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**The profile of breast cancer among patients attending a Breast Clinic in Cape Town, South
Africa**

by

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Declaration

I, Valdiela Daries, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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List of Abbreviations

ACS	American Cancer Society
ASIR	Age-standardised incidence rate
ASMR	Age-standardised mortality rate
BA	Breast awareness
BHGI	Breast Health Global Initiative
BSE	Breast self-examination
CANSA	Cancer Association of South Africa
CBE	Clinical breast examination
DoH	Department of Health
HRT	Hormone replacement therapy
IARC	International Agency for Research on Cancer
IQR	Inter quartile range
LMC	Low-and-middle income countries
NCI	National Cancer Institute
NCR	National Cancer Registry
NHLS	National Health Laboratory Services
RR	Relative risk
SA	South Africa
TBH	Tygerberg Hospital
TNM	Tumour-Node-Metastasis
WCPG	Western Cape Provincial Government
WHO	World Health Organization
WC	Western Cape

Abstract

Background: Breast cancer is the leading cancer among women in South Africa (SA). Studies conducted in developing countries have shown that the majority of women present with advanced stage breast cancer at diagnosis. There is a gap in terms of recent data on the profile of breast cancer patients in SA.

Purpose: The purpose of the study was to obtain recent data with regards to the socio-demographic, clinical and risk factor profile of breast cancer in patients who presented at a Breast Clinic linked to a tertiary public hospital in the Western Cape in order to underpin the development of strategies for earlier detection and diagnosis of breast cancer.

Methods: A cross-sectional descriptive medical record review was conducted. The study population included all newly diagnosed patients with histological or cytological confirmed breast cancer who presented at the Breast Clinic during the period 01 January 2009 to 31 December 2010. All patients with a previous diagnosis of breast cancer were excluded. Data on the socio-demographic, clinical and risk factor profile of breast cancer patients were collected using a standardised data capture sheet. Data was entered using Epidata version 3.1 and analysed using Stata Statistical package version 12.

After calculation of initial descriptive analysis for the whole sample, male subjects were excluded and further analysis was restricted to 585 female subjects. Stage at presentation was categorised as “early stage” (stage 0, I, IIA, IIB) and “late stage” (stage IIIA, IIIB, IIIC, IV). Crude associations of potential predictors with stage at presentation were tested using Wilcoxon rank-sum tests for medians and Chi-square tests and Fischer Exact tests for proportions.

Logistic regression was used to create a model with stage at presentation as dependent variable. Age and racial group were introduced in the model as possible confounders. Based on literature findings other variables present in the dataset were considered as potential predictors of stage at presentation (namely place of residence, employment status, medical aid status, family history of breast cancer, menopausal status, parity, having ever smoked or used alcohol, clinical signs of breast cancer as well as duration of symptoms) and introduced in the model if their bivariate association with the outcome (adjusted for age and race) was statistically significant. A significance level of $p < 0.15$ was used. The only variable showing a significant association according to this criterion was the ordinal variable duration of symptoms. The final logistic

regression model, therefore, included stage at presentation as the dependent variable and age, racial group and symptom duration as predictors.

Results: The overall median age was 54 years (IQR 44-64 years) with no significant difference in age by stage at presentation. The median age at presentation for Black females was 45 years (IQR 38-52 years); 54 years (IQR 44-64 years) for Coloured females and 59 years (IQR 44-64 years) for White females. The difference in age at presentation between women in the various race groups was significant ($p = 0.000$). The majority of women resided in urban areas, were employed and did not have medical aid membership. None of the latter variables showed any significant association with stage at presentation. History of breastfeeding, smoking and alcohol use were poorly documented.

The majority of women (56.6%) presented in late stage i.e. stages III and IV. Women with symptoms > 12 months were significantly more likely to present with late stage breast cancer (adjusted OR 10.44, 95% CI 3.44, 31.68) compared to women with symptoms between 1-6 months (adjusted OR 3.07, 95% CI 1.43, 6.58). Race was associated with stage at presentation, with White females having a significantly lower odds (adjusted OR 0.33, 95% CI 0.16, 0.70) of presenting at late stage compared to Black females.

Conclusion: In keeping with findings in other developing countries and previous SA studies, the majority of women in this study presented at late stage breast cancer which is associated with a poorer survival rate and limited treatment options. This study highlights the need for public health interventions in SA to increase awareness regarding breast cancer signs and symptoms. Further research is needed to determine possible barriers to early presentation to health facilities.

SECTION I: PROTOCOL

1.1 Introduction

Breast cancer is the most common cancer in women worldwide and it is the leading cause of death among females worldwide. In 2008 the estimated age-standardised incidence rate (ASIR) for breast cancer was 66.4 per 100 000 in developed countries compared to 27.3 per 100 000 in developing countries. The estimated age-standardised mortality rate (ASMR) was 15.3 per 100 000 in developed countries compared to 10.8 per 100 000 in developing countries (Ferlay et al., 2010). Africa is not exempt from the burden of cancer; in fact the American Cancer Society (ACS) views cancer as “an emerging health problem in Africa” and argues that cancer receives low public health priority partly due to the lack of understanding of the scale of the disease among policymakers, the general public as well as private and public health organisations (ACS, 2011). The GLOBOCAN 2008 summary statistics for the most common type of new cancer cases among females in Africa is shown in Table 1.

Table 1: Most common type of new cancer cases among females in Africa, 2008

Region	Type of cancer	Proportion of all female cancers
Eastern Africa	cervix	26.2%
Middle Africa	breast	22.1%
Northern Africa	breast	33.8%
Southern Africa	breast	23.4%
Western Africa	breast	26.4%

Source: Ferlay et al., 2010

Summary statistics for Southern Africa specifically revealed that breast cancer was the most frequent cancer among women in 2008 (Ferlay et al., 2010). Breast cancer could be considered to be a humanitarian burden in view of the fact that if the disease is not treated and the spread not controlled, it can result in premature death. Considering the staggering statistics with regards to breast cancer incidence, it has become a large health burden which needs to be addressed in the public health arena.

A number of studies, conducted outside of South Africa (SA), have investigated the demographic, clinical, reproductive, epidemiological, diagnostic, treatment and/ or surgical profile of breast cancer patients (Batool et al., 2005; Burson et al., 2010; Kemfang Ngowa et al., 2011; Nissan et al., 2004 & Sandhu et al., 2010). Breast cancer in African countries are generally characterised by a relatively advanced stage presentation which has been highlighted by Anderson et al. (2006). Advanced stage breast cancer is associated with a poorer prognosis with a survival rate of 25% and below (NCI, 2010).

Currently, breast cancer is the most common cancer among SA females. The 2008 GLOBOCAN estimated breast cancer ASIR for SA was 41 per 100 000 while the ASMR was 20.7 per 100 000 indicative of a significant public health problem.* The most recent National Cancer Registry (NCR) summary statistics of 2003 for histologically diagnosed breast cancer in SA females are shown in Table 2.

Table 2: NCR summary statistics for histologically diagnosed breast cancer among SA females, 2003

Group	% of all cancer cases (adjusted)	ASIR per 100 000	Lifetime risk
All females	20.3	28.8	31
Asian females	35.5	44.7	20
Black females	18.1	14.7	62
Coloured females	24.5	45.8	19
White females	20.4	71.9	13

Source: NHLS, 2011

In SA some degree of research has been undertaken to highlight the burden of breast cancer in the country however few studies have looked specifically at the socio-demographic, clinical and risk factor profile of breast cancer among women. Hacking et al. (1984) conducted a study at Groote Schuur hospital, Cape Town covering a period from 1971 to 1981. The main aim of the study was to measure the frequency of breast cancer by age, race and stage at presentation.

* In SA, a justification for the use of race in data collection includes monitoring of progress related to disparity in health care services especially post 1994 and another is to understand race-associated differences in a given medical condition (Myer & Ehrlich, 2007).

The results showed that of the females who presented with breast cancer, 1085 (49%) were White, 1063 (48%) were Coloured and 66 (3%) were Black. Interestingly, Hacking et al. (1984) established a marked difference in stage of presentation when race groups were compared. In this study, White women presented with breast cancer at an earlier stage compared to Coloured and Black women who presented with the disease at an advanced stage. A similar 10-year review by Ostyn et al. (1987) looked at breast cancer tumours at Coronation hospital, Johannesburg during June 1974 to June 1984. Most patients treated at the hospital were Coloured or Indian. The findings highlighted the large number of young females (below the age of 40) with breast carcinoma (25%) and that overall 50% of the patients presented with advanced lesions. Study conclusions by Hacking et al. (1984) and Ostyn et al. (1987) are similar to conclusions made in studies conducted in other African countries and Asian countries in that most women presented with advanced stage breast cancer.

Pegoraro et al. (1985) analysed data of 640 women with breast cancer who were enrolled in a university steroid hormone receptor study in Durban, KwaZulu-Natal. The study compared the clinical patterns of breast cancer in women of different racial groups. Findings revealed that the overall mean age of patients were 52 years however more than 50% of White patients presented with breast cancer after the age of 60 years whereas 88%, 72% and 70% of Indian, Black and Coloured patients respectively presented below 60 years. With regards to histological grade, Black and Indian women had a significantly higher incidence of poorly differentiated tumours compared to White women. It was found that breast cancer presented at a younger age in Black women, that tumour size was large and furthermore the cancer was at a more advanced stage compared to findings in White women. Coloured and Indian women were diagnosed with smaller tumour masses and the stage at diagnosis was likely to be intermediate. The authors proposed that the discrepancies in presentation of breast cancer between the race groups could be related to differences in cultural and educational attitudes to breast cancer in the various race groups.

A retrospective study at Hillbrow Hospital Radiation Therapy Department (Greenberg, 1993) revealed that between January 1988 and December 1992, breast cancer was the second most common cancer in Black women who received treatment at the hospital. Of the 2010 histologically proven breast cancer cases that presented during the period under investigation, it

was found that breast cancer presented ± 7 years earlier in Black women when compared to White women (as was revealed by Hacking et al., 1984 and Pegoraro et al., 1985) and at a more advanced stage (as was found by Hacking et al., 1984, Pegoraro et al., 1985 and Ostyn et al., 1987).

In another study, Walker et al. (2000) obtained data of breast cancer patients who presented at King Edward VIII Hospital in Durban during the period 1994-1999. It should be noted that this study only focussed on Black African women. Similar to African and Asian studies as well as other studies within SA, it was found that the majority of patients (84.3%) presented with advanced stage breast cancer at time of admission.

All these South African studies had similar conclusions in that breast cancer presented at a more advanced stage in Coloured and Black women when compared to White women.

In the NCR report by Mqoqi et al. (2004) it is interesting to note that the then Minister of Health, Dr. ME Tshabalala-Msimang commented on the disturbing increase in breast cancer among all population groups in the period 1998 to 1999 and commented that "...these patterns are sending strong and bold messages for prevention and control". Government initiatives to prevent and control cancer have included the amendment of the Tobacco Products Control Act as well as the implementation of a cervical screening programme. With regards to breast cancer, organisations such as the Cancer Association of South Africa (CANSA) have taken the lead concerning breast cancer awareness however campaigns are few and funding is predominantly reliant on public contributions.

Although a few studies have been conducted in SA to highlight the profile of breast cancer patients in SA (Hacking et al., 1984, Pegoraro et al., 1985, Ostyn et al., 1987, Walker et al., 2000.), these studies were conducted a number of years ago and reflect data between 1971 – 1999. More recent data is required to determine whether there have been changes in the profile of patients with breast cancer considering the efforts by non-governmental organisations such as CANSA to create public awareness around cancer and in particular breast cancer.

1.2 Motivation for the study

Breast cancer is an important public health problem in SA however breast cancer receives low public health priority despite the fact that it poses an increasing health burden. Studies, both

internationally and locally have shown that when breast cancer is detected and diagnosed at an advanced stage of the disease it is associated with a poorer prognosis (NCI, 2010). The motivation for the study is to obtain data as there is a gap in terms of recent data on the profile of breast cancer in SA.

1.3 Purpose of the study

Cancer incidence rates in SA are reported to be among the highest in Africa and increased attention needs to be given to the burden of non-communicable diseases such as cancer. With regards to breast cancer, SA lacks public health strategies to aid in early detection and diagnosis. The purpose of the study is to obtain recent data with regards to the socio-demographic, clinical and risk factor profile of breast cancer to underpin the development of strategies for earlier detection and diagnosis of breast cancer.

1.4 Aim and objectives

1.4.1 Aim

To determine the socio-demographic, clinical and risk factor profile of breast cancer in newly diagnosed patients who presented at the Breast Clinic at Tygerberg Hospital (TBH), Cape Town during the period 01 January 2009 to 31 December 2010.

1.4.2 Objectives

- To describe the socio-demographic profile of breast cancer patients. Socio-demographic details will include age at diagnosis, sex, race, place of residence, employment status and membership to a medical aid.
- To describe the clinical presentation at initial visit. Clinical presentation will refer to the signs and symptoms associated with breast cancer; this will include presence of breast lump, breast pain, nipple discharge, nipple retraction, nipple erosion, axillary nodes, breast oedema, peau d'orange, breast erythema, breast ulceration.
- To establish the proportion of histopathological confirmed types of breast cancer.
- To determine the stage of breast cancer at initial diagnosis.

- To describe risk factors associated with breast cancer including family history of breast cancer, menopausal status, parity status, hormonal therapy i.e. contraceptive use or hormone replacement therapy.
- To determine factors associated with stage at presentation.

1.5 Definition of terms

- The type of breast cancer will be based on the final diagnosis indicated on the histopathology or cytology report. This may include in-situ carcinoma (Not otherwise specified -NOS, Intraductal, Paget's disease and intraductal) and invasive carcinoma (NOS, Ductal, Inflammatory, Medullary, Mucinous, Papillary, Tubular, Lobular, Paget's disease and infiltrating, Undifferentiated, Squamous cell, Adenoid cystic, Secretory, Cribriform).
- Breast cancer will be staged using the Tumour-Node-Metastasis (TNM) classification into Stage 0, I, II, III or IV at initial diagnosis.
- Urban versus rural status - if place of residence falls outside a 150km radius from Cape Town, it will be classified as rural (Hoffman et al., 2000).

1.6 Methods

1.6.1 Study design

A cross-sectional retrospective descriptive medical record review will be conducted.

1.6.2 Study population

The study population will include all patients with histopathological or cytological confirmed breast cancer who presented at the Breast Clinic at TBH from 01 January 2009 to 31 December 2010.

1.6.3 Study setting

The study will be conducted at TBH, a tertiary hospital situated in the Western Cape (WC). TBH is the largest hospital in the WC and plays a major role in the provision of healthcare services to a large and diverse population, within and beyond the borders of the WC. The Breast clinics at TBH and Groote Schuur Hospital are the tertiary public hospitals for referral of breast cancer

patients in the WC. The 2009/ 2010 TBH annual report indicated that a total of 59 943 patients were admitted to TBH while 437 351 outpatients were seen at the various outpatient clinics. During 2009, a total of 1 363 new patients were seen at the Head, Neck and Breast clinic (Department of Health: WCPG, 2009).

1.6.4 Exclusion criteria

All patients with previous diagnosis of breast cancer will be excluded.

1.6.5 Measurement

A data capture sheet will be used to record relevant information from the medical records (Refer to Appendix A). Categorical and numerical variables will be measured and will be as follows:

Table 3: Classification of variables

Sex	Male versus Female	Categorical: Binary
Age	Age at diagnosis measured in years	Numerical: Continuous
Race	Black or Coloured or Indian or White	Categorical: Nominal
Place of residence	Urban versus Rural	Categorical: Binary
Employment status	Employed versus unemployed	Categorical: Binary
Membership to medical aid	Membership versus no membership	Categorical: Binary
Duration of symptoms prior to first visit	Time delay in days/ weeks/ months/ years	Numerical: Continuous
Cancer types	Refer to 1.5 bullet one	Categorical: Nominal
Signs and symptoms at presentation	Presence versus absence of a breast lump, breast pain, nipple discharge, nipple retraction, nipple erosion, axillary nodes, breast oedema, peau d'orange, erythema, ulceration.	Categorical: Nominal
Stage at diagnosis	Stage 0, I, II, III, IV	Categorical: Ordinal
Risk factors	Family history of breast cancer, menopausal status, parity status, hormonal therapy, breast feeding, alcohol use, smoking	Categorical: Nominal
Parity status	Number of children	Numerical: Discrete
Weight	At time of diagnosis in kilogram	Numerical: Continuous

The principle researcher will solely be responsible for all data collection which will assist in consistency of the data collection process. The data collection process will be as follows: The Breast clinic statistics record (a clinic-based book where all the breast cancer patient details are recorded for statistical purposes) will be accessed to verify the total number of breast cancer cases that presented during the period 01 January 2009 to 31 December 2010. The researcher will then capture the reference number of each patient with newly diagnosed breast cancer on the data capture sheet. The reference number will be used to find the specific medical records that are located in the folder room in the Breast clinic. The data capture process will take place over an estimated period of two months.

1.6.6 Pilot study

Before commencement of the study, a pilot study will be conducted to test the adequacy of the data capture sheet. The data of the first five (5) breast cancer patients who presented at the Breast clinic on or after 01 January 2011 will be used to assess the suitability of the data capture sheet.

1.7 *Time schedule

As the researcher is solely responsible for all aspects of the research process, all activities linked to the research process will be carefully planned. The time schedule is as follows:

Month	Anticipated progress
December 2011	Departmental approval
January 2012	Submit proposal to Human Research Ethics Committee
February-May 2012	Data collection / Literature review
June-July 2012	Data cleaning and analysis
Aug-October 2012	Write-up results
November 2012	Final feedback from supervisor
December 2012	Final changes
January 2013	Submit mini-dissertation

***Time schedule has been modified from the original proposal to reflect current progress**

1.8 Data management

The researcher will enter all case information onto identical data capture sheets. The researcher will double-check that all categories or fields on the data capture sheet have been completed to eliminate the chance of missing data at a later stage. Each clinic folder that has been scrutinised will be marked with a red sticky label to ensure that no data are accidentally duplicated. After each data collection session, the data capture sheets will be securely stored in a locked cabinet with access only by the researcher.

The researcher will capture data directly from the data sheets into Epidata. A data checking procedure will be performed using Epidata to ensure that categorical and numerical variables have no unlikely codes. Should there be any missing information the researcher will be able to go back to the raw data or medical records to verify information.

1.9 Analysis

Initial data exploration will include graphical representation of data collected. Categorical data will be explored through frequency tables, bar graphs and pie charts while numerical data will be explored through histograms and box plots.

Statistical analysis will be conducted using STATA 12. Descriptive statistics will be calculated regarding socio-demographic details, clinical presentation at initial diagnosis, types of breast cancer diagnosed, stage of breast cancer at initial diagnosis, risk factors associated with breast cancer and factors associated with stage at presentation. For categorical variables, a table will be used to summarise frequencies and percentages. For numerical variables that follow a normal distribution, a table will be used to summarise the mean and standard deviation. For numerical variables that are not normally distributed, the median and interquartile range will be used as summary statistics. To determine factors associated with stage at presentation (early stage breast cancer versus late stage breast cancer), bivariate analysis will be done to determine odds ratios, 95% confidence intervals and *p*-values. A two sample t-test will be used to compare continuous variables in early stage breast cancer and late stage breast cancer. To determine an association between risk factors and breast cancer, multiple logistic regression analysis will be performed. Risk factors that are significant on bivariate analysis as well as risk factors based on literature will be considered in the regression model.

1.10 Budget

This study is self-funded and the following expenses are anticipated:

Printing of data capture sheets	R 500-00
Statistician	R 3000-00
Petrol	R 800-00
Stationery	R 200-00
Total	R 4500-00

1.11 Ethical and legal considerations

Ethical approval will be sought from the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town prior to the commencement of the study (Refer to Appendix B). The study will not require any direct human participation therefore no risk of harm is posed to any individual. The study could potentially have public benefit as the results of the study could initiate public health policies or health service strategies to improve early detection and diagnosis of breast cancer. No personal identifying details of cases will be recorded for the study hence anonymity will be maintained at all times. All data will be treated confidentially and no information will be linked to a specific individual, either during dissemination or possible publication of study results. Permission to use the patient medical records at TBH will only be considered once ethics approval has been granted by the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town (Refer to Appendix C).

1.12 Reporting of results

The findings of the study will be communicated to the hospital management of TBH as well as the head of department of the Breast clinic to facilitate future resource planning. The findings of the study will also be presented to representatives of the Department of Health (DoH), Western Cape Provincial Government for deliberation. Representatives of CANSA will be informed of the outcome of the study. The findings will also be submitted to a peer-reviewed journal for publication.

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SECTION II: LITERATURE REVIEW

2. Literature Review

2.1 Objective of the Literature Review

The objective of the literature review is to summarise and identify gaps in research that has been done on breast cancer, both internationally and in SA. The focus of this literature review will be on:

- The burden of breast cancer globally and in SA
- Breast cancer risk factors
- The profile of breast cancer among patients in developed and developing countries including SA. This includes the socio-demographic, risk factor and clinical profile of breast cancer
- Breast cancer screening methods and control initiatives

Literature search strategy involved the following: The electronic databases PROQUEST, MEDLINE, PUBMED and SCIENCE DIRECT were searched for free full text reports of journal articles from the year 2000 onwards except for South African research studies where all breast cancer research studies were included.

Search words used included the following: breast cancer incidence, breast cancer burden, breast cancer epidemiology, profile breast cancer, breast cancer Africa, breast cancer South Africa, breast cancer risk factors, breast screening, and breast cancer control.

2.2 Burden of disease

2.2.1 Global burden of breast cancer

Breast cancer is the most common cancer among women worldwide. It is estimated that in 2008 there were 1.4 million new cases of breast cancer globally (Ferlay et al., 2010). The estimated new cancer cases by level of economic development indicate that the breast is the leading cancer site in women in developed and developing countries. In 2008 the ASIR for breast cancer was 66.4 per 100 000 in developed countries compared to 27.3 per 100 000 in developing countries. The estimated difference of breast cancer incidence between developed and developing countries are possibly related to the presence of breast screening programmes as well as diet and lifestyle (Parkin & Fernández, 2006; ACS, 2011).

In 2008 breast cancer was the leading cause of cancer death in 10 out of 21 world regions (Ferlay et al., 2010). The estimated ASMR was 15.3 per 100 000 in developed countries compared to 10.8 per 100 000 in developing countries (Ferlay et al., 2010). The estimated differences in mortality rates between developed and developing countries have been partially attributed to lack of death registries and inaccurate population data especially in Asia and Africa (Parkin et al., 2008; Ferlay et al., 2010).

2.2.2 Burden of breast cancer in Africa

In 2008 there were 92 600 new breast cancer cases in Africa of which 9 000 cases occurred among women in Southern Africa (Ferlay et al., 2010).

The ASIR and ASMR for female breast cancer in Africa in 2008 are reflected in Table 1.

Table 1: ASIR and ASMR for breast cancer in females in Africa, 2008

Region	ASIR per 100 000 women	ASMR per 100 000 women
<i>All African regions</i>	<i>28.0</i>	<i>16.0</i>
Eastern Africa	19.3	11.4
Middle Africa	21.3	13.1
Northern Africa	32.7	17.8
Southern Africa	38.1	19.3
Sub-Saharan Africa	26.3	15.3
Western Africa	31.8	18.9

Source: Ferlay et al. (2010)

Southern Africa has the highest ASIR and ASMR of all African regions- 38.1 per 100 000 and 19.3 per 100 000 respectively (Ferlay et al., 2010).

2.2.3 Global trends in breast cancer

Key et al. (2001) report that both incidence of and mortality from breast cancer vary five-fold among populations around the world and that breast cancer incidence rates are high in most developed countries and low in less developed countries.

Althuis et al. (2005) reported on the worldwide increase in breast cancer incidence between 1973 and 1997 in eighteen countries (both developed and developing countries). The authors observed that in most countries, breast cancer incidence rose by 30-40% from the 1970's to the 1990's with peak increases among women ≥ 50 years of age. For example in Sweden, the breast cancer incidence rate increased from 55.2 per 100 000 (1973-1977) to 76.5 per 100 000 (1993-1997). Botha et al. (2003) analysed data (1950's to 1990's) from sixteen European countries and found increases in breast cancer incidence rates; these increases occurred in countries both with and without a population-based breast screening programme. More recently, Cronin et al. (2009) reported a decline in breast cancer incidence rates in the United States (US) among women ≥ 50 years of age and initially associated the decline to a decrease in the use of hormone replacement therapy (HRT). The authors compared incidence from 2000-2002 and 2003-2005 and reported a decrease of 12% (in women 50-69 years of age) and 7.8% (in women > 70 years of age). However, due to inconsistency with Surveillance, Epidemiology and End Results (SEER) data collected in the US, they were unable to conclusively attribute the decrease in breast cancer rates to a decrease in use of HRT.

In developed countries the increased breast cancer incidence rates have been associated with the commencement of organised breast screening programmes. Increases have also been attributed to changes in reproductive patterns namely lower parity, delayed childbearing and reduced breastfeeding (Althuis et al., 2005; Parkin & Fernández, 2006) as well as improved health awareness among women (Botha et al., 2003).

With reference to mortality data, Althuis et al. (2005) noticed that in North-America, US white females had moderate reduction in mortality rate (12%) while US black women experienced an increase in mortality rate (17%) between 1973 and 1997. Reasons for the disparity between US whites and blacks are unclear but factors such as differential access to healthcare and diagnosis of tumours with less favourable prognosis in US black females are postulated.

In European countries, mortality rates have been decreasing since the late 1980s with estimated annual percentage decrease between 0.8%-2.8% in six countries (with screening programmes) and between 1.2%-3.0% in 10 countries (without screening programmes). Decreasing mortality trends in the European countries may reflect earlier stage at diagnosis and improved healthcare treatment (Botha et al., 2003). In the European countries without screening programmes,

decreasing mortality trends were largely due to improved access to care and better treatment options (Botha et al., 2003).

According to Porter (2008) and Parkin et al. (2008) trends in breast cancer incidence and mortality rates in Africa are difficult to assess. This is primarily attributed to the lack of cancer registries, death registries as well as accurate population data.

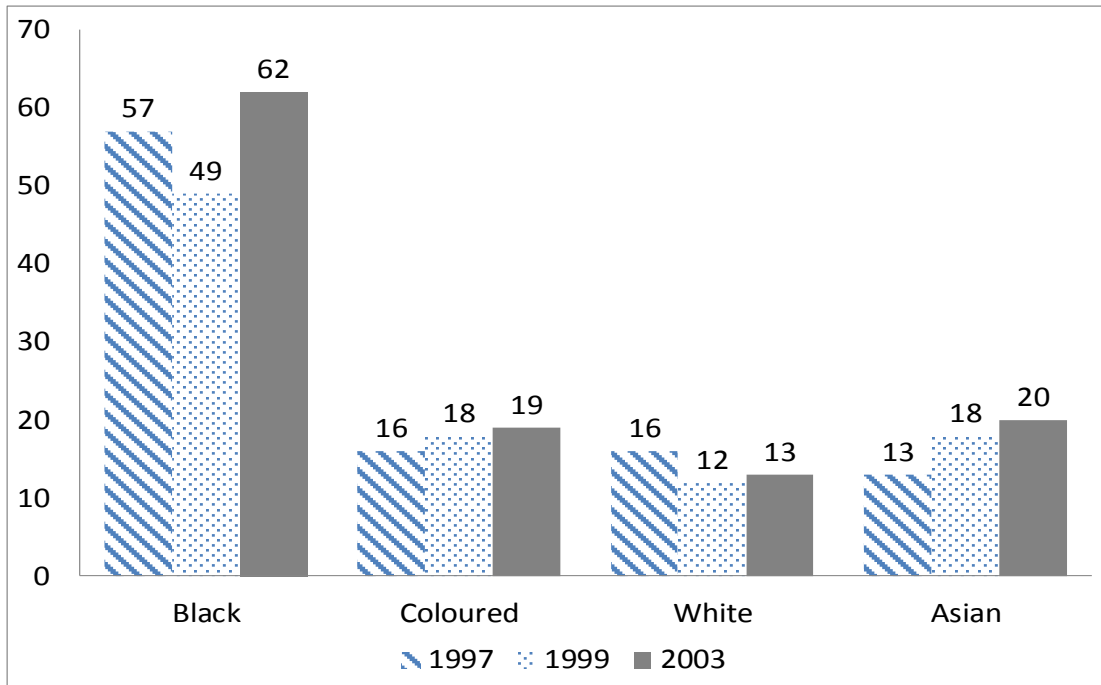
2.2.4 Burden of breast cancer in SA

In SA, cancer statistics are collected and reported by the NCR. The sources of data are the National Health Laboratory Services (NHLS) which provide data of the public health sector as well as private histopathology, cytology and haematology laboratories country wide. All data are sent on a goodwill basis (NHLS, 2011). Owing to the latter, the data reported by the NCR could underestimate the true incidence and patterns of cancer in SA. Nonetheless, statistics put forward by the NCR can be used to draw attention to the profile of breast cancer in SA. There are significant delays in collating the NCR data and the most recent breast cancer data is for 2003. For 2003, the ASIR for female breast cancer was 28.8. A total of 5602 histologically confirmed breast cancer cases were reported with the highest incidence in women in the age group 50-54 years (NHLS, 2011). Unfortunately, NCR data does not provide the median age of female population groups diagnosed with breast cancer which is an important gap in the planning and evaluation of early detection strategies.

Currently, breast cancer is the most common cancer among SA females. More recent estimate data for SA is obtainable from GLOBOCAN 2008. Data for SA were projected to 2008 using NCR pathology based breast cancer incidence rates of 1995-2001 and scaled by cancer, sex and age-specific percentages of microscopically verified breast cancer cases observed in Harare, Zimbabwe (Ferlay et al., 2010). The 2008 GLOBOCAN estimated breast cancer ASIR in SA was 41 per 100 000 while the estimated ASMR was 20.7 per 100 000 (Ferlay et al., 2010).

The lifetime risk of developing breast cancer in female population groups has changed over time and this is reflected in the following graph.

Figure 1: Lifetime risk of breast cancer in South Africa: 1997, 1999 and 2003



According to the latest NCR summary statistics of breast cancer diagnosed histologically in 2003 it is indicated that SA women have a lifetime risk of 1 in 31 of developing breast cancer. White females remain the subgroup at a greater risk of developing breast cancer with a lifetime risk of 1 in 13 compared to Asian, Black and Coloured females. It is also the only group in which lifetime risk appears to have worsened over the time period.

The only population-based cancer registry in South Africa is a registry in the Eastern Cape Province, set up by the Medical Research Council of South Africa (Somdyala et al., 2007). During the period 1998-2002, a total of 2 829 new malignant cases were recorded of which breast cancer accounted for 11.3% of all cancers in the Eastern Cape Province. A comparison between the population-based cancer registry and the nationwide NCR data of the same period showed that the proportion of breast cancer cases in the NCR 55 year (+) group was higher if compared to the same age group in the population-based cancer registry. Neither NCR data nor the Eastern Cape registry indicated mean or median age for female population groups. Conversely, Somdyala et al. (2007) reported a relatively high number of breast cancer cases from as early as 35 years of age which was not reflected in the NCR data of the same period. Somdyala et al. (2007) therefore established that there was a higher proportion of breast cancer

among younger women in the Eastern Cape Province compared to NCR data. Additional findings by the authors indicated that most women (80.5%) presented with late stage breast cancer i.e. stage III and IV.

In summary:

- Breast cancer is a major burden of disease globally.
- Increases in breast cancer incidence rates in developing countries have been associated with accessibility to mass breast screening and improved health awareness.
- Breast cancer mortality rates are decreasing in several developed countries as a result of earlier detection and diagnosis as well as improved breast cancer treatment programmes.
- Trends in breast cancer incidence and mortality rates in Africa are difficult to assess due to the lack of cancer and death registries as well as accurate population data.
- Breast cancer is the commonest incident cancer among women in SA.

2.3 Risk factors for breast cancer

It has not yet been possible to determine the aetiology of breast cancer (WHO, 2006) however several factors that increase risk have been identified and are outlined below.

Age and sex

The two major risk factors for developing breast cancer are being female and aging. The relative risk (RR) for breast cancer in females is >10 compared to breast cancer in males. The incidence of breast cancer increases with age and it doubles every 10 years until menopause commences (McPherson et al., 2000).

Family history of breast cancer

Woman with a BRCA1 or BRCA2 mutation have a RR of ≥ 6 compared to women without the gene mutation (Tucker & Rizk, 2011). Women with a strong family history of breast cancer but without a documented BRCA mutation still have a RR of ≥ 2 of developing breast cancer compared to women with no family history (Tucker & Rizk, 2011; McPherson et al., 2000). Key et al. (2001) argue that shared genes as well as shared physical environments and lifestyles could be responsible for increased risk in families.

Reproductive factors and hormonal status

Hormonal exposure i.e. endogenous hormones (high levels of free oestrogen) or exogenous hormones (long term use of oral contraceptives or HRT) place women at increased risk of developing breast cancer (Key et al., 2001; Sasco, 2001). HRT is associated with an increased risk of breast cancer for each year of use and the risk continues for four years after HRT has stopped. With HRT use of ≥ 10 years, a RR of 1.4 exists (McPherson et al., 2000).

The Million Women Study conducted in the United Kingdom (UK) aimed to determine the effects of specific types of HRT on incident and incurable breast cancer. Banks et al. (2003) found that current and recent use of HRT increased the risk of breast cancer by 1.66 (95% CI 1.58-1.75; $p < 0.0001$). Furthermore it was established that the relative risk of breast cancer in current HRT users (RR=2.00, $p < 0.0001$) significantly increased for oestrogen-progestagen combinations than for oestrogen only preparations.

Women who have a natural menopause after 55 years of age are twice as likely to develop breast cancer as women who experience menopause after 45 years of age (McPherson et al., 2000).

The risk of breast cancer is increased for current users of oral contraceptives (RR= 1.2) and the risk of breast cancer persists for 10 years after women stop taking it. Breast cancer diagnosed among oral contraceptive users is likely to be diagnosed at an earlier stage compared to non-users (McPherson et al., 2000).

With reference to childbirth, McPherson et al. (2000) claim that the risk of breast cancer in women who have their first child in their 30's is twice as high compared to women that have their first child before the age of 20. Furthermore, according to McPherson et al. (2000), women who have their first child after 40 years of age are three times more likely to develop breast cancer compared to women that have their first child before the age of 20. Studies conducted in India revealed that breastfeeding is a protective factor against development of breast cancer (Lodha et al., 2011; Pakseresht et al. 2009).

Lifestyle factors

Lifestyle factors such as alcohol consumption, smoking, physical inactivity and diet have been associated with an increased risk of developing breast cancer. Females who have a diet high in saturated fat have a RR of 1.5 of developing breast cancer compared to women who have a diet

low in saturated fat, while post-menopausal women with a body mass index of >35 have a RR of 2 of developing breast cancer compared to post-menopausal women with a body mass index of < 35 (McPherson et al., 2000). A study conducted in Australia found that lifestyle factors such as obesity, sedentary lifestyle and low fruit and vegetable intake were prevalent among younger women diagnosed with breast cancer. The authors therefore suggested that preventative strategies directed at modifiable risk factors be developed and younger women targeted (Protani et al., 2012).

McPherson et al. (2000) acknowledged that the excessive use of alcohol may increase the risk of breast cancer by 1.3 however the authors argue that alcohol use could possibly be linked to other dietary factors rather than alcohol use. The authors do not regard smoking as a risk factor for breast cancer. Similarly, Key et al. (2001) and Washbrook (2006) agree that the relationship of tobacco to breast cancer risk remains controversial due to the inconsistent results published to date and the fact that numerous studies could show no association.

In summary:

- The two major risk factors for breast cancer are being female and aging.
- Other risk factors which are significantly associated with an increased risk of breast cancer include: a family history of breast cancer, presence of BRCA genes, hormone replacement therapy and use of oral contraceptives.
- Breastfeeding appears to be a protective factor for development of breast cancer.
- Risk factors such as smoking, use of alcohol, diet and exercise requires further investigation to conclusively prove its contribution to risk of breast cancer.

2.4 Profile of breast cancer among patients in developing and developed countries: focus on stage at presentation, age at diagnosis and types of breast cancer diagnosed

Staging of breast cancer is essential to estimate the prognosis and to determine the choice of treatment (NCI, 2010). Stages 0-II are classified as early stage cancer and are associated with a more favourable prognosis (5-year survival rate: 83%-98%) while stages III-IV are classified as late stage cancer and are associated with a poor prognosis (5-year survival rate: 25% and below).

A number of studies, conducted outside of SA, have investigated the demographic, clinical, reproductive, epidemiological, diagnostic, treatment and/ or surgical profile of breast cancer patients (Batool et al., 2005; Burson et al., 2010; Kemfang Ngowa et al., 2011; Nissan et al., 2004; & Sandhu et al., 2010). Breast cancer in African countries is generally characterised by an advanced stage at presentation and a relatively young age at presentation. In Dar Es Salaam, Tanzania, a retrospective study was conducted where data was abstracted from the medical records of 488 breast cancer patients (Burson et al., 2010). The mean age at diagnosis was 43.4 years and 90.7% of cases (including male cases) were diagnosed with advanced breast cancer i.e. stage III and IV. Types of cancer found were ductal (85.5%), medullary (5.1%) lobular (2.3%), mucinous (2.3%) and other (2.3%). The mean duration of symptoms was 17.2 months and the authors pointed to various patient-mediated barriers in seeking care such as inability to pay for medical care, long distances to travel, ignorance, fear and cultural factors (Burson et al., 2010). Kemfang Nqowa et al. (2011) conducted a 20-year descriptive retrospective study in Yaounde, Cameroon. Data of 531 breast cancer patients were analysed. In this study, 66.1% of cases were younger than 50 years of age with a mean age of 45.2 years at diagnosis. The most common histopathological diagnosis was invasive ductal carcinoma (68.6%), invasive lobular carcinoma (11.1%) followed by invasive medullary carcinoma (5.2%). The findings also revealed that 62.8% of patients presented with advanced stage breast cancer. The studies by Burson et al. (2010) and Kemfang Nqowa et al. (2011) that were both conducted in African countries revealed fairly similar results in that most females presented with invasive ductal carcinoma i.e. advanced stage of the disease and the mean age at diagnosis was \pm 45 years.

Sandhu et al. (2010) conducted a study at a tertiary care hospital in North India and used the medical records of 304 breast cancer patients admitted over a five-year period to determine the epidemiology of breast cancer. The majority of the patients were female (98.7%). The mean age of the female breast cancer patients was 47 years which is a decade younger when compared to the western world (58 years) (Sandhu et al., 2010; Leong et al., 2010). Interestingly, the results revealed that in most cases a lump in the breast was detected by the women themselves. For this reason the authors recommended that education in breast self-examination was an important strategy for early diagnosis even though it is contrary to Cochrane recommendations. Similar to findings by Burson et al. (2010) and Kemfang Nqowa et al. (2011), Sandhu et al. (2010) also

reported that the majority of patients (99.3%) presented with invasive carcinoma i.e. late stage cancer.

In Pakistan, research has shown that women presented with breast cancer at a much younger age when compared to western populations (Batool et al., 2005). In the study conducted by Batool et al. (2005), medical records at Jinnah Hospital, Lahore covering a 5 year period, were reviewed. The majority of patients (69.3%) presented with malignant breast lesions; the mean age of patients was 35 years – the youngest mean age revealed by the literature searched. When stage of presentation was analysed, it was found that the majority of cases presented at stage III (60%). These findings are similar to findings from Tanzania, Cameroon and India (Burson et al., 2010; Kemfang Nqowa et al., 2011; Sandhu et al., 2010).

The clinical profile of breast cancer may differ among diverse ethnic or racial groupings living in the same country and this is illustrated in a study conducted in Israel by Nissan et al. (2004). A retrospective register review was conducted where ethnicity, age at diagnosis and stage at diagnosis were compared in Arab and Jewish women. The results indicated a significantly lower 5-year disease specific survival rate among various ethnic groups who were treated at the same hospital complex. The 5-year disease specific survival rate for Palestinian-Arab women was 55%; Ashkenazi-Jewish was 78% and Sephardic-Jewish, 72%. Nissan et al. (2004) further found that breast cancer in Palestinian-Arab women presented at a younger age and later disease stage compared to other ethnic groups. Since all the women irrespective of ethnicity had the same unrestricted availability to breast examination and screening mammography, the authors hypothesised that various explanations such as hormonal factors, family history, undescribed gene mutation and the traditional reluctance of the Arab society to participate in women's health programmes can explain some of the findings in the Palestinian-Arab group.

A study of 251 African-American and 580 White women in the US revealed that African-American women were more likely to be diagnosed with more advanced breast cancer compared to White women (Hahn, 2007). Reasons for the differences in stage at diagnosis between racial groups included insurance status, poverty, mammography screening history, method of breast cancer detection and obesity. The authors suggested that the observed differences between African-American and White women in breast cancer stage at diagnosis could be considerably reduced if attention could be given to strategies to address poverty and obesity, improvement in

health insurance coverage and through increased public awareness about mammography screening.

In 2007, a Breast Surgery International symposium was held in Canada to address epidemiological and clinical outcome data of women with breast cancer in Asian and Western Countries i.e. US and Europe (Leong et al., 2010). The following table summarises the comparison of characteristics of breast cancer based on a range of studies presented at the symposium.

Table 2: Summary of characteristics of breast cancer among Asian and Western women

Country	Incidence of breast cancer per 100 000	Peak age at presentation of breast cancer	Stage at initial presentation
China	24.0	45-50 years	Majority stage II
Taiwan	43.3	40-49 years	Not indicated
India	33.4	45-49 years	Stage I: 1-8% Stage II: 23-58% Stage III: 29-52% Stage IV: 6-24%
Japan	43.6	45-49 years	Stage II: 43.6%
South Korea	40.5	47 years	Stage I: 36% Stage II: 40% Stage III: 5%
Europe (Sweden)	153.0	63 years	Stage I: 56% Stage II: 37% Stage III: 5% Stage IV: 2%
Canada	104.0	50-59 years	Stage I: 65%
USA	131.0	61 years (mean age at diagnosis)	Stage I: 65%

Source: Leong et al. (2010)

From Table 2 it can be noted that there was a significant difference in age at initial diagnosis with Asian women presenting at a younger age and later stage compared to women from the US and Europe.

The clinical profile of breast cancer among younger and older women may differ. Breast cancer in the younger age group i.e. ≤ 35 years of age seems to be an understudied area. In young females, breast cancer may be less likely to respond to treatment, tumours may be more aggressive, disease outcome is typically poorer and young women with breast cancer are also more likely to have a genetic predisposition compared to older women (Althuis et al., 2003; Basro & Apffelstaedt, 2010). Furthermore, incidence of breast tumours with particularly poor prognosis is highest among pre-menopausal women aged 35-40 years (Althuis et al., 2003). A study conducted in Pakistan by Batool et al., (2005) found that the mean age of women who presented with breast cancer was 35 years; the majority of women (73.9%) were ≤ 40 years of age and that overall 61.9% of the women were ≤ 35 years of age. In Eastern Nigeria from 1998 - 2005, the peak age ranges of breast cancer incidence were between 30-39 and 40-49 pointing to occurrence at relatively young ages (Anyanwu, 2008).

In summary:

- In developing countries the majority of patients present with advanced stage breast cancer which is associated with a poorer survival rate.
- Women from developing countries (for example Africa and Pakistan) tend to present with breast cancer at a significantly younger age compared to women in developed countries.
- There is a gap in the knowledge regarding the profile of breast cancer among women ≤ 35 years of age.

2.5 Profile of breast cancer among patients in SA: focus on age, race and stage at presentation

In SA some research has been undertaken to highlight the burden of breast cancer in the country however few studies have looked specifically at the socio-demographic, clinical and risk factor profile of breast cancer among women. SA is a country with a very diverse population and due to the historical categories of population groups in SA (Black, Coloured, Indian, White) many researchers had collected or continue to collect data by race. In SA, a justification for the use of race in data collection includes monitoring of progress related to disparity in health care services

especially post 1994 and another is to understand race-associated differences in a given medical condition (Myer & Ehrlich, 2007). Table 3 reflects earlier research that has been published to highlight the profile of breast cancer among SA women.

Table 3: Summary of breast cancer research conducted in SA

Study site	Period	Purpose of study	Mean age at presentation in years	Stage at diagnosis
Groote Schuur hospital, Cape Town	1971-1981	To measure the frequency of breast cancer by age, race and stage at presentation.	Blacks: 49 Coloureds: 53 Whites: 60	White women ($\pm 60\%$) presented with breast cancer at early stage whereas $\pm 60\%$ of Coloured women and $\pm 75\%$ of Black women presented at advanced stage (Hacking et al., 1984).
Coronation hospital, Johannesburg	June 1974-June 1984	To review malignant breast tumours.	No mean age given; 25% of females presented with breast cancer below the age of 40.	50% of the patients presented at advanced stage (Ostyn et al., 1987).
University, Durban	1975-1983	To compare the clinical patterns of breast cancer in women of different racial groups.	Blacks: 50 Coloureds: 53 Indians: 47 Whites: 60 More than 50% of White patients presented with breast cancer after the age of 60 years whereas 88%, 72% and 70% of Indian, Black and Coloured patients respectively presented well below 60 years.	Breast cancer presented at a more advanced stage in Blacks compared to Whites (Pegoraro et al., 1985).
Hillbrow Hospital, Radiation Therapy Department	January 1988-December 1992	To assess breast cancer in the study population.	Blacks: 58 Coloureds: 52 Whites: 55 Indian: 49	74% of Black women and 25% of White women presented at advanced stage (Greenberg, 1994).
King Edward VIII Hospital, Durban	1994-1999	To evaluate breast cancer in black African women.	54	The majority of patients (84.3%) presented at advanced stage (Walker et al., 2000).

All the studies outlined in Table 3 had similar conclusions in that breast cancer presented at a more advanced stage in Coloured and Black women when compared to White women; and that breast cancer presented at a younger age in Black and Coloured women than in White women (except for the Greenberg study since the majority of patients were Black females). Pegoraro et al. (1985) proposed that the discrepancies in presentation of breast cancer between the race groups could be related to differences in cultural and educational attitudes to breast cancer in the various race groups. Pegoraro et al. (1985) did not explore whether differences in access to health services could have been a contributing factor in the outcome.

Although a few studies have been conducted in SA to highlight the profile of breast cancer among women in SA, these studies were conducted a number of years ago and reflect data from 1971 to 1999.

In summary:

- SA studies on the profile of breast cancer among patients are dated and information is only available for the period 1971 to 1999.
- The majority of SA studies revealed that breast cancer presented at a younger age in Black women when compared to White women.
- All SA studies revealed that breast cancer presented at a more advanced stage in Coloured and Black women when compared to White women.
- More recent data is required to determine whether the profile of breast cancer among women has changed.

2.6 Prevention of breast cancer

Secondary prevention through early breast cancer detection is the main focus of breast screening programmes with the aim to reduce mortality and morbidity. There are three commonly recognised screening techniques to aid in the early detection of breast cancer namely breast self-examination (BSE), clinical breast examination (CBE) and mammography screening. Breast awareness (BA) is also gaining increasing acceptance worldwide as a method in the early detection of breast cancer.

2.6.1 BSE

BSE is defined as a regular, repetitive monthly palpation of the breast by a woman. This breast screening method should be performed at the same time each month. Women who perform BSE should receive proper training before commencement of this monthly practice (Thornton & Pillarisetti, 2008).

According to Hackshaw and Paul (2003) there is the notion that among women who practice BSE, that those who develop breast cancer are more likely to find it at an earlier stage; that it will lead to earlier treatment and consequently lower the risk of dying from the disease. The authors conducted a meta-analysis of BSE and breast cancer mortality by reviewing published evidence from both observational studies and randomised trials. They investigated three aspects related to BSE namely women who practiced BSE, women who discovered their cancer during regular BSE, and women who were taught BSE and advised to practice it regularly. Hackshaw and Paul (2003) stated that in women who reported to have discovered their cancer during BSE, no evidence in decline in mortality rate was found compared to those who did not perform BSE.

The Cochrane review by Köster and Gøtzsche (2008) reviewed the evidence for the association between regular BSE and a reduction in breast cancer mortality. Two large, population-based randomised trials conducted in Russia and China were included. No statistically significant difference for breast cancer mortality was found between the intervention and control groups. The third study included in the Cochrane review was a large population-based randomised trial conducted in the Philippines which investigated the outcome of a combination of BSE and CBE. Unfortunately, the Philippines study was terminated early and a conclusive answer could not be reached whether a combination of screening by BSE and CBE reduces breast cancer mortality. Köster and Gøtzsche (2008) recommended that BSE cannot be suggested as a screening approach in the early detection of breast cancer.

2.6.2 CBE

CBE is defined as a standardised procedure where a health care professional examines a woman's breast, chest wall and axilla (WHO, 2008). According to WHO (2008) CBE can be used as either a screening examination or a diagnostic examination depending on the clinical setting in which it is applied.

A Canadian cohort study conducted by Chiarelli et al. (2009) compared the accuracy of screening among dedicated breast screening centres that offered CBE by trained nurses in addition to mammography with that among dedicated breast screening centres that offered only mammography. Study findings revealed that breast cancer detection rates, sensitivity, abnormal call rates and false-positive rates were higher among breast screening centres that offered CBE together with mammography compared to centres that only offered mammography alone. In fact, Chiarelli et al. (2009) found that women who were screened by both modalities were at a higher risk of false-positive tests than women screened by mammography alone. Hence, the authors point out that even though increased sensitivity from the addition of CBE to mammography is a benefit, it must be weighed against likely risks and costs of further follow-up caused by false-positive results as well as the anxiety coupled with additional medical investigations.

A Cochrane review by Köster and Gøtzsche (2008) reviewed the evidence for the association between regular CBE and a reduction in breast cancer mortality and morbidity. No statistically significant difference for breast cancer mortality was found therefore Köster and Gøtzsche (2008) finally concluded that CBE cannot be suggested as a screening approach in the early detection of breast cancer.

2.6.3 Breast Awareness (BA)

According to Thornton and Pillarisetti (2008) BA is defined as a woman becoming familiar with her own breasts and the way it will change throughout her life with the expectation that changes will be noticed to help detect breast cancer early. Globally BA is coming increasingly acceptable and has gained the support of numerous international breast cancer organisations. However Thornton and Pillarisetti (2008) caution that uncertainty exists about the benefit or harm in the practice of BA and stress the importance of further research.

2.6.4 Mammography screening

WHO (2008) define mammography screening as a standard two-view mammogram obtained of an asymptomatic women with the purpose to detect breast cancer early. Population-based mammography screening is widely utilised in developed countries.

Gøtzsche and Olsen (2000) conducted a meta-analysis of the effectiveness of mammography trials and their conclusions that mammography screening for breast cancer is unjustified caused

intense debate. The authors argued that there were many flaws and inconsistencies in the trials especially with regards to the randomisation method. The final conclusions by Gøtzsche and Olsen (2000) were that “the effect of screening programmes, if any, is small and the balance between beneficial and harmful effects is very delicate”.

In 2002, a working group of the International Agency for Research on Cancer (IARC) concluded that (a) there is ample evidence for the efficacy of mammography screening in women aged 50-69 years; (b) there is limited evidence for the efficacy of mammography screening in women aged 40-49 years and (c) there is no direct conclusion for the efficacy of mammography screening in women younger than 40 or older than 69 years.

In summary:

- BSE, CBE and mammography screening are the three commonly recognised techniques in the early detection of breast cancer.
- A Cochrane review concluded that BSE and CBE cannot be suggested as a screening approach in the early detection of breast cancer.
- BA is gaining increasing acceptance globally as a method in the early detection of breast cancer but further research on the benefits and harms are required.
- Mammography is widely used as a screening tool in developed countries. Evidence indicates that it is effective in women aged 50-69 years; of limited effectiveness in women aged 40-49 years and evidence for effectiveness in women younger than 40 or older than 69 years is inconclusive.

2.7 Initiatives in the control of breast cancer

It is widely recognised that breast screening through mammography is an effective method to aid in early detection of breast cancer in women 50 – 69 years of age; however screening through mammography is unaffordable in developing countries (WHO, 2008). In 2008, WHO suggested that to achieve a substantial effect on breast cancer mortality, an effective mammography screening programme needs to achieve coverage of no less than 70% of the target population. However, WHO realised that the majority of developing countries such as SA, would have difficulty to meet this recommendation and that several upper-middle resource countries would equally find this requirement economically unattainable. Therefore WHO (2008) and the Breast

Health Global Initiative (BHGI) 2010 summit identified less costly interventions that may be implemented in low-and middle-income countries (LMC) to aid in the early detection of breast cancer.

A variety of cost-effective breast cancer control programmes (compared to costly mammography screening programmes) are recommended by the BHGI and WHO to aid in early detection of breast cancer in LMC's. These cost-effective programmes would include community awareness, patient awareness and CBE. According to Anderson et al., (2010) essentially the BHGI recommend that breast care centres should be centralised and accredited breast care centres of excellence should be established. To ensure that larger proportions of the population are reached, outreach into rural and surrounding areas is important to increase access.

Community awareness where the public is educated about breast cancer and informed that breast cancer is a treatable disease if diagnosed early is an important strategy to improve participation in breast cancer control programmes (Anderson et al., 2011). WHO (2008) advocates patient awareness of early signs and symptoms which could lead to an earlier consultation with a health care professional who should then initiate prompt confirmation of diagnosis and treatment. The BHGI recommended the implementation of a combination of public awareness programmes and CBE in LMC's due to the higher incidence and the late presentation of breast cancer. CBE is recommended as a clinical diagnosis tool and is regarded as a basic and necessary resource in the early detection of breast cancer. CBE however should only be implemented on condition that healthcare professionals are appropriately trained (Anderson et al., 2011).

SA does not have a national mammography screening programme. In 2000 at a national Department of Health meeting, it was suggested that a gradual approach to CBE be introduced in SA however the suggestion was never put into practice (Sandelin et al., 2002).

Currently in SA, a non-profit organisation, Cause Marketing Fundraisers have initiated the PinkDrive community campaign. PinkDrive provides a service throughout SA with the message that "early detection saves lives". The main aim of this public benefit organisation is to provide free mammography and education to disadvantaged communities via local clinics, community health centres and hospitals with no oncology facilities (PinkDrive, 2012). PinkDrive currently has two mobile breast check/ educational units linked to four provincial hospitals in Gauteng. In the Western Cape, a mobile mammography screening unit operates via three community health

centres associated with a local academic hospital to provide free mammography services. Statistics as at 12 May 2012, indicate that since its inception, 4 032 mammograms and 28 950 CBE's have been performed while 37 699 women have been educated on breast health (PinkDrive, 2012). No studies have been documented on the significance of PinkDrive or the cost-effectiveness of this breast screening programme.

In SA, public awareness regarding cancer is spear-headed by the Cancer Society of South Africa (CANSA). This non-profit organisation's main mission is to lead the fight against cancer in SA through research, education to the public and by offering support to all people affected by cancer (CANSA, 2012). CANSA uses scientific research findings to create awareness regarding cancer and also strives to influence policy makers who are responsible for developing public health regulations. CANSA offers communities an opportunity to become actively involved in the fight against cancer by providing education and access to information. Community education focuses mainly on prevention of cancer. CANSA aims to ensure that communities will take ownership in the fight against cancer (CANSA, 2012).

In summary:

- Mammography screening is widely used in developed countries but is economically unattainable in developing countries including SA.
- WHO and BHGI 2010 have identified less costly breast screening interventions (compared to mammography screening) for LMC's which include public awareness programmes, breast education programmes as well as CBE by trained healthcare professionals.
- PinkDrive, a public benefit organisation provide SA women in various disadvantaged communities access to mammography screening, breast education, CBE and the opportunity to be educated on BSE.
- CANSA's main aims are to educate society regarding cancer and to influence health policy decisions.

2.8 Conclusion

Breast cancer is the most common cancer among females globally and in SA. Strong risk factors for breast cancer among females are aging, family history of breast cancer, presence of BRCA 1 and BRCA 2, exposure to HRT and oral contraceptives. Poorly defined risk factors include alcohol consumption, diet, bodyweight and physical inactivity however further research is required to conclusively prove its contribution to risk of breast cancer.

In developed countries, breast cancer mainly occurs in females 55 years and older however women in developing countries tend to present at a significantly younger age. A pattern identified in numerous studies conducted in developing countries including SA is that the majority of patients presented with advanced stage breast cancer which is associated with a poorer survival rate. Population-based mammography screening is a very costly breast screening method therefore developing countries such as SA are advised by WHO and IARC to implement less costly breast screening strategies such as CBE, BA and public awareness programmes to aid in the early detection of breast cancer.

SA studies on the demographic, clinical, reproductive, epidemiological, diagnostic, treatment and/ or surgical profile of breast cancer among patients are limited and dated and more recent data is required to underpin public health prevention efforts.

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SECTION III: JOURNAL MANUSCRIPT

3. Journal Manuscript

Title: The profile of breast cancer among women attending a Breast Clinic in Cape Town, South Africa

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Background: Globally, breast cancer is a public health burden. In developing countries the majority of women present with advanced stage breast cancer at diagnosis. Currently breast cancer is the leading cancer among women in South Africa (SA). No recent data is available on the profile of breast cancer patients in SA.

Objectives: To describe the socio-demographic, clinical and risk factor profile of breast cancer among women.

Design and Setting: A retrospective cross-sectional descriptive medical record review was conducted at a Breast Clinic linked to a tertiary public hospital in Cape Town, South Africa.

Methods: Data were abstracted from the medical records of 596 patients who were newly diagnosed with breast cancer from 01 January 2009 to 31 December 2010. Information on a wide range of variables at initial visit was recorded. Data were entered into EpiData version 3.1 and the database was imported to Stata Statistical package version 12. Data were analysed descriptively and multivariate logistic regression was conducted to determine factors associated with late presentation.

Results: The median age at presentation was 54 years (interquartile range of 44-66 years). The median age at presentation for Black females was 45 years; for Coloured females 54 years and 59 years for White females ($p = 0.000$). A total of 38 females (6.5%) were ≤ 35 years of age. History of breastfeeding, smoking and alcohol use were poorly documented. A breast lump was a dominant symptom and was discovered mainly by self-detection. The most common histopathological type diagnosed was infiltrating ductal carcinoma (83.7%). The majority of women (56.6%) presented at late stage breast cancer (stages III and IV). Thirty percent (30%) of women had signs or symptoms associated with breast cancer for > 6 months prior to a medical consultation. In the logistic regression, duration of symptoms (1-6 months OR 3.07, 95% CI 1.43, 6.58; 7-12 months OR 4.93, 95% CI 2.16, 11.28; > 12 months OR 10.44, 95% CI 3.44, 31.68) showed a significant association with stage at presentation. There was a significant association between race and stage at presentation with White females having a significantly lower odds (adjusted OR 0.33; 95% CI 0.16, 0.70) of presenting at late stage compared to Black females.

Conclusion: The majority of women presented with advanced stage breast cancer. There is a need in SA to create awareness regarding breast cancer signs and symptoms. Further research is needed to determine possible barriers to early presentation to health care facilities.

Introduction

Breast cancer is the most common cancer among women in both developed and developing countries.¹ Incidence rates are high (greater than 80 per 100 000) in developed regions (except Japan) and low (less than 40 per 100 000) in most developing regions.¹ In South Africa (SA) breast cancer is a major public health problem with an age-standardised incidence rate of 41 per 100 000 and an age-standardised mortality rate of 20.7 per 100 000.¹ The most recent National Cancer Registry (NCR) data indicate that SA females have a lifetime risk of 1 in 31 of developing breast cancer.²

Studies conducted in developing countries have shown that the majority of women present with advanced stage breast cancer at diagnosis.³⁻⁹ Poor socio-economic conditions, lack of medical facilities and trained medical staff, poor medical treatment as well as illiteracy have been found to be significant factors associated with late presentation of breast cancer.^{7,8,9} Factors such as fear of mastectomy, ignorance, stigma, a strong belief in traditional medicine and superstition also play an important role in late presentation of breast cancer.^{4, 6-9} Women in developing countries tend to present with breast cancer at a relatively younger age (median age of 45 years)³⁻⁹ compared to women in the developed world who generally present with breast cancer at 55 years and older.¹⁰ In young females (≤ 35 years of age), breast cancer may be etiologically different, may be less likely to respond to treatment, tumours may be more aggressive in character and disease outcome is typically poorer compared to breast cancer among older women.^{11, 12}

Studies on the profile of breast cancer patients in SA are dated (1971 to 1999).¹³⁻¹⁸ Previous SA studies have shown that the majority of patients present at an advanced stage, particularly Coloured and Black females compared to White females.¹³⁻¹⁸ In addition, some authors highlighted the relatively younger age of Black females i.e. 10-15 years younger than Coloured and White females when diagnosed with breast cancer.^{14, 16}

The aim of this study was to provide recent data on the socio-demographic, clinical and risk factor profile of breast cancer among women presenting at a Breast Clinic linked to a tertiary public hospital in Cape Town, South Africa.

Methods

A retrospective medical records review was conducted at the Tygerberg Hospital Breast Clinic in the Western Cape Province, South Africa. This tertiary public hospital provides healthcare services to a large and diverse population, within and beyond the borders of the Western Cape Province. A full range of general specialist and sub-specialist services are provided such as emergency care, high care, surgery, maternity care, paediatric services, oncology, human genetics and rehabilitation services.

The Breast Clinic statistics record (a clinic-based book where all the details of breast cancer cases are recorded) was accessed to verify the total number of breast cancer cases for the period 01 January 2009 to 31 December 2010. The medical records of patients were located, accessed and reviewed. A standardised data capture sheet was used for data collection. Data was collected for all patients with newly diagnosed breast cancer during the study period. All cases with previous history of breast cancer diagnosis were excluded. Information on a wide range of variables at initial visit was recorded which included socio-demographic details (age, sex, place of residence i.e. urban vs. rural, employment status, medical aid membership, race group) clinical details (family history of breast cancer, duration of symptoms, stage at presentation

based on the Tumour Node Metastasis-TNM- system, histopathological type of cancer, presenting signs and symptoms), reproductive details (menopausal status, gravida, parity, contraceptive use) and risk factor details (current or previous hormone replacement therapy (HRT) use, weight, history of breastfeeding, history of smoking and history of alcohol use). In cases where medical records were incomplete e.g. no staging information, it was captured as “not recorded”. Initial histopathology reports were reviewed, while initial cytology reports were reviewed in cases where the former was not performed due to clinical management of patient. A pilot study was conducted to test the suitability and practicability of the data capture sheet. Data collection took place over a period of four months.

Data was entered using EpiData version 3.1 and analysed using Stata Statistical package version 12. Summary statistics and box-and-whisker plots of continuous variables, and tabulations for categorical and binary variables were used to characterise the variables. After calculation of initial descriptive analysis for the whole sample, male subjects (n = 11) were excluded. For the purpose of the study, further analysis was restricted to female subjects (n = 585).

Stage at presentation was categorised as “early stage” (stage 0, I, IIA, IIB) and “late stage” (stage IIIA, IIIB, IIIC, IV). Crude associations of potential predictors with stage at presentation were tested using Wilcoxon rank-sum tests for medians and Chi-square tests and Fischer Exact tests for proportions.

Logistic regression was used to create a model with stage at presentation as dependent variable. Age and racial group were introduced in the model as possible confounders. Based on literature findings other variables present in the dataset were considered as potential predictors of stage at presentation (namely place of residence, employment status, medical aid status, family history of breast cancer, menopausal status, parity, having ever smoked or used alcohol, clinical signs of breast cancer as well as duration of symptoms) and introduced in the model if their bivariate association with the outcome (adjusted for age and race) was statistically significant. A significance level of $p < 0.15$ was used. The only variable showing a significant association according to this criterion was the ordinal variable duration of symptoms. The final logistic regression model, therefore, included stage at presentation as the dependent variable and age, racial group and symptom duration as predictors.

Results

A total of 724 breast cancer cases were diagnosed from 01 January 2009 to 31 December 2010. Of these, 73 had a previous diagnosis of breast cancer and were excluded from the study while a further 55 medical records were missing. Hence, data for 596 newly diagnosed breast cancer patients were included. Of the 596 patients, 585 were female (98.1%) and 11 (1.9%) were male. In males, the median age was 69 years with a range of 43-100. The majority of males presented with late stage breast cancer while infiltrating ductal carcinoma was the most common histopathological type diagnosed. Hereafter, only results on females will be presented.

Socio-demographics and prevalence of known risk factors for breast cancer

Table 1 illustrates the socio-demographics and prevalence of known risk factors for breast cancer for the overall population. The overall median age was 54 years (IQR 44-64 years). The majority of women resided in urban areas, were employed and did not have medical aid membership. The majority of women were Coloured, in keeping with the population profile of the Western Cape Province. No Indian/ Asian females attended the Breast Clinic during the period of investigation.

The highest proportion of cases was among Coloured females in the 40-49 year age group while overall 38 females (6.5%) were ≤ 35 years of age (data not shown). The median age at diagnosis for Black females was 45 years (IQR 38-52 years); 54 years (IQR 44-64 years) for Coloured females and 59 years (IQR 44-64 years) for White females (data not shown). The difference in age at presentation between women in the various race groups were significant ($p = 0.000$). Menopausal status was well documented with the majority of women (64.8%) being post-menopausal. Women had a median of 3 children while 8.6% of women were nulliparous. History relating to HRT use at time of diagnosis was indicated in 574 (96.0%) cases. The majority of women (96.7%) did not use HRT at time of diagnosis and a very small number of females (8) had previously used HRT for a period of more than 10 years (data not shown). History of breastfeeding, smoking and alcohol use were not routinely documented (see Table 1 for levels of missing data). A history of smoking was documented in only 368 cases; of these 60.9% ever smoked. Alcohol use was documented in only 331 cases; of these 75.8% have never used alcohol. History of breastfeeding was only documented in 58 cases; of these 50 ever breast fed (data not shown). Data on body weight or body mass index (BMI) was not documented at all.

Histo-pathology, stage at diagnosis and symptoms

Invasive breast carcinoma accounted for 99.0% of cases ($n = 579$). The most common histopathological type diagnosed was infiltrating ductal carcinoma (82.7%; $n = 479$). Of the 585 cases, 578 cases had complete data relating to stage at diagnosis and were as follows: Stage 0 (1.2%), Stage I (3.1%), Stage II (39.1%), Stage III (44.8%) and Stage IV (11.8%). Overall, the majority of cases (56.6%; $n = 327$) presented with advanced stage of the disease i.e. Stage III & IV. Women reported having signs and symptoms for varying periods prior to medical consultation: 7.7% ($n = 40$) had signs and symptoms < 1 month prior to medical consultation; 62.8% ($n = 325$) for between 1 and 6 months; 22.8% ($n = 117$) for between 7 and 12 months and 6.7% ($n = 35$) for > 12 months. Association between race group and symptom duration were significant ($p < 0.001$) (data not shown). Overall Black and Coloured females tend to present for a medical consultation later compared to White females (data not shown). In general, clinical signs and symptoms were poorly recorded with the exception of presence or absence of breast lumps and axillary nodes. The majority of cases presented with a breast lump (96.9%; $n = 564$) while 285 cases (48.7%) presented with axillary nodes.

Factors associated with stage at presentation

Table 2 summarises results of the bivariate analysis comparing 251 early stage cases and 327 late stage cases. The bivariate analysis showed that race was associated with stage at diagnosis ($p = 0.001$). Signs and symptoms of axillary nodes were significantly associated with stage at presentation ($p = 0.000$). Place of residence, employment status, medical aid status, family history of breast cancer and menopausal status showed no significant association with stage at diagnosis.

Table 3 summarises results of the multivariate logistic regression comparing 251 early stage cases and 327 late stage cases. After adjusting for race in the logistic regression model, a significant association was found between stage at presentation and race group with White females having a significantly lower odds (adjusted OR 0.33, 95% CI 0.16, 0.70) of presenting in late stage compared to Black females.

A significant association ($p < 0.001$) between stage at presentation and duration of symptoms was found. Women with symptoms > 12 months were significantly more likely to present with late stage breast cancer (adjusted OR 10.44, 95% CI 3.44, 31.68) compared to women with symptoms between 1- 6 months (adjusted OR 3.07, 95% CI 1.43, 6.58).

Discussion

The majority of cases (56.6%) in our study presented at Stage III and IV i.e. advanced stage of the disease. SA research covering a period from 1994-1999 indicate that 84% of cases presented with advanced stage breast cancer.¹⁸ Although the proportion of patients presenting at advanced stage breast cancer in our study was much lower than previously recorded, it is still much higher than that seen in developed countries.

In comparison, in many developing countries, breast cancer is diagnosed at an advanced stage.³⁻⁹ The proportion of patients presenting with advanced stage was 63% in Cameroon⁴, 70% in Iran⁶, 81% in Nigeria⁹ and 91% in Tanzania.³ The proportion of women presenting late in SA is lower than other developing countries but higher than that seen in middle and high-income countries.¹⁰ Research, especially in African countries, has attributed late presentation mainly to strong beliefs in traditional medicine, religious beliefs and cultural barriers.^{6-9, 17} The difference in proportions in late presentation compared to other developing countries (especially other African countries) could be explained by the fact that in SA, Coloured and White females generally are less likely to opt for traditional medicine as a first line of treatment compared to Black females.¹⁷ In this study, a minority of women were Black, possibly explaining part of the difference. African studies in particular have also found that apart from cultural factors, socio-economic factors directly or indirectly affect health seeking behaviour.^{4, 8} It is also possible that access to breast cancer services in the Western Cape might be better compared to other developing countries. Our study did not examine the reasons for delay in health seeking behaviour in the study population, however future studies could shed more light on this.

In African countries such as Tanzania and Nigeria, breast cancer is seen at a younger age^{3, 9} compared to developed countries where breast cancer peaks between 55-60 years of age.¹⁰ Findings from Cameroon⁴, India⁵, Iran⁶, Nigeria⁹ and Tanzania³ indicate that the mean age at diagnosis was approximately 10-15 years earlier than peak incidence for women in developed countries. The median age at diagnosis in this study was 54 years. This is consistent with the most recent 2003 National Cancer Registry (NCR) data which indicate that the peak incidence of breast cancer is in the 50-54 year age group.² In addition in our study, the median age in Black women was 45 years; this is about ± 10 years earlier than the median age in Coloured women and ± 15 years earlier than the median age in White women. No comparative data regarding median or mean age of females in the race groups are available from the NCR. In our study, 6.5% of females were ≤ 35 years of age while the most recent NCR data indicate that 5.1% of females presented with breast cancer at ≤ 35 years of age.² Our results and NCR data are slightly less than findings in Israel where 11% of Arab women were ≤ 35 years of age.¹⁹ A significant difference was found between median age and race group ($p = 0.000$). Our finding is in keeping with results from Israel where Arab women presented with breast cancer at a younger age compared to Jewish women.¹⁹ Similarly in the United States (US), African-American women were more likely to be younger at time of diagnosis.²⁰ Our results indicate that Black women in

SA follow breast cancer age patterns similar to women in developing countries while White women follow breast cancer age patterns similar to women in developed countries.

In this study most women diagnosed during the period under investigation resided in urban areas and had no medical aid, however no significant association between stage at presentation and place of residence or medical aid membership was found. This suggests that distance to the health facility and having no medical aid were not contributing factors to presenting with advanced stage breast cancer. In contrast, a study published in 2000 which incidentally was also conducted in Cape Town found that late stage at presentation was significantly associated with rural residence and having no medical aid membership.²¹ The difference in result between this study and the latter could be that access to health care facilities for people living in rural areas could have improved since 2000. Furthermore, the lack of urban-rural association with stage at presentation in this study could be due to better general health care infrastructure in the Western Cape; the urban-rural association with stage at presentation may be different in other provinces.

Various risk factors are associated with breast cancer and are well documented.^{22, 23} In our study, a positive family history of breast cancer was recorded in 21.7% of cases, higher than most developing countries. In Queensland, Australia²⁴ 16.1% of cases reported a positive family history of breast cancer while in less developed countries like Cameroon⁴, India⁵ and Nigeria⁹, positive family history accounted for 8.7%, 0% and 7.3% of cases respectively. In many developing countries there is still stigma attached to having breast cancer^{6, 17} and this medical information would not necessarily be shared among family members.⁶ In our study, the proportion of cases with a positive family history was higher compared to other developing countries however under reporting of family history of breast cancer could still be possible. Menopausal status was well documented in our study with the majority of women (64.8%) being post-menopausal. This is in keeping with findings conducted in India⁵ and Pakistan⁷ where the majority of women were post-menopausal (55.8% and 53.0% respectively).

Endogenous or exogenous hormones i.e. long term use of oral contraceptives (OC) or hormone replacement therapy (HRT) place women at increased risk of developing breast cancer.²³ In our study, 96.7% of females have never used HRT previously while data on OC use was extremely poor. In Cameroon, a very low proportion of HRT and OC use (6.3% combined) was reported pointing to a similar dilemma as with our study concerning poor documentation of medical information.⁴ Data regarding modifiable risk factors such as lifestyle factors associated with breast cancer was poorly documented. As a result analysis was limited due to the high levels of missing data (>44% for ever use of alcohol and >38% for smoking). Data on history of breastfeeding in our study was also limited. Obesity is associated with a two-fold increase in risk of breast cancer in postmenopausal women²⁴ however analysis regarding weight and/ or BMI was not possible due to non-routine documentation of weight or BMI at initial visit.

Medical records regarding presenting clinical signs and symptoms at initial visit were poorly documented. Of note in this study is the fact that if no clinical sign or symptom was documented, it does not imply that the patient did not present with it. In the majority of cases a breast lump was a dominant symptom and was self-detected. In studies conducted elsewhere a breast lump was also found to be the main complaint and was mainly self-discovered.^{4, 5} For this reason many authors have recommended public health interventions such as education and breast awareness campaigns^{8, 17} in an effort to detect and diagnose breast cancer earlier. In our study, the majority of women presented within 6 months after onset of signs and symptoms. In comparison in Pakistan the average time since awareness and first visit to a health care facility was 14 months⁷.

A Nigerian study⁹ revealed that 63% of patients presented within 1 year of noticing a lump while 7% did not present until 2 years after the onset of symptoms. In the US, women presented to health care facilities within 1-2 months of noticing signs and symptoms.²⁰

In the bivariate analysis, a statistically significant difference between stage at presentation and race groups was found ($p = 0.001$). This finding is consistent with previous studies of a late stage at presentation in SA among Black and Coloured women.¹³⁻¹⁸ During the logistic regression the association between stage at presentation and race groups remained, with White females having a significantly lower odds (adjusted OR 0.33; 95% CI 0.16, 0.70) of presenting in late stage compared to Black females.

The association between race group and symptom duration was statistically significant ($p < 0.001$). Black and Coloured females tend to present for a medical consultation at later periods after onset of signs and symptoms, compared to White females. This finding could possibly be explained by lack of awareness of the signs and symptoms associated with breast cancer^{6,7} by Black and Coloured women. Alternatively, the disparity can be explained by differences in access to health care services among the various race groups. Nonetheless, this difference needs to be explored in future research. In the US, African-American women similarly presented with advanced stage breast cancer compared to White women however an explanation for the racial difference was explained by factors such as no medical aid, poor socio-economic status, obesity and history of mammography.²⁰

Results from our multivariate logistic model revealed a significant association ($p < 0.001$) between stage at presentation and duration of symptoms. Women who presented with signs and symptoms for 7-12 months were 4 times more likely to present with advanced stage breast cancer (95% CI 2.16, 11.28; $p = 0.000$) while those women with signs and symptoms longer than 12 months were 10 times more likely to present with advanced stage breast cancer (95% CI 3.44,31.68; $p = 0.000$). This highlights the importance of educating women about the signs and symptoms of breast cancer and emphasising the importance of attending health care services early. It is possible that early signs and symptoms could have been present but not recognised by women. Improved health awareness could assist with down-staging of breast cancer.

This study provides the most recent data on the profile of breast cancer patients in SA. One of the main limitations of this study is the lack of information on risk factors associated with breast cancer due to poor routine documentation. It is therefore recommended that a comprehensive, standardised document or checklist is developed to aid in routine recording of medical data including signs and symptoms of breast cancer that could be of value in future research. Another limitation was the issue of missing medical records. Even though, we managed to obtain medical records for a fairly large sample of cases, missing medical records were problematic consequently data of 55 cases could not be analysed. Data collection and comprehensive analysis of medical data could be enhanced with a digital hospital information system.

Previous research conducted in SA indicated that the majority of women presented at late stage breast cancer which is associated with a poorer survival rate and limited treatment options. This study finding confirmed that late stage at diagnosis remains a problem in SA. As this study has provided information from one tertiary hospital in the country, further research is warranted to establish whether late stage at diagnosis holds true in other settings in SA.

In conclusion, breast cancer is a public health burden and a humanitarian burden. If breast cancer is detected early, it can lead to successful treatment. The stage of breast cancer at diagnosis may

well be a reflection of women's awareness of the disease. Hence, feasible and cost-effective public health interventions such as breast awareness campaigns should be implemented by the SA government in order to counteract the persistent late presentation among SA women. In addition, research exploring barriers to early presentation is required.

Acknowledgements

The author wishes to thank Mr. Annibale Cois for statistical support.

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Table 1: Socio-demographics and prevalence of known risk factors for breast cancer in study sample

Variable	Overall Distribution (%) N=585
Age at diagnosis in years	
Median	54
Interquartile range	44-66
Age categories	
<30	11 (1.8%)
30-39	63 (10.8%)
40-49	148 (25.3%)
50-59	153 (26.2%)
60-69	119 (20.3%)
70-79	66 (11.3%)
>=80	25 (4.3%)
Place of residence	
Urban	520 (88.9%)
Rural	65 (11.1%)
Employment status	
Employed	378 (64.6%)
Unemployed	61 (10.4%)
Pensioner	146 (25.0%)
Medical aid	
Yes	40 (6.8%)
No	545 (93.2%)
Race group	
Black	65 (11.1%)
Coloured	414 (70.8%)
White	106 (18.1%)
Family history of breast cancer	
Yes	125 (21.4%)
No	450 (76.9%)
Missing data	10 (1.7%)
Menopausal status	
Pre-menopausal	199 (34.0%)
Post-menopausal	379 (64.8%)
Missing data	7 (1.2%)
Parity	
Median	3
Nulliparous	50 (8.6%)
Parous	505 (86.3%)
Missing data	30 (5.1%)
Ever smoked	
Yes	139 (23.7%)
No	222 (38.0%)
Missing data	224 (38.3%)
Ever used alcohol	
Yes	77 (13.2%)
No	248 (42.4%)
Missing data	260 (44.4%)

Table 2: Bivariate association with stage at diagnosis

Variable	Early stage *N=251 (43.4%)	Late stage *N=327 (56.6%)	Early vs Late stage <i>p</i>-value
Age at diagnosis in years			
Median	54	53	0.191 ^a
Interquartile range	45-64	43-63	
Place of residence			
Urban	221(88.1%)	292 (89.3%)	0.691 ^c
Rural	30 (11.9%)	35 (10.7%)	
Employment status			
Employed	162 (64.5%)	214 (65.4%)	0.803 ^b
Unemployed	24 (9.6%)	35 (10.7%)	
Pensioner	65 (25.9%)	78 (23.9%)	
Medical aid			
Yes	19 (7.6%)	20 (6.1%)	0.507 ^c
No	232 (92.4%)	307 (93.9%)	
Race group			
Black	21(8.4%)	44 (13.5%)	0.001 ^b
Coloured	170 (67.7%)	241(73.7%)	
White	60 (23.9%)	42 (12.8%)	
Family history of breast cancer			
Yes	53 (21.1%)	71 (21.7%)	0.838 ^c
No	197 (78.5%)	248 (75.8%)	
Missing data	1 (0.4%)	8 (2.5%)	
Menopausal status			
Pre-menopausal	82 (32.7%)	117 (35.8%)	0.480 ^c
Post-menopausal	165 (65.7%)	207 (63.3%)	
Missing data	4 (1.6%)	3 (0.9%)	
Parity			
Median	3	3	0.426 ^b
Nulliparous	16 (6.4%)	34 (10.4%)	
Parous	223(88.8%)	275 (84.1%)	
Missing data	12 (4.8%)	18 (5.5%)	
Ever smoked			
Yes	63 (25.1%)	74 (22.6%)	0.827 ^c
No	98 (39.0%)	122 (37.3%)	
Missing data	90 (35.9%)	131 (40.1%)	
Ever used alcohol			
Yes	44 (17.6%)	31 (9.5%)	0.012 ^c
No	103 (41.0%)	143 (43.7%)	
Missing data	104 (41.4%)	153 (46.8%)	
Duration of symptoms			
< 1 month	30 (11.9%)	10 (3.1%)	0.000 ^a
1-6 months	149 (59.4%)	176 (53.8%)	
7-12 months	40 (15.9%)	77 (23.5%)	
>12 months	7 (2.8%)	28 (8.6%)	
Missing data	25 (10.0%)	36 (11.0%)	

Breast lump			
Present	242 (96.4%)	322(98.5%)	0.248 ^b
Absent	5 (2.0%)	2 (0.6%)	
Missing data	4 (1.6%)	3 (0.9%)	
Axillary nodes			
Present	73 (29.1%)	212 (64.8%)	0.000 ^b
Absent	47 (18.7%)	12 (3.7%)	
Missing data	131 (52.2%)	103 (31.5%)	

a=Wilcoxon rank-sum, b= Chi-square test, c=Fischer's exact test

*N: medical records of 578 cases were complete relating to stage at diagnosis

Table 3: Multiple logistic regression model* assessing the factors associated with stage at presentation (early vs late stage) among women who were newly diagnosed with breast cancer during 01 January 2009-31 December 2010

Variable	Adjusted OR	95% CI	<i>p</i> -value
Age**			
<55 years	1.00	-	0.785
>55 years	0.95	0.65, 1.38	
Race group			
Black	1.00	-	0.190
Coloured	0.67	0.36, 1.22	
White	0.33	0.16, 0.70	
Symptom duration			
< 1 month	1.00	-	0.004
1-6 months	3.07	1.43, 6.58	
7-12 months	4.93	2.16, 11.28	
>12 months	10.44	3.44, 31.68	

*Logistic regression comparing 251 early stage cases and 327 late stage cases

**Median age has been used to create two age categories

SECTION IV: APPENDICES

Appendix A:

Data capture sheet

The profile of breast cancer amongst patients attending a Breast Clinic in Cape Town, South Africa

Case number

*Not recorded: N/R ; Not applicable: N/A

Reference number	
Year of initial diagnosis	2009 <input type="checkbox"/> 2010 <input type="checkbox"/>
Sex	Female <input type="checkbox"/> Male <input type="checkbox"/>
Age at diagnosis	<input type="text"/> years
Place of residence	Name of town: Urban <input type="checkbox"/> Rural <input type="checkbox"/> Not known <input type="checkbox"/>
Employment status	Employed <input type="checkbox"/> Unemployed <input type="checkbox"/> Pensioner <input type="checkbox"/> N/ R <input type="checkbox"/>
Medical aid membership	Yes <input type="checkbox"/> No <input type="checkbox"/> N/ R <input type="checkbox"/>
Race group	Asian/ Indian <input type="checkbox"/> Black <input type="checkbox"/> Coloured <input type="checkbox"/> White <input type="checkbox"/> Not known <input type="checkbox"/>
Duration of symptoms prior to first visit	<input type="text"/> days <input type="text"/> weeks <input type="text"/> months <input type="text"/> years <input type="text"/> N/R

Type of cancer	<p>In situ Carcinomas (Non-invasive):</p> <p>In situ NOS <input type="checkbox"/></p> <p>(DCIS) Intraductal <input type="checkbox"/></p> <p>Paget's disease and intraductal <input type="checkbox"/></p> <p>Invasive Carcinomas:</p> <p>NOS <input type="checkbox"/></p> <p>Ductal <input type="checkbox"/></p> <p>Inflammatory <input type="checkbox"/></p> <p>Medullary <input type="checkbox"/></p> <p>Mucinous <input type="checkbox"/></p> <p>Papillary <input type="checkbox"/></p> <p>Tubular <input type="checkbox"/></p> <p>Lobular <input type="checkbox"/></p> <p>Paget's disease and infiltrating <input type="checkbox"/></p> <p>Undifferentiated <input type="checkbox"/></p> <p>Squamous cell <input type="checkbox"/></p> <p>Adenoid cystic <input type="checkbox"/></p> <p>Secretory <input type="checkbox"/></p> <p>Cribriform <input type="checkbox"/></p>
Staging at diagnosis	<p>Stage 0 <input type="checkbox"/></p> <p>Stage I <input type="checkbox"/></p> <p>Stage II A <input type="checkbox"/> Stage IIB <input type="checkbox"/></p> <p>Stage III A <input type="checkbox"/> Stage IIIB <input type="checkbox"/> Stage III C <input type="checkbox"/></p> <p>Stage IV <input type="checkbox"/></p> <p>N/R <input type="checkbox"/></p>
Signs and symptoms/ Clinical presentation	<p>Breast lump: present <input type="checkbox"/> absent <input type="checkbox"/> N/R <input type="checkbox"/></p> <p>Breast pain: present <input type="checkbox"/> absent <input type="checkbox"/> N/R <input type="checkbox"/></p> <p>Nipple discharge: present <input type="checkbox"/> absent <input type="checkbox"/> N/R <input type="checkbox"/></p> <p>Nipple retraction: present <input type="checkbox"/> absent <input type="checkbox"/> N/R <input type="checkbox"/></p> <p>Nipple erosion: present <input type="checkbox"/> absent <input type="checkbox"/> N/R <input type="checkbox"/></p>

	Axillary nodes: present <input type="checkbox"/> absent <input type="checkbox"/> N/R <input type="checkbox"/> Skin retraction: present <input type="checkbox"/> absent <input type="checkbox"/> N/R <input type="checkbox"/> Skin infiltration: present <input type="checkbox"/> absent <input type="checkbox"/> N/R <input type="checkbox"/> Oedema: present <input type="checkbox"/> absent <input type="checkbox"/> N/R <input type="checkbox"/> Peau d' orange: present <input type="checkbox"/> absent <input type="checkbox"/> N/R <input type="checkbox"/> Erythema: present <input type="checkbox"/> absent <input type="checkbox"/> N/R <input type="checkbox"/> Ulceration: present <input type="checkbox"/> absent <input type="checkbox"/> N/R <input type="checkbox"/> Fungating: : present <input type="checkbox"/> absent <input type="checkbox"/> N/R <input type="checkbox"/> Other (specify): _____
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Risk factors	<p>Family history of breast cancer: Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/R <input type="checkbox"/></p> <p>Menopausal status: Premenopausal <input type="checkbox"/> Postmenopausal <input type="checkbox"/> Unknown <input type="checkbox"/> N/R <input type="checkbox"/> N/A <input type="checkbox"/></p> <p>Gravida (number of pregnancies) <input type="checkbox"/> N/R <input type="checkbox"/> N/A <input type="checkbox"/> Parity (number of births) <input type="checkbox"/> N/R <input type="checkbox"/> N/A <input type="checkbox"/></p> <p>Contraceptive use (past): Yes <input type="checkbox"/> No <input type="checkbox"/> N/R <input type="checkbox"/> N/A <input type="checkbox"/> Most recent method e.g. Pill, IUD, condoms N/R <input type="checkbox"/> N/A <input type="checkbox"/></p> <p>Duration: Weeks <input type="checkbox"/> Months <input type="checkbox"/> Years <input type="checkbox"/> N/R <input type="checkbox"/> N/A <input type="checkbox"/></p> <p>Other methods used: N/R <input type="checkbox"/> N/A <input type="checkbox"/></p>
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	<p>Hormone replacement therapy at time of diagnosis:</p> <p>Yes <input type="checkbox"/> No <input type="checkbox"/> N/R <input type="checkbox"/> N/A <input type="checkbox"/></p> <p>Duration:</p> <p>Weeks <input type="checkbox"/> Months <input type="checkbox"/> Years <input type="checkbox"/> N/R <input type="checkbox"/> N/A <input type="checkbox"/></p> <p>Previous hormone replacement therapy use:</p> <p>Yes <input type="checkbox"/> No <input type="checkbox"/> N/R <input type="checkbox"/> N/A <input type="checkbox"/></p> <p>Duration:</p> <p>Weeks <input type="checkbox"/> Months <input type="checkbox"/> Years <input type="checkbox"/> N/R <input type="checkbox"/> N/A <input type="checkbox"/></p> <p>Weight at time of diagnosis:</p> <p>.....kg N/R <input type="checkbox"/></p> <p>Ever Breastfed Yes <input type="checkbox"/> No <input type="checkbox"/> N/R <input type="checkbox"/> N/A <input type="checkbox"/></p> <p>Ever smoked Yes <input type="checkbox"/> No <input type="checkbox"/> N/R <input type="checkbox"/></p> <p>Ever used alcohol Yes <input type="checkbox"/> No <input type="checkbox"/> N/R <input type="checkbox"/></p>
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Date loaded to Epidata: _____

Appendix B

15 Coral Road
Highbury
Kuilsriver
7580
08 December 2011

The Faculty of Health Sciences Human Research Ethics Committee
Room 24, E52
Old Main Building
Groote Schuur Hospital

Application for Ethics approval

My name is Valdiela Daries and I am currently registered as a part-time student at the University of Cape Town with the aim to obtain a Masters degree in Public Health. As part of the academic requirements, it is expected of me to conduct research and write-up a mini dissertation. The study I want to conduct is titled: “The profile of breast cancer among patients attending a Breast Clinic in Cape Town, South Africa”. The period under investigation is from 01 January 2009 to 31 December 2010.

For this study, I have to access the medical folders kept at the Breast clinic at Tygerberg Hospital of those patients who have been diagnosed with breast cancer during the period mentioned. The study will not require any human participation therefore no risk of harm is posed to any individual. The study could potentially have public benefit as the results of the study could initiate public health policies or health service strategies to improve early detection and diagnosis of breast cancer. No personal identifying details of cases will be recorded for the study hence anonymity will be maintained at all times. All data will be treated confidentially and will only be used for the purpose of the study. No information will be linked to a specific individual; either during dissemination or possible publication of study results.

The researcher will be responsible for all aspects of data collection. Data capture sheets will be securely stored at all times with access only by the researcher. Permission to use the medical records at the Breast clinic at TBH will only be granted once ethics approval has been granted by the Faculty of Human Sciences Research Ethics Committee of the University of Cape Town. Please refer to the letter attached.

Please contact me should you require additional information.

Thank you for your time.

Regards,

Valdiela Daries

021 928 3327 (office)

082 7888 652

dariesv@cput.ac.za

Appendix D



Tygerberg Hospital and
Mitchells Plain & Tygerberg Oral Health Centres
ENQUIRIES : Dr M Mukosi
TELEPHONE: 021 938-5966

(University of Cape Town): Student Number drsva1001

The profile of breast cancer amongst patients attending a Breast Clinic in Cape Town, South Africa

Dear Ms Valdiela Daries

PERMISSION TO ACCESS HOSPITAL PATIENT RECORDS

Permission is hereby granted that you have access to hospital patient records for the abovementioned research.

Kind regards.

Signature removed

DR M MUKOSI
MANAGER: MEDICAL SERVICES

Date : 09/02/2012

Francie van Zijl Avenue, Parow, 7505
tel: +27 21 938-4136 / fax: +27 21 938-4890

Private Bag X3, Tygerberg, 7505
www.capegateway.gov.za

Appendix E

UNIVERSITY OF CAPE TOWN



Health Sciences Faculty
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

10 January 2012

HREC REF: 004/2012

Ms V Daries
c/o Dr J Moodley
Public Health & Family Medicine

Dear Ms Daries

PROJECT TITLE: THE PROFILE OF BREAST CANCER IN PATIENTS ATTENDING A BREAST CLINIC IN CAPE TOWN, SOUTH AFRICA.

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year till the 30th January 2013.

Please submit a progress form, using the standardised Annual Report Form (FHS016), if the study continues beyond the approval period. Please submit a Standard Closure form (FHS010) if the study is completed within the approval period.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

Signature removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council

s.thomas

Appendix F

Author Guidelines

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

AUTHORSHIP

Named authors must consent to publication. Authorship should be based on substantial contribution to: (i) conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; and (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

RESEARCH ETHICS COMMITTEE APPROVAL

Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to www.icmje.org.

ETHNIC CLASSIFICATION

References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Research articles (previously 'Original articles') not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to clinical medicine and related fields. References should preferably be limited to no more than 15. Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results, and Conclusion.*

Scientific letters will, in future, be incorporated as shorter **Research articles**.

Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the SAMJ peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.

Forum articles must be accompanied by a short description (50 words) of the affiliation details/interests of the author(s). Refer to recent forum articles for guidance. Please provide an accompanying abstract not exceeding 150 words.

Book reviews should be about 400 words and must be accompanied by the publication details of the book.

Obituaries should be about 400 words and may be accompanied by a photograph.

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - www.icmje.org.

Manuscripts must be provided in **UK English**.

Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and <) should be placed immediately preceding the relevant number, i.e. 'women >40 years of age'. The same applies to \pm and $^{\circ}$, i.e. '35 \pm 6' and '19 $^{\circ}$ C'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'

Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting

The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file or provided as '**supplementary files**'. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data

representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...'

All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable, but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached individually as '**supplementary files**' upon submission (not solely embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft Powerpoint or Excel must be accompanied by the original workbook.

REFERENCES

Authors must verify references from the original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference manager software.

References should be inserted in the text as superscript numbers, e.g. These regulations are endorsed by the World Health Organization,² and others.^{3,4,6}

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Book references:

Jeffcoate N. *Principles of Gynaecology*. 4th ed. London: Butterworth, 1975:96-101.

Chapter/section in a book:

Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA jun, Sodeman WA, eds. *Pathologic Physiology: Mechanisms of Disease*. Philadelphia: WB Saunders, 1974:457-472.

Internet references:

World Health Organization. *The World Health Report 2002 - Reducing Risks, Promoting Healthy Life*. Geneva: World Health Organization, 2002. <http://www.who.int/whr/2002> (accessed 16 January 2010).

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