Occupations and breast cancer in women treated at a tertiary hospital in Johannesburg.

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DECLARATION

I, Odette Natasha Abrahams, declare that this research report is my own work. It is being submitted a requirements for the degree of Master of Medicine in the branch of Community Health (Occupational Medicine). It has not been used, either wholly or partially, for any other degree or examination at this or any other university.

Signed:  Date: 17/11/2014

DEDICATION

This research report is dedicated to my Lord and Saviour who helped me maintain my sanity through this difficult process. This is also for my two boys; one big and one almost big boy; you are my inspiration and my joy.

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ABSTRACT

Introduction

This is the first study in South Africa to look for an association between breast cancer and occupations in black women. Breast cancer is one of the commonest forms of malignancy experienced by women in South Africa and its incidence is increasing (1). Approximately six million women work in South Africa, some of these women are likely to be exposed to carcinogenic agents during their daily working lives. Many occupational carcinogens to the breast have been described and there is some evidence suggesting that many more synthetic chemicals used in different industries may also have carcinogenic properties that have not fully been explored as yet (2).

This study plans to identify occupations that place black women at risk of breast cancer in the South African context. Thereafter, it will assess if there is an association between shift work (a known carcinogen to the breast) and breast cancer in black women in South Africa.

The findings of the study could be of particular significance to the local context, given that women are entering the workforce in increasing numbers possibly putting more women at risk.

Aims

The aims of the study are to identify occupations that possibly increase the risk of breast cancer in South Africa, and to specifically assess if there is an association between shift work and breast cancer in black South African women.

Objectives

To determine whether there are associations between different occupations and breast cancer in black women by calculating the odds ratios (ORs) for breast cancer in different occupations in South Africa.

To examine the association between shift work and breast cancer in black women adjusting for variables that may confound the association.

Methods

The study is an unmatched case-control study using secondary data from the existing Johannesburg Cancer Case Control Study (JCCS) database. The JCCS study is a large ongoing study that recruits black male and female cancer patients with all types of cancers receiving treatment at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a tertiary hospital in Johannesburg.

All women patients recruited from 1 January 2001 to 31 December 2009 were included in the analysis. This included 1 903 cases and 3 990 controls.

An expert group was set up to estimate the likelihood of occupational engagement in shift work for the existing occupational groupings present in the JCCS database. These occupations were classified into: a) high probability of shift work; b) possibility of shift work and c) unlikely to do shift work.

ORs were estimated using logistic regression. Those who had never worked were the reference category.

Bivariate analysis was then carried out to estimate ORs between individual occupations and breast cancer and later to estimate ORs between the likelihood of involvement in shift work and breast cancer. Multivariate logistic regression followed a forward stepwise approach and all the possible confounders present in the JCCS database were considered. These included age, smoking, drinking alcohol, age at first menarche, parity, age at menopause, use of oral contraception and retroviral status.

Results

With regards to occupation, the bivariate analyses showed significant ORs for breast cancer in the occupational categories of health, education, social services, retail, hospitality, construction, food, textile and manufacturing, with the highest OR in education (OR 2.33, 95% CI: 1.44 – 3.78) and social service (OR 2.39, 95% CI: 1.24 – 4.58) followed by office workers (OR 2.17, 95% CI: 1.47-3.20) and health workers (OR 2.01, 95% CI: 1.33-3.04). Agriculture (OR 0.55, 95% CI: 0.32 – 0.94) and domestic workers (OR 0.96, 95% CI: 0.75 – 1.22) had ORs under one.

Following the adjustments for possible confounders, no statistically significant ORs were found between specific occupations and breast cancer. However, manufacturing had the highest OR (OR 1.44, 95% CI: 0.42- 4.94), followed by office workers (OR 1.44 95% CI: 0.31-5.94) and health workers (OR 1.31, 95% CI: 0.36-4.76) as compared to the never worked group.

In the bivariate analyses there was an association between a possibility of doing shift workers and breast cancer (OR 1.66, 95% CI: 1.41-1.97). Similarly, women who had a high likelihood of participating in shift work had an elevated odds ratio for the disease (OR 1.76, 95% CI: 1.44-2.15). After adjusting for confounders in the multivariate model the ORs for both shift work groups were increased with women who possibly did shift work having an OR of 2.18 (95% CI: 1.34- 3.56) and those who had a high likelihood of carrying out shift work having an OR of 2.13 (95% CI: 1.26- 3.61).

Conclusions

The bivariate analyses identified elevated ORs for breast cancer in some occupations but in multivariate analyses no statistically significant OR were found. Nevertheless ORs>1 were found for the occupational categories of manufacturing, office and health workers. This study reports a strong association of breast cancer and shift work, which is supported by the literature. However shift work still remains necessary for the functioning of many industries.

Many gaps still exist, however, and this study has tried to address one of the neglected areas of occupational risks for breast cancer development.

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ABBREVIATIONS

BCEA	Basic Conditions of Employment Act No 75 of 1997
CERG	Cancer Epidemiology Research Group
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
IARC	International Agency for Research on Cancer
JCCS	Johannesburg Cancer Case Control Study
NCR	National Cancer Registry
NIOSH	National Institute for Occupational Safety and Health
OR	Odds ratio
SASHON	South African Society of Occupational Health Nursing Practitioners (SASHON).
SASOM	South African Society of Occupational Medicine (SASOM)

GLOSSARY OF TERMS

Benign breast disease	A group of lesions of the breast that are non cancerous
Breast cancer	A malignancy arising from the breast tissue
Carcinogen	A substance that plays a role in causing cancer
Circadian rhythm	Physical, mental and behavioural changes that occur in the body in a 24 hour cycle. This impacts sleep- wake cycles, hormonal release, body temperature changes and other body functioning
Mammography	X ray image of the breast
Menarche	Start of the first menstrual period in a woman
Night work	Work between 18h00 and 06h00
Nulliparous	A woman who has not given birth to a live baby

Oestrogen receptor-positive tumours	Breast cancer that has receptors in the cells that bind to oestrogen
Parity	Number of children born
Postmenopausal	A woman who has reached menopause and no longer menstruates
Shift work	A work schedule that requires shifts other than the usual 09h00-17h00 working hours

Chapter One

1. Introduction

The question of a possible association of breast cancer with certain occupations has been considered for centuries. Berardino Ramazzini, the father of occupational health first described the link between occupations and breast cancer in the 1700s when he observed that nuns suffered high rates of breast cancer. At the time, he attributed this to a "mysterious sympathy" between the uterus and the breast brought on by the occupational celibacy practiced by the nuns (3).

In the 1800's, Rigoni-Stern managed to quantify the excess of breast cancer in nuns in Verona, Italy. Later epidemiological research has shown that nulliparity and delayed childbirth are risk factors associated with the development of breast cancer and hence can explain the high prevalence in nuns (3). Subsequent research has been undertaken on the possible associations between breast cancer and a range of occupations.

1.1. Background

Breast cancer is one of the commonest forms of malignancy experienced by women in South Africa and it incidence is on the increase (1). Occupational risks are amongst the many factors that have been associated with breast cancer.

Approximately six million women work in South Africa, mainly in community and social services, private households, finance, trade and manufacturing industries (4). Some of these women are likely to be exposed to agents that are carcinogenic to the breast during their daily working lives. Occupational carcinogens that have been described include exposure to radiation, ethylene oxide and polychlorinated biphenyls. However there is some evidence suggesting that many more synthetic chemicals have an oestrogen-like effect such as

organochloride pesticides, polycyclic aromatic hydrocarbons, organic solvents and plastics. In animal studies over 200 chemicals have been identified to trigger breast cancer. However these have not been adequately studied in humans as yet. In addition to physical and chemical risks, shift work has been associated with breast cancer due to its effect on circadian rhythms and consequent hormonal dysregulation (2).

There are many complexities around toxic carcinogenesis of the breast and it is thought that the dose and timing of exposure in relation to breast development may also play a role in carcinogenesis. It has been documented that the most vulnerable times of exposure may be during breast development and biochemical and morphological change which starts at gestation and continues through puberty to first pregnancy and possibly throughout the reproductive years (2).

It may then be possible that some of the six million South African women may be placed at risk due to their occupational duties as well as the other, more well-described changes in reproductive and behavioural risk factors.

The economic impact of an increasing prevalence of breast cancer is also significant given the mortality and morbidity associated with this disease. In the United Kingdom, for example, it was estimated that a total cost of £243 million per annum was used for diagnosing and treating breast cancer (5).

Globally there is limited information available on the occupations that are associated with an increased risk of breast cancer, and even less has been documented in South Africa. It appears that occupational cancer epidemiology has largely focused on studying white males as the population of interest and women, particularly of black decent, have largely been

neglected in this area of research (6). In South Africa, there are no studies identifying occupation and risk of breast cancer. In particular, there are no studies related to black women.

This study plans to identify occupations that place black women at risk of breast cancer in the South African context. Thereafter, it will assess if there is an association between shift work and breast cancer in black women in South Africa. The reason for studying black women is two-fold: first, no studies of this nature have been done in South Africa, and more especially in black women (whose previous protective factors against breast cancer appear to be diminishing) and, second, the Johannesburg Cancer Case Control study (JCCS) database that will be used in this study only contains data on black people with cancer.

The findings of the study could be of particular significance to the local context, given that women are entering the workforce in increasing numbers. Furthermore, there are no data on occupations that may increase the risk of breast cancer or on the risk factors associated with these occupations. Finally, as a more long term goal, if high risk occupations can be identified, these could potentially be targeted for screening and prevention programmes. This, could, ultimately contribute to a decrease in morbidity and mortality associated with breast cancer due to early detection and treatment.

1.2. Rationale for the study

Breast cancer poses a significant threat to South African women causing major morbidity and mortality as well as significant economic costs. An increasing number of black women are entering the labour market in South Africa and, simultaneously, it is noted that there is an increasing incidence of breast cancer amongst black females. Many of these women entering the workforce may be exposed to occupational risk factors for malignancy.

Despite this there have been no South African studies to identify occupations where women are at increased risk of developing breast cancer. Furthermore, an association between shift work and the risk of breast cancer has not been studied in South African women and there is a lack of studies of this nature particularly in black women globally.

1.3. Arrangement of the chapters

- Chapter 2: This chapter focuses on the literature around breast cancer in particular the epidemiology, non occupational and occupational risk factors and then briefly on the female labour workforce in South Africa.

- Chapter 3: In this chapter the methodology of the study will be detailed.

- Chapter 4: This chapter will outline the results of the study in terms of descriptive and analytical findings.

- Chapter 5: The results, and their implications, will then be discussed in detail in this chapter.

- Chapter 6: Lastly, conclusions will be documented and recommendations made.

Chapter Two

2. Literature Review

2.1. Chapter overview

This literature review will commence by considering the relevant literature on the epidemiology of breast cancer. Global statistics will be briefly reviewed and then what has been published on Africa, and then South Africa, noting the differences in extent of the disease between the developed and under-developed worlds. Risk factors for breast cancer will then be examined in terms of non-occupational risk factors and occupational risk factors. A focus on the literature on occupational risk factor will address the known occupational carcinogenic agents of the breast and then the occupational groups that have shown a higher than usual risk for breast cancer. Lastly, the literature pertaining to female workers in South Africa and the types of jobs they predominate in will be reviewed to assess the potential of occupations which may play a role in increasing the risk of breast cancer in South African women.

2.2. **Epidemiological Overview**

2.2.1. Global burden of breast cancer

Breast cancer is the commonest cancer in females with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers), causing more than half a million deaths globally (7). There are only a few places in the world where cervical cancer supersedes it as the most common cancer in women (8) and when looking at the incidence of cancer in both sexes, it is the second most frequently diagnosed new cancer in both sexes combined (9).

2.2.2. Incidence trends

It is of concern that the global incidence of breast cancer is projected to increase to 3.2 million new cases per year by 2050 due to expected population growth, increasing life expectancy and the adoption of more western lifestyle habits in developing countries. The above notwithstanding, recent years have seen the stabilization of incidence rates in developed countries, including the United States of America, Canada, Australia and Europe. The only exception is the incidence rate of breast cancer in females in the fifth and sixth decades of life which has increased in Europe. However, in many other developed countries a declining trend in mortality has been noted in this age group due to the decrease in use of hormone replacement therapy, early screening and advances in treatment (8,10,11). However, an increase has been noted in developing countries in Asia and Africa. This change has been attributed to the effects of westernisation, particularly around lifestyle changes and reproductive habits, which have recently become more prevalent in developing countries (8).

2.2.3. Prevalence

Prevalence differs from incidence in that it measures all the living individuals in a population at a given period of time, who have been diagnosed with the disease as opposed to incidence which measures individuals who have newly acquired the disease during the given time period. Prevalence, therefore, includes new cases as well as survivors from past disease (7).

The 5-year prevalence of breast cancer is estimated to be 5.2 million cases in both sexes which is the highest 5-year prevalence amongst all cancers worldwide. This is true for the majority of countries except some areas in sub-Saharan Africa and Asia where cervical cancer has the highest 5-year prevalence. The high prevalence is most likely due to increased screening and early recognition of breast cancer as well as advancements in medical treatment which have lead to improved survival, especially in developed countries.

2.2.4. Developed versus undeveloped countries

There are distinct differences seen in the epidemiology of breast cancer in developed and developing countries, particularly around incidence rates, which are more than double in developed countries as compared to developing countries. This has largely been attributed to changes in the reproductive habits of women in developed countries (8,10,11). Women in developed countries tend to have fewer children, often at an older age, and often breastfeed less than women in developing countries. Women in developed countries also have a greater use of oral contraceptive and, until recently, used hormone replacement therapy more frequently than women in developing countries, further contributing to the higher incidence of breast cancer in these populations (8,10,11). Lifestyle habits have also been implicated in contributing to the higher incidence of breast cancer in developed countries as high levels of obesity, increased alcohol consumption and low levels of physical activity (8,10,11) have all been identified as risk factors in the development of breast cancer.

Although, it is clearly established that developed countries have a higher rate of breast cancer, under-diagnosis as a result of poor access to adequate health care and poor cancer surveillance systems also contribute to the lower incidence of breast cancer in developing countries (8). Some of the literature also suggests that the lower life expectancy in developing countries further decreases the incidence of breast cancer in these areas (12). Furthermore, women with breast cancer in developed countries often present, and are

diagnosed, at an earlier stage with the majority of cancers being localised at the time of diagnosis. This contrasts greatly with developing countries, where more than three quarters of cases are diagnosed at a late stage of the disease (8).

2.2.5. Africa

With regards to cancer in Africa, the exact burden of disease is not fully understood due to poor surveillance systems in the continent. Despite this, the available data show an estimate of 715 000 new cases of cancer being diagnosed in a population of about one billion people (13). Furthermore, cancer contributed to approximately 542 000 deaths in 2008 (13), and individuals in Africa have a lifetime risk of cancer of 10%, which is 30% lower than in developed countries (14). The next 20 years is expected to see a growth in life expectancy of both males and females in Africa and with this, the burden of cancer is expected to almost double from 0.7 million to 1.3 million from 2008 to 2030 (13).

Breast cancer was the leading cause of cancer in women in Africa in 2012, with 99 760 cases, and accounted for about 50 000 deaths (7,15). The region with the highest incidence rates was sub-Saharan Africa; the rate was estimated to be 9 new cases per 100 000 of breast cancer in females in 2008 (9). It has also overtaken cervical cancer as the most commonly diagnosed cancer in this region, probably due to changes in behaviour patterns following urbanisation and economic development in this area (7)(15). Breast cancer has also been shown to have a predominance in the white and urban population within this region (14).

Many studies have been done in the USA on ethnicity and breast cancer. These have shown that black females have a lower incidence of breast cancer, present at a later stage, have a shorter survival and an increased mortality as compared to white females (even when adjustments were made for differences in access to healthcare) (14). The aggressive clinical

presentation and poor outcome has been attributed to the presence of hormone receptor-negative breast cancer being predominant in black women (14,15).

2.2.6. South Africa

The World Health Organization estimated that cancer accounts for 3% of the total burden of diseases in South Africa (16). The incidence of cancer was estimated to be 774 000 cases with an age standardised rate of 187 per 100 000 in 2012, as published in GLOBOCAN (7). Cancer was the third leading cause of mortality (resulting in approximately 40 000 deaths) in South Africa in 2009, following tuberculosis and influenza with pneumonia (16).

The commonest cancers that were noted in South African women were breast, uterine, cervix, oesophagus, colorectal, lung and uterine corpus (16). The incidence of breast cancer was estimated to be 41.5 per 100 000 in 2012 (17). Indeed, South Africa has demonstrated the highest incidence rates of breast cancer amongst females in Africa (17), with this type of cancer being the leading cancer in women (16.6%) in the country after it overtook cervical cancer in 1993 (1).

The burden of disease differs significantly among the races and between rural and urban settings. The National Cancer Registry shows an age standardised incidence of breast cancer of 76.3 per 100 000 in white females as opposed to 18.2 per 100 000 amongst black females (14) . Furthermore, the incidence of breast cancer is historically low in in black rural women, but has been on the increase in urban communities. The protective factors that were previously noted in black rural women were late menarche, first child at an early age, high parity with prolonged lactation and high physical activity and a low fat diet (18,19). These

protective factors have been diminishing with westernization, and as many as 922 cases of breast cancer were diagnosed in black South African women between 1993 and 1995 (1). Breast cancer in black women also tends to occur at a younger age, almost a decade earlier, as compared to the white population in South Africa (18,19).

The mortality rate, although not entirely reliable due to limitations in data (14), for breast cancer for females in South Africa, between 1998 and 2005, has been estimated by the WHO to be 11 per 100 000 (17). It has been noted that breast cancer in black women has been associated with a low survival rate, particularly in South Africa. Some of the reasons cited for the low survival include the late presentation seen in black women and black patients presenting at a later stage of disease, with 63.1% presenting at stage IV (19). Furthermore, there is an over-representation of triple negative breast cancer which has been linked to the worst prognosis (17).

2.3. Risk factors

Breast cancer has a multifactorial aetiology, comprising non-occupational and occupational risk factors. There are many ways of classifying risk factors, however for the purposes of this study, the risk factors will be discussed under the occupational and non-occupational categories. Non-occupational risk factors that will be examined will include genetic factors, age, a previous history of benign breast disease, hormonal factors, lifestyle and other risk factors. Occupational risk factors will include workplace exposure to ionizing radiation, ethylene oxide, polychlorinated biphenyls (although now a banned substance) and shift work.

2.3.1. Non-occupational risk factors

2.3.1.1. Genetic risk factors

It has long been known that individuals with a family history of breast cancer have an increased likelihood of developing breast cancer, despite the fact that breast cancer has multiple aetiologies. Women with a relative that has breast cancer have a two-fold or even three-fold increased risk of developing breast cancer (depending on the age at diagnosis, the number of relatives affected and the generational distance between the women) (20). Gene studies have isolated some mutations on two major breast cancer susceptibility genes, BRCA1 and BRCA2, which result in a very high risk for breast cancer. It has been documented that 5-10% of all breast cancer cases can be explained by the inheritance of mutations in one of these two genes (21).

The first breast cancer susceptibility gene, BRCA1, was isolated in 1994. Females who carry this mutation have a 60-80% lifetime risk of developing breast cancer which often has distinguishable clinical characteristics (21). These include early age of onset, higher prevalence of bilateral breast cancer and association with other tumours, particularly ovarian and colon cancers (21). BRCA1 functions in transcription, cell cycle control, DNA repair pathways and regulating apoptotic cell death, hence a mutation to this gene is likely to impact tumour suppression (21).

The BRCA2 gene has been isolated as a second dominant breast cancer susceptibility gene. BRCA2 mutation carriers also have an increased lifetime breast cancer risk between 60-85% (21). Although the molecular function of BRCA2 is not well understood, it is also thought to play a role in DNA damage repair pathways(21). Other suspected alleles have also been identified and are still being studied (21).

2.3.1.2. Age

The incidence of breast cancer increases with age, usually by a factor of two every 10 years, until the menopause; thereafter the incidence decreases dramatically (20). Before the age of 30, the incidence of breast cancer is extremely low (<25 cases per 100 000). This then increases till menopause.

2.3.1.3. Previous history of benign breast cancer

A history of a previous benign breast lesion is said to increase the risk of breast cancer in women. However, it has been noted in the literature that there is no fixed definition of "benign breast disease" and only benign disease of a proliferative nature is associated with an increased risk, as opposed to non-proliferative lesions (such as cysts). Complex fibroadenomas, duct papillomas, sclerosis adenosis and moderate to florid epithelial hyperplasia have also been linked to an increased risk of the development of breast cancer (23). The risk of breast cancer increases four-to five-fold in women who have severe atypical epithelial hyperplasia (23).

2.3.1.4. Hormonal risk factors

It is well established that hormonal factors influence the development of breast cancer in women, with exposure to oestrogen being of particular importance. Prolonged or increased exposure to oestrogen puts women at risk of developing breast cancer while decreased exposure to oestrogen is protective against breast cancer. Factors that bring about a

prolonged or increased exposure to oestrogen occurs in women who have menarche at an early age, nulliparous women, women who have their first child later in life, those who take in exogenous hormones and women with a late onset of menopause (21).

Exogenous hormone intake can occur in the form of oral contraceptives or hormone replacement therapy. Diesthylstilbestrol, oestrogen-progesterone contraceptives and oestrogen-progesterone menopausal therapy have been classified by the International Agency for Research on Cancer (IARC) as Group 1 carcinogens for the breast (which means that there is sufficient evidence to confirm the carcinogenicity in human breast) (24).

Diethylstilbestrol is a synthetic oestrogen that was previously mainly used to prevent miscarriages, treat menopausal symptoms and for post-coital emergency contraceptives. The monograph published by IARC reviews all the available literature on diethylstilbestrol and concludes that there is a modest association between exposure to this substance during pregnancy and an increased incidence and mortality of breast cancer (24).

Oestrogen-progesterone contraceptives are also a Group 1 carcinogen as classified by IARC and have been documented to increase the risk of breast cancer among women who currently use, or have used, these types of contraceptives. Most of the scientific evidence used to decide this is drawn from the a meta-analysis done in 1996 (24). The study showed a striking increase in risk among women who had used this type of contraceptive for many years and started using this at a young age (<20 years) and were diagnosed with breast cancer under the age of 35. The risk was noted to decrease in women who were diagnosed at an older age and who had stopped using contraceptives for more than 10 years. Furthermore the body of evidence appears to suggest that the use of oral contraceptives increases the risk of breast cancer, particularly in carriers of BRCA1 or BRCA2 mutations (24).

Oestrogen-progesterone menopausal therapy was initially used for the treatment of menopausal symptoms and the prevention of osteoporosis. This combination treatment was encouraged to decrease the risk of endometrial cancer (which was increased in unopposed oestrogen therapy in peri-menopausal and menopausal women) (24). In 2007, IARC established that there was sufficient evidence to classify oestrogen-progesterone menopausal therapy as a carcinogen to the breast. Four systematic reviews have been published since 2004, all of which confirmed these results and more recent studies that have looked at incidence trends have shown that with a decrease in post-menopausal hormone use, the incidence of breast cancer has decreased. The current monograph published by IARC states that there is additional evidence that the increased risk of breast cancer starts after five years of constant use of oestrogen-progesterone menopausal therapy, and the risk increases the longer one takes this treatment. It was also noted that insufficient evidence was available to link the risk to the type, dosage and route of administration of either oestrogen or progesterone or type of regime used. Furthermore, there was insufficient evidence to show an association between the histological type of cancer and oestrogen-progesterone menopausal therapy (24). The risk posed from this is rapidly changing as a result of decreased use of hormone replacement therapy (24).

Oestrogen-only therapy has been implicated by IARC, with limited evidence, as a suspected human carcinogen for the breast. This type of therapy is still currently used in the treatment of menopausal symptoms and the prevention of osteoporosis and ischaemic heart disease in postmenopausal women, mainly following a hysterectomy (24).

The IARC monograph in which the link between unopposed oestrogen therapy for menopause and breast cancer was presented, published in 1999, considered data from 51 studies and concluded that there was a small risk of breast cancer in current users who had been taking this treatment for approximately five years or longer. Numerous studies have

been done since then, the largest of which is the United Kingdom Million Women Study, which had a study population of more than a million women aged between 50 and 64 years. This study showed an increased risk of breast cancer according to the duration and type of preparation used, and also showed an increased risk with less than five years of use (24).

Lastly, as previously stated, a decreased exposure to oestrogen is protective against breast cancer; hence decreasing the number of ovulatory cycles can be protective. Factors that play a role here include increased parity and longer lactation periods. Moderate exercise is also thought to influence oestrogen and, therefore, may also be protective (21).

In black South African women, the previous low incidence of breast cancer had been attributed to later onset of menarche, early age at first birth, high parity and prolonged lactation which is a protective factor, however with westernization this trend is changing (1).

2.3.1.5. Lifestyle risk factors

2.3.1.5.1. Alcohol

IARC has classified alcohol consumption as a Group 1 carcinogen in humans and confirms that the risk of breast cancer increases as the level of alcohol consumption increases. There have been many postulations concerning the mechanism responsible for this. One hypothesis is that alcohol stimulates the metabolism of acetaldehyde, a known carcinogen. It has also been postulated that alcohol reduces DNA repair efficiency directly or by impeding nutrition absorption (22) and that alcohol increases circulating oestrogen especially in women who are taking exogenous oestrogen (25).

Research on the lifetime effect of alcohol consumption on the risk of breast cancer is inconsistent. One study showed a 31% increase in risk per 13g of alcohol consumed per day, but this was refuted by another study which found no association after adjusting for current alcohol use (26). Further research that was undertaken to determine if there was a link between the starting age of alcohol consumption and the risk of breast cancer showed no positive associations (27).

Although the evidence varies, there may be some association with increased alcohol consumption and oestrogen receptor-positive tumors after two large studies showed this effect. One study, comprising 1000 cases, showed an increased risk for all oestrogen receptor-positive tumors (27), and a meta-analysis done in 2008 reported an increased risk of oestrogen positive-tumors per 10 g/ day increase in alcohol intake (27).

2.3.1.5.2. Smoking

Hundreds of studies that have examined the association between cigarette smoking (active or passive) and breast cancer have been published. An IARC monograph done in 2004 found some evidence suggesting a lack of carcinogenicity of smoking in cancer of the breast, but more recent studies have found conflicting results. Moreover, it has been documented in a recent IARC monograph that many of the studies may be limited due to methodological issues, and smoking has been classified as a suspected carcinogen of the breast (although the data supporting this are still limited) (27).

2.3.1.5.3. Obesity and diet

There is some controversy over the role of obesity in the risk of breast cancer. Some of the literature has found an association between obesity in postmenopausal women and the risk of breast cancer. This is biologically plausible, given that adipose tissue facilitates the conversion of androstenedione to estrone in postmenopausal women - this mechanism is a major source of oestrogen and hence prolongs exposure to the hormone in postmenopausal females (21). However, some studies have found that it is of limited importance as a direct risk factor in postmenopausal women, but rather that obesity is associated with increased mortality due to delays in diagnosis that have been noted to be more in obese women (23). The available evidence relating breast cancer to dietary food is inconsistent (20).

2.3.1.5.4. Physical activity

There seems to be much debate around the role of physical activity on the risk of breast cancer. One study showed that higher levels of physical activity for a longer duration decreased the risk of breast cancer in women (28). However, it is thought that this could be due to many confounders; people who exercise may, for example, have different dietary patterns as compared to people who do not exercise (25). IARC has not classified physical activity a risk factor or breast cancer.

2.3.1.6. Other risk factors

2.3.1.6.1. Digoxin treatment

Digoxin is a drug widely used in the treatment of cardiac abnormalities. This drug has been

studied by IARC and been classified as a Group 2B carcinogen of the breast (a possible cause of breast cancer) after a review of the available literature which consisted of four case control studies across a few developed countries, all of which showed significant increases in the incidence of breast cancer in digoxin users (24).

A criticism of the studies was that no clear effects of duration or dose were seen, although a decrease in incidence was observed on stopping the drug. Furthermore, there appeared to be stronger association with oestrogen receptor-positive tumours as opposed to negative tumours (24).

2.3.1.6.2. Mammographic breast density

The use of mammography to determine who is at increased risk of developing breast cancer is controversial. The breast is composed of different types of tissues, namely adipose tissue, stroma and epithelial tissue. The percentage of each type varies by individual. Furthermore, they have different radiographical patterns, fat appears darker and epithelial tissue and stroma appears light or white (this is referred to as mammographic density). Many of the studies show extensive breast density is associated with an increased risk of breast cancer. However, as stated earlier, this is not a widely accepted school of thought, as some argue that the dense breast tissue masks an underlying breast neoplasm that is then only picked up on subsequent mammograms (29).

When assessing the determinants of non-occupational risk, the Gail model is often cited. Gail et al. used unstratified logistic regression analysis to assess a variety of potential risk factors. This study reported that the major determinants of risk in the study population were: family history in a first degree relative; late age of child birth; early menarche; and multiple previous benign breast lesions (22).

2.3.1.7. Risk factors according to hormonal receptor expression.

More recently, breast cancer has been classified according to the hormone receptor expressions (oestrogen receptor and progesterone receptor). It has been noted that these have distinctly different clinical, pathological and molecular features. Hormone receptor-positive tumours exhibit a stronger response to hormonal treatment, have a better differentiated morphological appearance and show increasing incidence rates with age as opposed to slowing down after menopause (30).

A systemic review done by Lthuis et al. examined the aetiology of hormone receptor breast cancers concluded that they may have separate risk factor profiles for each oestrogen or progesterone receptor subtype (30). It was suggested from this review that reproductive related risks, nulliparity and delayed childbearing tended to be associated with oestrogen receptor-positive tumours but not oestrogen receptor-negative tumours. Furthermore, early menarche was found to be more consistently associated with oestrogen receptor-positive/ progesterone receptor-positive tumours as compared to oestrogen receptor-negative/ progesterone receptor-negative tumours. Postmenopausal obesity was also associated with an increased risk of hormone receptor-positive forms of breast cancer while the other risks like breast feeding, alcohol consumption, cigarette smoking, family history of breast cancer and premenopausal obesity did not differ according to hormonal receptor status (30).

In the African context, black women have been noted to have a higher frequency of triple negative breast cancer. Triple negative breast cancer occurs when the malignancy is oestrogen receptor-negative, progesterone receptor-negative and human epidermal growth factor receptor 2-negative. Although this type of cancer occurs infrequently, it is responsible

for a high number of breast cancer related deaths. The risk factors for triple negative breast cancer are not as well defined as those for oestrogen receptor-positive disease, and much research is still underway in this area (31).

2.3.2. Occupational risk factors

It has been documented that 53% of the incidence rate of breast cancer cannot be explained by established risk factors, and that environmental exposures which include occupational risk factors, may play an important role here (32). A few agents that are used in occupational settings have been classified as human breast carcinogens by IARC. These exposures include radiation, ethylene oxide, less commonly polychlorinated biphenyls and, more recently, shift work. These exposures occur in a wide variety of industries.

2.3.2.1. Exposure to radiation

Exposure to X-rays and gamma radiation can occur in an occupational and a non-occupational setting. Non-occupational exposure to X-rays and gamma radiation can happen in the environment from natural sources, or after nuclear production explosions have occurred. A large percentage of exposure occurs as a result of medical investigations or interventions. These include conventional radiography, nuclear medicine, computed tomography and fluoroscopic procedures. Occupational exposure to radiation occurs during nuclear power production, fuel recycling, military and industrial activities, aviation and in medical settings (33).

In 2000, IARC classified X- and gamma radiation as a Group 1 carcinogen of the breast in women exposed before menopause. (33).

Much of the epidemiological data have been taken from exposures to all sources of radiation. However the Life Span Study (where the study population is women who have been exposed to radiation following a nuclear explosion) showed a strong association between exposure and the risk of breast cancer in a linear dose-response relationship. This relationship decreased with increasing age at the time of exposure, with women exposed before the age of 20 having a five times higher risk than women exposed after the age of 40 (34).

2.3.2.2. Exposure to ethylene oxide

Ethylene oxide is a chemical used as a sterilizing agent, fumigant and insecticide. It can be used alone or with a combination of other chemicals. As a sterilizing agent, it has uses in many settings and is often used in the medical industry to sterilize drugs, hospital equipment, medical items and packing material. However, its sterilization uses extend to food, books, museum artifacts, scientific equipment, clothing, furs, railcars and aircraft (35).

In a study on the industries that use ethylene oxide, published by the US Occupational Safety and Health Administration (2005), estimated employment numbers of people exposed to this chemical were 1 100 ethylene oxide- production workers, 4 000 ethoxylators (those who use ethylene oxide to make chemical derivatives) and 40 000 workers who use ethylene oxide as a sterilant or fumigant in hospitals. It was estimated that an additional 2 700 workers were also employed by the manufacturers of medical and pharmaceutical products, as well as producers of food spices to be used as sterilizers (35).

The exposures are noted to vary according to job category, with loaders and distributers of ethylene oxide documented as having the highest exposure. A decreasing trend over time has been noted due to improvement in control measures (35).

In hospitals, ethylene oxide is often used as a sterilant for heat sensitive medical items, surgical equipment, other objects and fluids that have been exposed to biological tissue. The large sterilizers are often located in the central supply areas of hospitals and smaller sterilizers are place in clinics, operating rooms, tissue banks and research facilities. The main exposure occurs when opening the sterilizer, and unloading and transferring sterilized material (35).

Studies into the risk of breast cancer in women exposed to ethylene oxide have showed varied results with some studies showing no overall risk while others finding an excess risk of 60% and a study by the National Institute for Occupational Safety and Health (NIOSH) showed increased relative risks for breast cancer at the highest level of cumulative exposure to ethylene oxide after controlling for confounders (35)

2.3.2.3. Exposure to polychlorinated biphenyls

Polychlorinated biphenyls are chlorinated compounds that were used in capacitators and transformers as well as building materials. However, their use has been banned in most countries (36). While the occupational exposure was highest during the manufacturing process, today exposures can still occur during demolition and in recycling of polychlorinated biphenyl containing structures (36). When reviewing the collection of studies done, IARC found that exposure to polychlorinated biphenyl was associated with an increased risk of breast cancer, however the associations were inconsistent and limited (36).

2.3.2.4. Shift work

More recently, shift work has been described as an occupational risk factor for breast cancer. Shift work is defined by the International Labour Organization as “a method of organization of working time in which workers succeed one another at the workplace so that the establishment can operate longer than the hours of work of individual workers”(37). This is often synonymous with irregular, odd, flexible, variable, unusual, non-standard working hours and is a growing trend in developing nations. Shift work may be permanent or continuous, and with or without night work. Shift systems can differ greatly according to the length of the shift cycle, duration of the shift, start and end times, speed of shift rotations, direction of the shift, rest periods between shifts and the regularity of shifts. The different shift systems can have different health effects brought about by the disruption to the circadian rhythm (which is essential for many biological functions in the body).

Shift work involving night work usually impacts circadian rhythm. Night work is very variable, and the definition of this type of work differs from country to country. In the South African context, the Basic Conditions of Employment Act no 75 of 1997 defines night work as “work that is performed between the hours of 18:00 on one day and 06:00 hours the next day” (38).

An employee’s tolerance to shiftwork and night work may be influenced by many factors both within and outside of the working environment. Some of these factors include individual characteristics, family situations, social conditions and working conditions.

No information was found on the frequency of shiftwork (including night work) in South Africa. However, globally it has been documented that two and a half billion people are shift workers, with the majority working in Asia. In the USA men worked more commonly in shift work than women, but in Europe men and women were almost equally involved in shiftwork which included night work. In the USA, the service and leisure and hospitality industries have the highest prevalence of shift work, whereas in Europe the prevalence of shift work was highest in the health industry, followed by plant and machine operators, hotels and restaurants, service, shop and market sales workers and the manufacturing and mining industries (37).

In 2007, IARC classified 'shift work that involves circadian disruption' as a probable human carcinogen (group 2A) (37). At the time when the monograph was written, eight studies had been done that found a higher risk of breast cancer in shift workers. One of the largest cohort studies, which included about 78 000 nurses, found an increased risk of breast cancer in those nurses who did shift work that involved night work. The risk of breast cancer grew with an increase in the duration of the shiftwork.

Another cohort study, done on 115 000 nurses in the NHS, showed similar results. Furthermore, a meta-analysis done in 2005 found an increased risk of breast cancer (RR,1.5; 95% CI: 1.36-1.68) in women who did night work. While a retrospective Swedish cohort study on more than a million participants showed no increased risk of breast cancer, there were some weaknesses associated with this study. The weaknesses that were cited included inadequate control for confounding and the fact that less than 0.3% were in occupations where 40% of shift workers worked at least 20 hours a week) (37).

The pathophysiology around the shift work hypothesis is that light, including artificial light, suppresses the normal night time production of melatonin by the pineal gland. Melatonin is synthesized and released in a dose-response relationship with the stimulus of darkness and

is inhibited by exposure to light. Melatonin peaks at night during sleep and is responsible for circadian rhythms and for inhibiting tumour growth. Other protective actions of melatonin against breast cancer have also been postulated, and include an increase in the immune response, scavenging of free radicals and modulation of the tumour expression gene (37).

2.3.2.5. Occupations at risk for developing breast cancer

Although IARC has identified a limited number of workplace agents as carcinogenic to the breast, many separate industries have been studied in an attempt determine if there is an increased risk for breast cancer in these settings. This includes industries without exposure to a known carcinogen.

In 1995, a review of occupational investigations into breast cancer in the preceding 25 years was undertaken. Several studies showed an excess risk in several "white collar," professional and managerial workers, clerical and secretarial workers, teachers, nurses, scientists and physicians and other health professionals. Not all these industries had a notable exposure to a known carcinogenic occupational agent in the workplace and there was suspicion that some of the apparent risk may be due to confounding by reproductive issues. However, some industries, such as healthcare, may have exposures to multiple occupational carcinogens (39).

The study also showed that there was limited evidence of an association of breast cancer with women employed in the pharmacology, cosmetology and beauty industry (cosmetologists, for example, may be exposed to several toxins in the form of hair dyes and solvents). Associations were found in women who worked as chemists and those exposed to low frequency electromagnetic fields. Furthermore, there was little support for an increased

risk in the textile, dry cleaning and nuclear industry (39). Interestingly, although radiation exposure is a known risk factor, none of the studies that examined radiation workers or X-ray technicians showed an excess in risk (39).

An assessment of the epidemiological evidence on breast cancer done in 2006, which looked at environmental and occupational associations with breast cancer, found that there was a possible link with exposure to organic solvents and breast cancer. However, the evidence is still inadequate to evaluate an association, although benzene has been documented as a mammary carcinogen in animals and some occupational studies have shown an increased risk of breast cancer with longer duration of employment in solvent exposed workplaces. One study showed a doubled risk in women with more than 10 years exposure and a 15 year lag time. Some of the occupations that have been studied that do have exposure to solvents are in dry cleaning, hairdressing, glass manufacturing and aircraft maintenance (40).

A number of studies have explored breast cancer risk in nurses, whose carcinogenic exposures include solvents, therapeutic agents, ethylene oxide and shift work. An elevated risk of breast cancer was found in nurses in British Columbia and Iceland (40).

Another review, that considered the evidence on environmental and occupational causes of cancer from studies done between 2005 and 2007, showed that exposure to polychlorinated biphenyls in women with a specific genetic anomaly (polymorphism in the CYP1A1 gene) resulted in a greater risk of breast cancer. A few studies also supported the link between pesticide exposure and the risk of breast cancer. With regards to this, it has been documented that the carcinogenic effect is strongest when exposure occurs just before puberty or early in the women's breast development. One study also showed an increased risk of breast cancer in women whose husbands were exposed to specific chlorinated pesticides (41). It was, however, documented that most studies that were

reviewed had important methodological weaknesses and that the precise exposure assessment was often limited. Furthermore, when comparing incidence rates with the general population, confounders such as reproductive history could be missed (40).

2.4. Women in the workplace in South Africa

The South African Quarterly Labour Force Survey published for the first quarter of 2014 showed that the female labour workforce in South Africa (economically active) consists of approximately nine million women; of whom over six million were employed (42). The main industries in which South African women work are (in descending order) community and social services; trade; private households; finance; manufacturing and agriculture (42). Women did not predominate in the transport, construction, utilities or mining industries.

When stratified by occupation, the highest number of South African women were employed as elementary school workers, followed, in order of frequency, by clerks, sales and service, domestic workers, technicians, managers, professionals, craft and related trades, plant and machine operators and skilled agricultural workers (42). The labour force survey also gives some information on the working hours of employees, with over half of the female working population working between 40-45 hours a week, and just less than a quarter of the same population working over 45 hours a week. However, there are still substantial gaps in relation to research on South African working women. For example, there is no information to determine whether the different racial groups of working women have a preponderance for a particular industry or occupation.

According to the 2005 EU study on working conditions, the highest prevalence of shift work occurred in health, hotels, restaurants and service industry, transport, communication,

manufacturing and mining (42). These represent some of the industries that women predominate in in South Africa. However, although there is some information about working hours, there is no information on whether this entails shift work and, more particularly, working at night.

2.5. Summary of the literature review

This literature review has attempted to give a brief synopsis of the relevant literature around breast cancer. Epidemiological data show breast cancer to be the commonest cancer worldwide, with increasing incidence noted in developing countries. This finding is reflected in the admittedly sparse literature available on Africa, and is expected to increase even further in the future. Cancer data also show that breast cancer has recently become the leading site of cancer in South Africa affecting all races in the country.

Many risk factors have been identified for breast cancer. Age, lifestyle habits and reproductive factors are well established risk factors in the literature. There are also other non-occupational factors that may have a link in increasing the risk of breast cancer in women, but these associations are not as well established.

Less information on occupational risk factors is available. However, IARC has noted an increased risk following exposure to radiation, ethylene oxide, polychlorinated biphenyls and shift work. A few studies have noted that white collar workers and women involved in the beauty, textile, dry cleaning, agriculture and nuclear industry are at increased risk of breast cancer.

Nine million women are in the economically active age group in South Africa, with six million in active employment. They predominate in the community and social service industry, trade and finance industry, manufacturing and agricultural industry and also work in private households. There is limited information on the main risks in each of the industries or the racial distribution of female workers by industry.

In conclusion, it is clear that there are still unexplored areas in the literature, some of which are:

1. Other than the changes in reproductive and lifestyle habits of South Africans, particularly black South African women, are there other factors, possibly occupational in origin (as more women enter the workforce), that may be responsible for the increasing incidence of breast cancer in black South African women who were previously protected?

2. Many South African women have jobs that have been described in the literature as having a higher than expected risk of breast cancer, yet there is a paucity of evidence on the prevalence and risk of breast cancer within the South African occupational setting.

3. Finally shift work has been identified as a breast carcinogen, yet there is no information on the prevalence of shift work in South African women, or even by industry in South Africa, and the effect of this on the risk of breast cancer within the South African black population.

These three gaps in the literature provide the rationale for this exploratory study. Indeed, the objectives have been set with these points in mind. Moreover, the focus will be on occupations where there is a potentially high risk of developing breast cancer, and the possible role of shift work in increasing the risk of this disease in the South African setting.

I. Aim

The aims of the study are to identify occupations that possibly increase the risk of breast cancer in South Africa, and to specifically assess if there is an association between shift work and breast cancer in black South African women.

II. Objectives

a) To determine whether there are associations between different occupations and breast cancer in black women by calculating the odds ratios (ORs) for breast cancer in different occupations in South Africa.
b) To examine the association between shift work and breast cancer in black women adjusting for variables that may confound the association.

Chapter Three

3. Methodology

3.1. Chapter Overview

This chapter will detail the design of the study. It will provide information on the setting, the study subjects and the period of the study. Thereafter it will describe the cases and controls included, and will discuss the analyses that were undertaken to meet the objectives.

3.2. Study design

The study is an unmatched case-control study using secondary data from the existing Johannesburg Cancer Case Control Study (JCCS) database of black cancer patients treated at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). Black in this context means any patient who does not consider themselves as belonging to the white population.

3.3. Study setting

The National Cancer Registry (NCR) of South Africa is a pathology-based cancer registry capturing histologically confirmed cancer cases. Within this Registry, is the sub-division of the Cancer Epidemiology Research Group (CERG) which houses the JCCS. The JCCS study is a large ongoing study that recruits black male and female cancer patients with all types of cancers receiving treatment at CMJAH, a tertiary hospital in Johannesburg. There are over 18 000 mainly cancer patients included. Some patients who, after histological examination, are found not to have a malignancy are still kept on the database and have been used for controls in other studies (43).

The patients on the JCCS database have been recruited from the CMJAH, a referral hospital that has about 1 088 beds and 4 000 professional and support staff (44). The hospital has an oncology unit which is responsible for the treatment of most non-benign tumours within the

larger Johannesburg area. In the southern area of Gauteng, it is the only hospital that offers both medical and radiological oncology services and it boasts the largest radiation oncology unit in South Africa, treating about 3 500 patients a year. This unit is followed by Tygerberg Hospital, which sees about a 1 000 fewer patients a year (45).

3.4. Study period

All women patients recruited from 1 January 2001 to 31 December 2009 were included in the analysis. The database initially recruited patients from other hospitals but recruitments have been limited to CMJAH since 2001. The data are available and cleaned for the period until 2009 and hence the study period is as such.

3.5. Sample size

No sampling was used for the collection of data in the JCCS, as all eligible cases and controls were used. This included 1 903 cases and 3 990 controls.

3.6. Inclusion and exclusion criteria

3.6.1. Inclusion and exclusion criteria for cases

The cases were incident, histologically confirmed, female breast cancer patients who had consented to be entered into the JCCS database between 2001 and 2009 and who were over the age of 35 years. One thousand nine hundred and three (1 903) cases of breast cancer had been recorded in the database for this time period and were accepted into the study.

Males with breast cancer were excluded from the study given the rarity of this diagnosis as well as the fact that breast cancer in males may have a different aetiological mechanism from that of female breast cancer.

3.6.2. Inclusion and exclusion criteria for controls

The controls included all women over the age of 35 years diagnosed with cancer on the JCCS database with the following exclusions:

a) Breast cancer patients.
b) Patients diagnosed with cancer where the origin is unclear. They were excluded as the malignancies could have originated from the breast which would potentially result in diagnostic misclassification of controls. Excluded from the controls were women with cancer from undefined sites [unknown primary sites *(n=78)*, ill-defined sites *(n=27)*, as well as other ill-defined digestive organ cancers *(n=7)*] as they could not be assigned to either the cases or the controls.
c) For the analysis of shift work, additional exclusion criteria were those with a cancer that may be associated with shift work. These have been identified as endometrial (*n=224*) and colorectal (*n=193*) cancer (37). This exclusion was done to prevent the introduction of cancers that may be associated with the exposure under investigation. The above mentioned cancers were only excluded when analysing the data for an association with shift work).

3.7. Matching of cases and controls

The cases and controls were not matched as all the eligible cases and controls were included in the study, no sampling was done and the study population was large.

3.8. Data collection and entry

As part of the JCCS, trained nurses used a standard questionnaire to interview newly diagnosed black cancer patients in their preferred language (generally Zulu or Sotho). A copy of the interview sheet is provided in Appendix 1. Participants were interviewed as soon as possible after diagnosis, but prior to receiving oncological treatment. The type of information gathered included age, birthplace, residence, years of education, alcohol consumption, tobacco use, and reproductive and sexual history. The questionnaires are collected and reviewed by the study manager who does quality checks. Incomplete questionnaires are returned to the nurses to get complete information. Questionnaires are entered into the JCCS database using a double entry system by a clerk specialist, initially onto Epi-info. Thereafter the data are transferred to STATA where simple frequency analysis is done to check for consistencies.

3.9. Data analysis

3.9.1. Software used for statistical analysis

The data were imported from the JCCS database into STATA (version 12). The data were analyzed using STATA 12.

A) <u>Demographic and occupational characteristics of cases and controls.</u>

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STATA 12 was used to tabulate and describe the data by cases and controls and to present this by the variables outlined below. No hypothesis testing was done to test differences between cases and controls.

The variables that were used include:

a) Demographic and risk factor variables

Age

This information was collected during the interview. Age was taken as the age at diagnosis and was a continuous variable for which the median, together with the interquartile range (IQR), was described in keeping with non-normally distributed data. This was incorporated into the multivariate model and adjusted for as a possible confounder as a continuous variable.

HIV status

An Elisa test was done to determine retroviral status during the work up of the patient prior to the onset of treatment. This was a binomial categorical variable (of positive or negative).

Alcohol consumption

This risk factor for breast cancer was categorised into either ever or never consuming alcohol and was, thus, a categorical binomial variable.

Smoking

This was also captured as a categorical binomial variable of ever smoked or never smoked

Age at menarche

These were continuous data. Again, the median and IQR were presented given that the data were not normally distributed. In the case control analysis this variable was continuous.

Parity

This variable was categorical ordinal data and classified according to:

i. Nulliparous
ii. $\leq$ three births
iii. > three births

These categories were selected according to the literature concerning risk which supports that nulliparity increases the lifetime incidence of breast cancer (20) and with each increase in child bearing this risk decreases. Three or fewer births and greater than three births are commonly used cut-points in breast cancer research (43).

Menopausal status

This information represents the menopausal status of the women at the time of diagnosis of breast cancer, as provided by categorical data in terms of two distinct categories of yes or no.

Age at menopause

This was a continuous variable that was not normally distributed. Again, the median and IQR was used to describe in keeping with the distribution of data. In the case control analysis, this was a continuous variable.

Oral contraceptive use

This variable was arranged as ordinal categorical data that were grouped into:

i. Never
ii. $\leq$5 years
iii. 6-10 years

iv. ≥11 years

According to IARC the increased risk of breast cancer increases with increasing use of oral contraceptives (20,24). More than 5 years of use and more than 10 years of use are commonly used cut-points in breast cancer research (20).

B. Classification of the exposure variables

i) Occupations

At the time of the interview information was obtained from the patient about their usual occupation and workplace. Occupations were either coded or written in free text in the database. The data were then cleaned and sub-divided into occupational categories that were non-ordinal. Table 1 describes the breakdown of the occupational groups. The groups were largely based on the European Union survey on working conditions.

Table 1: Composition of occupational groups as per usual occupation data.

No.	Occupation	Included occupational groups as they appear in the database:
1.	Never worked	Housewife, never worked
2.	Student	Student/scholar
3.	Unemployed	Unemployed
4.	Health	Nurse/nursing assistant, pharmacist/assistant, technician (medical and scientific), other health services
5.	Education	Tertiary lecturer, teacher, other educational
6.	Social services	Childminder, caregiver, old age home worker, minister, priest, nun, social worker
7.	Office/clerical workers	Personnel, human resources, clerk/bank, secretary, typist,

		receptionist
8.	Retail/sales	Cashier, sales supervisor, sales- technical, shop assistant including hawker, sales- insurance, property, services, sales rep, food trade e.g. baker, butcher, miller
9.	Transport	Delivery, driver, transport, taxi driver, train driver, transport conductor, inspector
10.	Security/ law enforcement	Defence/ military, law enforcement, police, security
11.	Hospitality	Catering, waitress, barmaid, accommodation proprietor/supervisor
12.	Domestic workers	Domestic worker
13.	Service workers	Service- e.g. lift operator, cleaner (not domestic), waste collector, car wash attendant, petrol attendant, laundry/ dry cleaning (commercial), telecommunications IT, beautician, hairdresser, barber.
14.	Agriculture	Farming own/communal land, subsistence, farm worker, gardener
15.	Metal workers	Metal and engineering artisan, production worker: metal
16.	Electrical	Electric and electronic artisan, electrical equipment maintenance, production worker: electrical
17.	Construction	Building: skilled (brick layer, builder etc.) Production worker: building and construction, building and construction: unskilled, painter: unskilled, unskilled labourer
18.	Printing	Printing
19.	Food	Food handling/processing e.g. canning, baking
20.	Textile and leather	Dressmaker/ sewing machinist/tailor, leather worker
21.	Manufacturing/production	Production worker: wood & paper and products, production worker: chemical, petrol, coal, rubber, plastic, production worker: semi- skilled, packer/ unskilled material handling
22.	Mining	Miner
23.	Informal sector	Informal sector
24.	Legislators, senior officials and managers	Director/manager in government, manager, businessman
25.	Craft and related trades	Performing artist, motor vehicle artisan; mechanic, furniture artisan, carpenter, plumber (domestic)

ii) Shift work

Currently there are no South African literature sources that classify different industries or even job categories according to the prevalence of shift work, and, although there is some information available for other countries, international data may not be entirely appropriate to use in the South African context. For this reason an expert panel was set up to classify occupations by the likelihood of participating in shift work.

Definition of shift work

There are many types of shift work and IARC has described shift work that disrupts circadian rhythm to be carcinogenic; therefore for purposes of the study occupations classified as having shift work will be work that includes night work for a large portion of the time.

The expert group

An expert committee was assembled consisting of three volunteers with substantial experience in occupational health in a variety of industries in South Africa. The volunteers were selected following recommendations from professional bodies, namely the South African Society of Occupational Medicine (SASOM) and the South African Society of Occupational Health Nursing Practitioners (SASHON). The co ordinators of the organizations were asked to recommend and approach members of their organization who had experience in a wide variety of industries and had ideally also had an interest in shift work. The co ordinator then approached the most appropriate member who expressed interest in participating. One member was selected from each society. The third member was a sleep researcher and clinician involved with management of sleep disorders. All three agreed to participate. The experts were then contacted by the researcher by email and a questionnaire (Appendix 2) was distributed to them for their response. The questionnaire was only filled out by the experts once and returned by email to the researcher.

The experts were given a list of occupational groups as per the occupational data available. As stated earlier, the groups were largely based on the European Union survey on working conditions (37) and allowed for a comparison to be made on the likelihood of shift work in the specific industry with other countries.

The experts were asked to estimate the likelihood of occupational engagement in shift work for all occupational groupings. These occupations were classified into: a) high probability of shift work; b) possibility of shift work and c) unlikely to do shift work.

If there no consensus was reached between all three experts, the median opinion was taken for the classification and if all three opinions of the experts differed, the job category was dropped from the study for the shift work analysis.

Table 2 presents a summary of the descriptive variables used in the study.

Table 2: Summary of variables used in descriptive and case control analyses

No	Variable	Type of variable	Further classification of variable
1.	Age	Continuous[1]	Not normally distributed
2.	Alcohol	Categorical[2]	Binary
3.	Smoking	Categorical	Binary
4.	Age at menarche	Continuous	Not normally distributed
5.	Parity	Categorical	Ordinal (categorised in an order)
6.	Menopausal status	Categorical	Binary
7.	Age at menopause	Continuous	Not normally distributed
8.	Oral contraceptive use	Categorical	Ordinal
9.	HIV status	Categorical	Binary
10.	Occupations	Categorical	Nominal- allocation of observations into more than 2 categories (not related to each other)
11.	Shift work	Categorical	Ordinal
12.	Dependant variable:	Categorical	Ordinal

[1] *Definition of a continuous variable*: "A numerical variable taking on a continuum of values is called *continuous "(46)*

[2] *Definition of a categorical variable:"* A categorical variable is *ordinal* if the categories can be logically ordered from smallest to largest in a sense meaningful for the question at hand (we need to rule out silly orders like alphabetical); otherwise it is unordered or *nominal*. " (46)

	Breast cancer		

B. Determination of associations between occupations and breast cancer by calculating the odds ratio (OR) for breast cancer in different occupations in South Africa.

i. Potential confounders

Risk factors for breast cancer used from the JCCS data

- Demographic information: age
- Lifestyle habits: smoking history, alcohol history
- Reproductive information: age at first menarche, parity, age at menopause, use of oral contraception
- Retroviral status

The risk factors for breast cancer were identified from the literature and were analysed based on availability in the JCCS data. Retroviral disease (HIV) status, although not a established risk factor (instead usually not inversely associated with breast cancer) (47), was also adjusted for in the multivariate analysis. This was done based on the contextual importance of the disease within the South African population. These confounders were added and adjusted for in the multivariate model which will later be described.

ii. Case control analyses

Logistic regression was used for the estimation of odds ratios in the case control analyses. The “never worked” occupational category was used as the reference population in the case control analyses.

The following steps were carried out for logistic regression:

1. Creation of binary variables.

For the exposure variable of occupation, binary variables were created where 1 constituted individuals who usually were employed in the occupation compared to 0 (individuals who had never worked).

All occupations that had a frequency less than 30 were dropped from the study as the number of observations were too small to make inferences for both bivariate and multivariate analysis.

2. Bivariate logistic regression:

Bivariate analysis was then carried out to estimate ORs between individual occupations and breast cancer. This was an unadjusted OR (that is, unadjusted for confounding).

3. Multivariate logistic regression:

All the possible confounders present on the JCCS database were considered. These included age, ever smoked, ever drank alcohol, age at first menarche, parity, age at menopause, use of oral contraception and retroviral status

Multivariate logistic regression followed a forward stepwise approach using the STATA command:

xi: sw, pe (0.1) forward lockterm1 : logistic breast_ca (occupation) age alcohol smoking age_period_begin age_period_end parity retro oral_contraceptive_use

to retain the variables in the model. Occupation was locked into the model.

C. Determination of associations between shift work and breast cancer

The same method was used to carry out logistic regression for this objective. First, binary variables were set up where 1 represented the exposure (possibility of shift work or high probability of shift work) and 0 represented unlikely to do shift work. Thereafter, bivariate analysis was done to determine the OR between the shift categories and breast cancer. All the confounders previously listed were forced into the multivariate model and were added in forward stepwise approach using the STATA command:

xi: sw, pe (0.1) forward lockterm1 : logistic breast_ca (shift work category) age alcohol smoking age_period_begin age_period_end parity retro oral_contraceptive_use

To retain the variables in the model, the category of shift work was locked into the model. The category of "Unlikely to do shift work" was used as the reference group.

4. Goodness of fit test

The final multivariate logistic model was analyzed using the Hosmer and Lemeshow's goodness of fit test, with a p-value of ≥ 0.05 being considered as acceptable with regards to the model's fit to the data.

3.10. Ethics Approval

Ethics approval to conduct this research was obtained from the Human Research Ethics Committee (Medical), University of the Witwatersrand, before initiating the study. Clearance was obtained on the 26/02/2014 (Clearance certificate M131126) (Appendix 3). It is not envisioned that anyone would be harmed by the study. All patient information from the JCCS database was anonymized before being given to the researchers.

3.11. Summary of the chapter

Figure 1 provides a graphical representation of a brief summary of the methodology used for the study.

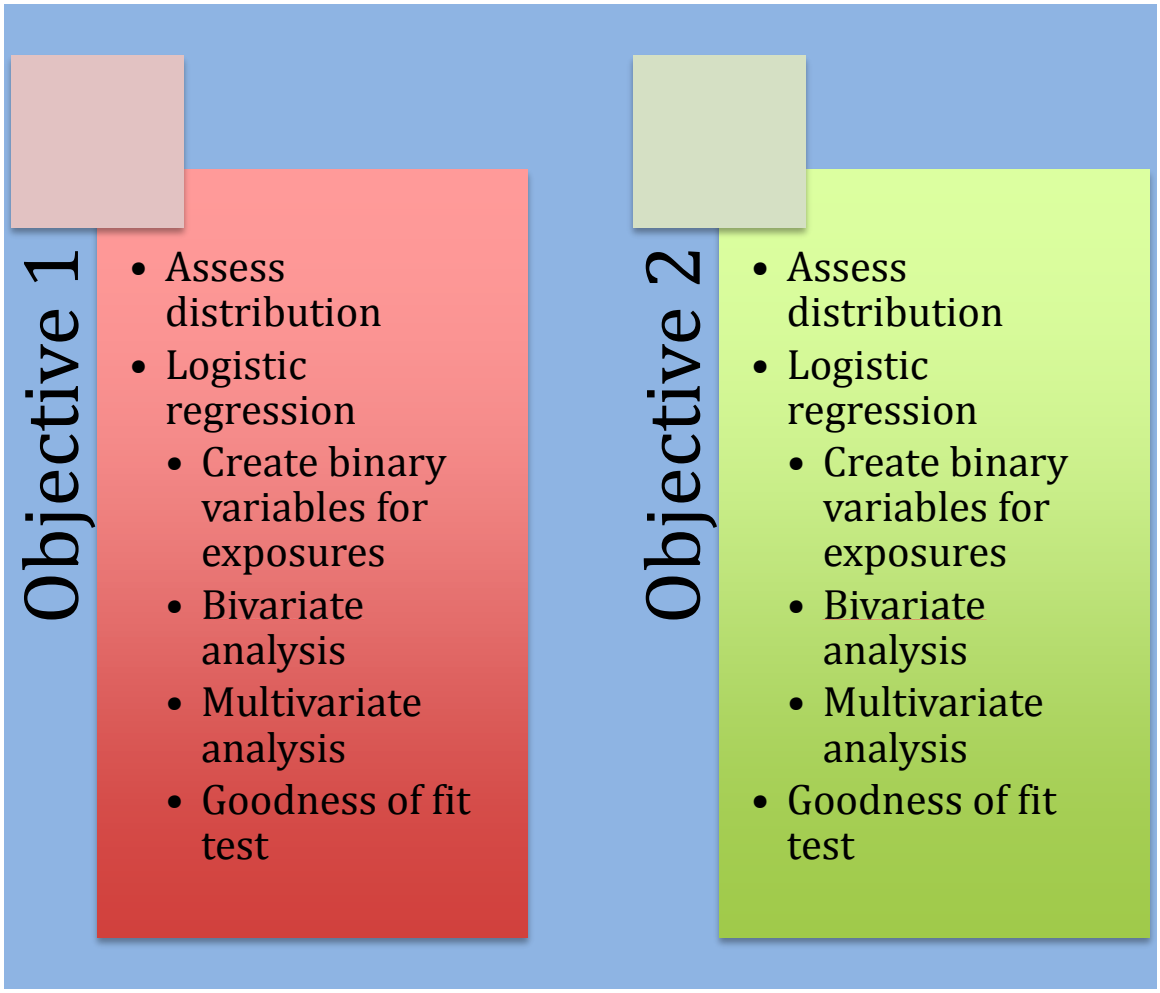

Figure 1: A graphical representation of the methodology

Chapter Four

4. Results

4.1. Chapter Overview

This chapter will detail the results of the study. First, it will give a brief description of the distribution of the cases and controls within the occupation groups as well as their engagement in shift work. The results for the bivariate and multivariate analyses will then be presented to show the relationship, in the study population, between (1) occupations and breast cancer and (2) the likelihood of performing shift work and the risk of breast cancer.

4.2. Demographic and occupational characteristics of the cases and the controls.

4.2.1. Cases and controls

The number of women diagnosed with breast cancer (cases) between 2001 and 2009 was 1 903 (32.3% of all subjects interviewed in the JCCS) and the eligible controls numbered 3 990 (67.7%) . All were entered into the study, although not all for the shift work analyses.

The ages of women with breast cancer ranged between 35 and 88 years of age, while the controls were between 35 and 97 years of age. Table 3 lists the median and IQR for the age at diagnosis, start of menarche and onset of menopause. The data on reproductive and gynaecological history showed the median age of menarche was 15 years for both cases and controls.

Table 3: Age at diagnosis, age at menarche and age at menopause by cases and controls

	Cases		Controls	
	Median	IQR	Median	IQR
Age (years)	51	44 - 60	53	44 - 61
Age at menarche (years)	15	14-17	15	14-17
Age at menopause (years)	48	45-50	48	45-50

Analysis of the behavioural habits of the study participants showed that 15 % of breast cancer cases and 24% of the controls within the study population had a positive smoking history, and around 30% of both cases and controls had used alcohol. Sixteen percent of the cases had a positive Elisa test result for HIV as opposed to 26 % of the controls. Further description of behavioural habits and HIV status are shown in Table 4.

Table 4 : Behavioural habits and HIV status of study participants by cases and controls

	Cases	Controls
	Number (%)	**Number (%)**
Total	1 903 (32.3%)	3 990 (67.7%)
HIV (Elisa result)		
Positive	287 (15.5%)	987 (25.9%)
Negative	1 560 (84.4%)	2 822 (74.1%)
Smoking		
Ever smoked	294 (15.5%)	970 (24.3%)

Never smoked	1 607 (84.5%)	3 018 (75.7%)
Alcohol		
Ever used	579 (30.4%)	1 302 (32.6%)
Never used	1 324 (69.6%)	2 687 (67.4%)

Fifty- six percent of the breast cancer cases were diagnosed post menopause. Sixty- four percent of the controls were diagnosed with cancer pre-menopausally. Slightly more women cases (58%) had three or fewer children in the cases as compared to the controls (49%). The majority of cases (51%) and controls (59%) used five or less years of oral contraceptives. The distributions of cases and controls according to reproductive and gynaecological variables are given in Table 5.

Table 5: Parity, menopausal status and years of oral contraceptive use of study participants by cases and controls

	Cases	Controls
	Number (%)	**Number (%)**
Parity		
Nulliparous	43 (2.3%)	59 (1.5%)
≤3	1 066 (58.1%)	1 907 (49.5)
>3	726 (39.6%)	1 887 (49.0%)
Menopausal status at diagnosis		
Post menopausal	1 048 (55.7%)	2 444 (61.7%)
Pre menopausal	755 (40.2%)	1 354 (64.2%)
Unsure	77 (4.1%)	162 (4.1%)
Oral contraceptive use		

Never	2 (0.3%)	4 (0.4%)
≤ 5 years	316 (51.3%)	554 (58.6%)
6-10 years	102 (16.6%)	191 (18.8%)
≥ 11 years	196 (31.8%)	266 (26.2%)

4.2.2. Occupational distribution of the study participants

Domestic workers represented the major occupation of the study population, with 38% of cases and 47% of the controls engaging in this type of work. The second largest occupational group represented was from the retail and sales industry, with 8% and 6% of the cases and controls respectively. A large proportion of the study participants had never worked and very few participated in transport, security, metal, electrical, printing, mining, management and trade related work. Detailed distributions of cases and controls according to occupational categories are given in Table 6.

Table 6 : Occupation distribution of study participants by cases and controls

	Cases		Controls	
Occupation	**Number**	**Percent**	**Number**	**Percent**
Never worked	109	5.7	273	6.9
Student	0	0	3	0.1
Unemployed	14	0.7	40	1.0
Health	57	3.9	71	1.8
Education	40	2.1	43	1.1
Social services	20	1.1	21	0.5
Office/Clerical workers	71	3.7	82	2.1
Retail/Sales	148	7.8	250	6.3
Transport	2	0.1	6	0.2
Security/Law enforcement	7	0.4	12	0.3
Hospitality	56	2.9	75	1.9
Domestic workers	715	37.6	1 870	46.9

Service workers	85	4.5	173	4.3
Agriculture	19	1.0	87	2.2
Metal workers	5	0.3	11	0.3
Electrical	10	0.5	16	0.4
Construction	47	2.5	76	1.9
Printing	7	0.4	7	0.2
Food	29	1.5	44	1.1
Textile and leather	97	5.1	163	4.1
Manufacturing/Production	70	3.7	108	2.7
Mining	1	0.1	2	0.1
Legislators, senior officials and management	5	0.3	6	0.2
Craft and related trades	5	0.3	6	0.2
Missing information	284	14.9	545	13.7
Total	**1 903**	**100**	**3 445**	**100**

4.2.3. Description of shift work engagement by the participants

4.2.3.1. Classification of shift work

There was full consensus from the expert group that the health, transport, security, metal, manufacturing and mining industry had a high probability of shift work. The majority of experts (2/3) decided that hospitality and printing also had a high probability of shift work.

There was also consensus that individuals who had never worked, the unemployed, office and clerical workers and legislators, senior officials and managers were unlikely to do shift work. However, although the majority decision was that students, domestic workers and informal sector workers were not likely to participate in shift work, consensus on this was not reached.

The majority of experts (2/3) decided that there was a possibility of engagement in shift work in the education, social services, retail, electrical, construction, food and craft/trade

industries. No consensus on the engagement in shift work was reached for service workers, agricultural worker and textile and leather workers. Table 7 details the likelihood of shift work being done in each occupational group represented in the study.

Table 7: Expert panel's opinion on shift work engagement categories by occupational groups.

	Occupation	Expert consensus
High probability of shiftwork	Health	3/3
	Transport/delivery	3/3
	Security/Law enforcement	3/3
	Hospitality	2/3
	Metal workers	3/3
	Printing	2/3
	Manufacturing/Production	3/3
	Mining	3/3
Possibility of shiftwork	Education	2/3
	Social services	2/3
	Retail/ Sales	2/3
	Electrical and electronic	2/3
	Construction	2/3
	Food	2/3

	Craft and related trade	2/3
Unlikely to do shiftwork	Never worked	3/3
	Scholar/student	2/3
	Unemployed	3/3
	Office/clerical workers	3/3
	Informal sector	2/3
	Domestic workers	2/3
	Legislators, senior officials and managers	3/3
No agreement between experts (i.e. no categories chosen by experts were the same)	Service workers	1/3
	Agriculture	1/3
	Textile and Leather	1/3

4.2.3.2. Engagement in shift work distribution of the study participants

After classifying the occupations into categories of likelihood of engagement in shift work, the majority of the study participants were categorized as unlikely to participate in shift work in both the cases (75.5%) and controls (64.5%). Almost 15% of the cases had a possibility of participating in shift work compared to 21.1% of the controls. Lastly, 14.5 % of the controls and 9.6% of the cases had a high probability of engagement in shift work in the

study population. Figure 2 graphically represents the engagement in shift work of the participants.

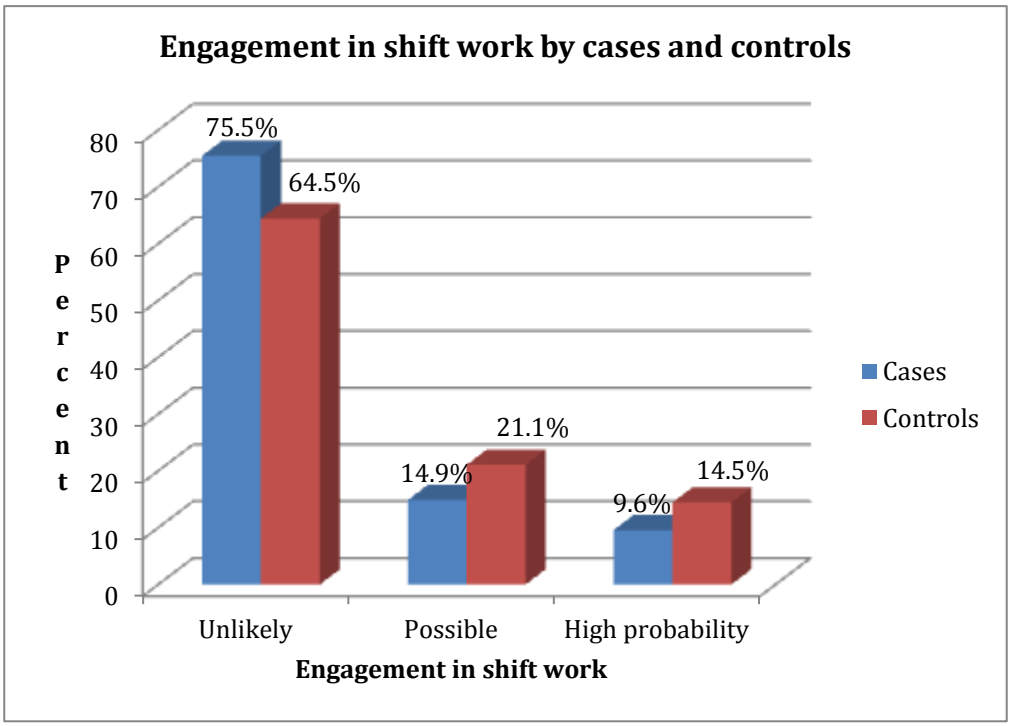

Figure 2: Distribution of participants engaged in shift work by cases and controls

4.3. Determination of associations between different occupations and breast cancer by calculating the odds ratio (OR) for breast cancer in different occupations in South Africa.

4.3.1. Bivariate logistic regression

The bivariate logistic regression findings are shown in Table 8. The strongest associations between increased risk of breast cancer and occupation are seen in the education (OR 2.33, 95% CI: 1.44 – 3.78) and social service (OR 2.39, 95% CI: 1.24 – 4.58) industries followed by office workers (OR 2.17, 95% CI: 1.47-3.20) and health workers (OR 2.01, 95% CI: 1.33-3.04). The unemployed (OR 0.88, 95% CI: 0.46 – 1.68), domestic (OR 0.96, 95% CI: 0.75 – 1.22) and agriculture (OR 0.55, 95% CI: 0.32 – 0.94) categories had ORs below one.

Table 8 : Unadjusted ORs of breast cancer for specific occupational groups as compared to women who never worked.

	Cases	Controls	OR	95% CI	P value
Never worked	109	273	1		
Unemployed	14	40	0.88	0.46- 1.68	0.690
Health	57	71	2.01	1.33-3.04	0.001
Education	40	43	2.33	1.44- 3.78	0.001
Social services	20	21	2.39	1.24-4.58	0.009
Office worker	71	82	2.17	1.47-3.20	0.000
Retail/Sales	148	250	1.48	1.10-2.00	0.010
Hospitality	56	75	1.87	1.24- 2.82	0.003
Domestic workers	715	1870	0.96	0.75- 1.22	0.722
Service workers	85	173	1.23	0.87-1.73	0.234
Agriculture	19	87	0.55	0.32- 0.94	0.030
Construction	47	76	1.55	1.01- 2.37	0.044
Food	29	44	1.65	0.98- 2.77	0.058
Textile	97	163	1.49	1.07- 2.08	0.020
Manufacturing	97	108	1.62	1.12- 2.36	0.011

4.3.2. Multivariate analysis

The findings of the multivariate logistic regression are displayed in Table 11. After adjusting for the potential confounders, manufacturing (OR 1.44, 95% CI: 0.42- 4.94), office workers (OR 1.44, 95% CI: 0.31-5.94) and health workers (OR 1.31, 95% CI: 0.36-4.76) had OR > 1. However all associations were not statistically significant. The goodness of fit test was significant in health workers, office workers, retail and sales workers, agriculture and manufacturing workers showing that for these occupations the logistic regression model fitted the data. Table 9 lists the OR for breast cancer in each occupation after adjusting for the previously listed confounders in a multivariate logistic regression model. It also shows the results of the goodness of fit tests.

Table 9: Adjusted ORs of breast cancer for specific occupational groups as compared to women who never worked and goodness of fit test results

	Cases	Controls	Adjusted OR	95% CI	P value	Goodness of fit test P value
Never worked	109	273	1			
Unemployed	14	40				
Health	57	71	1.31	0.36-4.76	0.685	0.16
Education	40	43	0.47	0.09-2.57	0.385	0.02

Social services	20	21			[3]	
Office worker	71	82	1.35	0.31-5.94	0.694	0.6
Retail/Sales	148	250	1.14	0.33-3.94	0.837	0.3
Hospitality	56	75	0 .89	0.21-3.91	0.880	[4]
Domestic workers	715	1870				
Service workers	85	173				
Agriculture	19	87			[5]estimability	0.3
Construction	47	76	0.875	0.23-3.3	0.845	[5]
Food	29	44	0.74	0.10-5.36	0.768	[5]
Textile	97	163	0.63	0.20-1.91	0.410	[5]

[3] Adjusted OR could not be calculated as convergence not achieved

[4] The statistical software was unable to calculate the goodness of fit test because there were not enough degrees of freedom.

[5] Adjusted OR could not be calculated due to estimatability i.e. not being able to esimate the variable.

Manufacturing	97	108	1.44	0.42-4.94	0.567	0.5

4.4. Determination of associations between shift work and breast cancer

4.4.1. Bivariate analysis

Table 10 shows unadjusted ORs for breast cancer in shift workers. Shift work was associated with breast cancer in possible shift workers (OR 1.66, 95% CI: 1.41-1.97) and those who had a high likelihood of participating in shift work (OR 1.76, 95% CI: 1.44-2.15).

Table 10: Unadjusted OR for breast cancer in women workers who may participate in shift work relative to women workers who are unlikely to participate in shift work

	Cases	Controls	OR	CI	P value
Shift work unlikely	914 (64.3%)	2 064 (75.5%)	1		
Possibility of shift work	299 (21.1%)	406 (14.9%)	1.66	1.41-1.97	0.000
High likelihood of shift work	205 (14.5%)	263 (9.6%)	1.76	1.44-2.15	0.000

4.4.2. Multivariate analysis

Multivariate logistic regression, after adjusting for the potential confounders, showed a significant increase in OR (OR 2.18, 95% CI: 1.34- 3.56) in women who possibly do shift work and those who have a high likelihood of carrying out shift work (OR 2.13, 95% CI: 1.26- 3.61)

as seen in Table 11. The goodness of fit for both models was significant and showed a fit with the data. There was no trend in increasing ORs as the likelihood of shift work increased.

Table 11: Adjusted OR for breast cancer in female workers who may participate in shift work relative to female workers who are unlikely to participate in shift work

	Cases	Controls	OR	CI	P value	Goodness of fit test P value
Shift work unlikely	914 (64.3%)	2 064 (75.5%)	1			
Possibility of shift work	299 (21.1%)	406 (14.9%)	2.18	1.34-3.56	0.002	0.3
High likelihood of shift work	205 (14.5%)	263 (9.62%)	2.13	1.26-3.61	0.005	0.5

4.5. Summary of the results

This chapter briefly describes the important findings of the study. It described the cases and controls and stratified them into risk factors that are known to be associated with breast cancer. It also showed the distribution of cases and controls in the different occupational groups. The findings of the expert group were then presented and the occupations sorted according to the likelihood of participation in shift work for both cases and controls. Bivariate and multivariate analyses was then presented.

With regards to occupation, the bivariate analysis showed significant ORs for breast cancer in health (OR 2.01, 95% CI: 1.33 – 3.04), education (OR 2.33, 95% CI: 1.44 – 3.78), social services (OR 2.39, 95% CI: 1.24 – 4.58), retail (OR 1.48, 95% CI: 1.10 – 2.00), hospitality (OR 1.87, 95% CI: 1.24 – 2.82), construction (OR 1.55, 95% CI: 1.01 – 2.37), food (OR 1.65, 95%

CI: 0.98-2.77), textile (OR 1.49, 95% CI: 1.07 – 2.08) and manufacturing (OR 1.62, 95% CI: 1.12 – 2.36).

Following the adjustments for possible confounding, no significant ORs were found between specific occupations and breast cancer. Despite the highest ORs found for manufacturing (OR 1.44, 95% CI: 0.42- 4.94), followed by office workers (OR 1.44 95% CI: 0.31-5.94) and health workers (OR 1.31, 95% CI: 0.36-4.76), the wide confidence interval for all these groups of workers, the implied effect should be treated with caution, given that at the lowest end, these occupations could exert a protective effect and at the highest end of the confidence interval a causative effect.

In the bivariate analyses there was an association between a possibility of doing shift worker and breast cancer (OR 1.66, 95% CI: 1.41-1.97). Similarly, women who had a high likelihood of participating in shift work had an elevated odds ratio for the disease (OR 1.76, 95% CI: 1.44-2.15). After adjusting for confounders in the multivariate model the ORs for both groups were increased with women who possibly did shift work having an OR of 2.18 (95% CI: 1.34- 3.56) and those who had a high likelihood of carrying out shift work having an OR of 2.13 (95% CI: 1.26- 3.61).

CHAPTER FIVE

5. Discussion

5.1. Chapter overview

This study aimed to identify occupations associated with breast cancer in black women registered in the JCCS database and then to evaluate if the likelihood of shift work was associated with a diagnosis of breast cancer.

Following the adjustments for possible confounding, no significant ORs were found between specific occupations and breast cancer however after adjusting for confounders in the multivariate model, the ORs for women who possibly did shift work (OR 2.18, 95% CI: 1.34-3.56) and those who had a high likelihood of carrying out shift work (OR 2.13, 95% CI: 1.26-3.61) showed double the odds than women who were unlikely to do shift work.

This research report will discuss these results further looking particularly at occupational groups and breast cancer, shift work and breast cancer and then lastly the limitations of the study will be highlighted.

5.2. Occupational groups and breast cancer

The results of this study, on bivariate analysis, showed that significantly high odds ratios were observed in women working in education (OR 2.33, 95% CI: 1.44 – 3.78), social services (OR 2.39, 95% CI: 1.24 – 4.58) and in office workers (OR 2.17, 95% CI: 1.47-3.20). Although, these high odds ratios are in keeping with some studies found in the literature the wide confidence interval suggest that these results should be treated with caution.

Specific predisposing exposures associated with breast cancer are not obviously apparent amongst education workers, but some studies have noted an increased risk in this group. One such study, that examined breast cancer related deaths in different occupations representing 23 states of the USA, found that teachers accounted for more than 5% of all breast cancer deaths with black teachers, in particular, having double the expected frequency of breast cancer mortality. In the study, increased proportionate mortality ratios and odds ratios were found in all teachers when stratified for age and even when stratified into different levels of teaching (namely primary and secondary school teachers and post secondary school teachers)(3). Similar results were seen in a Californian cohort of teachers where a much higher risk of breast cancer was observed, with a 51% higher age standardized invasive breast cancer incidence rate and a 67% higher in situ breast cancer incidence rate than expected based on race specific nationwide rates (48). A Shanghai study also showed higher risks amongst teachers (OR = 1.5, CI 1.1-2.1) (49).

Numerous studies have also reported a higher risk of breast cancer for administrative (office workers) and professional jobs (39,50). It has also been documented that white collar workers, which included managers, clerical and secretarial work, teachers, scientists and the clergy, have all shown a higher risk in some studies (50,51). With respect to the occupational category of legislators, senior officials and managers our study did not have sufficient numbers to allow for appropriate conclusions to be drawn and, for this reason, this group was dropped from our study.

It is noteworthy that, in this study, the multivariate regression analyses, i.e. adjusted for age and other, mostly reproductive, factors no longer produced statistically significant ORs. An explanation is that occupational choices may accompany lifestyle choices with occupations that require higher levels of educational qualifications having a higher occurrence of non-occupational risk factors such as decreased parity, higher age at first pregnancy and higher

contraceptive use (3). This is supported by strong evidence that higher levels of education are associated with lower levels of fertility to the extent that educational levels have been used as a marker for fertility change (51–53).

After adjusting for the potential confounders women in the manufacturing industry had the highest OR (OR 1.44, 95% CI: 0.42- 4.94) followed by office workers (OR 1.435, 95% CI: 0.31-5.94) and health workers (OR 1.31, 95% CI: 0.36-4.76).

It was anticipated that manufacturing industries would have an increased risk of breast cancer. But, even though the OR (OR 1.44, 95% CI: 0.42- 4.94) was the highest found in multivariate analyses, this was not statistically significant. The literature presents mixed results on increased risk in workers exposed to manufacturing involving rubber and plastic (possibly because of the release of oestrogenic chemicals), wood and paper and organic solvents. However, many of these studies examined breast cancer associated mortality rates (50).

Office workers showed an OR of 1.44 (95% CI: 0.31-5.94) which, again, was not statistically significant. Numerous studies have also reported a higher risk of breast cancer for administrative (office workers), professional jobs (39,50) and white collar workers in general (50,51).

Although health workers also showed an increased risk, after adjusting for confounders this result was also not statistically significant (OR 1.31, 95% CI: 0.36-4.76). This was unexpected, given that health workers may be exposed to many carcinogens in the workplace. These include exposure to ethylene oxide, chemotherapy drugs, organic solvents and radiation.

It should be noted that the multiplicity of carcinogenic exposures complicates the interpretation of the results. Furthermore, the risks may be diluted, and the findings confounded, because of the pooling of large groups of professionals in the health category (50).

More recent, and interesting, research concerning possible aetiological pathways of breast cancer explores the social stress pathway (54). Here it is postulated that prolonged exposure to steroid hormones produced by the adrenal cortex activates the glucocorticoid receptor. This receptor is expressed in human breast tissue and directly promotes mammary cell proliferation and inhibits apoptosis, increasing the risk of malignant transformation (54). This may be a further confounder, given the high prevalence of stress in our society (55) or it may even be part of a further consequence of occupational stress which is common in the health (56,57) and education (58–60) industries which have, in some of the literature, been linked to high prevalence of stress. This may help to shed light on why the literature cites white collar workers, professionals, health care workers and teachers to have a higher risk of breast cancer.

It was expected, from the literature, that agricultural workers would have an increased risk of breast cancer given their exposure to possible carcinogenic substances. Many pesticides have been described as mammary carcinogens in animal studies (61). However, this was not seen in this study, and there have been mixed results in other studies of agricultural workers and their risk of breast cancer (50,61). A paradox was seen in a Nordic study following up 15 million people in five countries where it was found that agricultural workers showed some of the lowest risks (51). One reason that has been postulated for this reduction in risk is that the high level of physical activity may account for the decreased risk; however, physical activity is still a disputed risk factor for breast cancer.

Service industry workers in this study included beauticians and hairdressers (who are also exposed to a large number of potentially toxic hair dyes, solvents etc). However no increased risk was noted (39,50). The literature shows mixed results when studying the risk in these occupational groups, despite IARC's classification that exposures from these occupations are probably carcinogenic to humans.

Dry cleaning workers were also represented in the service industry and it is postulated that this increased risk may be due to exposure to organic solvents. However, this was not shown in our study, and may, again, be a result of the pooling a large group of professions with exposures into this group.

Metal workers showed no increased risk in this study, despite this industry exposing workers to metallic fumes, metalworking fluids, polycyclic aromatic hydrocarbons (PAHs) and solvents. A few studies have shown an increased risk of breast cancer in women exposed to PAHs and benzene, particularly in pre-menopausal women, and a weak association was seen between exposure to soluble metalworking fluid and breast cancer (50).

This study found similar results to the majority of the literature around the risk of textile and clothing workers, where no significant association was found. While a few studies have shown an increased risk in this group, these were in the minority (39).

Other studies have also found higher rates of breast cancer in the military, journalists, administrators and artists (50). This study, again, did not find any increased risk of significance in these occupational groups, some of which were too small to give meaningful results.

In summary, although bivariate analysis showed some increased risk in a few industries, however after adjusting for confounding no statistically significant increased risk was shown with regards to specific occupations. Many studies that have shown a link with certain occupations and breast cancer have warned that the results should be interpreted with caution and that the excess risk may be confounded by previously mentioned reproductive factors (50). Also, many studies have not been able to quantify exposures, which may lead to exposure misclassification and biased findings.

5.3. Shift work and breast cancer

An important finding of this study was that the women who had worked in occupations that had a possibility of carrying out shift work had a more than doubled risk (OR 2.18, 95% CI: 1.34- 3.56) of developing breast cancer than women who were unlikely to do shift work. Furthermore women who were employed in occupations that had a high likelihood of engaging in shift work also had a more than double risk (OR 2.13, 95% CI: 1.26- 3.61) relative to women who worked in occupations that were unlikely to participate in shift work. It would be expected that employees with a higher likelihood of participating in shift work would be at higher risk of developing breast cancer, however the results of this study lack the dose response that is expected in a causal relationship.

These notable findings are in keeping with the available literature as well as the IARC classification, which categorises shift work as a probable human carcinogen. A few pathological mechanisms related to this have been described in the literature. Night-time light exposure decreases melatonin production. Melatonin is said to increase p53, shield DNA from oxidative damage and act as an immune modulating agent; in these ways it exerts a protective effect against cancer (62).

Some of the literature suggests that different types of night workers have differing risks of developing breast cancer. It has been proposed, for example, that while permanent night work may have an increased risk, the risk associated with rotating shift work is the highest

as workers are not able to regulate the circadian shift rhythm at all and, therefore, have the lowest melatonin levels (62). However, due to the limitations of our study (which are discussed below), data related to this level of exposure details were not available.

5.4. Limitations

5.4.1. Representativeness of study subjects relative to the female labour market during the study period.

The female labour market in South Africa has been growing since the 1960's with a peak noted between 1995 and 2000. Over these decades, the female working population grew by 12% as compared to the 33% increase that was noted in the male work force during that same time period. Over three million women became economically active after the end of apartheid, with more than half of them self-employed in the informal sector. The growth was more modest after 2000 and a slow decline was noted after the start of global economic crisis (63).

Domestic workers represented a substantial proportion of the study population: 38% of the cases and 47% of the controls having been employed in this industry. Although these figures are high, it seemed to be broadly representative of the nationwide frequency of women in the domestic industry over the study time period (domestic work constituted about 46% of the work force in 2007) (63).

The community and social services sector, as well as wholesale and retail sector, were also large employers of women during the time of the study (63). This coincides with the distribution of women workers in the study population. The retail industry accounted for the second largest occupation represented in the study population, with 8% of the cases

and 6% of controls belonging to this industry. It is difficult to ascertain the particular job types which were included in the nationwide assessment of the community and social service industry and, hence, adequately to compare this to the study population. Having said this, if health, education and social services are combined they make up 7% of the cases and approximately 4 % of the controls.

The other industries which employed large numbers of women in South Africa during this time period were manufacturing and finance, insurance and business (63,64). Manufacturing and production accounted for about 4% of cases and 3% of controls respectively. However, women in finance, insurance and business were not well represented in my study. Women in these industries may have had private medical aid and therefore may not have accessed the public oncology services from which the study population was recruited.

“Never worked” and “unemployed” represented about 8% of the study population. This was not truly reflective of the unemployment rates at the time of the study which fluctuated around 30% in women (63,64). This may be explained by the questionnaire which asked for the usual occupation of the participant, which may differ from whether the participant is currently employed at the time of answering.

In summary, the study subjects were likely broadly to represent occupational categories of South African women but with some deficiencies. For example, higher income occupations and those conducted in more rural settings. Generalisation of findings to South Africa as a whole should therefore be done with caution.

5.4.2. Exposure misclassification

5.4.2.1. Occupations

Some of the limitations of this study are that there may be misclassification of the exposure (occupation) due to broad occupational categorisations as surrogates for exposure. This grouping, which was done because of the restricted occupational data available, may not be reliable as women in the same occupational category may have vastly different exposures. This misclassification may have led to a loss of statistical power and an attenuation of risk ratios (39).

A major weakness of this study is potential exposure misclassification due to our limited knowledge of time-periods of the occupational history of participants. In terms of exposure to occupational carcinogens, a very relevant factor is the latency period (that is, the duration from initial exposure to onset of the disease or date of diagnosis). Some literature cites that solid tumours, such as breast tumours, require a latency period of 10 to 30 years before the onset of the disease. This may not be represented in the usual occupation, which may be the most recent occupation and hence not necessarily the work setting in which exposure to carcinogenic agents could have occurred. Additionally, ORs could not be calculated taking account of relevant latent periods.

As stated the JCCS database captures usual occupation or workplace. This could lead to bias away from the null hypothesis if subjects changed their occupation (39) i.e. had unrecorded occupations associated with a risk of breast cancer.

One of the benefits of using such a large database of cases and controls is that it is hoped that the large numbers would result in stable estimates of the risk of breast cancer (65).

However a few occupations had few observations and so could not be assessed. These occupations included transport, security, metal, electrical, printing, mining, management and trade related work. However, more data may be available for future analyses as women become more active in these industries.

5.4.2.2. Shift work

Issues around working hours have been particularly problematic in South Africa, and official statistics show a very high incidence of long working- hour weeks. Within the first quarter of 2009, 25% of all employed women worked more than 45 hours a week. However, there was no further information available on how this overtime was worked and if night work was involved (63).

While compiling a list of the likely industries to be involved in shift work, this study described a high probability of shift work (that includes night work for a large proportion of the time or regular night work) for workers involved in health, transport and hospitality. For the most part, similar occurrences of shift work have been described in other countries. With regards to the health industry, the European Union (EU) survey on working conditions (which takes into account a numerous countries within the EU), shows a prevalence of shift work within the health industry to be 35.5%. This differs from the US Bureau of Labor Statistics which records a prevalence of 12.8% (38). However the US statistics are combined with the education industry (38) which is likely to lower the true representation of shift work within the health industry

Transport in both the US and Europe show a prevalence of shift work of around 25-30%. (38) Similarly, in the South African setting, it was decided that there was a high likelihood of

shift work by the expert panel. The hospitality industry was another industry that was considered to have a high likelihood of shift work. These data are reflected in statistics from then the EU but even more so in the United States where a prevalence of 46% is documented (37). Manufacturing and mining also had a high prevalence of shift work in both the EU and the US surveys, with 26 % for the two industries combined in EU and in the US 31% for mining and 17% for manufacturing. Law enforcement had a moderate prevalence of shift work of 19% in the EU as compared to my results. Metal workers and printing industries could not be directly compared with international statistics as there was no such grouping. However, communication and production industries (which may have included these groups) did have a high prevalence of shift work internationally.

The expert panel classified education as being possibly associated with shift work. The EU survey gave a prevalence of shift work of 8% within this industry and the US data were difficult to interpret given that education was combined with health. A striking difference was noted in the retail/sales industry, where Western countries reported very high prevalence of shift work (37), but in the South African setting this was suggested as only possibly entailing shift work. This is likely to be due to the large retail culture in more developed countries, with 24-hour access and convenience being more prevalent, thus requiring more staffing at unusual hours. Construction had a very low prevalence of shift work internationally, with 5% or less reported in EU countries and the US. This contrasts somewhat with the opinion of the expert panel, however the poor definition of possibility of shift work may account for this.

Craft-related trades and the electrical industry had a moderate prevalence of shift work in the EU survey, which was in keeping with the opinion of the experts. The other industries within the possibility of shift work category could not be compared, as these categories did not exist in the survey.

Office workers were classified as unlikely to participate in shift work by the expert panel. This differed slightly with the EU findings where there was a prevalence of 13%. While shift work within this group was also documented as being high in the US, it was combined with sales and so cannot be adequately compared. Legislators were classified as unlikely to do shift work in our study and this sentiment was shared internationally (37). Very little is documented on shift work in the informal sector and domestic workers.

A considerable limitation to this study is the classification of shift work (37), which made it impossible to measure the nature, duration and intensity of shift work. For the purposes of this study a definition of shift work referred to women who did night work for a large proportion of the shifts worked. However, quantifying this exposure could not be done with the available information in the existing database. Specific information on shift load (time spent in shift work), the week load (the average length of a working week), type of shift work schedule, the availability of rest periods (and consistency of this) and the predictability of the shift pattern would have allowed the researcher to better assess the "dose response". Given the poor quality of data on shift work in this study as well as the lack of literature on the prevalence of this in the South African setting, the associations shown between shift work and breast cancer may be spurious and require confirmation by studies that reliably measure risky night shift work.

5.4.3. Disease misclassification

Although misclassification of the outcome is a potential limitation, this was addressed in the study by using data of histologically confirmed breast cancer cases and histologically confirmed non-breast cancer subjects as controls. Controls with unclear diagnoses were excluded. Misclassification of cases and controls sufficient to influence findings is considered unlikely.

5.4.4. Confounding

A limitation of using the JCCS database is that not all important risk factors may have been adjusted for due to the unavailability of data on these variables within the database. Although a variety of confounders were adjusted for (including age, alcohol, smoking, parity, age at menarche, age at menopause, and oral contraceptive use) important risk factors that were not available in the database include a family history of breast cancer or a previous history of benign breast neoplasm, socioeconomic status, physical activity, obesity and other environmental factors; these confounders could not, therefore, be adjusted for. Furthermore, although alcohol was adjusted for, the data was categorised into only 2 categories which could lead to residual confounding. Socioeconomic status is also an important confounder to be controlled for, however the study participants of the JCCS database is limited to black women using the public hospital which may limit the effect of socioeconomic status in the study. Retroviral disease was adjusted for in this exploratory approach given the importance of HIV in this setting. However in future studies the effect of HIV as an effect modifier needs to be more thoroughly explored and the model run separately for HIV positive and HIV negative individuals.

5.4.5. Analysis deviance.

5.4.5.1. Selection of the reference group

The reference group selected for the case control analyses comprised those participants who had never been employed. A review article suggested removing housewives from the reference group to control for reproductive related risk factors, since “housewives” may

have a different reproductive history to employed women (39). Housewives were not removed from the reference group in this study because detailed reproductive history was captured in the JCCS database.

The above limitations notwithstanding, the JCCS has been used in studying exposures and outcomes in poor resource settings effectively for more than a decade. Furthermore, the method of utilising cancer patients as controls has been used in investigating cancer risk in relation to HIV, Herpes virus 8, and tobacco smoking and has produced credible results. Using cancer controls also generally reduces the effects of referral bias, since both cases and controls have had the same referral drivers into the study hospital.

5.4.5.2. Analytical method

The method of analysis for this study employed a forward stepwise logistic regression model. This methodology may have resulted in partial adjustment by omitting established confounders from the analysis.

CHAPTER SIX

6. Conclusion and recommendations

6.1. In summary

The study showed no statistically significant association between breast cancer and occupations after adjusting for confounding. Moreover, women who possibly participated in shift work (OR 2.18, 95% CI: 1.34- 3.56) and those who had a high likelihood of performing shift working in their usual occupation (OR 2.13, 95% CI: 1.26- 3.61) showed a statistically significant increased risk of developing breast cancer.

6.2. Recommendations

6.2.1. Control of the hazard

To date very little has been done regarding protecting employees against the harmful effects of shift work in South Africa.

An important step would be to ensure that shift work is better regulated in South Africa (37). International codes of practice have been written in relation to working time, and a convention on night work has been drawn up by the International Labour Organization (ILO) (37).

South Africa, too, has legislation to regulate night work. Although the Occupational health and Safety act (Act No. 85 of 1993)(37) is the overarching legislation on hazard control in the workplace, control of night work falls within the Basic Conditions of Employment Act (BCEA). Specifically, within Chapter 2 of Section 17 of this Act there are regulations which lay down the conditions for night working. These conditions state that regular night workers need to

be informed of the health and safety risks as well as the need to undergo medical surveillance. It also details that the employee, at his/her request, should undergo a medical examination at the start (or within a reasonable period after starting) this type of work. Thereafter the employee should undergo regular medical surveillance. The Act stipulates that, where reasonably practicable, when a medical condition is associated with shift work, the person with the condition should be accommodated by day shift work. Within the BCEA, there is a Code of good practice on the arrangement of working time which aims to provide information and guidance on arrangements of working time and their effects on health, safety and family responsibility (66).

While there is some legislation and guidance around night work, it does not adequately cover how to control shift work. Moreover, there is no comprehensive guidance on how night work should be organised, the frequently of night work within the shift timetable, periodicity, shift load (that is, the average length of shifts) and week load (that is, the average length of the working week), frequency for night rest and constancy in night rest (variation in the week) or the predictability of the shift cycles that promote the health of the employees.

The guidance needs to be improved and should be referenced on the ILO Convention 171 on night work. Some of the conditions mentioned in the Convention are that normal hours for night workers should not exceed eight hours in a 24 hour period (during which they are performing night work), other than those periods of mere attendance or standby. Night workers should generally work less hours than day shift workers who perform the same job. Full-time shifts should not be done consecutively and rest periods of at least 11 hours should be taken between shifts (37).

6.2.2. Risk based medical surveillance

Risk-based medical surveillance needs to be considered as it takes into account the presence of the hazard in the workplace together with the health effects caused by the

hazard. It then offers targeted surveillance to ensure early detection of the medical effect caused in an attempt to treat early and also control the hazard so that other employees are not also exposed to health risks.

Breast cancer is one of the most successfully treated cancers. Breast cancer mortality has steadily dropped over the last few years due to advances in treatment and early detection of disease by screening mammography.

Mammograms are recommended for females over 40 and then usually every 2 years (1) thereafter. Initially it was thought that occupations with higher risks of breast cancer should be targeted to have on site mammography offered. However if such occupations exist they are poorly defined, making this approach problematic. However, there is more certainty regarding shift work and targeting women night shift workers has a sounder basis, although operational and cost-benefit aspects need much consideration.

The Occupational Health and Safety Act gives the responsibility to the employer to offer medical surveillance for known hazards in the workplace and the duty of the employee to present him/herself for the medical surveillance. There are some studies where worksite health screening programmes have provided assessment opportunities for health promotion in some instances (where cancer is not occupational) and these have been have allowed for access to a necessary health service (3). However, more research should be done on the effectiveness of implementing this type of screening in the workplace taking into account problems with quality and interpretation of onsite mammograms as well as cost effectiveness.

There are some studies where worksite health screening programmes have provided assessment opportunities for health promotion in some instances (where cancer is not occupational) and these have been have allowed for access to a necessary health service (3).

6.2.3. Future studies

This study serves as an initial, exploratory study. Further research, therefore, needs to be done in this area as many gaps continue to exist around occupational risk factors for breast cancer. Indeed, the increasing trend of breast cancer within the South African population requires urgent investigation into possible causes.

In conclusion, this study reports a strong association of breast cancer in shift workers, which is supported by the literature. However shift work still remains necessary for the economic development and progress in many industries. Many gaps exist, however, and this study has tried to address one of the neglected areas of occupational risks for breast cancer development. Understanding the shift patterns associated with breast cancer risk, the specific pathological mechanisms involved and how these can be avoided in the workplace will allow for the formation of good workplace practice and, ultimately, regulations that could improve healthy workplace policies around night work.

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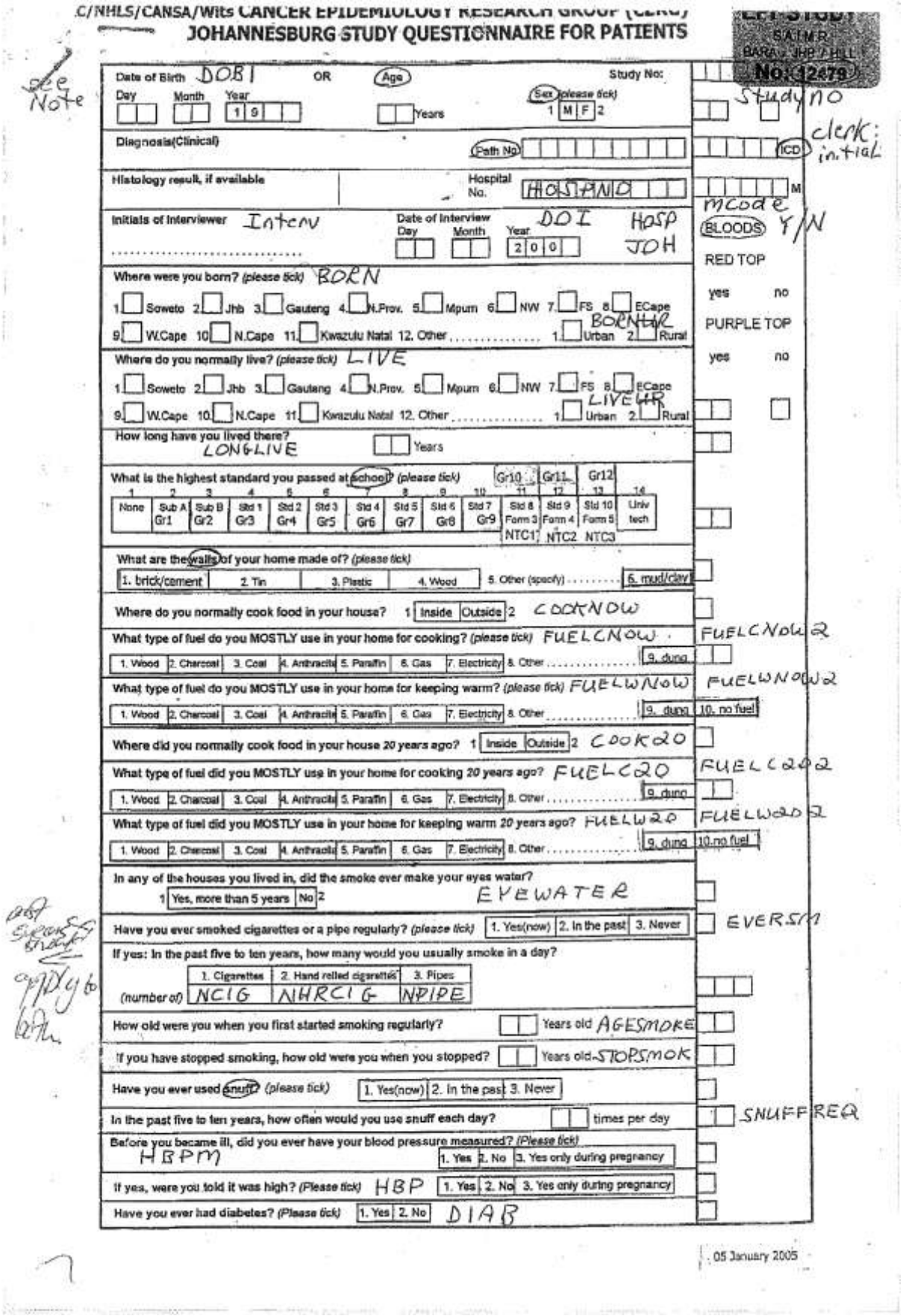
Appendix 1: Questionnaire filled in by nurses when patients are recruited for the JCC Study



C/NHLS/CANSA/Wits CANCER EPIDEMIOLOGY RESEARCH GROUP (CERG)

JOHANNESBURG STUDY QUESTIONNAIRE FOR PATIENTS

SAIMR BARA / JHB / HILL

No: 12479

See Note

Date of Birth DOB1 OR Age Study No: Study no

Day Month Year 1 9 Years Sex (please tick) 1 M F 2

Diagnosis(Clinical) Path No ICD clerk: initial

Histology result, if available Hospital No. HOSPNO M mcode

Initials of Interviewer Intcnv Date of Interview Day Month Year DOI 2 0 0 HOSP JOH

BLOODS Y/N

RED TOP yes no

PURPLE TOP yes no

Where were you born? (please tick) BORN

1 Soweto 2 Jhb 3 Gauteng 4 N.Prov. 5 Mpum 6 NW 7 FS 8 ECape 9 W.Cape 10 N.Cape 11 Kwazulu Natal 12. Other ..... BORNUR 1 Urban 2 Rural

Where do you normally live? (please tick) LIVE

1 Soweto 2 Jhb 3 Gauteng 4 N.Prov. 5 Mpum 6 NW 7 FS 8 ECape 9 W.Cape 10 N.Cape 11 Kwazulu Natal 12. Other ..... LIVEUR 1 Urban 2 Rural

How long have you lived there? LONGLIVE Years

What is the highest standard you passed at school? (please tick) Gr10 Gr11 Gr12

1	2	3	4	5	6	7	8	9	10	11	12	13	14
None	Sub A Gr1	Sub B Gr2	Std 1 Gr3	Std 2 Gr4	Std 3 Gr5	Std 4 Gr6	Std 5 Gr7	Std 6 Gr8	Std 7 Gr9	Std 8 Form 3 NTC1	Std 9 Form 4 NTC2	Std 10 Form 5 NTC3	Univ tech

What are the walls of your home made of? (please tick)

1. brick/cement 2. Tin 3. Plastic 4. Wood 5. Other (specify) ..... 6. mud/clay

Where do you normally cook food in your house? 1 Inside Outside 2 COOKNOW

What type of fuel do you MOSTLY use in your home for cooking? (please tick) FUELCNOW FUELCNOW2

1. Wood 2. Charcoal 3. Coal 4. Anthracite 5. Paraffin 6. Gas 7. Electricity 8. Other ..... 9. dung

What type of fuel do you MOSTLY use in your home for keeping warm? (please tick) FUELWNOW FUELWNOW2

1. Wood 2. Charcoal 3. Coal 4. Anthracite 5. Paraffin 6. Gas 7. Electricity 8. Other ..... 9. dung 10. no fuel

Where did you normally cook food in your house 20 years ago? 1 Inside Outside 2 COOK20

What type of fuel did you MOSTLY use in your home for cooking 20 years ago? FUELC20 FUELC202

1. Wood 2. Charcoal 3. Coal 4. Anthracite 5. Paraffin 6. Gas 7. Electricity 8. Other ..... 9. dung

What type of fuel did you MOSTLY use in your home for keeping warm 20 years ago? FUELW20 FUELW202

1. Wood 2. Charcoal 3. Coal 4. Anthracite 5. Paraffin 6. Gas 7. Electricity 8. Other ..... 9. dung 10. no fuel

In any of the houses you lived in, did the smoke ever make your eyes water?

1 Yes, more than 5 years No 2 EYEWATER

Have you ever smoked cigarettes or a pipe regularly? (please tick) 1. Yes(now) 2. In the past 3. Never EVERSM

If yes: In the past five to ten years, how many would you usually smoke in a day?

	1. Cigarettes	2. Hand rolled cigarettes	3. Pipes
(number of)	NCIG	NHRCIG	NPIPE

How old were you when you first started smoking regularly? Years old AGESMOKE

If you have stopped smoking, how old were you when you stopped? Years old STOPSMOK

Have you ever used snuff? (please tick) 1. Yes(now) 2. In the past 3. Never

In the past five to ten years, how often would you use snuff each day? times per day SNUFFREQ

Before you became ill, did you ever have your blood pressure measured? (Please tick) HBPM 1. Yes 2. No 3. Yes only during pregnancy

If yes, were you told it was high? (Please tick) HBP 1. Yes 2. No 3. Yes only during pregnancy

Have you ever had diabetes? (Please tick) 1. Yes 2. No DIAB

05 January 2005

you became ill, about how much wine, beer or spirits did you drink on average each week?
ase indicate glass/bottle size when you select block for each type of drink - eg. 3 large glasses of
ize beer per week would be: 3 e If none then 0

MAIZE		SORG		BEER		HOMECBR		HOMESPIRITS			WINE	OTHER
Maize		Sorghum "Clartoon"		Other homemade		COMBEER Commercial		Homemade (gavini)		COMSPR Commercial		OTHALC
A	B	A	B	A	B	A	B					

a: 2l wine bottle
b: bottle 750ml
c: 1l carton
d: 750ml wine bottle
e: 500ml beer glass
f: 375ml half jack/pint
g: 340ml beer can/dumpy
h: 250ml glass
i: 200ml wine glass/nip
j: 100ml (small glass)
k: 50ml miniature airplane bottle
l: 25ml tot
mother (please specify)

Are you? (please tick) MARSTAT
1. Single (never been married) 2. Married(living as married) 3. Widowed 4. Separated

How many husbands/wives have you had? HUSBWIV

FOR WOMEN ONLY: Have you ever been pregnant? (please tick) 1 Yes No 2 PREGNANT
If yes, how many times have you been pregnant? TIMESPR
If yes, how many times have you had a miscarriage? TIMESMIS
If yes, how many of your children were born alive? BORNALIV

FOR MEN ONLY: How many children (dead or alive) do you have? MENCHILD

ALL: How many mothers / fathers do the children have? MOTHFOTH

ALL: How old is your oldest child now? (include dead & alive) AGEOLDST Years old

ALL: How old is your youngest child now? (include dead & alive) AGEYOUNG Years old

ALL: How many boyfriends/girlfriends have you had? BOYFGIRF

FOR WOMEN ONLY
How old were you when your periods began? PERBEGIN Years old

Age now (from previous page) _____
Age at first birth _____
Age at last birth _____
for interviewer; not for capture

PEREND
Have your periods ended? Yes 1 No 2 Not sure 3 AGEENDED If yes, how old were you when they ended? years old

If Yes, did your periods stop: HYSTERNA
1. naturally | 2. due to surgery | 3. due to medical treatment | 4. due to IC use | 5. other | 6. unknown

Have you ever taken contraceptives? OC	Oral 1 Yes No 2	Injectable 1 Yes No 2	
If yes, how old were you when you started taking them? OCSTART			Years old
How old were you when you stopped taking them? OCSTOP			Years old
If yes, for how long in total did you take them? OCTOTAL			Years
Interruptions? OCINT1	1 Yes No 2	1 Yes No 2	

IC
ICSTART
ICSTOP
ICTOTAL
ICINT1

Main reason for stopping, the last time you stopped using the method: OCINT2 ICINT2

1 Nausea 2 high BP 3 headaches 4 wt.Gain 5.changed menstrual pattern 6. menopause 7.sterilization 8.hysterectomy 9. no partner.
10. to become pregnant 11 other 0.no specific reason

PAP Have you ever had a 'pap' smear?

0. Never	1. Yes	2. current illness only	9. Can't remember	If yes, how many? PAPNO	Age at first pap(yrs) FIRSTPAP	Age at last pap (yrs) LASTPAP

R ALL: Describe your usual or past occupation (eg. Driver, machine operator) OCCUP

Describe what your usual workplace does or did (eg. A bank, a chemical factory, a gold mine) WKPLACE

What language do you speak most at home? LANGYOU
What language does/did your father speak? LANGFATH
What language does/did your mother speak? LANGMOTH

1. Zulu 2. Xhosa 3. Sotho 4.Pedi 5. Tswana 6. Venda 7. Swazi 8. Shangaan 9. Ndebele
10 English 11. "Afrikaans" 12. Other

CB

Appendix 2: Expert panel questionnaire

Dear Expert Panel

Thank you so much for agreeing to participate in my study entitled: Occupations and breast cancer in women treated at a tertiary hospital in Johannesburg.

This is a case control study that uses secondary data analysis from the National Cancer Registry database.

Shift work is defined by the International Labour Organization (ILO) as "a method of organisation of the work time in which workers succeed one another at the workplace so that the establishment can operate longer hours than the hours of work of individual workers". There are many types of shift work and IARC has described shift work that disrupts circadian rhythm to be carcinogenic. Therefore for purposes of the study occupations classified as having shift work will be work that includes night work

Currently there are no South African literature sources that classify different industries or even job categories according to the risk of shiftwork and I am not sur e if the international literature is appropriate to use.

It is with this aim, that I am appealing for your expertise as experts in the industry.

I have listed the categories that I wish you to assess as 1-25. I have also listed the types of jobs that are included in the category for your information (from the database). I ask that you please that you look at the current categories and mark the last column as you deem appropriate into a) high probability of shiftwork; b)possibility of shiftwork and c) unlikely to do shiftwork. You are welcome to make any comments at the end of the questionnaire.

Thanking you in advance for your time and effort.

Kind regards,

Odette Abrahams

Occupational Medicine Registrar

NIOH

QUESTIONNAIRE

No	Usual Industry worked/Job category	Jobs included in this category (AS THEY APPEAR IN THE DATABASE)	Category to decide on: Likelihood of shiftwork (THAT INCLUDES NIGHT WORK)	Please choose only one which category of shiftwork that you feel is most suitable. Please mark with a cross.
1	**Never worked**	Never worked; housewife	High probability of shiftwork	☐
			Possibility of shiftwork	☐
			Unlikely to do shiftwork	☐
2	**Scholar/student**	Student/scholar	High probability of shiftwork	☐
			Possibility of shiftwork	☐
			Unlikely to do shiftwork	☐
3	**Unemployed**	Unemployed	High probability of shiftwork	☐
			Possibility of shiftwork	
			Unlikely to do shiftwork	☐ ☐

4	**Health**	Pharmacist/assistant; nurse/ nursing assistant; medical and scientific technician; health service other	High probability of shiftwork	☐
			Possibility of shiftwork	
			Unlikely to do shiftwork	☐
5	**Education**	Tertiary lecturer; teacher; other educational	High probability of shiftwork	☐
			Possibility of shiftwork	☐
			Unlikely to do shiftwork	☐ ☐
6	**Social services**	Childminder (not private home); caregiver; works in an old age home; minister; priest; social worker	High probability of shiftwork	
			Possibility of shiftwork	☐
			Unlikely to do shiftwork	☐
7	**Office/clerical workers**	Personnel/human resources; clerk/bank teller; secretary/typist; receptionist	High probability of shiftwork	☐
			Possibility of shiftwork	☐
			Unlikely to do shiftwork	☐
8	**Retail/ Sales**	Cashier, sales supervisor, sales: technical,	High probability of shiftwork	☐

		sales(shop assistant), sales: insurance, property, services; sales rep; food trade(retail)- baker, butcher, miller; other sales	Possibility of shiftwork	☐
			Unlikely to do shiftwork	☐
9	**Transport/delivery**	Delivery : driver/transport; taxi driver; train driver; transport conductor, inspector	High probability of shiftwork	☐
			Possibility of shiftwork	☐
			Unlikely to do shiftwork	☐
10	**Security/Law enforcement**	Defence/military; law enforcement; police; security	High probability of shiftwork	☐
			Possibility of shiftwork	☐
			Unlikely to do shiftwork	☐ ☐
11	**Hospitality**	Catering/waitress/barmaid; accommodation proprietor/supervisor	High probability of shiftwork	☐
			Possibility of shiftwork	
			Unlikely to do shiftwork	☐ ☐
12	**Domestic worker**	Indoor domestic worker e.g. maid, nanny	High probability of shiftwork	
			Possibility of shiftwork	☐

			Unlikely to do shiftwork	☐
13	**Service workers**	Laundry/dry cleaning(commercial; petrol attendant; car wash attendant; mail distribution; messenger other service; telecommunications(IT); beautician; hairdresser/barber	High probability of shiftwork	☐
			Possibility of shiftwork	☐
			Unlikely to do shiftwork	☐
14	**Agriculture**	Farm owner; farm worker; gardener	High probability of shiftwork	☐
			Possibility of shiftwork	☐
			Unlikely to do shiftwork	☐
15	**Metal workers**	Metal and engineering artisan; production worker: metal	High probability of shiftwork	☐
			Possibility of shiftwork	
			Unlikely to do shiftwork	☐
16	**Electrical and electronic**	Electrical and electronic artisan; electrician (domestic); production worker: electrical; electrical equipment maintenance	High probability of shiftwork	☐
			Possibility of shiftwork	
			Unlikely to do shiftwork	☐

17	**Construction**	Building: skilled brick layer; production worker: building and construction; building/construction: unskilled; painter: unskilled; other unskilled labourer	High probability of shiftwork	☐
			Possibility of shiftwork	
			Unlikely to do shiftwork	☐
18	**Printing**	Printing/ printing company/newspaper	High probability of shiftwork	☐
			Possibility of shiftwork	☐
			Unlikely to do shiftwork	☐
19	**Food**	Food handling/processing e.g. canning, baking	High probability of shiftwork	☐
			Possibility of shiftwork	☐
			Unlikely to do shiftwork	☐
20	**Textile and Leather**	Dressmaker/sewing machinist/tailor; leather worker	High probability of shiftwork	☐
			Possibility of shiftwork	☐
			Unlikely to do shiftwork	☐

21	**Manufacturing/Production**	Production worker: wood, paper and products; production worker: chemical, petrol, coal, rubber, plastic; production worker: semi skilled	High probability of shiftwork	☐
			Possibility of shiftwork	☐
			Unlikely to do shiftwork	☐
22	**Mining**	Miner	High probability of shiftwork	☐
			Possibility of shiftwork	☐
			Unlikely to do shiftwork	☐
23	**Informal sector**	Informal sector	High probability of shiftwork	☐ ☐
			Possibility of shiftwork	
			Unlikely to do shiftwork	☐ ☐
24	**Legislators, senior officials and managers**	Director/manager in government; other manager; businessmen	High probability of shiftwork	☐
			Possibility of shiftwork	
			Unlikely to do shiftwork	☐
25	**Craft and related trade**	Plumber(domestic); furniture artisan;	High probability of shiftwork	☐

		carpenter; motor vehicle artisan; mechanic; performing artist	Possibility of shiftwork	☐
			Unlikely to do shiftwork	☐

ANY COMMENTS:

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Appendix 3:Ethical Clearance Certificate

R14/49 Dr Odette Natasha Abrahams

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M131126

NAME: (Principal Investigator)	Dr Odette Natasha Abrahams
DEPARTMENT:	School of Public Health Community Health-Occupational Medicine The National Institute for Occupational
PROJECT TITLE:	Occupations and Breast Cancer in Women Treated at a Tertiary Hospital in Johannesburg
DATE CONSIDERED:	29/11/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof David Rees and Dr Spo Kgalamono
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	26/02/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES