discharge can be associated with breast cancer, most of the causes are benign. The current gold standard for diagnosis is microdochectomy and this means that many women will undergo this invasive procedure for benign causes. Demographic data of patients, clinical characteristics, and preoperative radiological investigations which can select patients at risk of cancer may help to reduce the number of patients operated for benign causes but there is little data to confirm this, especially from sub-Saharan Africa.

Aim

This study aimed to determine the prevalence of cancer in patients who had microdochectomy for pathological nipple discharge in a population in South Africa and evaluate patients' demographics and clinical characteristics as indicators of underlying cancer.

Patients and methods

Clinical, radiological and histological data from 153 patients who underwent a microdochectomy for a pathological nipple discharge at two South African breast clinics was collected.

Results

Invasive or in-situ cancer was found in 12 patients (7.84%) and in all patients, cancer was associated with a bloody nipple discharge. Bloody discharge had a sensitivity of 100% in indicating cancer, specificity of 55.32%, positive predictive value of 16%,

and negative predictive value of 100%. Patients with breast cancer were also more likely to be above 50 years (p=0.04). Preoperative mammogram and ultrasound were poor in detecting cancer (0/12).

Conclusion

In our population, patients with an isolated bloody nipple discharge (no mass) should have microdochectomy done, while many other patients can be managed expectantly with surgery only offered in individualised cases. Thorough clinical examination to determine the true colour and nature of the discharge is vital in the initial assessment of these patients. Preoperative radiology is not helpful in determining the presence of cancer (in an isolated pathological nipple discharge) and microdochectomy still remains the gold standard in diagnosing cancer in these patients.

CHAPTER 1

INTRODUCTION

A nipple discharge is the third most common cause for women presenting with breast complaints (1). This is an important finding because breast cancer can be the cause. From the literature, this incidence is up to 37.0% (2), with those with the highest percentage seen in patients with breast masses. In this group of patients with pathological nipple discharge, the diagnosis of cancer required duct excision in 20% cases. In the largest meta-analysis involving 3110 patients with a nipple discharge, 18.7% had cancer as a cause (1). Nipple discharges can be separated into physiological or pathological. A physiological nipple discharge is often seen following breast manipulation, it is typically bilateral and emanates from multiple ducts. Its causes are mainly benign (3). Other causes of physiological nipple discharge are idiopathic, pituitary adenoma, hypothyroidism, ectopic prolactin production, hypothalmic disorders, and medications (including some antidepressants, antipsychotics, and H2 antagonists).

A pathological nipple discharge is defined by the presence of one or more of the following: spontaneous nipple discharge, bloody nipple discharge and/or nipple discharge associated with a mass or skin changes (4). It is usually unilateral, uni-ductal and often persistent. A detailed patient history and examination can help separate the two types of nipple discharges.

Patients who have cancer as a cause of pathological nipple discharge are a challenge to ensure timeous diagnosis for the treating physician. Most studies have

shown an association between cancer and a bloody nipple discharge (5,6,7), although this is not always the case. Two studies found no association (2,8), but where bloody nipple discharge was not related to cancer, the cancer prevalence was either very small at 2.3% (8), or predicted by a breast mass (2). Old age was also suggested as a predictor (8,9). A study done in Ghana, with a comparable population to our own, showed cancer as a cause in 2.5% of patients with bloody nipple discharge without palpable masses and cancer went up to 31.7% when those with palpable masses were include (10).

The gold standard for diagnosis is a microdochectomy, a surgical procedure under general anaesthetic, that entails making a limited circumareolar incision and raising the areola skin flap. The discharging duct is dissected out and lacrimal probe or methylene blue dye can be used to help locate and follow the duct during dissection (11). Compared to complete sub-areolar tissue excision and mastectomy, which were done in the past to exclude malignancy, microdochectomy is less invasive, and also preserves ducts for future breast feeding in women of reproductive age (11). Furthermore, michrodochectomy remains the bench mark to exclude malignancy in patients with a pathological nipple discharge. In an attempt to avoid unnecessary operative procedures (including a microdochectomy), investigations can be done to help diagnose cancer. These include cytological investigations on the nipple discharge fluid including testing for occult blood, ductography, ductoscopy, as well as preoperative radiology such as ultrasound, mammogram, and magnetic resonance imaging (12,13,14), however few have been shown separately to have high sensitivity for predicting cancer (4,14). Mammogram,ultrasound,magnetic resonance imaging, and ductography had a sensitivity of 37.5%, 25.5%, 100%, 50.0% respectively in diagnosing malignancy (14).

In another study, magnetic resonance imaging had a sensitivity of 86% to 100% in detecting invasive cancer and a sensitivity of 40% to 100% in detecting ductal carcinoma insitu. Magnetic resonance imaging has the advantage of that it is non-invasive, has no radiation, can help differentiate between benign and malignant lesions, and can help with staging once cancer has been confirmed. Its disadvantage is that it is not readily available, it is expensive, and requires special skill in reporting the films. In duct cytology, nipple aspiration and subsequent cytological analysis is done. Ductography entails visualisation of of the affected duct system. Distortion, irregular stenosis, or obstruction of the ducts may indicate the presence of malignancy. Ductoscopy is an endoscopic technique that is used to visualise mammary ducts. It can provide accurate localisation of pathology, allow biopsy of lesions, and also enable ductal lavage for cytological analysis.

In Sub-Saharan Africa the implications of a surgical procedure and hospital admission will affect every domain of a patient's life. They require time off from scarce work, travel back and forth to a hospital capable of the procedure for initial and follow-up visits (which may be more than 100 kilometres away), as well as the high costs associated with an operation. These factors reiterate the importance that each operation should be justifiable or unavoidable. It is vital to find preoperative investigations or clinical parameters that can be associated with cancer in our patients. The purpose of this study was to evaluate the characteristics which may help predict cancer in patients with a pathological nipple discharge and to potentially make recommendations on how to best approach these patients in a resource-limited setting.

CHAPTER 2

METHODS

Patient selection

This was a retrospective records review of female patients undergoing microdochectomy for pathological nipple discharge at two specialist breast care centres in Johannesburg, South Africa, over a five year period. Ethical approval for the study was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) (clearance number M120974).

Data Acquisition

Pre-operative clinical and radiological records were reviewed in addition to patients' final histological reports. Demographic data was captured from hospital records and clinical consultation notes indicated the characteristics of the nipple discharge. The radiological records included imaging results that were carried out or supervised by radiologists with a special interest in breast radiology, as well as noted findings which were discussed in a multidisciplinary team meeting consisting of breast surgeons, pathologists and radiologists. Patients with a known history of breast malignancy, palpable mass, or any other features that suggested malignancy on clinical examination were excluded from the study, as were patients with physiological nipple discharges. At the time of the study, patients with palpable breast masses with or without nipple discharge were investigated by biopsy and treated according to the biopsy findings. Patients with suspicious breast findings on

mammogram (i.e calcifications) had either stereotactic or hook wire guided biopsy and were managed according to the biopsy results. Patients with pathological nipple discharge without any palpable breast masses had microdochectomy done, while those with physiological nipple discharge were followed up and the cause of the discharge treated if identified.

Statistical Analysis

Data was captured into MS Excel and imported into STATISTICA 12 for data analyses. The clinical characteristics of the nipple discharge were separated into categories of bloody (including brown and sero-sanguinous), serous and opaque (including white, yellow and green). Serous nipple discharge consisted of serous and clear discharges. Patients were also split into two groups of age ≤50 years and >50 years and analysed accordingly. Breast cancer is more prevalent in the older age group, especially in postmenopausal women. Fifty years was used as it is the mean age around which menopause starts. The imaging results were transcribed from free-text reports and, for the purpose of analysis, separated into groups based on the most common findings of retro-areolar abnormality (such as filling defects in the retroareolar area and lesion/papilloma in the retroareolar region), dilated ducts only and no significant abnormality. Histology was reported categorically as either *Cancer*, *Benign papilloma*, *Duct ectasia*, or *Other*: *Cancer* included premalignant lesions and invasive cancer; *Duct ectasia* included duct ectasia, ductal hyperplasia, duct ectasia and apocrine metaplasia; *Benign papilloma* consisted of benign papilloma, papillomatosis, and ductal papillomas; and, *Other* included non-specific pathology, fibrocystic change, inflammation, and tuberculosis. The relationship

between each nipple discharge and imaging category and their risk of cancer was analysed statistically.

CHAPTER 3

RESULTS

A total of 153 women underwent microdochectomy during the study period at any of the two study centres. The ages of the patients ranged between 20 and 80 years with a mean (±SD) age of 51.4 (13.5) years of which 45% (n=69) were aged less than or equal to 50.0 years. The patient demographics, clinical characteristics and radiology findings (mammogram and ultrasound) are shown according to histology in Table 1. The most common histopathological finding was benign papilloma in 87 patients (56.9%). Cancer was found in 12 women (7.8%), of which five patients had invasive cancer (3.3% of total cohort) and the remaining seven cancer patients had ductal carcinoma in-situ (4.6% of total cohort). Moreover, in the five patients with invasive cancers, three patients had ductal carcinoma, one patient had intra-cystic papillary carcinoma and the remaining patient had a tubular carcinoma. As could be expected, the cancer patients (n=12) were significantly older than those without cancer (n=141) with mean ages of 59.3 years and 50.7 years, respectively (P=0.04). However, of the 12 cancer patients, three patients were in the age category ≤50 years and no association was found between these age categories and prevalence of cancer. However, when we increased the cut-off in the age category to ≤55 years, a significant difference was found (Table 1).

When investigating the nipple discharge colour in this study population, a bloody nipple discharge was reported in 49% of patients, a serous nipple discharge in another 49% and opaque nipple discharge in the remaining 2%. Notably, women with a bloody nipple discharge were significantly older than those with a serous

nipple discharge (54.1 and 48.8 years, respectively; P=0.02). All cancer patients in this study reported a bloody nipple discharge, while the majority of patients with benign papilloma (n=47, 54.0%), duct ectasia (n=14, 50%) or other histological findings (n=14, 53.8%) reported a serous nipple discharge (Table 1). When compared to a serous nipple discharge alone, a bloody nipple discharge was significantly associated with having cancer in our study population (P=0.001).

Mammographic and ultrasound (US) imaging results were available for all patients in this study population. The most common mammographic finding was no abnormality for all of the histology groups. Specifically in the cancer group, half of patients had a no abnormality (n=6), 33.3% showed retro-areolar abnormalities (n=4) and the remaining 16.7% (n=2) showed dilated ducts. Furthermore, one cancer patient had a normal ultrasound, whereas 50.0% showed dilated ducts and the remaining 41.7% showed a retro-areolar abnormality with ultrasound. Only three cancer patients (25%) had retro-areolar abnormalities in both mammogram and ultrasound findings. There was no significant relationship between cancer diagnosis and any radiological imaging results. The sensitivity of mammographic imaging in identifying pathology was 32% compared to 63.4% for ultrasound imaging. Ultrasound imaging of the 87 patients with benign papilloma showed retro-areolar abnormality in 30 patients (34.5%). In the 28 patients with ducts ectasia, ultrasound imaging showed dilated ducts in 16 patients (57.1%).

CHAPTER 4

DISCUSSION

In this study of women treated in two South African hospitals with a pathological nipple discharge undergoing microdochectomy, the incidence of cancer was 7.8%. This falls within the range of up to 37.0% quoted in the literature (2). The study that quoted 37.0% included patients who also had a breast mass (2), which were excluded in this study. In this group of patients with pathological nipple discharge, the diagnosis of cancer required duct excision in 20% cases. Similar to other studies, benign papilloma was the commonest cause of a pathological nipple discharge in our study population at 56.9% (2,7,15). In this study, patients with breast cancer were older compared to patients in the other pathology groups. This reached significance when the non-cancer pathologies were grouped together.

The association between breast cancer and a bloody nipple discharge is well documented in the literature with the few studies that failed to show this association had either low prevalence of cancer or breast masses present (2,8). In this current study, the presence of a bloody nipple discharge was associated to breast cancer. Notably, where all cancer patients reported a bloody nipple discharge, they made up only 16% of those with a bloody nipple discharge. Furthermore, patients with a bloody nipple discharge were significantly older than those with a serous nipple discharge. A bloody nipple discharge had a sensitivity of 100% for cancer, with a negative predictive value (NPV) of 100% and this combination of a bloody nipple discharge and age as risk factors for cancer in this study would support the notion that, in patients with bloody nipple discharge over the age of 50 years, a

microdochectomy should be performed even though a negative finding can be expected in two-thirds of patients. More evident from our study is the NPV of 100% for cancer if there is no bloody nipple discharge. This finding, which is supported in some studies (7,15), should give the breast clinician confidence to recommend close surveillance of a serous nipple discharge rather than immediate microdochectomy. Moreover, this has an important implication for resource-limited settings with similar patient groups as it would immediately reduce the rate of microdochectomies by 50%.

This study concurs previous findings that pre-operative imaging with mammogram and ultrasound is not helpful in diagnosing cancer in patients with pathological nipple discharge (6,8,16). Sensitivity of a mammogram in elucidating any pathology in this study group was also poor (32%) and this too has been documented in the literature (6,7,16). Ultrasound imaging was more successful than mammography at detecting subtle changes such as retroareolar abnormalities and dilated ducts. It should be noted that our study was limited to patients requiring a microdochectomy for diagnosis, and therefore there may be a bias away from patients with a pathological nipple discharge and obvious lesion that could be percutaneously biopsied. Mammogram and ultrasound imaging do have a role in detecting other pathologies both in the presence of a nipple discharge and in the contralateral one, and for this reason they should always be done in patients with a pathological nipple discharge.

Other preoperative investigative modalities have been studied in the past and have also shown disappointing results. Cytology, ductoscopy and galactography have all shown poor sensitivity for cancer and thus cannot be used to diagnose cancer in pathological nipple discharge patients (17,18,19). Magnetic resonance imaging should be studied more as it has shown promising results in some studies

(13,20,21). Immune clinical studies also have to be studied further to see if they can diagnose cancer and help reduce the number of patients who undergo surgery unnecessarily (1). Immune clinical studies involves the detection of nipple discharge autoantibodies against tumour antigens. Examples of these are CA15-3, CA125 and CEA. Their role in further examination of the nipple discharge fluid is promising and need to be studied further. This study and other studies done before have shown that microdochectomy still remains the gold standard in diagnosing cancer and other pathologies in patients with pathological nipple discharge.

Another important limitation of this study is the retrospective nature, and therefore a reliance on clinical notes of the nipple discharge colour with no uniformity regarding the classification of colour. Whilst it would not be clinical good practice to carry out a prospective study operating on every pathological nipple discharge, the authors stress the importance of good surveillance and follow-up of any patients with a nipple discharge. In a resource-limited setting this is even more important as patients may not wish to come back, and education has a role to play in aiding patients to understand their disease. Determining the role of a microdochectomy for symptom control and comfort in a resource-limited setting is beyond the scope of this paper, but should be considered.

Conclusion

The findings from this study show that microdochectomy remains the gold standard in diagnosing cancer in women with a pathological nipple discharge. The prevalence of malignancy in patients who had microdochectomy for a pathological nipple discharge was 7.8% and benign papilloma was the most common histopathological

finding. Preoperative radiological investigations were inaccurate in diagnosing significant pathology in patients with pathological nipple discharge. However, simple steps can help reduce the burden of operative requirements in these patients. Step one is a good history and clinical examination to determine the age and the true colour or nature of the nipple discharge. Step two is adequate experienced breast imaging (defined to mean breast imaging done by a radiologist with experience in performing and interpreting breast images using different imaging modalities) to reduce the number of patients who remain undiagnosed non-invasively. Step three is microdochectomy of patients with bloody nipple discharge and age above 55 years and selective microdochectomy for those with bloody discharge and aged 55 years and below, with good education and close follow-up of all other women with a nipple discharge.

CHAPTER 5

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Table 1. Patient demographics, clinical characteristics and radiological findings according to histology

Demographic data	Cancer	Benign papilloma	Duct Ectasia	Other	ALL	P-value: Ca vs No Ca
n (% of all)	**12** (7.8%)	**87** (56.9%)	**28** (18.3%)	**26** (17.0%)	**153** (100%)	
*Continuous variable**						
Mean age (years)	59.3 ± 13.3	51.5 ± 12.2	47.9 ± 13.3	51.1 ± 16.7	51.4 ± 13.5	**0.04**
*Categorical variables***						
Age ≤ 50 years	3 (25.0%)	38 (43.7%)	16 (57.1%)	12 (46.2%)	69 (45.1%)	0.1
Age ≤ 55 years	4 (33.3%)	55 (63.2%)	21 (75.0%)	18 (69.2%)	98 (64.1%)	**0.03**
Nipple discharge colour						**0.02**
Bloody	12 (100%)	38 (43.7%)	13 (46.4%)	12 (46.2%)	75 (49.0%)	
Serous	0	47 (54.0%)	14 (50%)	14 (53.8%)	75 (49.0%)	
Opaque	0	2 (2.3%)	1 (3.6%)	0	3 (2.0%)	
Mammogram						0.4
Retro-areolar abnormality	4 (33.3%)	14 (16.1%)	3 (10.7%)	5 (19.2%)	26 (17.0%)	
Normal	6 (50.0%)	61 (70.1%)	19 (67.9%)	18 (69.2%)	104 (68.0%)	
Dilated ducts	2 (16.7%)	12 (13.8%)	6 (21.4%)	3 (11.5%)	23 (15.0%)	
Ultrasound						0.3
Retro-areolar abnormality	5 (41.7%)	30 (34.5%)	3 (10.7%)	6 (23.1%)	42 (27.5%)	
Normal	1 (8.3%)	35 (40.2%)	9 (32.1%)	11 (42.3%)	56 (36.6%)	
Dilated Ducts	6 (50.0%)	22 (25.3%)	16 (57.1%)	9 (34.6%)	53 (34.6%)	

*Value ± SD; **Number of patients *n* (% of group total); Ca: Cancer.

APPENDIX 1: Approved Protocol

Prevalence of breast cancer in patients undergoing microdochectomy for a pathological nipple discharge

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1. Full Title

Prevalence of breast cancer in patients undergoing microdochectomy for a pathological nipple discharge.

2. Introduction

Following only breast pain and breast lumps, nipple discharge is the third most common presentation seen in patients with breast disease presenting to breast surgical units. It also accounts for approximately 5 % of all referrals to breast units (1). About 80% of females will experience at least one episode of nipple discharge during their reproductive years (1). Nipple discharge is defined as the passage of liquid material through the nipple, either spontaneously or with manipulation of breast tissue (1). It is mostly caused by benign conditions, but in a small percentage of patients (10-15 %) the cause is an underlying malignancy (1). This small percentage of patients who can have malignancy as the underlying cause of nipple discharge, pose a challenge to the treating surgeon as neither the clinical predictors of malignancy nor preoperative investigations can reliably distinguish between benign and malignant pathology.

Nipple discharge can be classified into either physiological and benign or pathological and suspicious (2). The colour of the discharge can be of several types: 1) milky, 2) multi-coloured and sticky, 3) purulent, 4) clear and watery, 5) yellow or serous, 6) pink and serosanguinous, or 7) bloody or sanguinous (1). Studies have shown that pathological nipple discharge is characterised by being spontaneous, unilateral, uniductal, persistent, and bloody. In contrast, physiological nipple discharge, which is often a feature following breast manipulation, is typically considered bilateral and emanating from multiple ducts (1-7).

The causes of nipple discharge include carcinoma, fibrocystic lesions, inflammation, duct ectasiae, and papilloma. Such carcinomas include invasive cancers, ductal carcinoma in situ, high risk lesions, lobular carcinoma in situ and atypia (2). Moreover, papilloma is the most common pathological finding in

patients with pathological nipple discharge, accounting for 40% to 70% of cases (4).

While patients with physiological nipple discharge are managed conservatively, those with pathological discharge are best managed with microdochectomy, the latter of which is both diagnostic and therapeutic (3).Patients who present with pathological nipple discharge are evaluated by a thorough history and physical examination, preoperative investigations, and microdochectomy. The patient's history is recorded to include the colour of the discharge, the period of the discharge, previous history of breast disease, medications, and other associated symptoms. The physical examination will focus on a routine breast examination which includes looking at nipple discharge if present at that time, nipple inversion, skin dimpling and changes, breast lumps and axillary lymph nodes. All patients with pathological nipple discharge should have mammography and ultrasonography done. This enables the identification of a lesion responsible for the discharge if present, however it fails to reliably differentiate between benign and malignant lesions. In addition, other breast pathology that is unrelated to the discharge may be identified. With regards to nipple discharge, studies have shown that mammogram and ultrasound sensitivities are low at 60% and 65%, respectively (2,3), and thus their use as screening tools in the assessment of nipple discharge are limited. Furthermore, mammograms have a high negative predictive value and specificity, suggesting that, in the setting of physiological nipple discharge, it can be used to select and follow up patients for whom clinical observation alone is a reasonable management approach.

Other preoperative investigations include cytology, ductography, ductoscopy and immune clinical studies. In duct cytology, nipple aspiration and subsequent cytological analysis is done. The latter has been shown to be a poor indicator of underlying malignancy in nipple discharge (50%sensitivity)(3). It is therefore not widely used as it can miss up to 50% of malignancies.

A ductography is good for visualisation of the affected duct system in patients with pathologic nipple discharge. It can identify intraductal papillomas which are demonstrated by filling defects within the dilated ducts while solitary papillomas are seen in the collecting ducts. Multiple papillomas are seen in branching ducts.

Distortion, narrowing, or obstruction of the ducts may indicate the presence of malignancy (4). The disadvantage of the procedure is that it is painful and is limited in detecting lesions that do not fully obstruct the ductal lumen or in detecting multiple lesions in the same duct. Due to these reasons, it is rarely used in the evaluation of patients with spontaneous nipple discharge.

Ductoscopy is an endoscopic technique that is used to visualise mammary ducts. It has been evolving over the last 15 years and unlike ductography, it can provide accurate localisation of the pathology and also enable ductal lavage for cytological analysis. This increases the cytological yield when compared to simple discharge cytology (can increase by 100 fold) (4). The disadvantage of the technique is that it is not widely used, it is expensive, and has limited expertise.

Microdochectomy remains the gold standard to exclude malignancy in patients with pathological nipple discharge as clinical examination and preoperative studies can only identify patients with pathological discharge but cannot confirm malignancy. In the last 30 years, this conservative approach to patients with pathological nipple discharge has become accepted, as compared to the radical procedures used more than 50 years ago (4). A limited circum-areolar incision is made and the areola skin flap is raised. The discharging duct is dissected out and lacrimal probe or methylene blue dye can be used to help locate and follow the duct during dissection. Compared to complete subareolar tissue excision, microdochectomy is preferred as it is less invasive and also preserves ducts for future breast feeding in women in the reproductive age group.

From the literature it is evident that there is an association between pathological nipple discharge and underlying malignancy, with the incidence of malignancy in these patient groups ranging from 7% to 33% (2). This is a high percentage variation and would lead to microdochectomy being recommended for all patients with pathological nipple discharge to exclude malignancy. Also, it is known that a bloody nipple discharge could be a predictor of breast cancer risk. Clinical examination and preoperative evaluation of patients with pathological nipple discharge cannot reliably distinguish between benign and malignant causes. (1-7)

Published data on the prevalence and causes of pathological nipple discharge from South Africa is lacking. Therefore, the purpose of this study is to determine the prevalence of malignancy in patients who had microdochectomy for a pathological nipple discharge in two hospitals in Johannesburg, South Africa. This will enable us to compare our local population's prevalence to that of other international studies. The study will also determine the common causes of pathological nipple discharge in our local setting and enable the evaluation of the accuracy of preoperative radiological investigations in identifying significant pathology. Furthermore, any trend seen from the radiological investigations with regards to pathological nipple discharge could initiate prospective studies to investigate better tools for future diagnosis.

3. Study objectives

Primary endpoints

- To determine the prevalence of malignancy in patients who had microdochectomy for pathological nipple discharge.

- To determine common causes of pathological nipple discharge in our population setting.

Secondary endpoints

- To evaluate the accuracy of preoperative radiological investigations in the diagnosis of significant pathology in patients with pathological nipple discharge.

4. Methods

This is a retrospective analysis of all patients who had a microdochectomy done for a pathological nipple discharge at Helen Joseph Hospital Breast Unit and Milpark Hospital Breast Unit(Johannesburg, South Africa), over a 5 year period

between June 2007 and June 2012. Helen Joseph Hospital is a Government Hospital that mainly attends to patients without medical aid while Milpark Hospital sees private patients. The operations in both hospitals were done by the same team of surgeons.

Histopathological and preoperative radiological (mammogram and ultrasound) reports will be reviewed. Also patients' demographics will be included in the data collection.

Inclusion criteria

-all female patients who underwent microdochectomy for a pathological nipple discharge during the study period.

-patients who had both mammogram and or ultrasound investigations preoperatively.

Exclusion criteria

-patients with known breast malignancy

Study procedures

Patient data will be collected anonymously from histopathology and radiology records. The data will be analysed and variables recorded from both histology and radiology reports.

Data collection

Data will be collected by the candidate, with assistance from the breast surgeons. The data will include;

-name, age, gender, and medical history of patient

-histopathology reports from microdochectomy procedure

-preoperative mammogram and ultrasound reports

5. Data Analysis

Data collected will be entered into Excel spreadsheet and data analysed in statistica. Results will be presented in tables and graphs expressed as mean ± standard deviation and frequency (n). Where groups are compared, this will use a student t-test or non-parametric test, e.g. Mann-Whitney.

6. Ethics

Ethics application will be submitted to Human Research Ethics Committee of the University of the Witwatersrand in September 2012.

7. Timing

	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr
Literature review										
Preparing protocol										
Protocol assessment										
Ethics application										
Collecting data										
Data analysis										
Writing up thesis										
Submission										

8. Funding

No funding required. Stationary costs will be covered by the Department of Surgery, University of the Witwatersrand.

9. Problems/Challenges

Inability to access all the data required. This will be reviewed and inadequate data might lead to patients being excluded from the study.

10. References

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2.Morrogh M, Park A, Elkin E B, King T A,(2010) Lessons learned from 416 cases of nipple discharge of the breast. *The American Journal of Surgery* (2010) 200, 73-80

3.Dolan R T, Butler J S, Kell M R, Gorey T F, Stokes M A (2010) Nipple discharge and the efficacy of duct cytology in evaluating breast cancer risk. The Surgeon, *Journal of the royal Colleges of Surgeons of Edinburgh and Ireland* 8 (2010) 252-258

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6.Fajdic' J, Gotovac N, Glavic' Z, Hrgovic' Z, Jonat W, schem C (2011). Microdochectomy in the management of pathologic nipple discharge*. Archives of Gynecology and Obstetrics*(2011) 283: 851-854. DOI 10.1007/s00404-010-1481-6

7.Dillon F M, Nazri S R M, Nasir S, McDermott E W, Evoy D, Crotty T B, O'Higgins N, Hill A D K,(2006). The role of major duct excision and microdochectomy in the detection of breast carcinoma.*BMC cancer* 2006, 6:164. DOI:10.1186/1471-2407-6-164.

APPENDIX 2: Data recording sheet

DATA RECORDING SHEET *"Prevalence of breast cancer in patients undergoing microdochectomy for a pathological nipple discharge"*

Patient identification number:_____

Age (years):_____

Symptoms;_____

Nipple discharge side (R/L):_____

-Colour of discharge:_____

Operation: Unilateral/Bilateral;_____

Place of operation;_____

Histology report;

-Invasive cancer:_____

-Ductal carcinoma in situ:_____

-Lobular carcinoma in situ:_____

-Atypia:_____

-Benign papilloma:_____

-Benign duct ectasia:_____

-Benign nonspecific changes:_____

-Others (specify):_____

Breasts Ultrasound report;

-Normal:_____

-Abnormal (Specific findings):_____

Mammogram report;

-Normal:_____

-Abnormal (Specific findings):_____

APPENDIX 3: Ethics clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Chiapo Lesetedi

CLEARANCE CERTIFICATE	**M120974**
PROJECT	Pevalence of Breast Cancer in Patients Undergoing Microdochectomy for a Pathological Nipple Discharge
INVESTIGATORS	Dr Chiapo Lesetedi.
DEPARTMENT	Department of Surgery
DATE CONSIDERED	28/09/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 28/09/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Sarah Rayne

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...