UNIVERSITY OF THE WITWATERSRAND

FACULTY OF HEALTH SCIENCES

SCHOOL OF PUBLIC HEALTH

RESEARCH REPORT

Risk factors for breast cancer among women in Ekurhuleni Metropolitan Municipality, Gauteng Province of South Africa, 2017–2020: A case-control study

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A research report submitted in partial fulfilment of the requirements for the degree of Master of Science in Field Epidemiology in the School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg.

Johannesburg, February 2023

DECLARATION

I **Sizeka Aubrey Mashele** declare that the submitted research report is my original work and where ideas from other researchers have been used, I have referenced and acknowledged them accordingly. This research report is submitted in partial fulfilment for the degree of Master of Science in Field Epidemiology at the University of the Witwatersrand, Johannesburg. It has not been submitted for any degree or examination purpose before at the University of the Witwatersrand or any other University. I have been trained in plagiarism and am aware that plagiarism is misconduct.

Signature:  Date: 24 February 2023

DEDICATION

This work is dedicated to

MY BELOVED WIFE NTSHUXEKANI MAUREEN

FOR HER UNLIMITED SUPPORT

and

MY BELOVED CHILDREN NGALAVA AND NTSETSELELO

FOR BEING

THE HAPPINESS AND JOY OF MY LIFE

MAY THE BLESSINGS OF THE ALMIGHTY GOD OVERFLOW IN YOUR LIVES

and

MAY THIS DEGREE BE A TESTAMENT TO YOU THAT ANYTHING IS POSSIBLE WITH GOD THE ALMIGHTY.

PRESENTATIONS/PUBLICATIONS FROM THE STUDY

The study has been presented at the following conferences:

1. International Association of Cancer Registries (IACR) 2022 virtual scientific conference.

2. African Field Epidemiology Network (AFENET) 2022 regional (Namibia) conference

3. National Institute for Communicable Disease scientific forum

The draft article will be submitted for publication in the *ecancermedicalscience* journal.

SUMMARY

Background: Breast cancer (BC) is the most common cancer among women in South Africa (SA). In 2020, the age-standardized incidence rate (ASIR) and the age-standardized mortality rate (ASMR) were 52.6 and 16.0 per 100 000, respectively. There is a paucity of evidence on the risk factors for BC among women of all population groups in SA. The goal of this study was to determine the risk factors for BC, calculate the ASIR as well as explore epidemiological changes in BC among women in Ekurhuleni Metropolitan Municipality, Gauteng Province, SA.

Methods: An unmatched case-control study was conducted from 1 January 2017 to 31 December 2020 using secondary data extracted from the Ekurhuleni Population-Based Cancer Registry (EPBCR). Unconditional multivariable logistic regression analysis was carried out using the adjusted odds ratio (aOR). The variables race, employment, HIV, smoking and alcohol statuses were included in the multivariable logistic regression model while the model was adjusted for age. In addition to risk factor analyses, we calculated the ASIR for BC in women using the Statistics South Africa population estimates as a denominator and the Segi-World Standard Population (WSP) for standardization. The joinpoint regression program was used to estimate the average annual per cent change (AAPC) for the four years (2017–2020).

Results: A total of 3068 (2217 cases and 851 controls) participants were enrolled in the study. The mean age (±SD) in years of the participants was 55.2 (±15.2). The White population group, being self-employed and Human Immunodeficiency Virus (HIV) -positive status was significantly associated with reduced odds of BC development among women. Women who were HIV-positive were 61% less likely to have BC than women who were HIV-negative (aOR 0.39; 95%CI: 0.27–0.57). White women were 75% less likely to have BC than women of other races (aOR 0.35; 95%CI: 0.29–0.43). Self-employed women were 59% less likely to have BC than women who

were formally employed (aOR 0.41; 95%CI: 0.18–0.97). The ASIR for BC among all women in 2017 was 42.33 (95%CI: 39.25–45.59) and 23.39 (95%CI: 21.10–25.86) per 100 000 in 2020. White women had the highest incidence rate of BC throughout the study period (55.47 (95%CI: 47.57–65.08) in 2017, 69.70 (95%CI: 60.77–79.74) in 2018, 35.51 (95%CI: 29.29–42.85) in 2019 and 37.12 (95%CI: 30.74–44.62) in 2020) compared to other population groups. No significant reduction in BC incidence rate was observed among all women throughout the study period with an exception of Black women, whereby a significant reduction in BC incidence rate was observed between 2017 and 2020 with an AAPC of -23.5% (p=0.017).

Conclusion: In this study, the White population group, being self-employed and HIV-positive had lower odds of BC and thus necessitate more in-depth studies using primary data to effectively explore the risk factors of BC among women in SA settings. There was no significant change in AAPC except for Black women, this indicates disparities in screening uptake among population groups, and as such, there is a need to strengthen BC preventive strategies. There is a need for public health awareness to scale up BC screening uptake as well as the promotion of early detection through targeted awareness campaigns.

Keywords: Incidence, breast cancer, risk factors, age-standardized incidence rate, case-control study, odds ratio, women, average annual per cent change, Ekurhuleni Metropolitan Municipality, registries, standardization, South Africa

ACKNOWLEDGMENTS

I want to express my gratitude to the Almighty God for giving me the chance, the courage, and the strength to begin and ultimately finish this degree.

I owe my sponsor, the South African Field Epidemiology Training Program, a debt of gratitude for the scholarship and other support provided.

I want to express my sincere gratitude to Lactatia Motsuku for her guidance, encouragement, and supervision as well as for holding my hand during the research process and residence.

To Natasha Abraham, Thembekile Zwane, and Dr Mazvita Muchengeti, thank you both for your valuable supervision, guidance and support given throughout this research.

I wish to thank the management of the National Cancer Registry of South Africa for permission to use the data to conduct the research.

We would especially want to express our gratitude to the surveillance personnel of the Ekurhuleni Population-Based Cancer Registry for their excellent efforts during the collection of surveillance data.

I would also like to extend my sincere thanks to the late Dr Elvira Singh (Former Head of the Department, National Cancer Registry) for accepting me to do my Field Epidemiology training at the National Cancer Registry (NCR).

To my family and friends, thank you for your support and for believing in me until I believed in myself.

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LIST OF ACRONYMS/ABBREVIATIONS

AAPC	Average annual per cent change
AHI	Anova Health Institute
AICR	American Institute for Cancer Research
AIDS	Acquired Immune Deficiency Syndrome
aOR	Adjusted odds ratio
APC	Annual per cent change
ART	Antiretroviral treatment
ASIR	Age-standardized incidence rate
ASMR	Age-standardized mortality rate
BC	Breast cancer
BRCA	BReast CAncer gene
BSE	Breast self-examination
CA	Cancer Alliance
CANSA	Cancer Association of South Africa
CBE	Clinical breast examination
CCS	Cancer civil society
CHC	Community healthcentre
CI	Confidence interval

COVID-19	Coronavirus-19
CUMRISK	Cumulative lifetime incidence risk
EPBCR	Ekurhuleni Population-Based Cancer Registry
ER	Estrogen receptor
FETP	Field Epidemiology Training Program
HAART	Highly active antiretroviral therapy
HIV	Human Immunodeficiency Virus
HREC	Health Research Ethics Committee
ICD-O	International classification of disease for oncology
JCS	Johannesburg Cancer Study
LMIC	Low- and middle-income countries
LR	Lifetime risk
MRI	Magnetic resonance imaging
NCR	National Cancer Registry
NDHS	National Demographic and Health Survey
NDoH	National Department of Health
NHI	National Health Insurance
NHLS	National Health Laboratory Services

NICD	National Institute for Communicable Diseases
OR	Odds ratio
OR	Odds ratio
PBCR	Population-based cancer registry
PD	Pink Drive
PHC	Primary healthcare
PISCBE	Provider-initiated screening clinical breast examination
PLWHA	People living with HIV and AIDS
PMB	Prescribed minimum benefit
POPIA	Protection of personal information act
PR	Progesterone receptor
PSU	Primary site unknown
RBU	Regional breast unit
REDCap	Research Electronic Data Capture
SA	South Africa
SABC	South African Breast Cancer
SAFETP	South African Field Epidemiology Training Program
SBU	Specialized breast unit

SD	Standard deviation
SOWETO	South-Western Townships
SSA	sub-Saharan Africa
SSA	sub-Saharan African
STATS SA	Statistics South Africa
TNM	Tumour, Node, Metastasis system
TV	Television
USA	United States of America
WHO	World Health Organization
WSP	Segi-World Standard Population

PREAMBLE

This report consists of six chapters outlined as follows:

Chapter 1. Provides the background of the study, a comprehensive literature review of breast cancer, a problem statement, justification, and research questions as well as the aim and objectives of the study. It also contains the bibliography of references used in this chapter only.

Chapter 2. Consists of a draft of the manuscript written according to the *ecancermedicalscience* journal. The draft manuscript only reports on the risk factor analysis. The manuscript draft consists of the abstract, background, methods, results, discussions and conclusion. It also covers other aspects of the article such as the statements of declarations, ethical considerations, and declaration of conflict of interests among others. It also provides the bibliography of references used in the draft manuscript.

Chapter 3. Provides the methods used for the analysis of the objectives that are not included in the draft manuscript in chapter 2. It covers the ASIR and AAPC analyses. It defines the objectives as well as the analysis methods used.

Chapter 4. Provides the findings for the extended results (standardization and trends) that are not included in the draft manuscript in chapter 2. It also discusses the results found as well as discussing the overall strengths and limitations of the entire study. The references for this chapter are also included.

Chapter 5. Provides the overall conclusion of the study as well as the recommendations.

Chapter 6. Consists of three appendices, namely: Turnitin report, Ethics clearance certificate as well as *ecancermedicalscience* journal guidelines.

CHAPTER 1: INTRODUCTION

Introduction to the section

This chapter details the background and literature review of breast cancer and breast risk factors. It starts by proving a detailed background of breast cancer followed by a detailed review of the literature, problem statement, justification of the study as well as the research question, aim and objectives. The section ends by providing a list of references used in this chapter

1.1. BACKGROUND

Breast cancer (BC) is a condition in which the tissue of the breast develops uncontrollably. BC commonly develops in the lobules, adipose tissues or ducts of the breast due to host or environmental factors [1]. It is classified as either in situ (ductal and lobular) or invasive disease. It consists of five progressive tumour stages described based on the Tumour, Node, Metastasis (TNM) system [2]. Stage zero is a non-invasive ductal carcinoma in situ (DCIS), and stages one to four (1–4) are described as invasive BC. Invasive BC is defined as a malignancy that has invaded the extra ductal or extra lobular tissues and can metastasize [3].

BC is the most common cancer diagnosed in women worldwide. The age-standardized incidence rate (ASIR) of BC increased by approximately five per cent between 2019 and 2020 [4, 5]. One in eight women is estimated to develop BC in their lifetime [5, 6]. It is among the top five leading causes of cancer-related mortality in women worldwide [7]. The sub-Saharan African (SSA) region was estimated to have the highest number of BC-associated deaths in Africa, with a mortality rate of 19.1 deaths per 100 000 women in 2020 [5].

Risk factors are anything that may increase the chances of an individual developing BC disease [8]. The successful prevention of BC relies on the successful identification and elimination of BC risk factors as well as reducing the exposure of humans to these risk factors where possible. The World Health Organization (WHO) classifies risk factors into modifiable and non-modifiable risk factors, and certain risk factors are common to certain population groups [9]. These risk factors include among others, genetic predisposition, ageing, parity, age at first child, exogenous estrogens, obesity, dietary fat and heavy smoking [10-12].

Several BC risk factor studies have been conducted in South Africa (SA), however, these studies were limited to one population group and had a small sample size [13-16]. The above limitations impact the generalization of findings. The population diversity among women in SA impacts their overall health conditions [15, 17]. Therefore, the investigation of BC risk factors in a multiracial population becomes an important element for risk factor identification and research. Comprehensive population-based data on cancer incidence across all demographic categories in SA has been lacking.

In 2011, SA promulgated regulation No. 380 of the National Health Act (Act 61 of 2003), which formalized the National Cancer Registry (NCR) and mandated the establishment of population-based cancer registration [18]. Population-based cancer registration can collect almost all cases occurring in a population and provides comprehensive data. The Ekurhuleni Population-Based Cancer Registry (EPBCR) was established in 2015 as a pilot site for future population-based cancer registries in SA [19]. EPBCR covers about six per cent of the SA population and appropriately represents SA's multiracial diversity [19]. It has been five years of successful cancer registration for EPBCR since the six years of data collection in 2017 [20]. This has been a major success in cancer registration as well as cancer research in SA and enables us to study the BC risk factors in a multiracial population.

1.2. LITERATURE REVIEW

1.2.1. Epidemiology of breast cancer

BC is the most common type of cancer among women in SA, with an ASIR of 52.6 per 100 000 and a mortality rate of 16.0 per 100 000 in 2020, which corresponds to 15 491 new cases and 4 664 deaths [21]. The new cases of BC in SA increased from 6 224 in 2009 to 10 174 new cases in 2019 [22]. BC mortality ranks second in SA with an age-standardised mortality rate (ASMR) of 16.0 per 100 000 [5]. SA is not different from other countries in Africa where modifiable lifestyle factors such as type of occupation, dietary intake and physical activity as well as non-modifiable factors such as population growth, age and race are the key factors that influence BC risk [13, 17, 23, 24]. The extent to which these factors contribute to BC risks, and the population groups at risk is not yet fully explored in SA. The WHO estimates that avoiding a combination of risk factors could prevent about 30 to 50% of all cancer cases [16].

1.2.2. Breast cancer control and management

1.2.2.1. Breast cancer prevention

Apart from the non-modifiable factors, several studies have identified lifestyle as a major contributing factor to the increase in BC incidence worldwide [5, 9, 15, 25-30]. Primary and secondary prevention has a significant impact on the prevention and detection of cancer [26]. Primary prevention consists of eliminating the causes leading to the disease occurrence and enhancing the protective abilities of the immune system [29]. Primary prevention can be achieved by raising knowledge and awareness of the disease, its symptoms, and risk factors, encouragement of a healthy diet and physical activity, and discouragement of excessive alcohol consumption, tobacco smoking and other possible risky behaviours and exposures [29].

According to the American Institute for Cancer Research (AICR), a healthy diet in cancer prevention is a diet that helps maintain proper body weight [29]. This diet is rich in fruits, vegetables, cereals and legumes [29]. It contains a little red meat and salt and does not consist of processed meat [29]. A healthy diet is also characterized by avoiding sweet beverages and reducing the consumption of high-calorie food and alcoholic beverages [29]. Excessive consumption of high-calorie meals leads to weight gain and eventually obesity, which is related to an increased risk of cancer [31]. Secondary prevention aims at terminating the process of disease development before its full symptoms are diagnosed, which may impede or prevent the development of a malignant tumour [29]. Through screening, high-risk individuals are identified and referred for diagnostic services. BC awareness has been identified as a vital tool for BC prevention [26, 29].

1.2.2.2. Breast cancer awareness

The increase in BC incidence in the past years has prompted awareness in women, however, there is only a small number of women who are aware of breast symptoms and risks [32]. Studies show that many women still present to healthcare facilities with advanced BC [33]. It is important for women to be aware of the symptoms, risks, and signs of BC as well as how to self-examine their breasts [34]. Part of community health awareness is to teach women how to conduct breast self-examinations (BSE), and encourage them to have a clinical breast examination (CBE) by a qualified healthcare professional from their local community healthcare (CHC) facilities should they detect something from BSE [35].

The policy on BC management and control recommends BC education in all primary healthcare (PHC) facilities to increase awareness [35]. BC is associated with myths and stigma, this

necessitated the National Department of Health (NDoH) to raise awareness amongst the general public, including families and community leaders through the distribution of pamphlets, television (TV) and radio shows as well as BC education [36]. The educational content includes an understanding of BC risk factors as well as BC symptoms [35, 37]. The cancer civil society (CCS) organizations and the PHCs play a pivotal role in BC awareness and education through community outreach programmes [35]. The CCS organizations such as the Cancer Alliance (CA), Pink Drive (PD), Anova Health Institute (AHI), and the Cancer Association of South Africa (CANSA), are advocating for BC control in SA.

1.2.2.3.Breast cancer screening

Being breast aware helps women to recognize early warning signs and can help to detect breast changes. Mammography, magnetic resonance imaging (MRI), ultrasound as well as CBE and BSE are the recommended secondary prevention measures in SA [38]. WHO recommends mammography screening for women above 39 years old [37]. MRI is not recommended for general population screening but is recommended for high-risk women under the age of 30 years [37]. High-risk women include those with known BReast CAncer gene (BRCA) mutation carriers, first-degree relatives of known BRCA mutation carriers as well as women who had radiation to the chest between ages 10 and 30 [35]. Mammography, MRI and ultrasound screening programmes may not be feasible for all women, hence the consideration of BSE [33, 39].

Several studies do not recommend BSE because it may cause harm and increase breast biopsy procedures due to false positives [40-43]. In countries such as SA where many women present to healthcare facilities with advanced stages of BC, a simplified BSE at the individual level is

recommended [29]. BSE and CBE were found to be important in detecting BCs at an early stage by many studies [33, 40, 44]. The SA policy on BC management and control recommends BC screening for women with symptoms at the first point of contact (the PHC). It also recommends that irrespective of the reason for the visit to the health facility, all women should receive provider-initiated screening clinical breast examination (PISCBE) [35]. If any abnormality is detected irrespective of the severity, a referral letter should be given, detailing the findings to the regional breast unit (RBU) or specialized breast unit (SBU) for detailed examination [35]. RBU or SBU classified further referrals based on the suspicion of malignancy into immediate (next-day referral), intermediate (within 21 days), or routine referrals (within 60 days) for further investigations [35].

Referral to genetic services is offered to women whose family history meets the criteria for referral [35]. Eligible women are recommended for two breast screening services annually, however, the referral and screening programme is delayed due to the backlog in the public health facilities resulting from the lack of resources among other reasons [8, 45-47]. The aforementioned process applies to public healthcare institutions, where patients are not required to pay for any of the aforementioned services. For patients with health insurance, depending on the health plan, the health schemes cover the cost of the screening once every two years [48]. Referrals are done according to the protocols of the health insurance and the severity of the findings of the screening as well as the prescribed minimum benefit (PMB) requirements [48].

1.2.3. Breast cancer treatment

The treatment of BC is done through surgery, chemotherapy, radiation, palliative services or a combination of two or more [46]. The treatment of BC is an expensive and long process that patients have to go through. The treatment is delivered through SBUs and RBUs on a referral basis

in the public healthcare system [35]. The referral can take longer than expected due to the limitations of public healthcare in SA. For patients with health insurance, oncology services are also offered in private healthcare facilities. Cancer treatments that are a PMB are always covered in full [48]. For the treatments outside the PMB, health insurance covers the PMB cost with the patient covering the outstanding costs. This depends on the health plan, treatment procedure and the cost of the procedure [48]. This is also the limitation of private healthcare insurance. Palliative services are also available to assist the patients throughout the process. These services come at a minimum cost or sometimes free of charge depending on the service provider or the services required [35].

1.2.4. Risk factors for breast cancer

1.2.4.1. Known risk factors for breast cancer

The WHO identified many risk factors for BC [49]. Research studies indicate that risk factors affecting women in high-income or developed countries are similar to those affecting women in low- and middle-income countries (LMICs) [50]. Modifiable BC risk factors include among others, lack of physical exercise and unhealthy diet, obesity, alcohol consumption, and tobacco smoking [8, 16]. Non-modifiable factors such as age and race are also identified [31]. Furthermore, first-degree relatives of women with BC as well as women with increased breast density are at an increased risk of BC [51]. Early menarche, late onset of first pregnancy, lack of breastfeeding, nulliparity, use of oral contraceptives, late menopause, and post-menopausal hormone replacement therapy are among the reproductive risk factors [52]. Exposure to endogenous or exogenous oestrogens is an important risk factor in the development of BC [52]. Risk factors such as alcohol consumption, tobacco smoking, and lack of a healthy diet are detailed below.

1.2.4.1.1. Alcohol consumption

There is substantial evidence to demonstrate that excessive alcohol consumption increases the risk of BC in women. The risk of BC is dependent on alcohol dose in combination with biological mechanisms with or without considering the effects of other risk factors [10-12, 29]. Alcohol influences the development of BC by impacting the level of estrogens, estrogen receptors (ER) and the development of alcohol metabolism by-products [11, 29, 53]. Each alcoholic (ethanol) drink (10g) per day increases the risk of BC by 10% among women in their reproductive age [12, 29, 31]. This relationship is stronger for women with ER or progesterone receptor (PR)-positive than for those with tumours without receptor status [12]. The contribution that alcohol consumption makes to the risk of BC is quite clear and can be controlled by individual behaviours and public health awareness.

1.2.4.1.2. Tobacco smoking

In studies of passive and active tobacco smoking and BC, inconsistent results have been observed. However, the evidence for an increased risk of BC is consistent among active tobacco smokers [54]. Inconsistencies in the literature have been attributed to differences in the definition of smoking behaviour as well as inadequate sample sizes [54]. The meta-analysis study by Macacu et al to clarify the inconsistencies concluded that the association between smoking (active and passive) and the increased risk of BC is real [54]. However, the smoking and BC area needs more research to clarify whether this is true for different populations and settings.

1.2.4.1.3. Lack of healthy diet

Dietary intake is one of the important factors that can modify the BC risk in women [55]. Lack of a healthy diet may lead to obesity which was most frequent in populations of developed countries [16]. LMICs have undergone a transition in lifestyle and adopted a western diet [56]. The Johannesburg Cancer Study (JCS) investigated whether the cancer risk factors identified in the western countries are similar to those identified in SA's Black population [50]. This study found that an unhealthy diet was among the risk factors common to the western and the SA Black population [50]. The JCS study findings were supported by the South African Breast Cancer (SABC) studies conducted in South-Western Townships (SOWETO) that found an association between the intake of savoury snacks, and starch grains, and the risk of BC development [16].

1.2.4.2. Suspected risk factors for breast cancer

There is a sentiment that risk factors are unique to countries, population groups and dwellings. A study conducted in the SSA region found that insecticide exposures are associated with an increased risk of BC development [57]. Insecticides are widely used in the prevention of malaria most commonly in malaria-endemic regions of SSA, particularly in the Northern and Eastern parts of SA. Risk factors for BC among women in SA may be different from the WHO-identified risk factors because of population diversity, unique lifestyles, cultures, beliefs and socio-economic status. Because of the uniqueness and diversity of countries, it is important to investigate suspected BC risk factors.

1.2.4.2.1. Occupation

There is considerable evidence to suggest that the occupation status or type of occupation may have a relationship with BC risks among women [58]. Nightshift work has been associated with

the risk of BC because of the disruption of the circadian cycles by light exposure at night [23]. Exposure to light at night, the reduction in the production of melatonin, and stress-related mediators production disrupt normal sleep-wake cycles [24]. The evidence of a relationship between night shift work and the risk of BC was supported by various research studies such as the Nurse's Health Study I and II as well as murine studies [23, 24]. Agricultural occupations are also associated with BC risk, this was confirmed by a study among Moroccan women [24]. Therefore, occupation was an important risk factor to be studied among SA women of all diversities.

1.3. PROBLEM STATEMENT

BC is one of the most common cancers affecting women of all races in SA [21, 59]. Little has been documented about the risk factors for BC among all women in SA [5, 22, 53]. Several studies on BC among women in SA focused mostly on risk factors among Black women with limitations such as inadequate sample size [13, 15, 16, 50]. It would be important to examine risk factors for BC in an inclusive population with an adequate sample size.

1.4. JUSTIFICATION

Despite several studies carried out in SA, risk factors for BC among women of all races have not been established [15, 50]. Studies are needed to establish factors associated with the risk of BC among women of all races in SA. Population group (race) is a proxy for access to cancer diagnosis in SA due to historical inequalities. EPBCR is the first urban population-based cancer registry (PBCR) in SA to provide an opportunity to explore BC risk factors in a diverse urban population. Information on the risk factors of BC among women of all races in SA is therefore needed to inform BC prevention guidelines.

1.5. RESEARCH QUESTIONS

This study was designed to answer the following questions:

- What are the factors associated with the risk of BC development among women in Ekurhuleni Metropolitan Municipality?
- What are the changes in BC patterns among women in Ekurhuleni Metropolitan Municipality?

1.6. AIM

The study aimed to identify the risk factors for BC, determine the ASIR, and examine trends in the incidence rate of BC among women in the Ekurhuleni Metropolitan Municipality, 2017–2020.

1.7. OBJECTIVES

- To determine the socio-demographic and clinical characteristics of women diagnosed with cancer in Ekurhuleni Metropolitan Municipality, 2017–2020.
- To identify the risk factors associated with the development of BC among women in Ekurhuleni Metropolitan Municipality, 2017–2020.
- To measure the ASIR for BC in Ekurhuleni Metropolitan Municipality, 2017–2020.
- To estimate the average annual per cent change (AAPC) of BC among women in Ekurhuleni Metropolitan Municipality, 2017–2020.

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CHAPTER 2: SUBMISSIBLE DRAFT MANUSCRIPT

Introduction to the section

This section introduces the draft of the manuscript that is written according to the *ecancermedicalscience* journal guidelines. The background, methods and results included in this chapter are those that answer objective 1, "To determine the socio-demographic and clinical characteristics of women diagnosed with cancer in Ekurhuleni Metropolitan Municipality, 2017–2020", and objective 2, "To identify the risk factors associated with the development of BC among women in Ekurhuleni Metropolitan Municipality, 2017–2020".

Risk factors for breast cancer among women in Ekurhuleni Metropolitan Municipality, Gauteng Province of South Africa, 2017–2020: A case-control study

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ABSTRACT

Background: Breast cancer (BC) is the most common cancer among women in South Africa (SA), with an age-standardized incidence rate (ASIR) of 52.6 and an age-standardized mortality rate (ASMR) of 16.0 per 100 000. There is a paucity of evidence on the risk factors for BC among women of all races in SA. In light of the increased incidence rate of BC in SA, literature-based evidence is essential for the effective distribution of prevention resources. This study aimed to identify the risk factors associated with the development of BC among women in Ekurhuleni Metropolitan Municipality.

Methods: An unmatched case-control study was conducted from 1 January 2017 to 31 December 2020 using secondary data extracted from the Ekurhuleni Population-Based Cancer Registry (EPBCR). Unconditional multivariable logistic regression analysis was carried out using the adjusted odds ratio (aOR). The variables race, employment, HIV, smoking and alcohol statuses were included in the multivariable logistic regression model while the model was adjusted for age. A p-value of less than 0.05 was considered statistically significant.

Results: Among 2217 cases and 851 controls enrolled in the study, the mean age (±SD) in years was 55.2 (±15.2). The White population group, being self-employed and Human Immunodeficiency Virus (HIV) -positive status was significantly associated with reduced odds of BC development among women. Women who were HIV-positive were 61% less likely to have BC than women who were HIV-negative (aOR 0.39; 95%CI: 0.27–0.57). White women were 75% less likely to have BC than women of other races (aOR 0.35; 95%CI: 0.29–0.43). Self-employed women were 59% less likely to have BC than women who were formally employed (aOR 0.41; 95%CI: 0.18–0.97). No significant association was observed between tobacco smoking and BC as well as alcohol consumption and BC.

Conclusion: White women were 75% less likely to have BC and HIV-positive women were 61% less likely to have BC and self-employed women were 59% less likely to have BC. The White population group, being self-employed and HIV-positive appears to be protective factors against BC. Further research is required to confirm these findings and elucidate the underlying explanations for these results.

Keywords: Breast cancer, risk factors, incidence, age-standardized incidence rate, case-control study, odds ratio, women, Ekurhuleni Metropolitan Municipality, South Africa

2.1. BACKGROUND

Breast cancer (BC) is the most common cancer among women and is among the top five leading causes of cancer-related deaths worldwide [1-3]. In 2020, the number of new cases diagnosed in women was 2.3 million, with more than 700 000 new cases reported in low- and middle-income countries (LMIC) [4]. With over 10 500 new cases reported in South Africa (SA) in 2019, BC accounted for 23% of all cancers in women in 2019 [5-7]. Several risk factors have been associated with the development of BC among women worldwide. However, a paucity of studies on BC risk factors exists in SA, and a lack of generalizability due to inadequate sample size and limitation to one population group [8, 9]. There may be cancer risk factors that are peculiar to a given environment but are rarely seen in high-income countries.

The World Health Organization (WHO) defines a BC risk factor as anything that may increase the chances of developing BC disease [10]. Risk factors such as age, race, sex, family or personal history of BC are beyond the individual's control [11]. Behavioural factors such as poor eating habits, physical inactivity, tobacco smoking, excessive alcohol consumption, obesity and use of oral contraceptives among others are associated with the increased risk of BC development [1, 12, 13]. It is well documented that reproductive factors such as late childbearing, low parity and lack of breastfeeding increase the risk of BC [8]. Prolonged endogenous estrogen exposure owing to early menarche, late age at first childbirth and late menopause also increases the risk of BC [14]. Exposure to exogenous estrogen mostly due to hormone replacement therapy and the use of oral contraceptives has also been associated with an increased risk of BC [8]. The role of certain factors such as race, occupation, and residential status in the development of BC in SA remains controversial [15, 16].

A large proportion of BC cases in SA has been observed among the White population group, this may reflect the role of some specific risk factors in this population group [15, 17]. The population group has been used as a proxy for access to cancer screening and diagnosis in SA due to historical inequalities [15]. HIV, obesity, and alcohol may also vary by race. A study in SA reported a doubling incidence rate of BC among women living in urban areas [15]. The BC burden in urban areas is characterized by westernized behaviours and lifestyles that favour high BC incidence rates [17]. Comprehensive national data on cancer incidence to study BC risk factors among women across all demographic categories in SA has been lacking.

In 2011, the National Department of Health (NDoH) established the Ekurhuleni Population-Based Cancer Registry (EPBCR) through the enaction of regulation number 380 of the National Health Act 61 of 2003 [18]. The purpose of this establishment was to increase cancer incidence reporting and registration as well as to capacitate cancer research and education in SA [19]. It has been five years of successful cancer registration of incidence data for all population groups in EPBCR. However, no research studies have been conducted using EPBCR data. This case-control research study was conducted to identify the possible risk factors for BC in women living in the Ekurhuleni Metropolitan Municipality using the data from the EPBCR.

2.2. METHODS

2.2.1. Study setting and data sources

The study used secondary cancer incidence data extracted from EPBCR collected between 1 January 2017 and 31 December 2020, to identify the risk factors for BC among women. EPBCR is a population-based active cancer surveillance site of the National Cancer Registry (NCR) of SA.

EPBCR collects information on cancer incidence among the residents of the Ekurhuleni Metropolitan Municipality. Ekurhuleni Metropolitan Municipality is located in the East Rand region of Gauteng Province in SA. It occupies a 1975 km^2 area with small towns, townships, and informal settlements [20]. It has a population of 3,894,000 persons, a population density of 1609 persons/km^2, and a population growth rate of 1.9% in 2020 [20, 21]. It covers about six per cent of the SA population and appropriately represents SA's multiracial diversity with 79% Blacks, 16% Whites, 3% Coloureds, and 2% Asians/Indians [20].

EPBCR's procedures are described in full elsewhere [19, 22, 23]. Briefly, cancer incidence data are actively collected from all identified sources within the catchment area of the EPBCR by surveillance officers [20]. The identified sources of EPBCR include private and government healthcare facilities, laboratories, mortuaries, hospices, and referral hospitals of Ekurhuleni Metropolitan Municipality [20]. Cancer incidence data are collected using the Research Electronic Data Capture (REDCap) system hosted in Johannesburg, SA by the University of the Witwatersrand [24, 25]. The cases are coded based on the international classification of disease for oncology version 3 (ICD-O-3) guidelines and stored within the REDCap system.

2.2.2. Study design and population

We conducted an unmatched case-control study to identify risk factors for BC in women between 2017 and 2020. The study included all women who were registered in the EPBCR database with BC diagnosed between 1 January 2017 and 31 December 2020. The study was conducted using a study design methodology described by Muchengeti et al., in a study that was published in 2021 to investigate the evolving association between HIV and cancer in the context of antiretroviral

treatment (ART) availability as well as compare to the available literature on HIV-associated cancers in Africa [26].

A case was defined as any woman residing in Ekurhuleni Metropolitan Municipality with a primary BC diagnosis during the study period. Controls were defined as any cancers diagnosed among Ekurhuleni Metropolitan Municipality women, with an exception of BC as well as hormonal-, smoking- and alcohol-related cancers during the study period. Controls were selected using an established case-control methodology for four scenarios for potential control selection for cancer types as described by Chen et al, 2020 [27]. Cancers of the bone, endocrine gland, melanoma, myeloma, small intestine, testis, eye, Hodgkin lymphoma, non-Hodgkin lymphoma, non-myeloid leukaemia, and squamous cell were used as controls. Among these controls, non of them are hormonal-, smoking- and alcohol-related cancers and their association are null. All males, non-residents of Ekurhuleni Metropolitan Municipality, women under 18 years old and those with cancer diagnosis before or after the study period, women who were not registered in the EPBCR database during the study period, as well as metastatic and primary site unknown (PSU) cancers, were excluded.

2.2.3. Sampling procedure

All women who met the requirements for case and control definition were enrolled in the study. A total sample of 3 068 (2 217 cases and 851 controls) was extracted from the EPBCR database. The 2:1 case-to-control ratio method was previously used in a case-control study to examine risk factors for Melanoma in a highly exposed population in America by Lazovic et al., 2010 [28]. Several power calculations were done with the various candidate's risk factors such as race, HIV status, smoking status, and alcohol consumption. The candidate's risk factor which could yield the

largest power to detect at least 50% odds of BC was the participants with a history of employment. The power of the study was calculated using Stata IC version 15.1 based on a 95% confidence interval (CI), 31.0% of cases, and 24.0% of controls with no history of employment. A 97.4% power of the study was achieved.

2.2.4. Data cleaning and analysis procedure

Before analysis, all data were checked for completeness, and internal consistency, and then cleaned, coded and analyzed using Stata IC version 15.1. Observations with missing values on key variables such as age and sex were dropped from the analysis. Descriptive statistics such as means for normally distributed continuous variables, frequencies and proportions for categorical variables were used to summarise the socio-demographic and clinical characteristics of the participants. A univariate logistic regression analysis was conducted for all the variables and adjusting for age. Every variable was incorporated into the model for the multivariable logistic regression analysis. The variables included in the multivariable logistic regression model were race, employment, HIV, smoking, and alcohol status and the model was adjusted for age. A p-value of ≤ 0.05 was considered statistically significant.

2.3. RESULTS

2.3.1. Socio-demographic characteristics of cancer-diagnosed women

A total sample of 3 238 newly diagnosed cancer participants were enrolled in the study from 2017 to 2020. We excluded 49 participants for missing sex (0.3%) and age (1.9%), 62 participants were less than 18 years (1.9%) of age and eight (0.2%) participants with in-situ cancers for a final sample of 3 068 participants. There was a final total of 2 217 cases and 851 controls. The participants' mean (±SD) age at diagnosis was 55.7 (±15.2) years (cases= 58.0 (17.9) and controls= 54.9 (13.9)),

with a minimum age of 18 years and a maximum age of 105 years. The majority of the cases (n=1061) and controls (n=270) were among the age group 40–59 years. Among all participants enrolled, 1.7% (n=43 cases and n=10 controls) were Asian, 56.6% (n=1387 cases and n=354 controls) were Black, 1.9% (n=49 cases and n=10 controls) were Coloured and 39.8% (n=745 cases and n=478 controls) were White women. A significantly higher proportion of Black women (n=1387, 62.4%) had developed BC compared to Asian, Coloured and White women ($p< 0.001$). About 8.1% (n=180) of cases and 6.5% (n=55) of controls were alcohol consumers while 8.2% (n=182) of cases and 6.6% (n=56) of controls were tobacco smokers. Regarding occupational status, about 26% of all participants were unemployed while 8.5% were employed, with less than one per cent (<1%) of patients who have reported self-employment (Table 1).

2.3.2. Clinical characteristics of cancer-diagnosed women

Among the total participants, 9.6% (n=206 cases and n=90 controls) were reported to be HIV positive at diagnosis. Among all participants, 386 participants were diagnosed with cancer stage two (stage II) while a majority (n=2258) of the participants had unknown cancer stage at diagnosis. A larger proportion (n=2553, 83.0%) of participants were diagnosed with cancer through histological means. A significantly higher proportion of women who were HIV negative (n=424, 13.8%) had developed BC compared to those who were HIV positive ($p< 0.001$) (Table 2).

Table 1. Socio-demographic characteristics of women diagnosed with cancer in Ekurhuleni Metropolitan Municipality, South Africa, 2017–2020.

Characteristics	**Controls n (%) N=851**	**Cases n (%) N=2217**	**p-value**
Age cohort			
18-35	99 (11.6)	146 (6.6)	**<0.001**
36-39	62 (7.3)	164 (7.4)	
40-59	270 (31.7)	1061 (47.7)	
60-79	316 (37.1)	765 (34.4)	
80+	105 (12.3)	86 (3.9)	
Race			
Asian	10 (1.2)	43 (1.9)	**<0.001**
Black	354 (41.5)	1387 (62.4)	
Coloured	10 (1.2)	49 (2.2)	
White	478 (56.1)	745 (33.5)	
Alcohol consumption			
No	113 (13.3)	507 (22.8)	**<0.001**
Yes	55 (6.5)	180 (8.1)	
Undisclosed	684 (80.3)	1537 (69.1)	
Tobacco smoking			
No	132 (15.5)	569 (25.6)	**<0.001**
Yes	56 (6.6)	182 (8.2)	
Undisclosed	664 (77.9)	1473 (66.2)	
Employment status			
Employed	72 (8.8)	188 (8.5)	**<0.001**
Self Employed	13 (1.5)	13 (0.6)	
Unemployed	264 (31.0)	534 (24.0)	
Undisclosed	500 (58.7)	1489 (67.0)	

Table 2. Clinical characteristics of women diagnosed with cancer in Ekurhuleni Metropolitan Municipality, South Africa, 2017–2020.

Characteristics	**Controls n (%) N=851**	**Cases n (%) N=2217**	**P-value**
HIV status			
Negative	70 (8.2)	352 (15.9)	**<0.001**
Positive	90 (10.6)	206 (9.3)	
Undisclosed	691 (81.2)	1659 (74.8)	
Cancer stage at diagnosis			
Stage I	59 (6.9)	118 (5.3)	**<0.001**
Stage II	57 (6.7)	329 (14.8)	
Stage III	34 (4.0)	165 (7.4)	
Stage IV	17 (2.0)	31 (1.4)	
Unknown	684 (80.3)	1574 (70.8)	
Basis of diagnosis			
Autopsy with History	1 (0.1)	1 (<1)	**<0.001**
Biochem. /Immuno. test	0 (0.0)	1 (<1)	
Clin. Invest./ Ult. Sound	30 (3.5)	39 (1.8)	
Clinical only	25 (2.9)	22 (1.0)	
Cytology/Haematology	22 (2.6)	45 (2.0)	
Death Certificate Only	2 (0.2)	11 (0.5)	
Histology metastases	67 (7.9)	242 (10.9)	
Histology of primary	696 (81.7)	1857 (83.5)	
Surgery/Autopsy	1 (0.1)	0 (0.0)	
Unknown	8 (0.9)	6 (0.3)	

2.3.3. Identification of risk factors for breast cancer

In the multivariable logistic regression analysis, race, employment and HIV status were significantly associated with reduced odds of BC development among women. White women were 65% less likely to have BC than Black women (aOR 0.35; 95%CI: 0.29–0.43). Self-employed women were 59% less likely to have BC than women who were in formal employment (aOR 0.41; 95%CI: 0.18–0.97). Women who were HIV-positive were 61% less likely to have BC than women who were HIV-negative (aOR 0.39; 95%CI: 0.27–0.57CI). We could not identify a statistically

significant association between tobacco smoking and BC as well as alcohol consumption and BC development (Table 3).

Table 3. Factors associated with BC among women in Ekurhuleni Metropolitan Municipality, South Africa, 2017–2020.

Characteristics	Controls n (%)	Cases n (%)	Total n (%)	OR (95% CI)	p-value	aOR (95% CI)	p-value
Race							
Black	354 (41.6%)	1382 (62.3%)	1736 (56.6%)	1.00		1.00	
Asian	10 (1.2%)	43 (1.9%)	53 (1.7%)	1.11 (0.55–2.23)	0.767	0.99 (0.49–2.00)	0.974
Coloured	10 (1.2%)	49 (2.2%)	59 (1.9%)	1.26 (0.63–2.52)	0.509	0.96 (0.49–2.01)	0.991
White	477 (56.1%)	743 (33.5%)	1220 (39.8%)	0.41 (0.35–0.49)	**<0.001**	0.35 (0.29–0.43)	**<0.001**
Alcohol status							
No	113 (13.3%)	503 (22.7%)	616 (20.1%)	1.00		1.00	
Yes	54 (6.3%)	180 (8.1%)	234 (7.6%)	0.77 (0.53–1.11)	0.162	1.22 (0.80–1.85)	0.347
Smoking status							
No	131 (15.4%)	565 (25.5%)	696 (22.7%)	1.00		1.00	
Yes	56 (6.6%)	182 (8.2%)	238 (7.8%)	0.78 (0.54–1.11)	0.166	1.09 (0.73–1.63)	0.676
Employment status							
Employed	74 (8.7%)	188 (8.5%)	262 (8.5%)	1.00		1.00	
Self Employed	13 (1.5%)	13 (0.6%)	26 (0.8%)	0.38 (0.17–0.85)	**0.019**	0.41 (0.18–0.97)	**0.042**
Unemployed	264 (31.0%)	531 (24.0%)	795 (25.9%)	0.85 (0.85–1.52)	0.366	0.91 (0.65–1.28)	0.601
HIV status							
Negative	70 (8.2%)	352 (15.9%)	422 (13.8%)	1.00		1.00	
Positive	90 (10.6%)	206 (9.3%)	296 (9.6%)	0.41 (0.29–0.57)	**<0.001**	0.39 (0.27–0.57)	**<0.001**

NB. OR, odds ratio; aOR, adjusted odds ratio; **Bold**, statistically significant associations at $p \leq 0.05$.

2.4. DISCUSSION

This study enrolled 3 068 women diagnosed with cancer in Ekurhuleni Metropolitan Municipality over four years (2017–2020) to identify risk factors for BC among women. The study found that the White population group, self-employment and being HIV-positive were significantly associated with lower odds of BC development in Ekurhuleni Metropolitan Municipality. There was no significant association identified between BC and alcohol consumption as well as BC and tobacco smoking.

Several studies have been conducted to describe the risk factors for BC globally [11, 29-34]. The study by Williams et al, 2016 conducted to understand the social context of BC risks in African American women found a lower risk of BC among White women [30]. BC is a genetic and lifestyle disease. Lifestyle factors such as breastfeeding and obesity are likely the factors associated with the reduced odds of BC among White women compared to Black women. A study by Jones et al, 2015 [31] shows that Black women in urban areas are likely not to breastfeed or are likely to discontinue breastfeeding as compared to White women. Socioeconomic disparities between Black and White women are among the reason for not breastfeeding or discontinuing breastfeeding in Black women due to the need to go back to work or start a new job [35]. The need for employment has led to many children being introduced to complementary feeding, which anyone can do when the mother is at work. Ekurhuleni Metropolitan Municipality is an urban area in the Gauteng Province (GP) of SA. GP is an economic hub of SA where people migrate from other provinces to seek employment and a better living. Nglazi et al, 2022, also highlighted the high prevalence of obesity among urban Black women in SA as compared to White women [35]. This may also explain the reduced odds of BC among White women in Ekurhuleni Metropolitan Municipality. Another explanation for the high incidence of BC among the Black population in

Ekurhuleni Metropolitan Municipality is the occupational exposure to risk factors due to historical reasons where Blacks did not share similar occupations with Whites, and environmental exposure to risk factors due to differences in living arrangements amongst Black and White persons in SA. Singh and colleagues previously found that White women in SA have a higher incidence of BC [18]. This study found a higher incidence of BC among Black women. The contradiction may also likely be due to the sources of BC data in the EPBCR. Investigation into the sources of BC data is likely to clarify the contradictions outlined.

We have identified that self-employed women have lower odds of BC as compared to those who are employed. Several industries have been associated with an increased risk of BC [36, 37]. Some agricultural employment such as those that use pesticides is associated with the risk of BC development [38]. Most of the self-employed women are likely to have employed others, they are also likely not to involve themselves frequently on the ground or in baseline activities. This may somehow explain the lower odds of BC among women in this setting. Self-employed women have more time to seek healthcare services when they have problems and are thus more likely to have BC diagnosis while women who are not self-employed might find it more difficult to take a day off from work to go to healthcare facilities if they want a check-up or they are ill.

Women who were HIV-positive had lower odds of BC as compared to women who were HIV-negative. There is a paucity of evidence on the lower odds of BC in HIV-positive women, however, the study conducted in the United States of America (USA) to determine the incidence of BC among people living with HIV and AIDS (PLWHA) found a lower incidence rate among the PLWHA as compared to the HIV-negative population [11]. Another study by D'Andrea and colleagues to identify the possible links existing between HIV infection, highly active

antiretroviral therapy (HAART) and BC risk found that PLWHA has slightly lower odds of BC when compared to the general population [29].

Like any other cancer type, BC is an age-associated disease. In this study, about 82% of cases were diagnosed with BC at the age of 40 years old and above. In SA, the prevalence of HIV is higher (19.8%) in younger women aged between 15 and 39 years old [11, 26]. Because of the fact highlighted above, we have a small proportion (9.3%) of HIV-positive cases registered in the EPBCR. The risk of BC increases with age, however, the HIV population is primarily young in SA. The reduced odds of BC among HIV-positive women might also be explained by the antiretroviral treatment (ART) rollout in SA. The studies by Williams et al and D'Andrea et al highlight the importance of ART in BC epidemiology [29, 30]. We do not have evidence of HIV-positive BC cases being enrolled in the ART program in this study. However, in SA, before 2004, mortality due to HIV was high with a low survival rate and reduced life expectancy [30]. After the implementation of the ART program, low mortality due to HIV and improved life expectancy were observed among PLWHA [30, 39].

When we investigated alcohol consumption and tobacco smoking on the risk of BC, we could not establish a significant association with BC in this population. Studies demonstrated that alcohol consumption and smoking increase BC risk in a dose-dependent manner [40, 41]. Active and passive variations, as well as personal behaviour in tobacco smoking, have also been cited in the association between smoking and BC [10]. A large proportion of incompleteness of smoking and alcohol variables may likely explain the no association between these variables and BC.

Our study had several limitations. The fact that we have used secondary data rather than primary data limited us to exploring only factors that were available in the dataset. Therefore, other factors of importance such as occupational factors, reproductive factors as well as details on smoking and drinking behaviours could not be explored. Also, this study used controls that are diagnosed with different cancer types. While we acknowledge that this type of control selection may introduce unexpected referral bias, careful selection of controls was done using an established cancer control selection method [27]. As outlined in previous studies [26, 27], a careful selection of controls produces prevalence rates that resemble background levels. The large proportion (>60%) of missing information observed on the variables such as alcohol consumption, tobacco smoking, HIV and employment status may have introduced some levels of bias in the analyses and therefore need for further studies in this regard.

Our study also had some strengths. This is the first study to explore the factors associated with the risk of BC using multiracial population-based cancer registry data in SA. As previously outlined in previous studies [12, 18, 19, 23, 27], this setting mimics the structure and cultural background of SA, therefore, the representativeness was adequate. Our study found lower odds of BC in the White population group and lower odds of BC in HIV-positive women as well as lower odds of BC among self-employed women. There were no identified risk factors associated with the development of BC in our study. Further analyses of lifestyle, reproductive and environmental factors may provide further insight into the determinants of BC in this setting. The protective effects of HIV and the White population group need confirmation in this setting. It is now pertinent to conduct a primary study to determine the risk factors for BC in Ekurhuleni Metropolitan Municipality. Primary studies will allow for the inclusion of other important factors such as

reproductive factors and behavioural factors among others. There is also a need to improve data collection tools to allow for the collection of other variables of importance in this cancer registry.

2.5. CONCLUSION

White women were 75% less likely to have BC and HIV-positive women were 61% less likely to have BC and self-employed women were 59% less likely to have BC. The White population group, being self-employed and HIV-positive appears to be protective factors against BC. Further research is required to confirm these findings and elucidate the underlying explanations for these results.

2.6. DATA SHARING STATEMENT

All data for this study is available upon reasonable request from the corresponding author.

2.7. ETHICAL CONSIDERATIONS

This study was ethically cleared by the Human Research Ethics Committee (HREC) for health science-related research at the University of the Witwatersrand, Johannesburg, SA (Ref. No. M220374). Following approval, written data access permission was obtained from the NCR. Confidentiality of information was maintained.

2.8. ACKNOWLEDGEMENTS

We would like to thank the University of the Witwatersrand for academic registration, SAFETP and NCR for technical and financial support. Special gratitude to the surveillance officers, coding

clerks, coding supervisor and NCR leadership for cancer registration and support throughout the study.

2.9. AUTHOR CONTRIBUTIONS

Sizeka Mashele, Lactatia Motsuku and Mazvita Muchengeti conceived the study. Sizeka Mashele conducted data analysis, and interpretation of the results and wrote the manuscript. Lactatia Motsuku provided the data, and interpretation of the results and gave critical comments. Thembekile Zwane, Lazarus Kuonza and Mazvita Muchengeti gave critical comments on the manuscript. All authors approved the final draft of the manuscript.

2.10. FUNDING

This study was equally supported financially by the NCR and SAFETP. The publication fees were covered by the University of the Witwatersrand, Johannesburg.

2.11. DISCLOSURE

No competing interests are declared by the authors.

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CHAPTER 3: EXTENDED METHODS

Introduction to the section

The section outlines the methods used to determine the ASIR of BC among women in Ekurhuleni Metropolitan Municipality for the period 2017 to 2020. The method outlined in this section was not part of the draft paper.

3.1. OBJECTIVES

- To measure the ASIR for BC among women in Ekurhuleni Metropolitan Municipality, 2017–2020.
- To estimate the annual per cent change in BC incidence rate among women in Ekurhuleni Metropolitan Municipality, 2017–2020.

3.2. METHODS

3.2.1. Sampling

A total sample of 2 224 BC-diagnosed women between 1 January 2017 and 31 December 2020 was enrolled in the study. The sample included all women who met the criteria for a case definition as outlined in chapter two of this report.

3.2.2. Data analysis procedure

We checked data completeness, and we then cleaned, coded and analyzed using Stata IC version 15.1. ASIR were calculated per 100 000 women using the Segi-World Standard Population (WSP). Statistics South Africa (STATS SA) mid-year population estimates for Ekurhuleni Metropolitan Municipality were used as a denominator. The calculated rates and risks were stratified by

population group. The ASIR formula was as follows: Crude = (Number of new cases ÷ Mid-year population) × 100 000. WSP weighting = (WSP per age group) ÷ Total WSP for all age groups) * 100 000. ASIR = Crude × WSP weighting. ASIRs were imported into Joinpoint regression statistical software for trend analysis. The model used by Joinpoint statistical software to create the trend patterns was described by Kim et al, 2000 [1]. The average annual per cent change (AAPC) was considered statistically significant at a p-value of less than 0.05. The analysis was stratified by population group.

CHAPTER 4: EXTENDED RESULTS

Introduction to the section

The section outlines the standardization and trend results of BC among women in Ekurhuleni Metropolitan Municipality for the period 2017–2020. The results outlined in this section were not included in the paper. The standardization was conducted for all women combined and in different population groups. Frequency and proportions, crude rate, age-standardized rate, cumulative and lifetime risk were reported.

4.1. RESULTS

4.1.1. Age-standardized incidence rate for breast cancer.

A total of 2224 BC women aged 18 years and above were enrolled for the standardization study. A higher incidence of BC was observed in 2017 (n=718) and 2018 (n=706). A reduction in BC incidence was observed in 2019 (n=409) and 2020 (n=391). The ASIR for BC among all women in 2017 was 42.33 (95%CI: 39.25–45.59), 41.62 (95%CI: 38.57–44.85) in 2018, 24.90 (95%CI: 22.52–27.46) in 2019 and 23.39 (95%CI: 21.10–25.86) in 2020. The higher incidence rate in 2017 (ASIR=55.75, 95%CI: 47.57–65.08) and 2018 (ASIR=69.70, 95%CI: 60.77–79.74) was among White women followed by Asian women. In 2017, the lifetime risk of BC among women in EPBCR was one in 23, while the lifetime risk of BC among women in 2020 was one in 17 (Table 4).

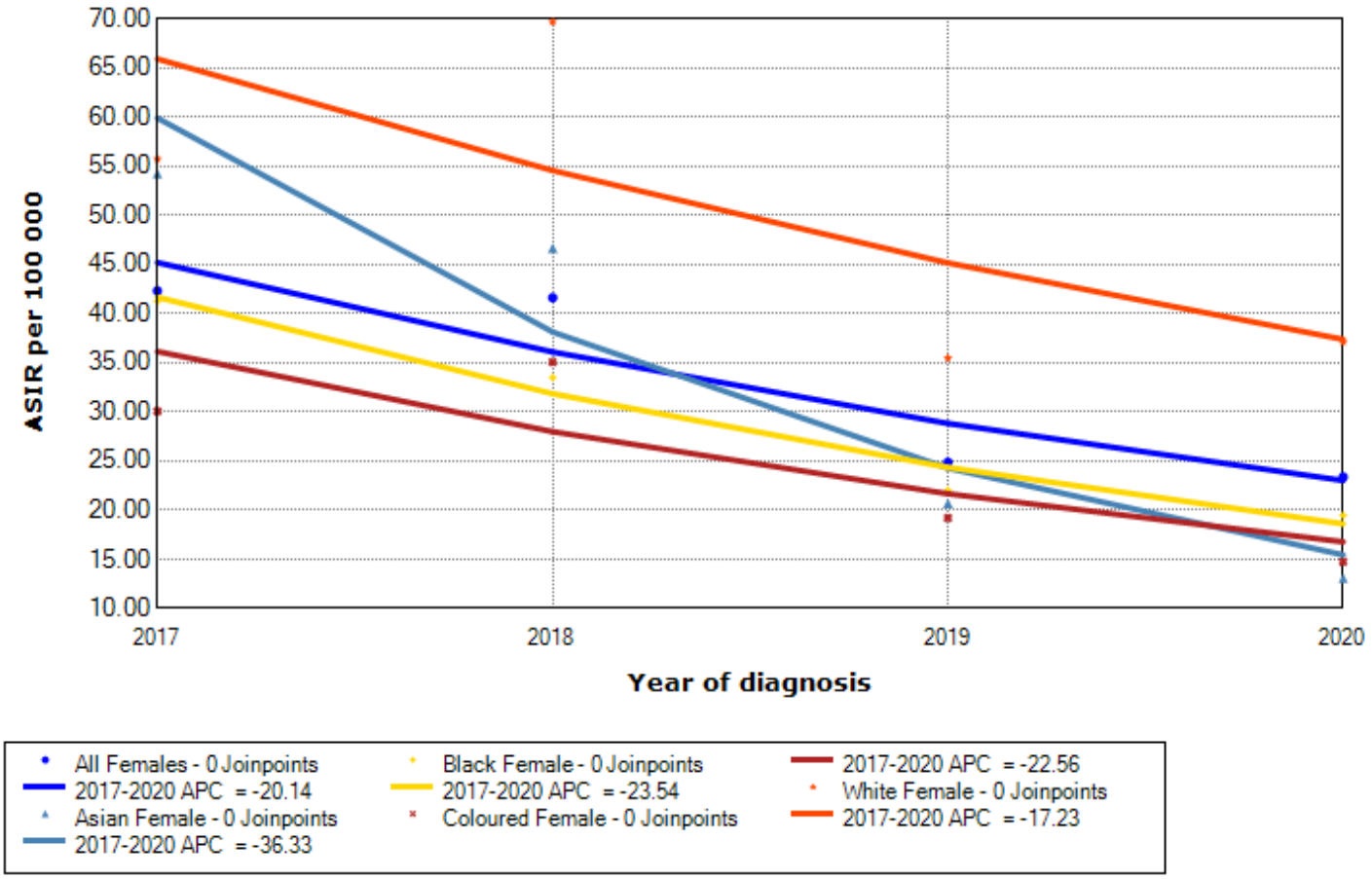

Figure 1. Trends of breast cancer incidence among women in EPBCR by population group, South Africa, 2017–2020.

Table 4. The annual age-standardized incidence rate for breast cancer among women in Ekurhuleni Metropolitan Municipality, South Africa, 2017–2020

Population	Diagnosis year	Frequency n (%)	CRUDE	ASIR (95%CI)	CUMRISK 0_74	LR0_74
All Females	2017	718 (32.27)	43.72	42.33 (39.25–45.59)	4.34	23
	2018	706 (31.73)	42.99	41.62 (38.57–44.85)	4.54	22
	2019	409 (18.38)	24.90	24.90 (22.52–27.46)	2.64	38
	2020	391 (17.57)	23.81	23.39 (21.10–25.86)	2.77	36
Asian Female	2017	17 (0.76)	52.52	54.24 (31.21–87.65)	5.74	17
	2018	15 (0.67)	46.34	46.67 (25.90–77.65)	4.68	21
	2019	7 (0.31)	21.62	20.71 (8.16–43.68)	2.39	42
	2020	4 (0.18)	12.36	13.09 (3.50–33.84)	1.88	53
Black Female	2017	490 (22.02)	36.79	41.26 (37.52–45.26)	3.82	26
	2018	405 (18.20)	30.41	33.51 (30.18–37.11)	3.65	27
	2019	258 (11.60)	19.37	22.04 (19.34–25.01)	2.36	42
	2020	234 (10.52)	17.57	19.49 (16.97–22.27)	2.17	46
Coloured Female	2017	14 (0.63)	31.38	30.08 (16.09–51.50)	3.45	29
	2018	18 (0.81)	40.35	35.08 (20.69–56.36)	3.66	27
	2019	9 (0.40)	20.18	19.22 (8.68–37.22)	2.00	50
	2020	8 (0.36)	17.93	14.76 (6.19–30.56)	1.53	65
	2017	197 (8.85)	84.32	55.75 (47.57–65.08)	5.67	18
	2018	268 (12.04)	114.71	69.70 (60.77–79.74)	6.99	14
	2019	135 (6.07)	57.78	35.51 (29.29–42.85)	3.61	28
White Female	2020	145 (6.52)	62.06	37.12 (30.74–44.62)	4.18	24

NB. LR 0–74, Lifetime (0–74) risk of developing cancer expressed as 1 in X number of people; CUMRISK 0–74, Cumulative lifetime incidence risk (0–74 years) (per 100 people); CRUDE, Adjusted cases per 100 000/year

4.1.2. Trends in age-standardized incidence rate among women in EPBCR, 2017–2020.

A reduction in ASIR for BC among all women in EPBCR was observed between 2017 (ASR=42.33) and 2020 (ASR=23.39). The change in ASIR for BC among all women was not statistically significant with an AAPC of -20.1 (p=0.088). A statistically significant change in ASIR was observed among Black women with an AAPC of -23.5 (p=0.017). A reduction was also observed among Asian, Coloured and White population groups, however, the reduction was not statistically significant (Table 5, Figure 1).

Table 5. Estimated average annual per cent change in age-standardized incidence rate among women in Ekurhuleni Metropolitan Municipality, 2017–2020.

Population group	Age-standardized incidence rate (ASIR)		Joinpoint analysis (2017–2020)				
			Trend 1			Average	
	2017	2020	Period	APC	P-value	AAPC	P-value
All females	42.33	23.39	2017–2020	-20.1	0.088	-20.1	0.088
Asian females	54.24	13.09	2017–2020	-36.3	0.068	-36.3	0.068
Black females	41.26	19.49	2017–2020	-23.5	0.017*	-23.5	0.017*
Coloured females	30.08	14.76	2017–2020	-22.6	0.199	-22.6	0.199
White females	55.75	37.12	2017–2020	-17.2	0.293	-17.2	0.293

APC, annual per cent change; AAPC, average annual per cent change. *The estimated average/annual percentage change is statistically significant (P≤ 0.05).

4.2. DISCUSSION

This study has found that in the four years of data collected in EPBCR, ASIR of BC in women was high in 2017 and low in 2020. The ASIR was higher among White women in 2017 compared to other population groups throughout the trend period. We have also found a statistically significant reduction in the incidence rate of BC among Black women.

The higher ASIR (42.33) of BC among women in 2017 is comparable to the ASIR (35.35) of the pathology-based cancer incidence in SA [2]. Similarly, the low ASIR (23.39) of BC among women in 2020 is comparable to the low ASIR (29.39) of the pathology-based cancer incidence in SA. There was a downward trend in the ASIR among all population groups, however, low ASIR in 2020 may be partly due to inadequate access to healthcare facilities due to the restrictions of movements and services caused by the COVID-19 pandemic. The downward trend in ASIR in all population groups is likely due to an insufficient amount of cases collected annually which may be exacerbated by the restriction of access to data sources because of the enacted second part of the protection of personal information act (POPIA). High ASIR among White women as compared to other population groups is comparable to the national pathology-based cancer registry report of SA which observed that the ASIR of BC is high among White women [3]. This is likely due to the health-seeking behaviour and socioeconomic status of the White women.

Most White women seek medical attention as soon as they observe changes in their lives as compared to other population groups. This behaviour makes it possible to detect any BCs at the early stages. Policy on BC control and management encourages all women who qualify to undergo BC screening at least twice per annum [4]. Limited resources at the level of public healthcare facilities make BC screening access difficult for the majority of women, mostly Black women.

This leads to women with better socioeconomic status seeking alternative BC screening services. Alternative BC screening in SA is a paid service in private healthcare facilities. This result in women with poor socioeconomic status not getting equitable access to BC screening services. The disparities in screening uptake among population groups, together with the health-seeking behaviour of Black women among others, may partly explain the significant reduction in BC incidence among women in this setting.

The observed pattern of BC incidence rate highlights disparities in access to BC screening and diagnostic services in SA. Barriers to accessing BC screening and diagnostic facilities should be addressed. There is a need to strengthen BC prevention strategies and public health awareness. These will scale up BC screening uptake as well as the promotion of early detection through targeted awareness campaigns.

4.2.1. Overall limitations

There is no study without limitations, one of the limitations was that we used secondary data rather than primary data, which limited us to exploring only factors that were available in the dataset. Therefore, other factors of importance such as occupational factors, reproductive factors as well as smoking and drinking behaviours could not be explored. The large proportion (>60%) of missing information observed on the variables such as alcohol consumption, tobacco smoking, HIV and employment status may have introduced some levels of bias in the analyses due to its incompleteness. Also, this study used controls that are diagnosed with different cancer types. While we acknowledge that this type of control selection may introduce unexpected referral bias, careful selection of controls was done using an established cancer control selection method [5]. As

outlined in previous studies [5, 6], a careful selection of controls produces prevalence rates that resemble background levels. EPBCR has not fully mapped all data sources and therefore numbers are continually changing as more data sources are discovered.

4.2.2. Overall strengths

Our study also had some strengths. This is the first study to explore the factors associated with the risk of BC using multiracial population-based cancer registry data. As previously outlined in previous studies [5, 7-10], this setting mimics the structure and cultural background of SA, therefore, adequate representativeness was achieved in terms of race and age cohorts. EPBCR collects all cancer incidence of Ekurhuleni Metropolitan Municipality diagnosed by all means of cancer diagnosis including cancers identified from the death certificates only. We were also able to report the trends in BC in this setting.

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CHAPTER 5: OVERALL CONCLUSIONS AND RECOMMENDATIONS

Introduction to the section

This chapter provides the overall conclusion of the study and the recommendations.

5.1. CONCLUSION

The study identified that the White population group, being self-employed and HIV-positive had lower odds of BC. These findings necessitate more in-depth studies using primary data to effectively explore the risk factor for BC among women in SA settings. There was no significant change in AAPC except for Black women, this indicates disparities in screening uptake among population groups, and as such, there is a need to strengthen BC preventive strategies. There is a need for public health awareness to scale up BC screening uptake as well as the promotion of early detection through targeted awareness campaigns.

5.2. RECOMMENDATIONS

Based on the identified limitations and findings of this study, we recommend the following:

- More in-depth primary data collection studies on BC risk factors are needed in this setting to confirm the findings of this study.
- The data collection tool should be improved to allow for the collection of other variables of importance for research purposes.
- Targeted BC awareness in communities to scale up BC screening uptake and strengthen BC preventive strategies.

CHAPTER 6: APPENDICES

APPENDIX 1. Plagiarism declaration

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Sizeka Mashele (Student number: 0702731Y) am a student registered for the degree of MSC in Field Epidemiology in the academic year 2021.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 13 December 2022

APPENDIX 2. Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Mr SA Mashele

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220374

NAME: (Principal Investigator)	Mr SA Mashele
DEPARTMENT:	School of Public Health Division of Epidemiology and Biostatistics Medical School University
PROJECT TITLE:	*Risk factors for breast cancer among women in Ekurhuleni Metropolitan Municipality, Gauteng Province of South Africa 2017–2020: A case-control study*
DATE CONSIDERED:	2022/03/25
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Ms L Motsuku; Drs L Kuonza and A de Voux
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/05/05

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **March** and therefore reports and re-certification will be due in the month of **March** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

05 May 2022
Date

APPENDIX 3: Journal authors' guideline (ecancermedicalscience)

TEMPLATE

The author guidelines are available on the following: https://ecancer.org/en/journal/author-guidelines

ecancermedicalscience template manuscript paper

Magnesium-wasting associated with epidermal-growth-factor receptor-targeting antibodies in colorectal cancer: a prospective study

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Abstract
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TRIAL REGISTRATION
Please list your trial registry and the unique identifying number.

Background
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Methods
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Results
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Discussion
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Conclusions
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Conflicts of interest
Declare if there is no conflict of interest, otherwise please complete the 'Conflict of Interest' form

Authors' contributions

Please complete the authors' contributions form.

Acknowledgements
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Figures

Figure 1: Sample figure title
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Figure 2: Another sample figure title
Figure legend text

Tables

Table 1: Sample table title
Table legend text

Table 2: Another sample table title
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The Accession Numbers of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript should be provided, in square brackets and include the corresponding database name; for example, [EMBL:AB026295, EMBL:AC137000, DDBJ:AE000812, GenBank:U49845, PDB:1BFM, Swiss-Prot:Q96KQ7, PIR:S66116].

End of sample article