Spring 5-2020

EXPLORATION OF BREASTFEEDING AS A PROTECTIVE FACTOR FOR BREAST CANCER IN SOUTH AFRICAN WOMEN: A NESTED CASE-CONTROL STUDY

BOOKER S. QUIERA

EXPLORATION OF BREASTFEEDING AS A PROTECTIVE FACTOR FOR BREAST CANCER IN SOUTH AFRICAN WOMEN: A NESTED CASE-CONTROL STUDY

by

QUIERA S. BOOKER, BS, MPH(C)

APPROVED:

DR. KATELYN K. JETELINA, PHD MPH

DR. SARAH E. MESSIAH, PHD MPH

DEDICATION

To the phenomenal women in my life who have inspired me to be my competition and be the best version of myself that I can see myself being, not others can see myself being.

EXPLORATION OF BREASTFEEDING AS A PROTECTIVE FACTOR FOR BREAST CANCER IN SOUTH AFRICAN WOMEN: A NESTED CASE-CONTROL STUDY

by

QUIERA S. BOOKER
BS, Christopher Newport University, 2017

Presented to the Faculty of The University of Texas

School of Public Health

in Partial Fulfillment

of the Requirements

for the Degree of

MASTER OF PUBLIC HEALTH

THE UNIVERSITY OF TEXAS
SCHOOL OF PUBLIC HEALTH
Houston, Texas
May 2020

PREFACE

My ultimate goal is to become an Epidemiologist, and Public Health Educator/Humanitarian who focuses on reducing the mortality rates of breast and female-related carcinomas in low-income communities as well as low- and middle-income countries (LMICs). Cancer epidemiology in women sparks my interest for various reasons. The first being, I find it extremely interesting how carcinoma is known as a complicated chronic disease due to the cancerous cells' intelligence in learning biochemical mechanisms and creating an infinite number of pathways for invading healthy cells. The second and third reasons correlate with one another. Both of my grandmothers had to receive breast lumpectomies. One of my grandmother's cancer was invasive and she had to undergo chemotherapy as a result. Even though they both survived, African American women are faced with a more aggressive subtype of breast cancer than any other race or ethnicity, triple-negative breast cancer. I desire to be a part of the team who not only figures out why but determines treatment alternatives. Lastly, women are the creators of life. I strongly support the fact that health equity should be provided to those in need to combat the aggressive, chronic disease that is slowly engulfing women in countries with low healthcare resources.

ACKNOWLEDGEMENTS

I would like not only to acknowledge but thank everyone who had a part in the development and success of my integrative learning project. To Dr. Katelyn K. Jetelina and Dr. Sarah E. Messiah, thank you for being a support system and mentors every step of my thesis, from my original proposal I couldn't comprehend how to execute to the presentation day. To Kent Long, thank you for providing a safe space for me and a shoulder to lean on when in need. To the scholarships and awards which funded my project, thank you for believing in my innovation to fund the execution of my project. To Groote Schuur Hospital and the Breast Ward team, thank you for welcoming me into your space, supporting my data collection, showing me the true meaning of collaboration, and teaching me about the clinical side of increased breast cancer burdens.

EXPLORATION OF BREASTFEEDING AS A PROTECTIVE FACTOR FOR BREAST CANCER IN SOUTH AFRICAN WOMEN: A NESTED CASE-CONTROL STUDY

Quiera Booker, BS MPH
The University of Texas
School of Public Health, 2020

Dr. Sarah E. Messiah, PhD MPH

ABSTRACT

Background. South African's (SA) breast cancer incidence rate is continually increasing (39 per 100,000 (2012) versus 46.2 per 100,000 (2018) with trends towards later-stage diagnosis. In previous literature, breastfeeding has been assessed as a protective factor for breast cancer; however, the SA population experiences inconsistent breastfeeding trends, rates, and support services. Therefore, this study will evaluate the inverse association between breast cancer and breastfeeding history. **Methods.** Cases (breast cancer) and controls (mastalgia) were matched 1:1 on clinical visit from May-August 2019 at Groote Schuur Hospital (GSH) in Cape Town, Western Cape, South Africa. Breastfeeding history, breast carcinoma diagnosis, and clinically relevant endocrinology data was extracted from GSH medical records. Bivariate conditional logistic regression (clogit) and χ^2 analyses compared predictor variables amongst breast cancer groups. Multivariable clogit models assessed the association between breast cancer diagnosis and breastfeeding history both unadjusted and adjusted for statistically and clinically relevant confounders. **Results. Results.** In a sample of 360 SA mothers (mean age= 53 years old, SD= 14.36), 79% of breast cancer patients breast cancer breastfed while 75% of

non-breast cancer patients breastfed, with the majority of the population (75%) having ever-breastfed overall. When controlling for all other covariates, SA mothers with breastfeeding history did not have a lower risk of breast cancer compared to women who never breastfed with OR=1.29 (95% CI 0.52 – 3.23). **Conclusion.** This pilot study did not show a protective effect of breastfeeding on breast cancer diagnosis. However, it contributes to the theory that race, ethnicity, and detailed exposure/outcome statuses are essential to concluding statistically, biologically, and clinically significant results for the assessment of a dose-response relationships.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

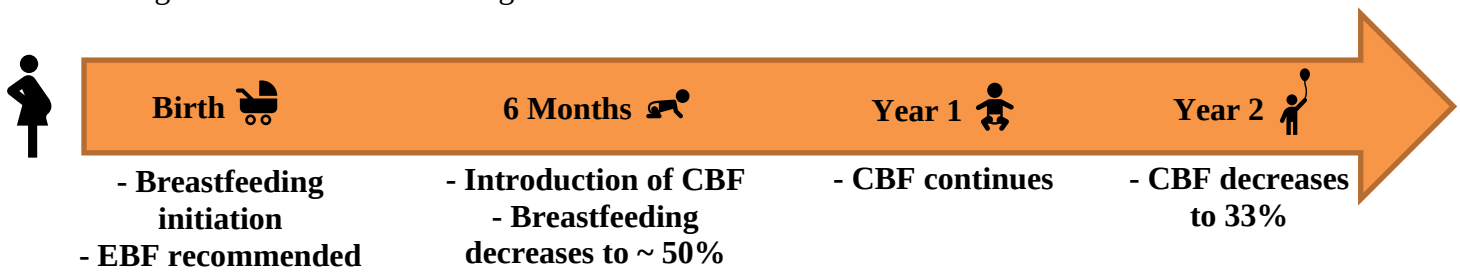
INTRODUCTION

Breastfeeding Benefits and Barriers

Breastfeeding is a natural and unique method of supplying infants with necessary nutrition in their early life that cannot be replaced by any other nutritional item, including infant formula, and encompasses health benefits for both the mother and baby (i.e. reduce pediatric mortality and morbidity, benefit neurocognitive functions, and are less likely to develop chronic diseases such as type 2 diabetes or become obese).[1,2] To receive these benefits, the World Health Organization (WHO) recommends 1) initiation of breastfeeding within the first hour of birth 2) exclusive breastfeeding (EBF) for at least six-months 3) complementary breastfeeding (CBF) up to two years of age and 4) breastfeeding on demand (i.e. when the child wants).[2,3]

EBF is defined as solely supplying infants with breast milk for proper growth and development since the milk will resource infants with 100% of the nutrients needed during those recommended first six months of life.[2] As indicated in Figure 1, after the first six months of EBF, CBF is introduced and breast milk need not be used as the sole food-source, but as an addendum to the introduction of solid foods and alternative drink options to the infant's diet. It has been recommended that the consumption of breast milk in an older infant's diet changes to 50% for the second six months of life, and 33% during the second year of life.[4]

Figure 1: WHO Breastfeeding Recommendations Timeline



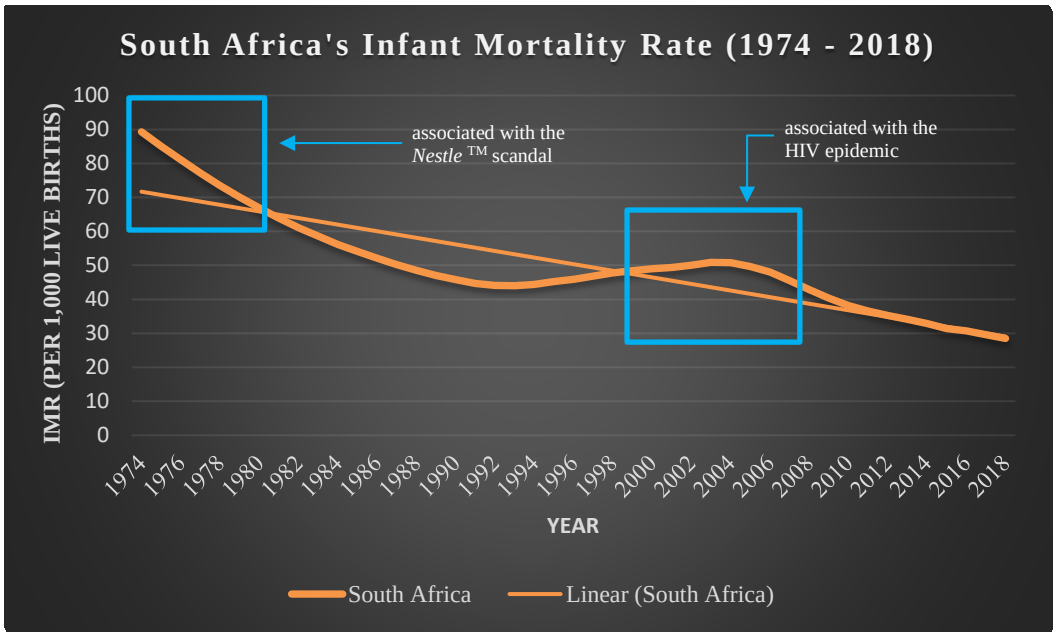
Overall, in the United States (US), breastfeeding can prevent 823,000 child deaths and boost the economy by approximately $300 billion (0.49% gross income improvement globally). These health and fiscal benefits make breast milk superior to manufactured breast milk substitutions (BMS) (i.e. infant formula). Therefore, BMS should be used as a tool, not a precedence to EBF or CBF.[5-8]

Although breastfeeding has seemingly infinite number of benefits, complications and frustrations can arise for the mother if their baby does not latch properly or if she is simply unable to breastfeed. When available, donor milk is a substitute for mothers who are not able to supply their children with their own breast milk for optimal nutrition.[9] Therefore, mothers can avoid the added expense of BMS which only provides secondary nutritional levels compared to traditional breast milk. Donor milk is especially essential and practical during instances where the infant is preterm or ill.[9] When donor milk is not an available practice, BMS can then be used to nourish the infant for adequate growth and development.

Conversely, the aggressive promotion and marketing associated with the BMS industry has had a negative impact on overall breastfeeding practices. Unethical marketing

ploys in low- to middle- income countries (LMICs), including South Africa, by *Nestle*^{TM} (Appendix A) caused mothers to live outside of their monetary means and purchase formula. Mothers became hooked on the formula by creating goals of westernization and middle-class acceptance. LMIC mothers were triggered to dilute their baby formula and inadvertently deprive their baby of the necessary nutrients to stay alive, increasing infant mortality rates (IMRs).[10] As seen in Figure 2 and Appendix A, South Africa had their highest IMRs during the *Nestle*^{TM} scandal allegations in the early to mid-1970s.[11]

Figure 2: World Bank's Data on South Africa Infant Mortality Rates (1974 – 2018)



Breastfeeding Culture in South Africa

South Africa is an LMIC which is harboring a substantial socioeconomic status (SES) gap. Therefore, women who cannot afford manufactured BMS introduce additional foods and

drink, like maize porridge and water, to ensure their baby's adequate nutrition (i.e. CBF).[12-14] Moreover, the current WHO recommendation of EBF for at least six months does not align with current South African breastfeeding practices. In a research study examining SA mothers breastfeeding practices, none of the Peri-urban community mothers reported to EBF their infants; however, 78% reported CBF practices.[12]

Sibeko et al. found other cultural beliefs such as the introduction of herbal preparations (occurring in 56% of their study population) were responsible for several CBF concerns.[12] The mother's diet is ultimately the régime the infant will receive whether directly or via breast milk. Hence, outside influences on the mother's decision-making (i.e., the socioecological framework) must also be taken into consideration when understanding the mother's decision to initiate breastfeeding, EBF, or CBF.

Generational knowledge and comprehension of breastfeeding mostly originates with clinical figures. If physicians were misinformed or inadequately translating information to patients, poor breastfeeding practices will recurrently circulate. Shah, Rollins, and Bland found that despite 92% of doctors South Africa knowing initiation should take place within 30 minutes to one hour of delivery, other WHO recommendations such as EBF were not mandated (i.e. 71% recommend water, 50% recommend solids, and 57% recommended glucose water within the first six months of infancy).[15] Difficulties associated with breastfeeding initiation and exclusivity rates also arise when hospitals and clinical care teams

are not breastfeeding-friendly environments (i.e. not initiating breastfeeding within the first 30 minutes to one hour of delivery or supplying baby formula).

South Africa is one of the most funded countries from President's Emergency Plan for AIDS Relief (PEPFAR).[16] Conversely, there is conflicting and lack of translating information to HIV-positive mothers regarding the transmission of HIV through breastmilk, causing mixed feeding practices amongst infected mothers.[17,18] During the early stages of the HIV epidemic, infected mothers were generally discouraged from breastfeeding altogether if they met certain South African mandated criteria to safely provide alternative methods to nourish the infant.[15] Many of the HIV-positive mothers did not meet said criteria. However, HIV-infected mothers have been shown to at least initiate breastfeeding and were more likely to initiate and report EBF compared to HIV-negative mothers.[17, 19-21]

Further research is required to assess prevention methods regarding female cancer development and childhood ailments when comparing HIV-positive with HIV-negative mothers. However, EBF has been shown to reduce the likelihood of HIV transmission from mother to baby compared to CBF.[22,23]

Breastfeeding Rates in South Africa

Overall, despite low- (LIC), middle- (MIC), or high-income (HIC) status of a country, the vast majority of children (95%) have ever been breastfed with trends of never breastfeeding being lower in LICs and MICs (4%), like SA, compared to HICs (21%) (Figure

3).[24] Although the general consensus is that LICs, MICs, and LMICs have higher breastfeeding rates than HICs, breastfeeding rates and duration vary between and within countries respective economic classifications. Nonetheless, the poorer the family, the higher the likelihood of the mother and baby indirectly abiding by WHO breastfeeding recommendations out of necessity to live within their means (Figure 4).[25]

Figure 3: High-Income Countries vs. Low- and Middle-Income Countries' Overall Breastfeeding Outlook Using 2018 UNICEF Data[23]

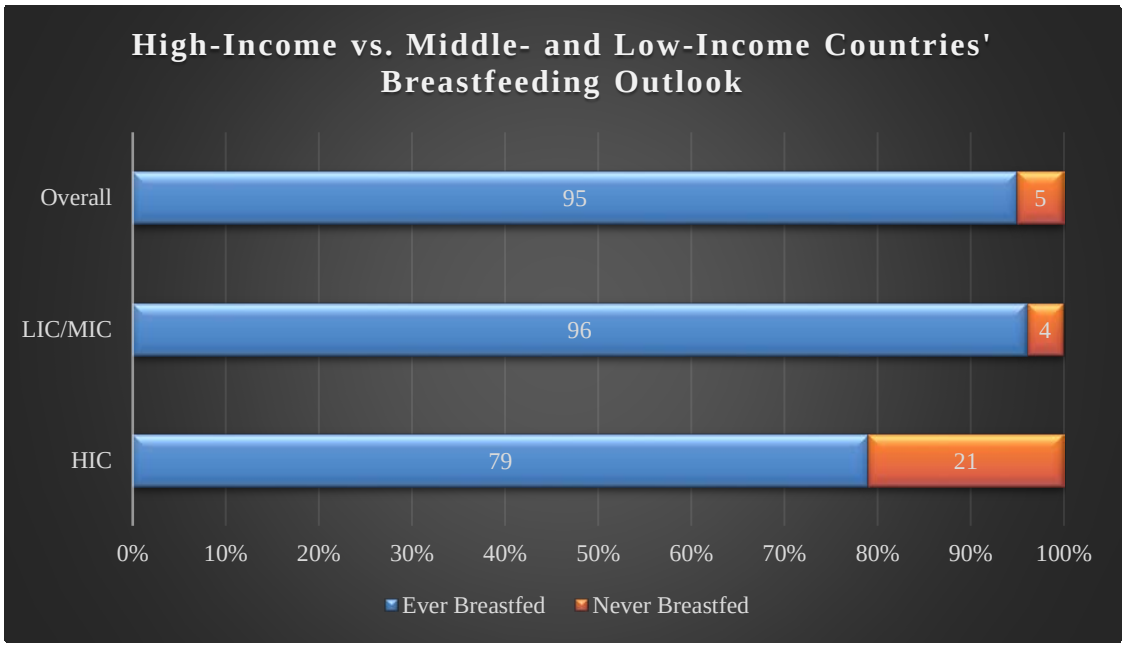


Figure 4: High-, Middle-, and Low-Income Countries' Breastfeeding Variation at 2 years of age[25]

* East Asia and the Pacific excluding China, Latin America and the Caribbean excluding Brazil, Eastern Europe and Central Asia Russian Federation.

** World excluding China, Brazil and Russian Federation.

Note: Analysis is based on a subset of 73 countries with recent (2010–2017) disaggregated data for continued breastfeeding at 2 years. Regional estimates are presented only where adequate population coverage is met (see page 9 for details).

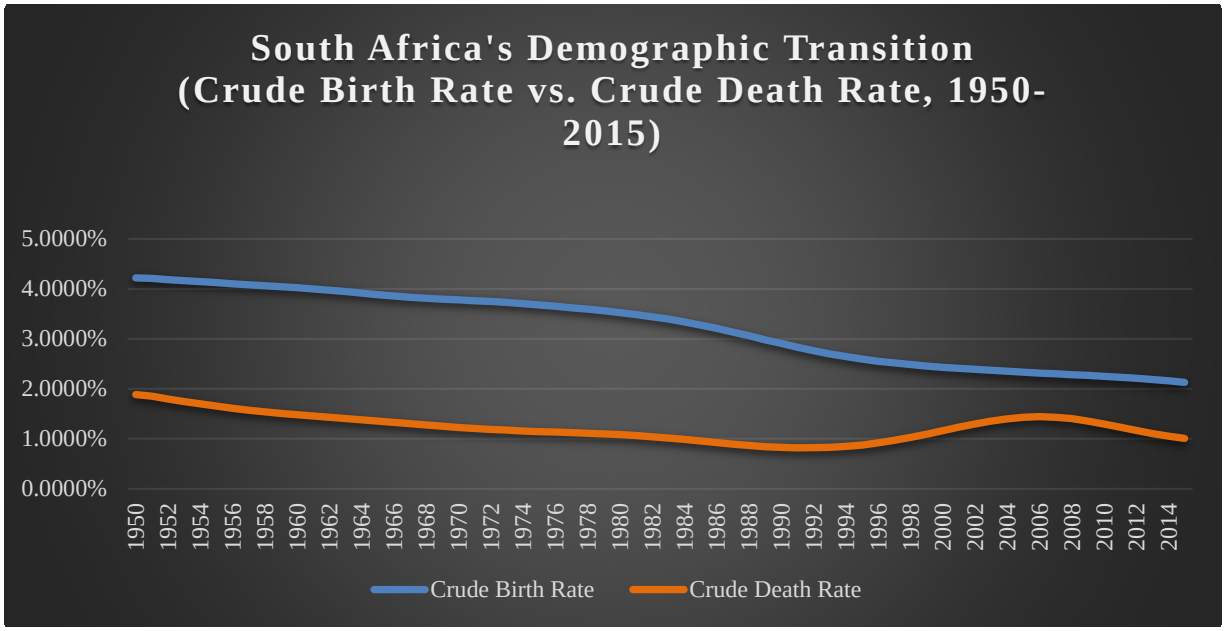
Source: UNICEF Global Databases: Infant and Young Child Feeding, 2018.

South Africa's mortality and birth rates (Figure 5) indicate the country is undergoing a phase in the demographic transition where developmental advancements are occurring while birth and death rates are simultaneously decreasing.[26,27] Westernization influences the transformation of women's roles in society into becoming more involved and having

increased responsibilities in the workplace. In response, breastfeeding practices have also evolved.

The 2012 iteration of the South African Demographic and Health Survey (SADHS) stated a decrease in breastfeeding duration (5.9 months) with 35.8% of children being breastfeed for 12-15 months and 13.4% of children being breastfed for 20-23 months compared to 2003's SADHS reports a breastfeeding median of 16.6 months.[28] SA breastfeeding rates are highly dependent on the province and SES, as well as other factors that are specific to South African municipals, like HIV status and overall breastfeeding knowledge.

Figure 5: South Africa's Demographic Transition Modeled from *Our World Bank* 1950 2015 Data[26,27]



South Africa has shown fluctuating breastfeeding rates throughout its history. Women have been reported to have very low EBF rates (7.4%) and high CBF (70-75%) rates before 6 months of age.[28] These breastfeeding rates directly coincide with the diverse racial and ethnic cultures which directly include breastfeeding practices within SA.[12,15]

Breastfeeding and Breast Cancer

Breastfeeding is known to have protective factors for the child who is consuming the breast milk, but proper breastfeeding practices can also be a prevention method for the mother as well. Health benefits include the risk reduction of estrogen-receptor (ER) related cancers (such as ovarian and estrogen-receptor-positive (ER+) breast cancer) and the prevention of 20,000 annual maternal-related breast cancer deaths in the US.[4,6]

Almost all breast cancer develops in the ducts or the lobules, developing a pre-cancerous lesion, ductal carcinoma in situ or DCIS.[29] During lactation, both health and potentially damaged breast tissues are shed; thus, reducing the risk of breast cancer cell development.[30] Moreover, the longer a woman lactates and breastfeeds, the more breast tissue cells will shed.

After 12 months, breastfeeding can slightly reduce the risk of both pre- and post-menopausal breast cancer by 4.3%.[30,31] Mothers who breastfed for a combined duration of 2 years, for all children, are expected to attain about twice the benefit of those who breastfed for a total of 1 year; whilst, mothers who breastfed for a lifetime total of more than two years

are expected to receive the most benefit with no significant difference for women in HICs compared to LMICs.[31,32]

PUBLIC HEALTH SIGNIFICANCE

Breast Cancer and the South African Healthcare System

Breast carcinoma proliferative lesion of the breast tissue that has both genetic and environmental risk factors, varying within each patient. South Africa (SA) is currently experiencing increased rates of female cancers; specifically, breast carcinoma, with troubling trends towards later-stage diagnoses. In 2012, southern Africa had an incidence of 39 breast cancer cases per 100,000 women compared to 46.2 breast cancer cases per 100,000 women 2018.[33,34] This increase was predicted by Globocan and is assumed to be caused by 1) all forms of cancers are increasing in South Africa 2) healthcare resources are inadequate to meet this growing need 3) breast cancer is the most common cancer amongst SA women 4) most women in SA present with late-stage diagnoses.[35-40]

Metastasis and lymph node spread is the major concern with breast cancer; otherwise, the disease can be mitigated, treated, and ultimately cured.[41,42] The hindrance with later stage diagnosis in SA is the higher probability of being diagnosed with metastatic breast cancer and the inability to effectively treat or cure due to low resources; therefore, increasing the mortality rate.[41,42] The mortalities of non-communicable diseases, like cancers, are a result in a shift away from pre-industrialization where infectious diseases are prominent, due to lack

of public health knowledge, and towards industrialization where chronic diseases are more prevalent, due to increases in technology, more advanced medical practices, and manufacturing.

Moreover, healthcare resources are being heavily allocated to the infectious disease that are also burdening the SA healthcare system (i.e. tuberculosis (TB), human immunodeficiency virus (HIV), and acquired immunodeficiency syndrome (AIDS)), so breast cancer patients who are at risk of metastasis or who present with larger tumors at risk of metastasizing may not receive as urgent care and management as desired.[44,45]

The proposed research aim, to evaluate the inverse association between breastfeeding history and breast cancer outcomes, will provide quantitative evidence to support policy decisions about how a low no-cost method (in terms of monetary value) may potentially aid in the reduction of the foreseeable increase of breast cancer incidence which is burdening the SA healthcare system. Using a method that is fiscally friendly is beneficial to LMICs like SA because it will prevent additional economic strain. Instead, breastfeeding will indirectly improve the economy because of breastfeeding's additional healthcare benefits (i.e. reducing childhood mortality/morbidity, childhood obesity prevention, infectious and chronic disease prevention for both baby and mother).[1,4,6]

SPECIFIC AIM

Aim

- To evaluate the association between breastfeeding history and breast cancer diagnosis while controlling for clinically and statistically relevant confounders (i.e. age, enrollment date, breast cancer family history, HRT use, smoking ever-use, alcohol consumption, HIV status, and menopausal status).

Hypothesis

- There is an inverse association between breast cancer diagnosis and breastfeeding exposure in South African mothers; while controlling for all other factors (i.e. age, enrollment date, breast cancer family history, HRT use, smoking ever-use, alcohol consumption, HIV status, and menopausal status).

METHODS

Study Design

This pilot study implemented a hospital-based, nested case-control design. A retrospective medical chart review was conducted and evaluated the association between breastfeeding history (Y/N) of South African mothers in those who were diagnosed with breast cancer (cases) or discharged with mastalgia (controls). The analysis controlled for clinically and statistically relevant confounders including age, enrollment date, breast cancer family history, HRT use, smoking ever-use, alcohol consumption, HIV status, and menopausal status.

Data was collected from a public hospital in Cape Town, Western Cape, South Africa during their Friday breast clinic where a combination of physician and pathology examinations were conducted, Monday telephone clinic where pathology results were given to patients from Friday's breast clinic, and Wednesday Collaborative Breast Clinic (CBC) where women's breast cancer care plan was discussed.

Study Setting

Data was collected at Groote Schuur Hospital (GSH) located in Cape Town, Western Cape, South Africa. GSH had a history of being a "Whites only" medical establishment during the Apartheid era but is now a government-funded public hospital who accepts all races, ethnicities, and patients with and without health insurance. Medical charts were

reviewed from patients who participated in the Friday breast clinic, Monday telephone clinic, or Wednesday CBC.

Study Subjects

GSH's Breast Ward patient population primarily consists of women who were coded as H1, annual income < R36 000, of racial or ethnic origin, and deprived of health insurance. Study participants were breast cancer patients at Groote Schuur Hospital from May-August 2019. Cases were diagnosed with breast cancer and required to meet the following inclusion criteria: 1) diagnosed with breast cancer; 2) a mother; 3) participated in GSH's Friday breast clinic, Monday telephone clinic, or Wednesday CBC from May-August 2019; 4) female; 5) African native or citizen.

Controls were defined as patients discharged with mastalgia and required to meet the following inclusion criteria: 1) patients who present with mastalgia and were not diagnosed with any other breast-related condition; 2) a mother; 3) participated in GSH's Wednesday CBC, Friday breast clinic, or Monday telephone clinic from May-August 2019; 4) female; 5) African native or citizen.

Overall motherhood status was included in this study to avoid ethical implication that may coincide with the title of a "mother". Thus, this study also included patients who had miscarriages or have children through another equivalent avenue. To avoid having a large

number of young women in the control group, patients were matched 1:1 on month of visit. GSH had never had a patient under 20 years of age with breast cancer; therefore, the age inclusion range was set at ≥ 20 years old. Potential control subjects who were diagnosed with another benign diagnosis other than mastalgia were excluded from the study to avoid further skew, residual confounding, and extensive effect measure modification.

Data Collection

The data collection for this study uses GSH's Breast Clinic's *RedCap*^{TM} database to collect cases and a retrospective medical chart review to collect controls. Cases and controls were matched 1:1 on clinical visit to take into account the later-stage diagnosis trend. Data were used to assess the association between breast cancer (outcome) and breastfeeding history (exposure) as well as other covariates and potential confounding factors, including age at clinical visit, breast cancer family history, HRT ever-use, smoking ever-use, alcohol consumption, HIV status, and menopausal status. Data collection for this study did not include personal health information or other identifiable factors.

Data Analysis

Univariate analysis including means and percentages were calculated to describe the patient population by outcome status; mastalgia patients (controls), and breast cancer patients (cases). Bivariate conditional logistic regression assessed the log odds difference in

continuous predictor variables (i.e. age at clinical visit, age of menarche, age at first delivery, and number of pregnancies) betweeen non-breast cancer and breast cancer groups; while, χ^2 analysis assess difference amongst categorical predictor variables (i.e. breastfeeding history, breast cancer family history, HRT ever-use, HIV status, and menopausal status) between non-breast cancer and breast cancer patient groups.

A crude model was initially constructed to assess the bivariate association between the main exposure (breastfeeding history) and main outcome (breast cancer). Mid data collection, medical forms were revised, removing alcohol consumption from the medical history collection; therefore, alcohol was not considered in the multivariable model building techniques due to inconsistent variability across the entire study period and population. Forward and backward variable inclusion/elimination was used to build the multivariable conditional logistic regression model. Both models had identical outcomes; therefore, AIC numbers were not needed to be taken into account for the best fit model.

The final model resulted in age and age at first delivery being statically significant. Due to multicollinearity between the two covariates, age at first delivery was removed, leaving age to be controlled for in the adjusted model. Since family history and menopausal status have genetic and clinical associations with breast cancer outcomes, respectively, both predictor variables were considered for the multivariable model. However, age and menopausal status were highly correlated, leaving age and family history to be controlled for in the final multivariable conditional logistic regression model.

Effect measure modification was evaluated between age and family history using an interaction term; however, a significant association was not observed. Predicted probabilities of breast cancer was plotted against breastfeeding history and family history, across age progression using post-estimation graphing techniques.

HUMAN SUBJECTS SAFETY CONSIDERATIONS

Ethical Considerations

Human Subjects ethics has been approved by the UTHealth Institutional Review Board (HSC-SPH-19-0263) and Groote Schuur Hospital's Ethics Committee (IRB number: IRB00001938). All data were saved on a password-protected computer and were not distributed to or viewed by any person that is not on either IRB application. No identifiers were available in the dataset, neither individually, nor appended.

RESULTS

Sample Description

Uni- and bivariate statistics of breast cancer cases and mastaglia discharged controls, matched on month, are presented in Table 1. In a sample of 360 South African mothers, 77% had a history of breastfeeding (main exposure) while 50% were diagnosed with breast cancer (main outcome) due to the 1:1 matching on clinic visit month. The majority of the mothers were not currently breastfeeding (99%) and post-menopausal (66%) which coincides with the age (mean= 53, SD= 14.23) of the patient population. The average age of menarche was 14 (SD= 2.12), average age of delivery was 22 (SD= 5.10), and average number of pregnancies was 3 (SD= 1.60). South African mothers also reported to have marginally higher percentages of not having a family history of breast cancer (74%), no HRT ever-use (91%), to be non-smoking (63%), consume no alcohol (83%), and were HIV-negative (91%).

Table 1: Description of Groote Schuur Hospital's Breast Cancer Cases and Mastalgia Controls Matched on Month of Clinical Visit

N= 360	**N (%)**
Age at Clinical Visit *(mean, SD)*	53, 14.14
Age of Menarche *(mean, SD)*	14, 2.12
Age at First Delivery *(mean, SD)*	22, 5.10
Number of Pregnancies *(mean, SD)*	3, 1.60
Breastfeeding History (*n=300)*	
No	69 (23)

Yes	231 (77)
Currently Breastfeeding *(n=228)*	
No	226 (99)
Yes	3 (1)
Family History of Breast Cancer *(n=329)*	
No	242 (74)
Yes	87 (26)
HRT ever-use *(n=159)*	
No	145 (91)
Yes	14 (9)
Smoking ever-use *(n=319)*	
No	201 (63)
Yes	118 (37)
Alcohol Consumption *(n=220)*	
No	182 (83)
Yes	38 (17)
HIV status *(n=260)*	
Negative	236 (91)
Positive	16 (6)
Not Done	8 (3)
Menopausal Status *(n=280)*	
Pre-menopausal	71 (26)
Peri-menopausal	21 (8)

Post-menopausal	185 (66)
Breast Cancer *(n=360)*	
Yes	180 (50)
No	180 (50)

Bivariate analyses of predictor variables, matched on month of clinic visit, compared breast cancer and non-breast cancer diagnosed SA mothers (Table 2). The odds of breast cancer significantly increased by 0.0267 with each increase year of age (p=0.016). The statistical significance of age is visually represented by the mean age difference in non-breast cancer (mean age 50, SD= 13.04) versus breast cancer (mean age 57, SD= 15.51) diagnoses. There is also a statistical difference between HIV status amongst non-breast cancer and breast cancer diagnoses. When SA mothers whose HIV test was "not done" were replaced as missing, the statistical difference between positive and negative HIV status remained (p= 0.045). However, age of menarche (p=0.704), age at first delivery (p=0.259), number of pregnancies (p= 0.961), currently breastfeeding (p=0.533), family history of breast cancer (p=0.327), HRT ever-use (p= 0.567), smoking ever-use (p=0.063), alcohol consumption (p= 0.325), and menopausal status (p=0.433) showed no significance difference between breast cancer and non-breast cancer groups.

Table 2: Conditional Logistic Regression and χ^2 Bivariate Analysis Comparing the Difference Between Breast Cancer Groups Amongst Predictor Variables

N= 360	Non-Breast Cancer	Breast Cancer	Clogit (β, p-value)	χ^2 p-value
Age at Clinical Visit *(mean, SD)*	50, 13.04	57, 15.51	0.0267, 0.016 *	
Age of Menarche *(mean, SD)*	14, 2.13	13, 0	- 0.275, 0.704	
Age at First Delivery *(mean, SD)*	22, 4.78	23, 5.35	0.040, 0.259	
Number of Pregnancies *(mean, SD)*	3, 1.55	3, 1.65	0.005, 0.961	
Breastfeeding History (*n=300)*				0.358
No	39 (25)	30 (21)		
Yes	116 (75)	115 (79)		
Currently Breastfeeding *(n=228)*				0.533
No	71 (99)	155 (99)		
Yes	1 (1)	1 (1)		
Family History of Breast Cancer *(n=329)*				0.327
No	120 (71)	122 (76)		
Yes	48 (29)	39 (24)		
HRT ever-use *(n=159)*				0.567
No	84 (92)	61 (90)		

	Yes	7 (8)	7 (10)	
Smoking ever-use *(n=319)*				0.061
	No	94 (58)	107 (68)	
	Yes	68 (42)	50 (32)	
Alcohol Consumption *(n=220)*				0.325
	No	68 (86)	114 (81)	
	Yes	11 (14)	27 (19)	
HIV status *(n=260)*				< 0.0001*
	Negative	148 (91)	88 (90)	
	Positive	14 (9)	2 (1)	
	Not Done	0 (0)	8 (8)	
Menopausal Status *(n=280)*				0.413
	Pre-menopausal	41 (30)	33 (23)	
	Peri-menopausal	11 (8)	10 (7)	
	Post-menopausal	86 (62)	99 (70)	

SD= standard deviation; χ^2 = chi-square; β= beta coefficient; clogit= conditional logistic regression

Conditional Logistic Models

A bivariate conditional logistic regression model, grouped by month of clinic visit, was conducted to examine the crude odds of breast cancer diagnosis with breastfeeding history (Table 3). Breastfeeding is shown to have a positive association that is not statistically significant (OR= 1.50, 95% CI [0.71 – 3.16]). Therefore, although not statistically significant, South African mothers who have a history of breastfeeding have a 50% higher odds of breast cancer compared to South African mothers who do not have a history of breastfeeding.

Table 3: Unadjusted and Adjusted Conditional Odds of Breast Cancer with Breastfeeding History, While Controlling for Statistically and Clinically Relevant Covariates (i.e. Age at Clinical Visit and Family History of Breast Cancer)

	Model 1 OR (95% CI)	**Model 2** AOR (95% CI)
Breastfeeding History		
No	**Ref**	**Ref.**
Yes	1.50 (0.71 – 3.16)	1.54 (0.69 – 3.43)
Age at Clinical Visit	---	1.03 (1.01 – 1.06)
Family History of Breast Cancer		
No	---	**Ref.**
Yes	---	1.04 (0.49 – 2.22)
R^2	0.0051	0.0400

OR= unadjusted odds ratio; AOR= adjusted odds ratio; CI= confidence interval; age is measured in years; Ref.= reference group

Model 2 in Table 3 contains statistically relevant confounders (i.e. age) in addition to family history which is clinically relevant effect measure modifiers for breast cancer

outcomes. Although not statistically significant, the increased odds of breast cancer with breastfeeding history increased from 50% in the crude model to 54% (AOR= 1.54, 95% CI [0.69 – 3.43]) in the adjusted model when controlling for age at clinical visit and family history of breast cancer. In addition, SA mothers with a family history of breast cancer have 4% higher odds of being diagnosed with breast cancer (AOR= 1.04, 95% CI [0.49 – 2.22]), when controlling for breastfeeding and age at clinical visit. With each yearly increase in age, the odds of breast cancer significantly increased by 3% (AOR= 1.05, 95% CI [1.01 – 1.06]), when controlling for breastfeeding and family history of breast cancer.

The graphic display of the association between breastfeeding history and breast cancer diagnosis while controlling for age (Figure 7) shows an increased predicted probability as age increases. The overlap in the confidence intervals for both breastfeeding exposure categories (Y/N) represents the non-statistical significance of the association between the main exposure (breastfeeding history) and main outcome (breast cancer diagnosis). Figure 8 shows a different result where family history differences were not affected by age, but also had an increased breast cancer outcome and confidence interval overlap between exposure groups, illustrating the non-statistically significant from the 4% increased odds of breast cancer diagnosis.

Figure 6: Predicted Probability of Breast Cancer with Breastfeeding History While Controlling for Age

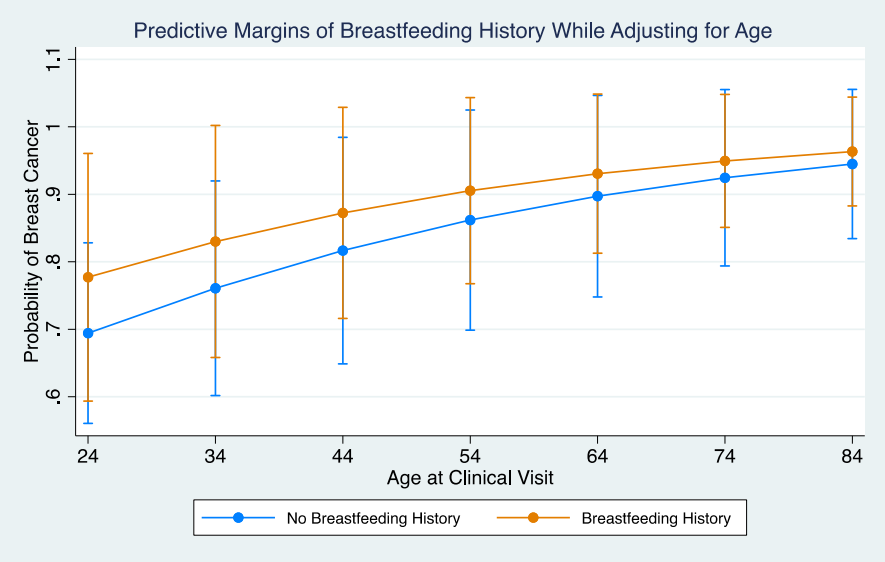
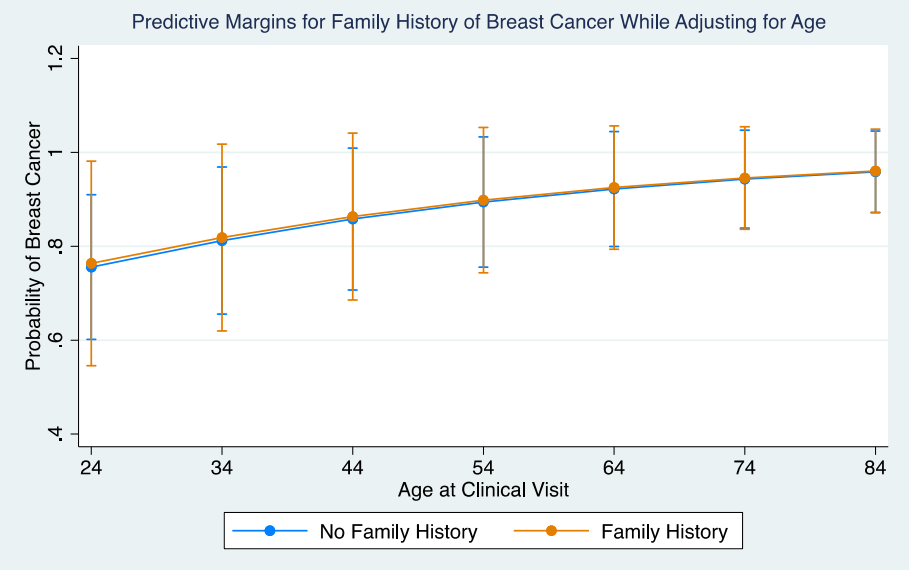


Figure 7: Predicted Probability of Breast Cancer with Family History of Breast Cancer While Controlling for Age



DISCUSSION

In this retrospective, nested case-control study that examined the association between breastfeeding history and breast cancer, results did not support a protective effect. Specifically, when assessing the direct relationship between breastfeeding history and breast cancer, South African mothers who have a history of breastfeeding have a 50% increase in odds of breast cancer compared to South African mothers who have no history of breastfeeding. The adjusted conditional logistic regression model also resulted in a positive relationship opposed to the hypothesized inverse association. When controlling for age at clinical visit and family history of breast cancer, South African mothers who have a history of breastfeeding have a 54% increased odds of breast cancer compared to not having a breastfeeding history. In favor of the unique characteristics within the patient population, neither of the cross-over effects were supported by previous literature outside of the South Africa setting, but is similar to literature that the same patient population attributes. Additionally, there is evidence of negative confounding by family history and age because of their influence in the odds of breast cancer in the adjusted model (Table3).

This positive association may be due to the limitations associated with the study in the design phase. The true inverse association between breastfeeding history and breast cancer odds could be hidden in light of residual confounding caused by race and ethnicity in addition to detailed breastfeeding history. However, age (3%) and family history (4%) have long been shown to be associated with increased odds of breast cancer diagnoses in previous

studies and are well-established causal risk factors which is also supported in this research study.[46-53]

Breast cancer and modern treatment methods are stigmatized in African communities. Therefore, information bias from recall and interviewer bias (i.e. patients hiding information) during the verbal genetic mapping process that is conducted in the SA healthcare system may be the source of the lack of statistical significance when assessing the association between family history and breast cancer outcomes.[54,55] Further research such as a qualitative study identifying themes and patterns in patients who undergo genetic testing, in addition to the physicians who conduct the genetic testing would need to be conducted to further isolate and assess the non-significant association.

Journal Article #1

Title: Lactation and Breast Carcinoma Risk in a South African Population

Target Journal: American Cancer Society

Demographically, most of South African women within the study sample (446 cases, 1471 controls) were defined as “colored” and between 35-49 years of age. Furthermore, the majority of the population in both cases (83%) and controls (85%) had a history of breastfeeding (OR = 0.9, 95% CI [0.7-1.3]). However, cases had a higher age at first delivery (20-24 (47.7%)) compared to controls (<20 (43.6)).[56]

Concerning the effects of lactation duration and history on breast carcinoma diagnosis, results concluded all breastfeeding odds were close to or equivalent to having a null effect for those who had accumulated a total breastfeeding period of less than three years (i.e. never (Ref.), ever (OR= 0.9 [0.7 – 1.3]), < 1 year (OR= 0.9 [0.6 – 1.3]), 1 year (OR= 1.1, [0.7 – 1.6]), 2 years (OR= 1.0, [0.6 – 1.5])).[56] Conversely, SA mothers who had a life-course of breastfeeding time of more than three years had a protective effect, although not statistically significant (i.e. 3-4 years (OR= 0.8 [0.5 – 1.2]), 5-6 years (OR+ 0.8, [0.5 – 1.4]), ≥ 7 years (OR= 0.7, [0.4 – 1.3]).[56]

The covariates of menopausal status (i.e. never (Ref.); ever (OR= 1.0 [0.7 – 1.4]), number of children (i.e. none (Ref.), 1 (OR= 0.9, [0.6 – 1.3]), 2 (OR= 0.9 [0.6 – 1.3]), 3 (OR= 1.0, [0.6, 1.5]), 4 (OR= 1.0, [0.6 – 1.6]), 5 (OR= 1.3, [0.7 – 2.3])), and age at fist lactation (i.e. never (Ref.), ≤ 18 (OR= 0.7 [0.5 – 1.1]), 19 – 20 (OR= 0.8 [0.6 – 1.2]), 21 – 24 (OR= 1.0, [0.7 – 1.4]), 25 – 29 (OR= 1.1, [0.8 – 1.7]), ≥ 30 (OR= 1.2, [0.7 – 2.1])) were also observed to have a null effect on breast cancer odds.[56]

Both this research study and Coogen et al.'s study was conducted in the form of a hospital-based, case-control design. However, Coogen et al. did not use a defined cohort for a nested case-control study design. The patient populations were similar in the sense that majority of women in both samples of mothers ever breastfed and the difference amongst breastfeeding groups were not statistically significant (i.e. 83% cases and 85% controls (OR = 0.9, 95% CI [0.7-1.3]) in Coogen et al. versus 79% cases and 75% controls (p= 0.358)).[56]

While both research studies failed to obtain an inverse association between breastfeeding exposure and breast cancer outcomes, this study resulted in a cross-over effect while Coogen et al.'s research study concluded a null effect respective to WHO guidelines (AOR= 1.54, 95% CI [0.69 – 3.43]; (1 year (OR= 1.1, [0.7 – 1.6], respectively).[56] The difference in concluding a null versus a positive association may be because Coogen et al.'s was able to obtain more detailed breastfeeding information (i.e. lactation duration). However, neither study was able to collect exclusivity versus complementary breastfeeding data which is essential is observing protective effects of breast milk for mothers.

Additionally, neither study included race and ethnicity in their final logistic model. This research study was not able to collect said data points while Coogen et al. omitted the variable due to ambiguity regarding the definition of the racial and ethnic terms used in South Africa. In addition, this study was also not able to collect breastfeeding duration information. Therefore, there may be residual confounding in both studies due to race, ethnicity, and more specific breastfeeding history data points.

Journal Article #2

Title: Prevalence of Comorbidities in Women with and Without Breast Cancer in Soweto, South Africa: Results from the SABC study

Target Journal: South African Medical Journal

The research study observing the effects of comorbidities on breast cancer was conducted in a matched case-control design. The 798 Black, South African women who participated in this study (mean age= 54.6, SD= 12.9) were categorized into two groups 1) advanced stage breast cancer cases 2) age and neighborhood match non-breast cancer controls.[57] Similar to this research study, majority of the population in Ayeni et al.'s study was HIV-negative (i.e. 90% cases and 91% controls versus 83.5% cases and 77.4% controls, respectively).[57]

Women with HIV had a significantly higher odds of presenting with advanced stage breast cancer compared to women without HIV (OR= 1.75, 95% CI [1.01 – 2.99]).[57] Furthermore, women who were HIV-positive have 1.44 [0.80 – 2.57] times the odds of presenting with advanced stage breast cancer compared to women who were HIV-negative, when controlling for age, household income, dyslipidemia, and hypertension.[57]

While Ayeni et al.'s study does not examine lactation history, it does take into account the effects of HIV on breast cancer. Comparable to Ayeni et al.'s study (p=0.032), this study observed a statistical difference (p= < 0.001) amongst HIV groups (negative, positive, not done) between breast cancer and non-breast cancer.[57] However, HIV was considered in the final model of this study due to lack of statistical significance. Therefore, the impact of HIV on breast cancer odds was not observed.[57]

Limitations

The theorized association between breastfeeding and the reduced risk of breast cancer has been studied for decades. The inverse association is a result of ovulation suppression from lactation, which lowers estrogen levels and suppresses the food supply of ER+ breast cancers. Also, when mothers breastfeed, they shed breast tissue cells, including those that may be cancerous. Therefore, lactation duration is an important aspect when considering the reduced risk of breast cancer. Critical data collection elements were not collected to make the inverse association between breastfeeding history and breast cancer (i.e. breastfeeding duration, initiation, exclusivity, and complementary).

The original study protocol was modified to a retrospective format for GSH Ethics Committee approval; therefore, eliminating the ability to collect detailed breastfeeding data along with accompanying qualitative interviews with staff and patients regarding the SA healthcare system. Collection of race and ethnicity data was also rejected and caused cultural interpretations and genetic dissimilarities about breastfeeding effects and practices to be combined; thus, leaving room for ambiguity in breastfeeding history and constituting variability. In addition, there are research gaps regarding the inverse association between breast carcinoma and lactation in South African women; nonetheless, previous studies in a South African failed to form an inverse relationship. Stratifying breastfeeding history and endocrinology data by race, ethnicity, and breastfeeding category, would enhance the comprehension of South African breastfeeding culture, effects, and breast cancer burden.

CONCLUSION

Although the inverse association between breastfeeding history and breast cancer outcome was not observed, this pilot study provides credible research in support of the evidence-based theory that race, ethnicity, and detailed exposure-outcome status information is vital when observing the association of chronic diseases. Especially when dealing with scopes of practices and subject matters like cancers which is affected by a combination of genetic, environmental, and behavioral practices.

Future Research

There are significant gaps in the field regarding South African women and breast carcinoma overall. Innovative solutions to the limitations of this study may include: a multidisciplinary team consisting of SA surgical leaders, oncologists, and physicians within the breast and OBGYN wards, where data collection will occur, will collaborate on the study protocol. New chart forms will be curated to include breastfeeding details (initiation, duration, exclusivity, and complimentary) within the present endocrinology subsection to ease data collection processes, especially considering multiple languages (i.e. Afrikaans, Xhosa, and English). World Health Organization (WHO) breastfeeding regulations will be used for consistent and accurate recordings. Qualitative methods will also need to be included in a future study to better understand the patient population for appropriately tailored data collection procedures and, if needed, intervention programs.

APPENDICES

Appendix A: Nestle` Formula Push Scandal Timeline[10]

REFERENCES

1. Persson Lars Åke. (2018). Breastfeeding in low-resource settings: Not a “small matter”. *Plos One, 15*(8) doi: https://doi.org/10.1371/journal.pmed.1002646
2. World Health Organization. (2019). Nutrition: Breastfeeding. Retrieved from https://www.who.int/nutrition/topics/exclusive_breastfeeding/en/
3. UNICEF. (2019). Infant and young child feeding. Retrieved from https://data.unicef.org/topic/nutrition/infant-and-young-child-feeding/
4. World Health Organization. (2019). e-library of evidence for nutrition actions (eLENA): Exclusive breastfeeding for optimal growth, development and health of infants. Retrieved from https://www.who.int/elena/titles/exclusive_breastfeeding/en/
5. Rollins Nigel C, Bhandari Nita, Hajeebhoy Nemat, Horton Susan, Lutter Chessa K, Martines Jose C, Piwoz Ellen G, Richter Linda M, Victora Cesar G, on behalf of The Lancet Breastfeeding Series Group. (2016). Why invest, and what it will take to improve breastfeeding practices? *Lancet, 387,* 491-504.
6. Victora Cesar G, Bahl Rajiv, Barros Aluísio J D, França Giovanny V A, Horton Susan, Krasevec Julia, Murch Simon Murch, Sankar Mari Jeeva, Walker Neff, Rollins Nigel C, for The Lancet Breastfeeding Series Group. (2016). Breastfeeding in the 21st century: Epidemiology, mechanisms, and lifelong eff ect. *Lacnet, 387,* 475-90.
7. McFadden Allison, Frances Mason, Jean Baker, Begin France, Dykes Fiona, Grummer-Strawn Laurence, Kenney-Muir Natalie, Whitford Heather, Zehner

Elizabeth, Renfrew Mary J Spotlight on infant formula: Coordinated global action needed. (2016). *Lancet, 387,* 413-415.

8. Breastfeeding: Achieving the new normal. (2016). *Lancet*, *387,* 404.
9. Sparks, H., Linley, L., Beaumony, J. L., & Robinson, D. T. (2018). Donor milk intake and infant growth in a South African neonatal unit: A cohort study. *International Breastfeeding Journal, 13*(41) doi:10.1186/s13006-018-0183-8
10. Krasny, J. (2012). Every parent should know the scandalous history of infant formula. *Business Insider* Retrieved from https://www.businessinsider.com/nestles-infant-formula-scandal-2012-6
11. The World Bank. (2019). Mortality Rate, Infant (per 1,000 live births)- South Africa.
12. Sibeko, L., Dhansay, M. A., Charlton, K. E., Johns, T., & Gray-Donald, K. (2005). Beliefs, attitudes, and practices of breastfeeding mothers from a Peri-urban community in South Africa. *Journal of Human Lactation: Official Journal of International Lactation Consultant Association, 21*(1), 31-38. doi:21/1/31
13. Sayed, Nazeeia & Schönfeldt, Hettie C. (2018). A review of complementary feeding practices in South Africa. *South African Journal of Clinical Nutrition,* doi:10.1080/16070658.2018.1510251
14. Nieuwoudt, S., Manderson, L., & Norris, S. A. (2018). Infant feeding practices in Soweto, South Africa: Implications for healthcare providers. *South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde, 108*(9), 756-762. doi:10.7196/SAMJ. 2018.v108i9.13358

15. Shah, S., Rollins, N. C., Bland, R., & Child Health Group. (2005). Breastfeeding knowledge among health workers in rural South Africa. *Journal of Tropical Pediatrics, 51*(1), 33-38. doi:10.1093/tropej/fmh071
16. The Office of the U.S. Global AIDS Coordinator. (2014). *PEPFAR 3.0- controlling the epidemic: Delivering on the promise of an AIDS-free generation*. Retrieved from https://aidsfree.usaid.gov/resources/prevention-update/editions/december-2014/pepfar-30-controlling-epidemic-delivering
17. *Improving breastfeeding in the context of HIV: KZN's breakthrough on breastfeeding (2010-2014).* Petoria: UNICEF South Africa.
18. Seidel, G., Sewpaul, V., & Dano, B. (2000). Experiences of breastfeeding and vulnerability among a group of HIV-positive women in Durban, South Africa. *Health Policy and Planning, 15*(1), 24-33. doi:10.1093/heapol/15.1.24 [doi]
19. Horwood, C., Haskins, L., Engebretsen, I. M., Phakathi, S., Connolly, C., Coutsoudis, A., & Spies, L. (2018). Improved rates of exclusive breastfeeding at 14 weeks of age in KwaZulu natal, South Africa: What are the challenges now? *BMC Public Health, 18*(1), 757-018-5657-5. doi:10.1186/s12889-018-5657-5
20. Nieuwoudt SJ, Ngandu CB, Manderson L, Norris SA. (2019). Exclusive breastfeeding policy, practice and influences in South Africa, 1980 to 2018: A mixed-methods systematic review. *Plos One, 14*(10) doi:10.1371/journal.pone.0224029
21. Doherty, T., Sanders, D., Jackson, D., Swanevelder, S., Lombard, C., Zembe, W., . . . PROMISE EBF study group. (2012). Early cessation of breastfeeding amongst

women in South Africa: An area needing urgent attention to improve child health. *BMC Pediatrics, 12*, 105-2431-12-105. doi:1471-2431-12-105

22. Coovadia Hoosen M, Rollins Nigel C, Bland Ruth M, Little Kirsty, Coutsoudis Anna, Bennish Michael L, Newell Marie-Louise. (2007). Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. *Lancet, 396*, 1107-16.
23. Bobat, R., Moodley, D., Coutsoudis, A., & Coovadia, H. (1997). Breastfeeding by HIV-1-infected women and outcome in their infants: A cohort study from Durban, South Africa. *AIDS (London, England), 11*(13), 1627-1633. doi:10.1097/00002030-199713000-00012
24. United Nations Children's Fund, Division of Data Research and Policy. (2019). *UNICEF global database on infant and young child feeding*. New York: UNICEF. Retrieved from Global UNICEF Global Databases: Infant and Young Child Feeding: Continued breastfeeding
25. Maaike Arts, Vrinda Mehra, Guy Taylor, Vrinda Mehra, Julia Krasevec, Chika Hayashi, France Bégin, Victor M. Aguayo, Xinyi Ge, Yasmine Hage, Nona Reuter, QUO Global, Kurtis Cooper, Shushan Mebrahtu, Sabrina Sidhu, Guy Taylor, Irum Taqi. (2018). *Breastfeeding: A mother's gift for every child.* (). New York, New York: United Nations Children's Fund (UNICEF).
26. The World Bank. (2019). Birth Rate, Crude (per 1,000 people)- South Africa.
27. The World Bank. (2019). Death Rate, Crude (per 1,000 people)- South Africa.

28. *National integrated early childhood development policy.* (2015). (Policy). Pretoria: Government Printers: Republic of South Africa.
29. National Institute of Health: U.S. National Library of Medicine. (2015). Breast cancer. Retrieved from https://ghr.nlm.nih.gov/condition/breast-cancer#inheritance
30. Cordeiro, B. (2014). Breastfeeding lowers your breast cancer risk. Retrieved from https://www.mdanderson.org/publications/focused-on-health/breastfeeding-breast-cancer-prevention.h19-1589046.html
31. Susan G. Komen. (2018). Breastfeeding and breast cancer risk. Retrieved from https://ww5.komen.org/Breastcancer/Notbreastfeeding.html
32. Collaborative Group on Hormonal Factors in Breast Cancer. (2002). Breast cancer and breastfeeding: Collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50 302 women with breast cancer and 96 973 women without the disease. *The Lancet, 30*(9328) doi:10.1016/S0140-6736(02)09454-0
33. Bray Freddie, Ferlay Jacques, Soerjomataram Isabelle, Siegel Rebecca L, Torre Lindsey A, Jemal Ahmedin. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians, 68*, 394-424. doi:10.3322/caac.21492.
34. Adeloye Davies, Sowunmi Olaperi Y, Jacobs Wura, David Rotimi A, Adeosun Adeyemi A, Amuta Ann O, Misra Sanjay, Muktar Gadanya, Auta Asa, Harhay Michael O, Chan Kit Yee. (2018). Estimating the incidence of breast cancer in Africa:

A systematic review and meta-analysis. *Journal of Global Health, 8*(1), `. doi:10.7189/jogh.08.010419

35. World Health Organization: Globocan. (n.d.). Estimated number of deaths from 2018 to 2040, breast, females, all ages: South Africa.
36. World Health Organization: Globocan. (n.d.). Estimated number of new cases in 2018, South Africa, females, all ages: South Africa.
37. Maphumulo, W.T. & Bhengu, B.R. (2019). Challenges of quality improvement in the healthcare of South Africa post-apartheid: A critical review. *Curationis, 42*(1) doi: 10.4102/curationis. v42i1.1901
38. Dickens Caroline, Joffe Maureen, Jacobson Judith, Venter Francois, Schüz Joachim, Cubasch Herbert, and McCormack1Valerie. (2014). Stage at breast cancer diagnosis and distance from diagnostic hospital in a peri-urban setting: A South African public hospital

    case series of over 1000 women. *International Journal of Cancer*, *135*(9), 2173-2182. doi:10.1002/ijc.28861
39. Moodley, J., Cairncross, L., Thurandrie Naiker, & Momberg, M. (2016). Understanding pathways to breast cancer diagnosis among women in the western cape province, South Africa: A qualitative study. *BMJ Open*, *6* doi:10.1136/ bmjopen-2015-009905
40. Coovadia Hoosen, Jewkes Rachel, Barron Peter, Sanders David, McIntyre Diane. (2009). The health and health system of South Africa: Historical roots of current public health challenges. *Lancet, 374*, 817-34. doi:10.1016/S0140- 6736(09)60951-X

41. Breast Cancer: Causes, Symptoms & Treatments. (2020, February 17). Retrieved from https://www.cancercenter.com/cancer-types/breast-cancer
42. Recommended Treatments for Metastatic Breast Cancer. (n.d.). Retrieved from https://ww5.komen.org/BreastCancer/RecommendedTreatmentsforMetastaticBreastCancer.html
43. BreastCancer.org. Metastatic Breast Cancer. Retrieved from https://www.breastcancer.org/symptoms/types/recur_metast
44. Tuberculosis (TB). (n.d.). Retrieved from https://www.afro.who.int/health-topics/tuberculosis-tb
45. HIV/AIDS. (n.d.). Retrieved from https://www.afro.who.int/health-topics/hivaids
46. Braithwaite D, Miglioretti DL, Zhu W, Demb J, Trentham-Dietz A, Sprague B, Tice JA, Onega T, Henderson LM, Buist DSM, Ziv E, Walter LC, Kerlikowske K. (2018). Family history and breast cancer risk among older women in the breast cancer surveillance consortium cohort. *JAMA Internal Medicine, 178*(8), 494-501. doi:10.1001/jamainternmed.2017.8642
47. Shiyanbola Oyewale O, Arao Robert F, Miglioretti Diana L., Sprague Brian L, Hampton John M, Stout Natasha K., Kerlikowske Karla, Braithwaite Dejana, Buist Diana S.M., Egan Kathleen M, Newcomb Polly A, and Trentham-Dietz1 Amy. (2018). Emerging trends of family history in breast cancer and associated risk. *Cancer Epidemiol Biomarkers Preview, 26*(12), 1753-60. doi:10.1158/1055-9965.EPI-17-0531

48. Kharazmi E, Chen T, Narod S, Sundquist K, & Hemminki K. (2014). Effect of multiplicity, laterality, and age at onset of breast cancer on familial risk of breast cancer: A nationwide prospective cohort study [Abstract]. *Breast Cancer Research and Treatment, 144*(1) 185-92. doi:10.1007/s10549-014-2848-3

49. Pharoah, P., Day, N., Duffy Stephen, Easton, D., & Ponder, B. (1998). Family history and the risk of breast cancer: A systematic review and meta-analysis [Abstract]. *International Journal of Cancer, 71*(5)

50. Moolgavkar, S., Stevens Richard G., & Lee John A. H. (1979). Effects of age on incidence of breast cancer in females [Abstract]. *JNCI: Journal of the National Cancer Institute, 62*(3) 493-501. doi:10.1093/jnci/62.3.493

51. Trichopoulos, D., MacMahon, B., & Cole, P. (1972). Menopause and breast cancer risk [Abstract]. *JNCI: Journal of the National Cancer Institute, 48*(3) 605-13. doi:10.1093/jnci/48.3.605

52. Susan G. Komen. (February 13, 2020). Age. Retrieved from https://ww5.komen.org/BreastCancer/GettingOlder.html

53. Susan G. Komen. (February 13, 2020). Family history of breast, ovarian, and prostate cancer. Retrieved from https://ww5.komen.org/BreastCancer/FamilyHistoryofBreastOvarianorProstateCancer.html

54. Mutebi M, J. E. (2014). Stigma, survivorship and solutions: Addressing the challenges of living with breast cancer in low-resource areas. *South African Medical Journal, 104*(5)

55. Wallace M, Bos A, Noble C. (2018). Cancer-related stigma in South Africa: Exploring beliefs and experiences among cancer patients and the general public [Abstract]. *Journal of Global Oncology*, *4*(2) doi:10.1200/jgo.18.53700

56. Coogan, P. F., Rosenberg, L., Shapiro, S., & Hoffman, M. (1999). Lactation and breast carcinoma risk in a South African population. *American Cancer Society, 86,* 982-90. doi:10.1002/(sici)1097-0142(19990915)86:6<982::aid-cncr13>3.0.co;2-b

57. Ayeni, O. A., Joffe, M., Cubasch, H., Rinaldi, S., Taljaard, C., Vorster, E., . . . Norris, S. A. (2019). Prevalence of comorbidities in women with and without breast cancer in Soweto, South Africa: Results from the SABC study. *South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde*, *109*(4), 264-271. doi:10.7196/SAMJ.2019.v109i4.13465