UNIVERSITY OF THE WITWATERSRAND

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RESEARCH REPORT

PROJECT TITLE

HORMONAL CONTRACEPTIVES AS A RISK FACTOR FOR INVASIVE BREAST CANCER IN BLACK WOMEN IN JOHANNESBURG, SOUTH AFRICA

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Research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in partial fulfillment of the requirements for the Degree of Master of Science in Medicine in the field of Epidemiology and Biostatistics

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DECLARATION

I, Wilson Rubanzana declare that this research report work is my own work. It is being submitted for the degree of Master of Science in Medicine in the field of Epidemiology and Biostatistics, in the School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature: _____

Full Name: **Wilson Rubanzana**

_____ day of **April** 2007

DEDICATION

DEDICATED TO

MY BELOVED WIFE JACQUELINE MUSAYIDIRE

FOR HER UNLIMITED SUPPORT

MY BELOVED CHILDREN

KATIA, INES AND LIONEL

FOR BEING

THE HAPPINESS AND JOY OF MY DAYS

AND

OUR FAMILIES, VICTIMS OF RWANDAN "HOLOCAUST"

WE WILL MOURN YOU FOREVER
MAY YOUR SOUL AND SPIRIT REST IN PEACE

ABSTRACT

Background: Black South African women are known to have a high usage rate of injectable contraceptives. Breast cancer is the second leading cancer after malignant cervical neoplasms in black South African women. There is evidence that sex hormones are associated with an increased risk of developing breast cancer. In the Western Cape, investigators suggested that injectable contraceptives, more specifically DMPA, may increase breast cancer risk. In another study conducted in the same province, a weak association between breast cancer and women taking combined oestrogen/progesterone oral contraceptives was found, though no risk associated with injectable progestogen contraceptives (DMPA) was confirmed.

Study Objective: This study aimed to determine whether there is an association between hormonal contraceptive use and an increased risk of cancer of the breast.

Methods: Data was obtained from an ongoing case control study set up by MRC/Wits/NHLS Cancer Epidemiology Research Group (CERG) in 1995 to investigate risk factors associated with cancer among the black population in Johannesburg. Data was processed using STATA, version8 and analysed using univariate, bivariate and multivariate unmatched logistic regression models.

Results: There was evidence that an overall use of oral contraceptives increases the risk of breast cancer; cases (n= 221), controls :(n= 153), OR=2.01 (95% CI: 1.45, 2.80), $p<0.0001$.

There was evidence of an association between use of injectable contraception and the risk of breast cancer; cases (n=244), controls (n=202), OR=1.51(CI: 1.14, 2.01), p=0.004

Surprisingly, no other use characteristic of either hormonal contraceptive method was statistically significantly associated with the risk of breast cancer in our dataset.

The combined use of both oral and injectable contraception was associated with an increased risk of breast cancer, OR=1.68(1.21, 2.33), p =0.002. There was a strong effect modification (interaction) between oral contraceptive use and injectable progesterone associated with the risk of breast cancer, (p=0.008).

Conclusion: After adjusting for all potential risk and confounding factors, as collected in the dataset, there was evidence of an association between combined oral contraceptive use and breast cancer. An association between cancer of the breast and overall use of injectable progesterone use was also established. There was evidence of association between the use of both hormonal contraceptive methods and an increased risk of breast cancer. However, whether these findings reflect the reality in terms of causal relationship or are the result of bias must be ascertained.

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CHAPTER ONE: INTRODUCTION

1.1 BACKGROUND INFORMATION

Reproductive and hormonal factors are the most important well established risk factors for breast cancer.[1,2] The link between breast cancer and oestrogen has been recognized for more than 100 years, since George Beatson showed that surgical removal of both ovaries - known as bilateral oophorectomy - was followed by the remission of breast cancer in premenopausal women.[2] Many years later, numerous studies demonstrated that breast cancer risk was strongly associated with various hormonal factors, and furthermore, a high serum concentration of oestradiol was shown to be an important determinant of breast cancer risk.[3] This finding was confirmed by numerous prospective studies that revealed that high blood levels of estradiol are related to an increased breast cancer risk in postmenopausal women exposed to hormone replacement therapy.[3] Subsequently, further scientific evidence has implicated both endogenous and exogenous oestrogen in the pathogenesis of malignant breast neoplasms. Indeed, hormonal preparations containing oestrogen and progestogen have been used as contraceptives since the early 1960s and appeared to be linked to the rise of breast cancer noted worldwide since then.[1, 2, 3]

The occurrence of malignant breast cancer is very rare in women before 25 years of age, increasing after menopause and declining in older women.[4] The low incidence of breast cancer among elderly women coincides with a decline in circulating oestrogen.[1,4] This observation confirms the role of reproductive hormones in the

occurrence of the disease. The risk is increased by early menarche, late menopause, late age at first childbirth, and low parity.[1,2,34] All of these factors demonstrate the role of high concentrations of endogenous oestrogen, in particular free oestradiol, in the development of breast cancer.

In addition, the risk of developing breast cancer may be increased by exogenous contraceptive hormones, either oral or injectable.[5,6] The possible effects of hormonal contraceptives on the risk of developing breast malignancy have been a subject of intensive research in the developed world.[1,2,3,4,5] The findings of many studies remain, however, controversial, and even contradictory.

In South Africa, since the 1970s, injectable progestogen contraceptives (IC) and oral contraceptives (OC), both progestogen only and combined oestrogen/progestogen containing preparations, have been the most commonly used contraceptive methods by black women.[6] More specifically, studies have shown that depot medroxyprogesterone acetate (DMPA; trade name Depo-Provera), an injectable progestogen contraceptive, was used more frequently and was taken for longer periods in South Africa than in any other country in the world.[7] Indeed, South Africa presents with the highest prevalence of use, with 27% of black women aged 15-49 estimated to be current users of injectable contraceptives.[8] Recently, another injectable progestogen, norethisterone enanthate, has also been introduced and used in South Africa.[7]

1.2 LITERATURE REVIEW

1.2. 1 INVASIVE BREAST CANCER:

Invasive breast cancers are defined as proliferation of malignant populations of cells that have the capacity to invade through the basement membrane and, therefore, are capable of distant metastasis.[9,10] Only primary invasive breast cancer arising from glandular components of the breast, ducts and lobules; such as invasive duct carcinoma, invasive lobular carcinoma, medullary carcinoma, tubular carcinoma, mucinous carcinoma or invasive papillary carcinoma are considered as invasive breast cancer in this study.[9,10]

1.2.2 RISK FACTORS FOR BREAST CANCER

A number of risk factors for female breast cancer have been identified. These include genetic predisposition (a family history of breast cancer is a risk factor)[3], benign proliferative breast disease (epithelial hyperplasia, sclerosing adenosis, small duct papilloma)[9], increasing age (breast cancer is rare before the age of 25 years), length of reproductive life (risk increases with early menarche and late menopause), parity (the risk of developing breast cancer is much higher in nulliparous than in multiparous), age at first child (the risk of breast cancer increases in women older than 30 years at the time of their first child's birth)[9], exogenous estrogens (postmenopausal hormonal therapy or oral contraceptives), obesity (increased risk in

postmenopausal obese women attributable to synthesis of estrogens in fat deposits)[3], dietary fat and heavy smoking.[3,9]

1.2.3 BREAST CANCER IN AFRICA

Cancer of the breast is by far the most common cancer affecting women worldwide, with an estimated 1.05 million new cases in the year 2000, accounting for 22% of all new cancers in women.[11] In Africa, 59,000 new breast cancer cases were estimated in 2000, corresponding to 18% of all cancers in women.[11] However, information concerning breast cancer remains scarce on the African continent, given that only six countries (Zimbabwe, Uganda, Algeria, Mali, South Africa and Gambia) have cancer registries that monitor and report the disease.[11, 12, 13] Within each of these countries, the reported rates are lower than in Western countries. For example, in Algeria (Algiers), an age standardized incidence rate of 21.3 per 100,000 was reported in 1999, compared to 74.4 and 92.1 per 100,000 for the United Kingdom and United States of America, respectively.[12] The same trend of much lower reported rates than Western countries was observed in other sub Saharan African countries in the same year.[12] Even in Zimbabwe, which has a good population-based registration system, the incidence and prevalence rates of breast cancer reported for the same period are lower than in Western populations.[11,12,13,14] An age standardized incidence rate (ASIR) of 20.3 per 100 000 was recorded in Zimbabwe in 1999.[11,14] Interestingly, in Bulawayo, 1963-1977, women registered with breast cancer had a higher level of literacy than women with other types of cancer.[11,16] The lower incidence rates in Africa are likely due in part to high parity, low age at first birth and late menarche, or may merely be the result of lack of medical facilities capable of diagnosing the

disease, as well as under-reporting due to the scarcity of registries - population-based registries in particular. However, it may also be a real effect of lower socio-economic status in Africa than in the rest of the world. This assumption concurs with the observed higher incidence rates in women of higher socio-economic status compared to lower social classes, and higher incidence rates in urban dwellers compared to women in rural areas.[14] In almost all developing countries with relatively low incidence rates of breast cancer, the risk appears to be increasing, even though data remain sparse.[11]

1.2.4 BREAST CANCER INCIDENCE IN SOUTH AFRICA

Breast cancer incidence rates in black South African females are generally comparable with those reported elsewhere in developing countries.[12,13] However, the South African National Cancer Registry (NCR) is only pathology based, which may lead to under-reporting of breast cancer cases in this country. The occurrence of breast cancer is very rare in black women before 30 years of age and thereafter the incidence steadily increases with increasing age.[6, 7,12,13,15] Reported breast cancer incidence is low among women living in rural areas in South Africa. However, in urban areas**,** it remains one of the most frequent cancers among black females of childbearing age.[6, 12, 13] In 1998 and 1999, breast cancer reached an average ASIR of 18 per 100,000, as reported by the NCR.[12] However, there is a strong suspicion that the incidence of the disease is underestimated, particularly in urban areas where Black South African women tend to embrace a Western lifestyle. The incidence of the disease still remains significantly lower in black compared to white, coloured and Indian South African women, who have ASIRs of 76.5, 49.8 and 49.6 per 100,000, respectively[12]. The

relatively low incidence of breast cancer among black females might be the result of under-reporting, the protective effect of high parity, extensive breast-feeding and a low fat diet in this population.[6,7, 8]

1.2.5 HORMONAL CONTRACEPTIVES:

a. Injectable contraceptives: these are progesterone preparations, which are a class of female synthetic sexual hormones that have been used by millions of women around the world over the past 25 years. The injectable contraceptive such as Depo–Provera® and norethisterone are administered at three and two month intervals, respectively. These hormonal preparations have been used more commonly by black South African women.[5,6,8]

b. Oral contraceptives: synthetic sexual hormone pills whose preparations include either progestogen only if they contain progestin molecules in each cycle, or a combination of oestrogen and progestogen in each cycle (i.e. a monophasic, multiphasic, or sequential formulation).[5,6] They come in several trademark names. (Melodene, etc.)

1.2.6 HORMONAL CONTRACEPTIVES AS A RISK FACTOR FOR BREAST CANCER IN BLACK SOUTH AFRICAN WOMEN

Studies on the association between hormonal contraceptives and breast cancer among black South African women are rare, and their findings contradictory.

In a case control study of breast cancers in black and 'coloured' women in Western Cape, South Africa, Baillie et al (1997) showed that black women used injectable progesterone for birth control more frequently and for longer time periods than other women world-wide.[7] Based on experimental evidence and previous studies in the United States, the investigators suggested that "unopposed progestogen", and more specifically DMPA, may increase breast cancer risk.[7]

The same research question was investigated by Shapiro et al. (2000), in the same study population.[6] An overall weak association between breast cancer and women taking combined oestrogen/progesterone oral contraceptives was found (Odds Ratio: OR =1.2). The association was strongest in young women under 35 (OR=1.7). They found no association within age categories, or with recency or duration of use. There was no risk associated with injectable progestogen contraceptives, particularly DMPA, even in those aged less than 35 at diagnosis.[6]

Thus, despite the two large-scale studies described above, the possible role, if any, of hormonal contraceptives in the occurrence of malignant breast neoplasm among black South African women has not been resolved.[6]

1.2.7 OTHER RISK FACTORS AND CONFOUNDING EFFECTS

In a study of the association between an exposure (risk factor) and outcome (disease), confounding can occur when another exposure exists in the study population that is associated with both the exposure and the outcome being studied.[17] Therefore, confounding is about alternative explanations. Confounding (from the Latin word 'confoundere', to mix together) is the situation where the association between a risk

factor and a disease is entirely or partially due to another exposure.[17,18,19] The most common concern over confounding is that it may create the appearance of a cause-effect relationship that in reality does not exist (positive confounding) or the effect can work in the opposite way, resulting in the association between a risk factor and a disease appearing to be weaker than it really is (negative confounding).[17,18,19] Confounding is a nuisance effect that needs to be controlled because it distorts the association between a risk factor of interest and the health outcome under study.[17,18,19]

Effect modification can be defined as a situation where the association between an exposure and an outcome is different for each level of the risk factor under study.[18,19] Effect modifier is not the same as confounder.[17, 18, 19] It is a real effect, independent of study design and needs to be detected and reported. However, effect modification and confounding are often considered together because the techniques of stratification and regression models are useful for both. To determine whether a risk factor is a confounder or an effect modifier, one must test whether the odds ratios can be considered to be constant over the strata.[17,18] This is done by performing tests of homogeneity. For that purpose, the most commonly used is the Mantel-Haenszel Chi Square test of homogeneity.[18, 19]

This study examined a number of potential confounders and other potential independent risk factors that were suspected to play a role in the relationship between hormonal contraceptive and cancer of the breast. The main objectives were to determine whether there is a relationship between different patterns of hormonal contraceptives use (overall contraceptive use, time since first use, duration of use, and time since last use) and cancer of the breast while controlling for potential

confounders and other well known risk factors that were available in the dataset, such as age, age at menarche, age at menopause, age at first pregnancy, parity, socio-economic status and smoking.[7,20,21,22,23,24,25] Logistic regression models were used to control for the possible confounding effects of these independent risk factors for breast cancer.

1.2.8 Problem statement

Breast cancer is one of the most common cancers affecting South African women of all races.[12,13] Among black South African women, breast cancer is the second most prevalent cancer after malignant cervical tumours, accounting for an average of 39% of all cancers diagnosed in this population group, and claiming lives of many black females of middle and childbearing age.[12,13] Thus, breast cancer is clearly a public health problem in black females, a population group known for its high use of hormonal contraceptives.[6,8] Indeed, in spite of scientific evidence incriminating oestrogen in the physiopathology of breast cancer, and some studies suggesting a possible increased risk associated with hormonal contraceptives, injectable or oral contraceptives remain the most widely used contraceptive method by black South African women.[1,2,6,8] The possible role of hormonal contraceptives in the occurrence of malignant breast neoplasm among black South African women has not been resolved, and only two studies have examined this question.[6 ,8]

I.2.9 Justification for the study

The only key to surviving breast cancer remains early detection and appropriate treatment including surgical procedure, chemotherapy, hormonotherapy and radiotherapy. Various screening programs, including mammography and ultrasound examinations, exist in South Africa. However, the screening techniques and treatment procedures are an expensive way to fight this deadly disease on large scale, and are therefore unaffordable to a large proportion of black South African women. Thus, it is of utmost importance to identify and understand the preventable risk factors for breast cancer, so as to plan and implement valuable epidemiological preventive programs and thus reduce the incidence of this deadly disease.

Numerous epidemiological studies conducted worldwide have revealed that hormonal contraceptive use and reproductive factors play a role in the development of breast malignancy.[2 ,3,5,6 8] However, few studies so far have examined in depth the role of hormonal contraceptives in general, and injectable progesterone in particular, in the development of breast cancer in black South African women.[6,8] Despite large-scale studies carried out in the Western Cape, the possible role, if any, of oral and injectable contraceptives in the occurrence of malignant breast neoplasm among black South African women has not been definitely established.[8] Clearly, further studies are needed to clarify any association between exposure to hormonal contraceptives and the development of breast cancer in this unique population, with its unique socio-demographic characteristics. In particular, no such study has been conducted in Johannesburg, the most populated South African city; providing justification for the current project. Information on the association between hormonal contraceptive use

and breast cancer risk in black South African women is therefore needed to inform public health policies of this country.

1.2.10 Hypothesis

1.2. 10.1 Null Hypothesis

There is no association between hormonal contraceptive use and the risk of breast cancer in black South African women attending tertiary hospitals in Gauteng.

1.2.10.2 Alternative Hypothesis

There is an association between hormonal contraceptive use and the risk of breast cancer in black South African women attending tertiary hospitals in Gauteng.

CHAPTER TWO: AIM AND STUDY OBJECTIVES

2.1 Aim of the study

To measure the association between hormonal contraceptives and the risk of breast cancer in black South African women attending tertiary hospitals in Gauteng.

2.2 Specific objectives:

a. To measure the association between injectable hormonal contraceptive (IC) use and the risk of breast cancer in black South African women

b. To measure the association between oral contraceptive (OC) use and the development of breast cancer in black South African women.

CHAPTER THREE: MATERIALS AND METHODS

This project entailed analysis of pre-existing data from an ongoing case-control study, which was initiated in 1995 in the three main public tertiary hospitals of Gauteng province, a predominantly urban province in South Africa. The study aimed at collecting data on potential risk factors for cancer in the black population of Greater Johannesburg (Johannesburg and Soweto). The background assumption was that since the vast majority of black residents of Johannesburg used public hospitals at that time, patients diagnosed with cancer in the referral hospitals would be representative of the black population as whole.

3.1 Study design

The dataset used in this project was obtained from a case control study carried out among black cancer patients admitted to Chris-Hani-Baragwanath, Hillbrow and Johannesburg General Hospital. The study began at Chris-Hani-Baragwanath in March 1995. In September of that year, the investigation expanded to include the Radiation Oncology facility at Hilllbrow hospital and the Medical Oncology Unit at Johannesburg hospital. From 1 November 2001, the study has only been conducted at Johannesburg General Hospital. Registered nurses trained in interview techniques questioned black patients aged 18 and older who presented with newly diagnosed cancers at the target hospitals. The interview was carried out using the patient's first language. Informed written or verbal consent was sought and obtained from the patients before their participation in the investigation. The data collected included socio-demographic characteristics, reproductive and hormonal contraceptive use

history. Confidentiality and anonymity of study participants was assured. Cancer diagnosis was confirmed by histology, haematology, or cytology.

For this research project, cases were selected from the overall database as black women, aged between 18 and 75 years, who presented with newly diagnosed invasive, parenchymal breast cancers at the target hospitals. Thus, breast ductal, lobular carcinoma in situ and breast skin cancers were not considered among cases. The controls were women, aged 18 to 75 years and diagnosed with cancers considered to be unrelated to hormonal contraceptive use. Furthermore, gynaecological malignancies were excluded because they may have similar risk factors to breast cancer. Thus, cancers of the vulva, uterine cervix, endometrium and ovary were not considered in the study. Cancers that were included in the control group originated from the following organs and systems: oesophagus, haematopoietic and reculo-endothelial system, colorectal region, lymph nodes, skin, lungs, bones, soft tissues, oral cavity, stomach, endocrine system, hepatobiliary system ,oto-rhino-laryngeal tract, pancreas, kidneys and lower urinary system, central nervous system, lower limbs ,eye and adnexa.

3.2 Study population

The study population consists of 6,363 black women aged 18 years and older, admitted with newly diagnosed cancers to the Chris-Hani-Baragwanath, Hillbrow, and Johannesburg hospitals from March 1995 to June 2004. These Government referral hospitals serve a large proportion of black women living in Greater Johannesburg (Johannesburg and Soweto) and black patients seen in those tertiary

medical institutions might be representative of a large proportion of black South African women of the same age groups.

3.3 Study sample

The study sample consists of 1,608 women. There were 753 cases and 855 controls, aged 18 years and older, obtained from the data set of this ongoing cancer case-control study over the period extending from March 1995 to June 2004.

3.4 Data analysis

Data were cleaned in Excel and processed using STATA, version 8. Invasive breast cancer cases and controls were classified according to the International Classification of Diseases for Oncology (ICD-O), 2nd edition. Breast Carcinomas in situ were excluded. Cases and controls were coded as 1 and 0, respectively. Similarly, hormonal contraceptive use was coded as follows: never use as 0, oral contraceptive use only as 1, injectable contraceptive use only as 2 and both oral and injectable contraceptives use as 3. Thorough cleaning of the dataset with regard to reproductive and socio-demographic variables of interest was carried out in Excel, and data was thereafter transferred to STATA for analysis. The reliability and consistency of reproductive factors were checked among cases and controls. For example, if the age of the respondent was less than the age at menarche, then age at menarche was set as a missing value. Similarly, if reported age at first birth was less than age at menarche then age at first birth was set as missing value. The fertility age interval was considered to be 15-49 according to the international demographic standard.[26]

Age at first childbirth was not available in the overall dataset and calculated by subtracting the age of the oldest child from the age of the mother. Similarly, time since first and last use of either hormonal contraceptive method were respectively obtained by subtracting the age at which women first used hormonal contraceptives or the age when they stopped using them from the age of the respondent. Some of the socio-demographic characteristics were measured by proxy. Thus, socio-economic status was measured by proxy using the level of education, area of birth and type of house.

The exposure of interest; hormonal contraceptive use and its related patterns were categorised and recorded in STATA. Likewise, potential confounders and other risk factors of interest were also categorised and recorded. Both univariate (frequency), bivariate (chi square statistical test through cross-tabulation) and multivariate logistic statistical analyses were carried out. The variables assessed in relation to invasive breast cancer were overall oral and injectable contraceptive use and their different patterns of use - such as age at first use, the duration of use, time since first use as well as time since last use of each of the hormonal contraceptive methods.

A frequency distribution of the controls and the distribution of reproductive and socio-demographic characteristics among cases and controls were produced using univariate analysis. This was followed by bivariate analysis aimed mainly at ascertaining whether there was statistical association between exposure of interest and the outcome. In addition, bivariate analysis was used to identify reproductive and socio-demographic factors that are statistically significantly associated with both the outcome and the exposure of interest.

Lastly, multivariate logistic analyses were conducted in order to measure the strength of any possible association between hormonal contraceptive use patterns and breast cancer. Multivariate analyses were adjusted for all reproductive and socio-demographic variables that were found statistically significantly associated with both the exposure and the outcome at the 5% significance level in bivariate analyses. Logistic regression model, the stratified analysis by combined Mantel-Haenszel method and its associated test of homogeneity were used to assess effect modification. Reproductive and socio-demographic variables that showed a borderline significance level (slightly greater than 5%) were also included in multivariate analysis.

3.5 Ethical consideration

The University of Witwatersrand Committee for Research on Human Subjects (medical) approved the use of the case-control study data for this MSc project (ethics approval number: M050925). Written permission to analyze the data was obtained from the MRC/NHLS/Wits Cancer Epidemiology Research Group.

CHAPTER FOUR: RESULTS

4.1 Univariate analysis

Univariate analysis presents the distribution and measure of spread of the characteristics of interest among cases and controls.

Table 1 shows the distribution of cancers in the control group. A total of 855 cancer types were selected. They were grouped into 20 types of malignancy according to the anatomical systems or specific organs from which they arose. Cancer of the oesophagus was the most common cancer among controls (21.70%), followed by cancers of the haematopoietic and reticulo-endothelial system (14%), colorectal cancer (8.98%), lymph node cancers (7.93%) and malignancies originating from the skin (7.58%). Cancer of the eye and adnexa were the least commonly represented cancers among the controls (0.35%).

Table 1: Distribution of cancers in the control group

Origin of cancer	Frequency	Percentage (%)
Oesophagus	185	21.70
Haematopoietic and Reticulo-endothelial system	119	14.00
Colorectal	77	8.98
Lymph nodes	68	7.93
Skin	65	7.58
Lungs	54	6.30
Bones, joints and soft tissues	50	5.83
Oral cavity	45	5.25
Stomach	44	5.13
Endocrine glands	30	3.50
Sinus,pharynx,larynx	26	3.03
Hepatobiliary tract	24	2.80
Pancreas	16	1.87
Kaposi sarcoma	12	1.40
Lower urinary tract	10	1.17
Salivary glands	9	1.05
Kidney	7	0.82
Central nervous system	7	0.82
Ill defined sites (pelvis-lower limbs)	4	0.47
Eye and adnexa	3	0.35
Total	855	100

Figure 1 shows the age distribution among cases and controls. The highest proportion of breast cancer cases occur in age group 40 to 49 (30.4%), followed by age group 50 to 59 (28.1%). Case respondents in the age group 15 to 19 years contributed the smallest proportion of cases participants (0.1%). The age distribution curve among controls was shifted to the right - in contrast to cases, the highest proportion of controls were in age

group 50 to 59 (29.3%). Women in the control group aged less than 20 years represented the smallest proportion (0.4%) of respondents. The age range was similar for cases and controls (19 to 75 and 18 to 75 years, respectively). The mean age of cases (52, SD 10.9) was significantly younger than that of controls (54, SD 12.7); p=0.0013.

Table 2 shows the distribution of reproductive characteristics among cases and controls. There was no significant difference at the 5% level between cases and controls with respect to the following reproductive characteristics normally associated with breast cancer (comparison of mean by Student test and test of proportions): The distribution of age at menarche among case subjects showed that the majority of women (63.8%) had their first menstrual period between 15 and 19 years. This was also the most common age group for menarche in the control group (66.6% aged 15 to 19 years). The mean age at menarche of cases and controls was 15.7 (SD 6.1) and 15.9 (SD 7.4), respectively.

The percentage of cases and controls who reported ever having being pregnant was 94.9% and 93.5%, respectively. The distribution of age group at first birth revealed that the majority (60%) of women in both groups had their first child in age groups 20-29 and 30-39 years. The mean age at first childbirth and its corresponding standard deviation among the cases and controls was 31.4 (10.1) and 31.2 (10.4) years, respectively. With regard to the parity of study participants, the nulliparous constituted 1.9% of the cases study participants and 1.5% of the controls group. In each study group, 2.9% of the women had their last periods at ages between 28 and 39 years.

However, the majority of cases and controls experienced the menopause when they were aged 46 years and above (45.2% and 53.5%, respectively). The age ranges at

menopause among cases and controls were 30-64 and 28-63 years, respectively. The mean age at menopause was 48.8 (SD 5.1) for the cases and 48.8 (SD 4.9) for the control participants.

Figure1: Age distribution of cases and controls

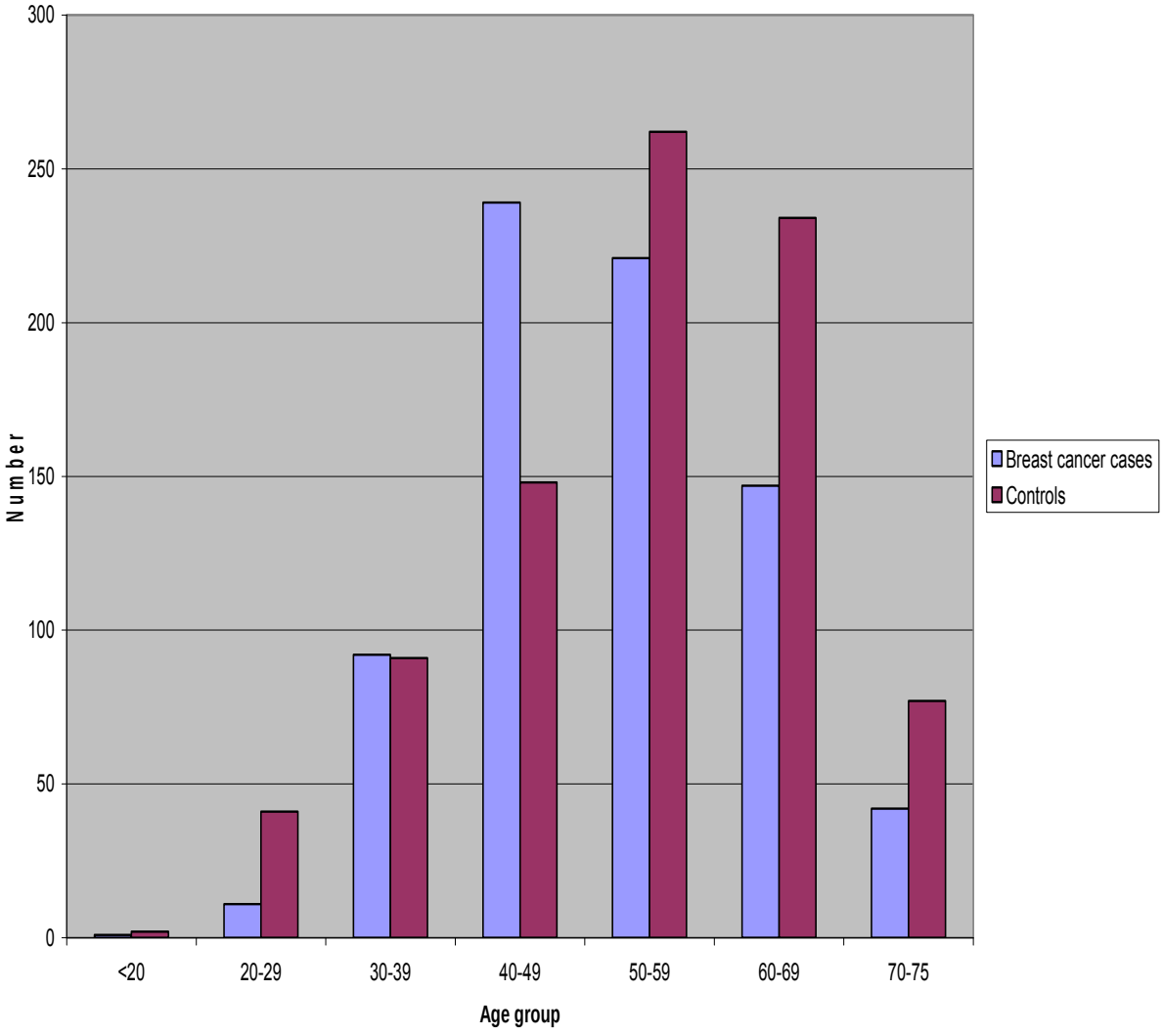

Table 2: Description of reproductive characteristics among cases and controls

Reproductive characteristics	Breast cancer cases N (%)*	Controls N (%)*
Age at menarche		
10-14	256(32.5)	264(29.5)
15-19	502(63.7)	595(66.7)
≥20	20(2.1)	23(1.9)
Ever pregnant		
Yes	747(94.9)	836(93.3)
No	39(5.1)	53(6.7)
Age at first birth		
15-19	102(13.5)	144(16.2)
20-29	244(31.3)	255(29.3)
30-39	242(30.8)	267(30.3)
40-49	184(19.0)	215(19.6)
Parity		
0	14(1.9)	11(1.3)
1-2	205(27.2)	220(25.7)
3-5	179(23.8)	240(28.0)
≥6	51 (6.8)	79(9.2)
Age at menopause		
28-39	22(2.9)	24(2.9)
40-49	192(24.5)	248(28.9)
≥50	222(29.5)	310(36.2)

* Because of very few missing responses with regard to some of the variables, the total percentages do not attain, but approach nearly 100% among cases and controls

Figure 2 shows the distribution of educational level among cases and controls. The mean level of education was significantly higher among cases (standard 8, SD 3.7) than among controls (standard 7, SD 3.8); $p<0.00001$. Cases and controls who reached between 8 and 11 years of schooling constituted the highest proportion; 42.4% and 42.7%, respectively. In contrast, 34.4% of case respondents attained 12 years of education or higher compared to 24.5% of the controls.

In contrast to education level, analysis of variance (by one way ANOVA command) demonstrated that there was no significant difference between cases and controls (5% level) with regard to the following socio-demographic characteristics: smoking status, marital status, urban vs rural area of birth, number of sexual partners and type of house (brick or cement). Table 3 shows the distribution of socio-demographic characteristics among cases and controls.

Figure 2: Distribution of education level among cases and controls

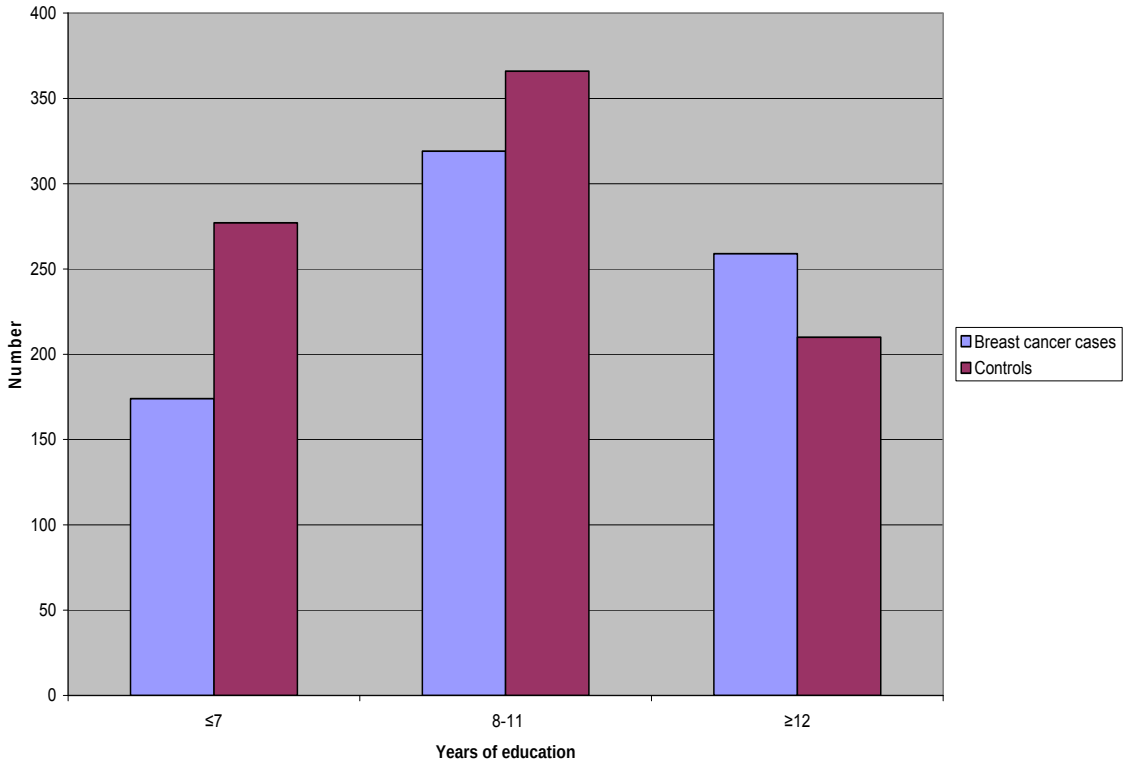

Table 3: Description of socio-demographic characteristics among cases and controls

Characteristics	Type of cancer	
	Breast cancer N (%)*	Control N (%)*
Smoking status		
Never	613(81.4)	648(75.6)
Past smoker	78(10.4)	130(15.2)
Current smoker	56(7.4)	77(9.0)
Marital status		
Single	203(26.9)	203(23.7)
Married	321(42.6)	363(42.4)
Widowed	149(19.8)	198(23.1.5)
Separated	79(10.5)	90(10.5)
Area of birth		
Rural	352(46.7)	455(53.1)
Urban	393(52.2)	390(45.5)
Number of partners		
Single	87(11.6)	108(12.6)
Multiple	645(85.7)	699(83.6)
House made of		
Other materials	122(16.2)	135(15.8)
Brick/cement	631(83.8)	720(84.0)

* Because of very few missing responses with regard to some of the variables, the total of the percents do not attain but approach nearly 100% among cases and controls.

Tables 4 and 5 describe different patterns of hormonal contraceptive use among cases and controls. The exposure under investigation is hormonal contraceptive use and cancer of the breast is the outcome of interest. The age range for starting hormonal contraceptive use among our study participants was found to be between 14 and 50 years.

A higher proportion of controls did not use any hormonal contraceptive method (570/855=66.7%), compared to women with breast cancer (389/753=51.7 %).

With regard to oral contraception among our study participants, the proportion of cases (221/753=29.3%) who used oral contraceptives (including those who also used injectable contraceptives) was higher than the proportion of controls (153/855=17.9%) who used the same hormonal contraceptive method. Further analysis revealed that among cases and controls, women who used solely oral contraceptives represented 15% (113/753) and 8.5% (73/855), respectively, ($p<0.0001$).

There was, however, no significant difference (5% level) between cases and controls for the following oral contraceptive use related characteristics (comparison of mean by Student T test): age at first use, age at last use, time since first use, time since last use and duration of use.

The mean age at starting oral contraceptive use was 24.6 (SD 6.8) in cases and 24.1 (SD 6.8) among controls. The age range at starting use of OC among cases and controls was 15-48 and 14-45, respectively. In addition, proportion of women starting the use of oral contraception was highest in age group 20 to 29 among both study arms. This age segment represented 12.6% (95/753) of cases against 9.0% (77/855) of the control group.

The mean age at last use of OC among cases and controls was 31.3 (SD 9) and 29.2 (SD 7.7), respectively. The age range of the variable was 16-50 for cases and 17-50

for controls. Surprisingly, the same age group, 20 to 29 years constituted the highest proportion of study respondents with regard to their age at last use of OC. They constituted 8.6 %(65/753) of cases and 7.3 % (62/855) of controls.

The mean time since first use of OC among cases and controls was 22.3(SD9.6) and 21.4(SD11), respectively. Further results show that women who reported the time since their first use of OC at 10 years and beyond constituted the highest proportion of study respondents, representing respectively 23.1% (174/753) of cases and 13.7% (108/855) of controls.

The mean time since last use of OC was 16.6(SD 10.4) for women with breast cancer and 16.5(SD10.7) for controls. The results also show that the highest proportion was found among cases and controls who presented the time since last use of OC of 10 years or more; 16.1%(121/753) and 9.7% (83/855),respectively.

The mean duration of use of OC among cases and controls was 8.5(SD15.5) and 8.6(17.6), respectively

There was a significant difference in the proportions of women who used injectable contraceptives (regardless of OC use or not) among breast cancer patients and controls. The proportion of women who used injectable contraceptives among cases was significantly higher than the proportion of controls who used ICs. This represented 32.4% (244/753) of cases compared to 23.6% (202/855) of controls (p=0.0001) who used ICs. Excluding women who, in addition, used oral

contraception, the number of cases and controls who used only injectable contraception dropped to 138 (18.3%) and 122(14.2%) respectively.

There were differences between cases and controls for age at first use and age at last use of ICs, in contrast to what was found for OC use.

The mean age at first use of ICs among cases was weakly significantly higher than among controls; 25(SD7.2) and 24(SD7) years, respectively (p=0.0485). The age range at first use of IC was 15-46 among cases and 15-47 in control participants. In addition, study participants who started using IC between 20 to 29 years constituted the highest proportions; 15.8% (119/753) of cases and 9.9% (85/855) of the control group.

Similarly, the mean age at last use of IC among cases was significantly higher than the mean age at last use of IC among control subjects; 33(SD 8.4) and 30(SD8.5), respectively (p=0.0072). The age at last use ranged from 16 to 50 in the case group and 17 to 50 among controls. In contrast to OC use, cases who reported stopping IC use during the age interval 30-39 constituted the highest proportion (9.4%), while among controls, the highest proportion was found within age group 20 to 29.

In contrast, there was no significant difference (5% significance level) between cases and controls for the following IC use related characteristics: mean time since first use, mean time since last use and mean duration of use.

The mean time since first use was 18.5(SD9) and 18(9.5), respectively, for cases and controls. The mean time since last use of IC among cases and controls was 12.8(10.5)

and 12.9(SD9.7) while the mean duration of use of injectable contraceptive was 7.6 (SD13.3) for cases and 7.2(SD14.7) among control participants.

The proportion of breast cancer patients who used both oral and injectable hormonal contraceptive methods was significantly higher than the proportion of controls who used similar hormonal contraception; 13.9 %(105/753) and 9.2 %(79/855), respectively, (p=0.0041)

Table 4: Description of oral contraceptive (OC) use among cases and controls

Oral contraceptive use related patterns	Types of cancer	
	Breast cancer N (%)	Controls N (%)
Oral contraceptive use		
Never	528(70.1)*	693(81.1)*
Oral contraceptive use(OC)**	221(29.3)	153(17.9)
Oral and injectable contraceptive use(OCIC)	105(13.3)	79(9.3)
Age at starting use of OC		
14-19	51(6.8)	33(3.8)
20-29	95(12.6)	77(9.0)
30-39	48(6.4)	23(2.7)
40-50	4(0.5)	4(0.5)
Unknown	23(3.1)	16(1.8)
Age at last use of OC		
14-19	15(2.0)	6(0.7)
20-29	65(8.6)	62(7.3)
30-39	59(7.8)	41(4.6)
40-50	40(5.3)	14(1.5)
Unknown	42(5.6)	30(3.5)
Time since first use of OC		
≤4	9(1.1)	12(1.4)
5-9	15(1.9)	18(2.1)
≥10	174(22.1)	108(12.6)
Unknown	23(2.9)	16(1.8)
Time since last use of OC		
≤4	32(4.1)	27(3)
5-9	26(3.4)	14(1.6)
≥10	121(16.1)	83(9.7)
Unknown	42(5.3)	30(3.5)
Duration of use of OC		
≤4	92(11.7)	72(8)
5-9	45(5.7)	41(4.6)
10-14	29(3.7)	16(1.8)
15-19	23(2.9)	9(1)
≥20	15(1.9)	8(0.9)
Unknown	17(2.2)	8(0.9)

***** Because of very high proportions of cases and controls that have ever used any oral contraceptives, the percentages related to oral use characteristics are small and thus, their sum does not attain 100%

** Oral contraceptive use: women who took oral contraceptives, including those who, in addition, used injectable contraception.

Table 5: Description of injectable contraceptive (IC) use among cases and controls

Injectable contraceptive use related patterns	Types of cancer	
	Cases N (%)	Controls N (%)
Injectable contraceptive use		
Never	502(66.7)*	644(75.3)*
Injectable contraceptive use (IC)**	244(32.4)	202(23.6)
Injectable and oral contraceptive use(OCIC)	105(13.3)	79(9.3)
Age at first use of IC		
14-19	43(5.7)	56(6.5)
20-29	119(15.8)	85(9.9)
30-39	50(6.4)	41(4.6)
40-50	16(2.1)	5(0.6)
Unknown	16(3.4)	15(3.1)
Age at last use of IC		
14-19	11(1.4)	12(1.4)
20-29	63(8)	70(8.2)
30-39	78(10.4)	45(5.3)
40-50	46(6.1)	29(3.4)
Unknown	46(6.1)	46(5.4)
Time since first use of IC		
≥4	14(1.8)	15(1.7)
5-9	23(2.9)	28(3.1)
≥10	191(24.3)	145(16.2)
Unknown	16(2.0)	15(1.7)
Time since last use of IC		
0-4	57(7.2)	45(5)
5-9	29(3.7)	20(2.2)
≥10	112(14.2)	92(10.3)
Unknown	46(5.8)	46(5.1)
Duration of use of IC		
≤4	119(15.1	99(12.6)
5-9	44(5.6)	49(5.5
10-14	29(3.7)	14(1.6)
15-19	23(2.9)	9(1)
≥20	8(1)	9(1)
Unknown	21(2.7)	23(2.6)

***** Because of very high proportions of cases and controls that have ever used any injectable contraceptives, the percentages related to injectable contraceptive use characteristics are small and thus, their sum are far less than 100%.

** Injectable contraceptives use: women who used injectable contraceptives including those who also took oral contraception.

4.2 BIVARIATE ANALYSIS:

Bivariate analysis examines the distribution of the exposure variables and other potential risk factors among cases and controls and most importantly, seeks to establish whether risk factors are associated with both the exposure and the outcome of interest at the 5% significance level. Only variables that met this latter condition were fitted in multivariate logistic regression models in order to measure the strength of the association between hormonal contraceptive use patterns and breast cancer.

Table 6 shows the distribution of age group, age group at menarche, pregnancy status, age group at first birth, parity and age group at menopause among cases and controls. The table also illustrates any statistical association between the aforementioned factors and the risk of developing invasive breast cancer (5% significance level). The results show that invasive breast cancer is strongly statistically associated with age group ($p<0.0001$). The age distribution differed significantly between cases and controls, with cases being in the majority in age groups 30--49, while among controls, the highest proportions are found among younger and older age (below 30 and above 60 years).The comparative age distribution of cases and controls is affected by the fact that the controls are not a sample of the background population but other recently diagnosed cancer cases, some of which occur in older or younger age groups than breast cancer cases. In addition, the distribution of age among breast cancer patients revealed a particular trend. The proportions of cases increase with age and attain the highest level at the age interval 40-49 and thereafter the proportions decrease with an increasing age. This is supported by a non-parametric test for trend p value as shown in the table ($p<0.0001$).

Age at menarche, pregnancy status, age at first birth, parity and age at menopause were not statistically associated with breast cancer.

Table 6: Reproductive characteristics among cases and controls

Characteristics	Types of cancer		Total	P value
	Breast cancer N (%)	Controls N (%)		
Age				<0.0001 <0.0001*
15-19	1(20.0)	4(80.0)	5	
20-29	11(21.2)	41(78.8)	52	
30-39	92(50.3)	91(49.7)	183	
40-49	239(61.8)	148(38.2)	387	
50-59	221(45.8)	262(54.2)	483	
60-69	147(38.6)	234(61.4)	381	
70-75	42(35.3)	77(64.7)	119	
Age at Menarche				0.426
10-14	256(49.2)	264(50.8)	520	
15-19	502(45.8)	595(54.2)	1097	
≥20	20(46.5)	23(53.5)	43	
Ever pregnant?				0.370
Yes	747(47.2)	836(52.8)	1583	
No	39(42.4)	53(57.6)	92	
Age at first birth				0.275
15-19	102(41.5)	144(58.5)	246	
20-29	244(48.9)	255(51.1)	499	
30-39	242(47.5)	267(52.5)	509	
40-49	184(46.1)	215(53.9)	399	
Parity				0.130
0	14(56)	11(44)	25	
1-2	205(48)	220(51.8)	425	
3-5	179(42.7)	240(57.3)	419	
≥6	51(39.2)	79(60.8)	130	
Age at menopause				0.654
28-39	22(47.8)	24(52.2)	46	
40-49	192(43.6)	248(56.4)	440	
≥50	222(41.7)	310(58.3)	532	

* The p value of a non-parametric test for trend

Table 7 shows a bivariate analysis of socio-demographic characteristic among cases and controls. Concerning education level, a strongly significant association between years of schooling and the occurrence of breast cancer is demonstrated, ($p<0.0001$).A total of 451women had education levels less than or equal to 7 years of education; of which 174(38.6%) had breast cancer. Of 685 women who had education level between 8 and 11 years of education, 319(46.6%) were cases. Out of 469 women who had greater than or equal to 12 years of education, 259(55.2%) had breast malignancy. Therefore, the largest proportion of women diagnosed with invasive breast cancer had an educational level greater than or equal to12 years of schooling. A non-parametric test for trend ($p<0.0001$) supports a trend of increasing proportions of breast cancer cases with increasing level of education.

Smoking appeared to be associated with breast cancer ($p=0.007$) in the bivariate analysis. The association is probably due to confounding with use of hormonal contraceptive. Out of 1261 women who had never smoked, 613(48.6%) developed breast cancer. There were a total of 133 women who were current smokers and 56(42.1%) of them developed cancer of the breast. Of the 208 women who had ever smoked in the past, 78(37.5%) developed cancer of the breast. This decreasing trend of proportions among breast cancer patients in relation with smoking status was supported by a non-parametric test, ($p=0.003$)

Area of birth (rural vs urban) was also found to be statistically associated to the development of breast cancer among study participants ($p=0.009$). A slightly higher

proportion of breast cancer cases were born in urban areas (50.2%) compared to controls. Among rural born women, 43.6% were cases and 56.4% controls.

Marital status, number of lifetime sexual partners and type of house were not statistically associated with breast cancer.

Table7: Socio-demographic characteristics among cases and controls

Characteristics	Types of cancer		Total	P value
	Breast cancer N (%)	Controls N (%)		
Years of education				<0.0001
≤ 7	174(38.6)	277(61.4)	451	<0.0001*
8-11	319(46.6)	366(53.4)	685	
≥ 12	259(55.2)	210(44.8)	469	
Smoking status				0.007
Never	613(48.6)	648(51.4)	1261	0.003*
Current smoker	56(42.1)	77(57.9)	133	
Past smoker	78(37.5)	130(62.5)	208	
Place of birth				0.009
Rural	352(43.6)	455(56.4)	807	
Urban	393(50.2)	388(49.8)	781	
Marital status				0.290
Single	206(49.6)	209(53.4)	415	
Married	329(46.9)	372(53.1)	701	
Widowed	169(43.4)	219(56.4)	388	
Separated	82(47.4)	91(52.6)	173	
Number of sexual partners				0.378
Single	93(44.1)	118(55.9)	221	
Multiple	668(48.1)	722(51.9)	1390	
House made of:				0.822
Other materials	126(47.2)	141(52.8)	267	
Brick/cement	661(46.8)	750(53.2)	1411	

* The p value of a non-parametric test for trend

Table 8 shows the distribution of socio-demographic characteristics that were earlier found to be significantly associated with breast cancer, among oral contraceptive users and non-users. It also seeks to demonstrate any statistical association between those factors (namely age group, education level, smoking status and place of birth) and the exposure variable under investigation.

There is a strong statistical association between age group and oral contraceptive use ($p<0.0001$). Out of a total of three women aged 15-19, one (25%) used oral contraceptives. Of 50 respondents aged 20-29, 19 (38%) used oral contraceptives. Among 180 women in the age group 30-39, 63 (35%) were oral contraceptive users. In the age interval 40-49, there was a total number of 385, 145 (37.7%) of whom used oral contraceptives. There were 106 (22.1%) out of 479 respondents, aged 50-59 years who used oral contraceptives. In summary, Table 8 shows that the highest proportions of oral contraceptive use were found among women between 20 and 49 years of age. In contrast from age 50, the results show a decreasing trend of proportions of oral contraceptive users among study participants. This is strongly supported by a non-parametric test for trend, ($p<0.0001$)

Level of education was strongly significantly associated with oral contraceptive use, ($p<0.0001$). The use of oral hormonal contraceptives increases with the increasing level of education. This is supported by a non-parametric test for trend ($p<0.0001$). Among 446 study participants who had up to 7 years of education, 9.6% were OC users. Out of 679 women who had between 8 and 11 years of education, 22.5% used OC. Of 467 women who reached 12 years of schooling or higher level, 38.3% used OC.

Smoking status and area of birth were also significantly associated with oral contraceptive use ($p<0.0001$). Women who had never smoked constituted the highest proportion among oral contraceptives users (26.3%), while those who were currently smokers represented the lowest proportion ($p<0.0001$ in non-parametric test for trend). The proportion of oral contraceptive users was significantly higher in urban than in rural born women, 29.4% and 18.2, respectively ($p<0.0001$).

Table 8: Oral contraceptives use and socio-demographic characteristics of interest among cases and controls

Characteristics	Oral contraceptive use		Total	P value
	Yes N (%)	No N (%)		
Age				<0.0001
				<0.0001*
15-19	1(25.0)	3(75.0)	4	
20-29	19(38.0)	31(62.0)	50	
30-39	63(35.0)	117(65.0)	180	
40-49	145(37.7)	240(62.3)	385	
50-59	106(22.1)	373(77.9)	479	
60-69	36(9.5)	344(90.5)	380	
70-75	5(4.2)	113(96.9)	118	
Years of education				<0.0001
				<0.0001*
≤7	43(9.6)	403(90.4)	446	
8-11	153(22.5)	526(77.5)	679	
≥12	179(38.3)	288(61.7)	467	
Smoking status				<0.0001
				<0.0001*
Never	328(26.3)	921(73.7)	1249	
Current smoker	21(15.8)	112(84.2)	133	
Past smoker	24(11.5)	184(88.5)	208	
Place of birth				<0.0001
Rural	146(18.2)	656(81.8)	802	
Urban	228(29.4)	547(70.6)	775	

* The p value of a non-parametric test for trend

Table 9 below describes socio-demographic characteristics of interest among IC users and non IC users and aims to show any statistical association between age, education standard, smoking status, place of birth and the exposure variable, IC use.

Age is strongly associated with injectable contraceptive use ($p<0.0001$). Women in this study population used ICs from an early age (75% of 18 to 19 year olds), and the use decreased after 39 years to reach the lowest proportion of use at the age interval 70 to 75 years where users represent only one percent ($p<0.0001$ in non-parametric test for trend).

As with OC use, education standard was also strongly statistically associated with injectable contraceptive use, ($p<0.0001$). Among 445 women who had seven years of schooling or less, 15.3% were IC users. Of 678 women who had between 8 and 11 years of education, 27.1% used IC while out of 466 women who attained 12 or more years of schooling, 41.8% were IC users. Thus the use of injectable hormonal contraceptives increases with increasing level of education, as supported by a non-parametric test for trend ($p<0.0001$).

Smoking status and area of birth were also strongly associated with injectable contraceptive use ($p<0.0001$ and $p=0.027$, respectively). In addition, smoking status and area of birth showed trends similar to those noted among OC users. Thus the highest proportion of IC use occurred among those who had never smoked (30.9%), followed by current smokers (18.9%), and then past smokers, among whom IC use was the lowest (16.9%). IC use was higher among those born in urban areas (30.8%) than those born in rural areas (25.9%).

Table 9: Injectable contraceptive use and socio-demographic characteristics among cases and controls

Characteristics	Injectable contraceptive use		Total	P value
	Yes N (%)	No N (%)		
Age				<0.0001
<20	3(75.0)	1(25.0)	4	<0.0001*
20-29	30(60)	20(40)	50	
30-39	116(64.4)	64(35.6)	180	
40-49	168(43.9)	215(56.1)	383	
50-59	106(22.2)	372(77.8)	478	
60-69	23(6.1)	357(94)	380	
70-75	1(0.9)	117(99.1)	118	
Years of education				<0.0001
				<0.0001*
≤ 7	68(15.3)	377(84.7)	445	
8-11	184(27.1)	494(72.9)	678	
≥ 12+	195(41.8)	271(58.2)	466	
Smoking status				<0.0001
				<0.0001*
Never	385(30.9)	862(69.1)	1247	
Current smoker	24(18.1)	109(81.9)	133	
Past smoker	35(16.9)	172(83.1)	207	
Place of birth				0.027
Rural	206(25.9)	592(74.2)	798	
Urban	239(30.8)	536(69.2)	775	

* The p value of a non-parametric test for trend

Table 10 presents the distribution of oral contraceptive use and its related characteristics among cases and controls. The table also shows any statistical association between oral contraceptive use characteristics and the development of breast cancer at the 5% significance level. The overall use of the oral contraceptive

method was strongly associated with the risk of developing breast cancer ($p<0.0001$). Out of 374 respondents who used oral contraceptives (the number includes women who used OC only as well as those who used IC in addition to OC), 221 (58.9%) had breast cancer and 153 (41.2%) presented with other cancer that was not of gynaecological origin.

With respect to oral contraceptives use patterns, the findings show that at the 5% significance level, age at last use of OC was significantly associated with breast cancer ($p=0.022$). Out of 21 women who were aged between 14 and 19 when they stopped using OC, 15(71.4%) were breast cancer patients. Among 127 women who stopped the use of OC at the age between 20 and 29, 65(51.2%) presented with breast cancer. There were100 women who stopped the use of OC when they were aged 30 to 39, and 59(59%) of them developed breast malignancy. Thirty five (72.9%) out of 48 women who stopped the use of OC between 40 and 50 years, developed breast cancer.

The time since first use of OC was also investigated. This is the period of time that elapsed between the first time when the patient used OC and the age when breast cancer was diagnosed. It was measured as the age at diagnosis of the cancer, minus the age at first use**.** A borderline significant association (5% level) was found between time since first use of OC and breast cancer ($p=0.060$). Breast cancer risk appears to increase with increasing time since first use. Among 21 women who had less than or equal to 4 years between the time they started using OC and the time breast cancer was diagnosed, nine (42.9%) developed breast cancer. Among 33 women of whom the time since first use of OC was 5 to 9 years, 15 (45.5%) were breast cancer

patients. Out of 282 women whose the time since their first use of OC and the diagnosis of breast cancer was 10 years and above 174 (61.7%) had breast cancer.

In contrast, there was no significant association between age at first use of OC and cancer of the breast. Similarly, there was no association between the time since last use of OC and breast cancer. Time since last use is the period of time that elapsed between the last time that the patient used OC and the age when breast cancer was diagnosed. Thus, it was calculated as the age at diagnosis of the cancer, minus the age at last use. There was no association between the duration of use of OC and breast cancer. Duration of use of oral pills was calculated as the difference between the age when women stopped the use of OC and the age when women started that contraceptive method.

Table 10: Patterns of oral contraceptives use among cases and controls

Oral contraceptive use Characteristics	Type of cancer		Total	P value
	Breast cancer N (%)	Controls N (%)		
Oral contraceptive(OC)				<0.0001
No	528(43.2)	693(56.8)	1221	
Yes	221(59.1)	153(40.9)	374	
Age at first use of OC				0.314
14-19	51(60.7)	33(39.3)	84	
20-29	95(55.2)	77(44.8)	172	
30-39	48(67.6)	23(32.4)	71	
40-50	4(50)	4(50)	8	
Age at last use of OC				0.022
14-19	15(68.2)	6(28.6)	21	
20-29	65(51.2)	62(48.8)	127	
30-39	59(59)	41(41)	100	
40-50	35(72.9)	13(27.1)	48	
Time since first use of OC				0.060
≤4	9(42.9)	12(57.1)	21	
5-9	15(45.5)	18(54.5)	33	
≥10	174(61.7)	108(38.3)	282	
Time since last use of OC				0.975
≤4	30(57.7)	22(42.3)	52	
5-9	28(59.6)	19(40.4)	47	
≥10	121(59.3)	83(40.7)	204	
Duration of use of OC				0.271
≤4	92(56.1)	72(43.9)	164	
5-9	45(52.3)	41(47.7)	86	
10-14	29(64.4)	16(35.6)	45	
15-19	23(71.9)	9(28.1)	32	
≥20	15(65.2)	8(34.8)	23	

Table 11 illustrates the distribution of injectable contraceptive use and its related characteristics among cases and controls and highlights IC use characteristics that are statistically associated with breast cancer. The overall use of injectable contraceptives was strongly associated with the risk of developing breast cancer ($p<0.0001$). Out of 446 women who used the IC method (alone or in conjunction with OCs), 244 (54.6%) developed breast cancer and 202 (45.4%) did not. There was also an association between the use of both hormonal contraceptive methods and the occurrence of breast cancer ($p<0.004$). Of 185 women who used both oral and injectable contraceptive methods, 105(56.8%) developed breast cancer and 79(43.2%) presented with other types of cancers not of gynaecological origin.

Age at first use of IC was significantly associated with cancer of the breast ($p=0.018$). Proportions of breast cancer among this study population tend to increase with an increasing age at first use of IC ($p=0.019$ in non parametric test). Among 99 women who were aged between 14 to19 when they started using injectable contraceptives, 43 (43.4%) developed breast cancer. Of 204 women who started the use of IC at the age interval 20-29, 119 (58.3%) were breast cancer patients. Among 91women who started using injectable hormonal contraception between ages 30 to 39, 50 (55.4%) were breast cancer patients. Out of 21 women who started injectable contraceptives when they were aged 40 years and above, 16 (76.2%) developed breast cancer.

Age at last use of IC was also significantly associated with breast cancer at the 5% level ($p=0.045$). Out of 23 women who were aged between 14 and 19 when they

stopped using IC, 11 (45.8%) were breast cancer patients. Among 133 women who stopped the use of IC between 20 and 29 years of age, 63 (47.4%) presented with breast cancer. There were123 women who stopped the use of IC when they were between30 and 39 years of age, and 78 (63.4%) of them developed breast malignancy. Therefore, proportions of breast cancer patients tend to increase with an increasing age at last use of injectable contraceptive method, up to age 39 ($p=0.021$ in non-parametric test).

A borderline statistical association (5% significance level) was found between the duration of use of IC and breast cancer, ($p=0.060$) and, surprisingly there was no significant trend of proportions of breast cancer cases observed with regard to the duration of use of IC ($p=0.157$ in a non-parametric test). Nevertheless, the proportion of breast cancer cases increased from 5 to 19 years of use of IC. Among 218 women who used injectable contraceptives for a period of 4 years or less, 119 (54.6%) of them had breast cancer. Out of 93 women who used IC for a period of 5 to 9 years, 44 (47.3%) developed breast cancer. Twenty nine (67%) out of 43 women who used IC for a period of 10 to 15 years, had breast cancer. Among 32 women who used IC for duration of 15 to 19 years, 23 (71.9%) developed breast cancer. Of 17 women who used IC for a period of 20 years and above, 8 (47.1%) of them had breast cancer.

There was no statistical association between the time since first use of IC and breast cancer at the 5% significance level. Similarly, no significant association was demonstrated between the time since last use and breast cancer.

Table11: Patterns of injectable contraceptives use among cases and controls

Hormonal use Characteristics	Type of cancer		Total	P value
	Cases N (%)	Controls N (%)		
Injectable contraceptive(IC)				<0.0001
No	502(43.8)	644(56.2)	1146	
Yes	244(54.6)	202(45.4)	446	
Injectable and oral contraceptive(OCIC)				0.004
No	640(45.5)	765(54.5)	1405	
Yes	105(56.8)	80(43.2)	185	
Age at first use of IC				0.018
14-19	43(43.4)	56(56.6)	99	
20-29	119(58.3)	85(41.7)	204	
30-39	50(55)	41(45)	91	
40-50	16(76.2)	5(23.8)	21	
Age at last use of IC				0.041
14-19	11(45.8)	12(54.2)	23	
20-29	63(47.4)	70(52.6)	133	
30-39	78(63.4)	45(36.6)	123	
40-50	46(59.7)	29(40.3)	75	
Time since first use of IC				0.223
≤4	14(48.3)	15(51.7)	29	
5-9	23(45.1)	28(54.9)	51	
≥10	191(56.8)	145(43.2)	336	
Time since last use of IC				0.863
≤4	57(55.9)	45(44.1)	102	
5-9	29(59.2)	20(40.8)	49	
≥10	112(54.9)	92(45.1)	203	
Duration of use of IC				0.060
≤4	119(54.6)	99(45.4)	218	
5-9	44(47.3)	49(52.7)	93	
10-14	29(67)	14(32.6)	43	
15-19	23(71.9)	9(28.1)	32	
≥20	8(47.1)	9(52.9)	17	

4.3 MULTIVARIATE ANALYSIS

Unadjusted and adjusted odds ratios with associated 95% confidence intervals were obtained from univariate and multivariate logistic regression models by considering the type of cancer (breast cancer vs controls) as the outcome variable. The exposures under investigation were oral contraceptive method used exclusively, injectable contraceptive use exclusively, combined oral and injectable contraceptive use and their related characteristics that were found in the bivariate analyses to be statistically significantly associated with breast cancer. In addition, hormonal contraceptive use patterns for which p values were slightly higher than the 5% significance level in the bivariate analysis were assessed in multivariate analysis in order to determine the strength of their association with breast cancer. In assessing the measure of effect (OR) associated with time since last use of OC and time since first use of OC, the multivariate analysis was restricted to women who used OC exclusively. Similarly, in order to precisely measure the strength of effect associated with age at first use of IC, age at last use of IC, the multivariate analysis was limited to study participants who used IC only. The justification of this separate analysis was that an effect modification (interaction) was first investigated and found between OC use and IC use in the development of breast cancer.

Reproductive and socio-demographic characteristics that were found in the bivariate analyses to be statistically associated with the outcome and the exposure variable were considered and fitted into the logistic regression models. These risk factors were: age, level of education, smoking status and place of birth.

At the 5% level of significance, both unadjusted and adjusted odds ratios obtained by univariate and multivariate logistic regression models in Table 12 below show that, after adjusting for independent risk factors, oral contraceptive use was associated with the risk of developing breast cancer. Women who used OC exclusively were two times more likely to develop breast cancer than those who never used any hormonal contraceptive method (OR: 1.92, 95%CI: 1.45, 2.80, p<0.0001).

Women who had used injectable contraceptives exclusively were 1.5 times more likely to present with breast cancer than study participants who never used any hormonal contraception during their fertile period (OR: 1.51, 95%CI: 1.14, 2.01, p=0.008). Women who used both injectable and oral contraception were roughly 1.7 times more likely to develop breast cancer than those who did not use any hormonal contraceptive method (OR: 1.68, 95% CI: 1.21, 2.33, p=0.004). There was strong effect modification between OC and IC use (p=0.008). This means that the effect of oral hormonal contraceptives on breast cancer decreases if women also used injectable contraceptives (from OR: 1.92 to 1.68). In contrast, the risk associated with IC goes up if women also took oral contraception (from OR: 1.51 to OR 1.68).

Education standard was the only socio-demographic factor found to be associated with the risk of breast cancer in the logistic regression model. After controlling for contraceptive use, age, smoking status and area of birth, women who had between 8 and 11 years of education had a 1.3 times higher risk of developing breast cancer than women who had less than or equal to seven years of schooling ;OR:1.3 ,95% CI 0.97,2.80, p=0.076).

Those with an education level greater than or equal to 12 years were 1.6 times more likely to develop breast malignancy compared to women who had seven years of education or less; OR:1.6,95%CI: 1.20,2.10 ,($p=0.001$). Thus, there is evidence that the risk of cancer of the breast increases with increasing level of education (non-parametric test for trend; $p<0.0001$)

The association between hormonal contraceptives use and breast cancer stratified by education level (Mantel Haenszel technique) showed crude OR: 1.89, 95%CI: 1.47, 2.39, and adjusted (combined) OR: 1.6, 95%CI: 1.36, 2.09 ($p<0.00001$). Further analysis showed that the effect of hormonal contraceptive use on breast cancer can be treated as homogenous over the three education strata (test of homogeneity: $p=0.1676$). Therefore, the stratified analysis by combined Mantel-Haenszel method and its associated test of homogeneity revealed that education level was confounding the association between hormonal contraceptive use and breast malignancy. Thus education attainment was a confounding factor and not an effect modifier. After adjusting (stratification) for education level, the combined Mantel-Haenszel estimate of OR 1.7 (95%CI: 1.36, 2.09, $p<0.00001$) meant that a woman who used hormonal contraceptives is 1.7 times more at risk of developing breast cancer compared to women who never used hormonal contraception.

TABLE12: LOGISTIC REGRESSION ANALYSIS OF THE RISK OF BREAST CANCER IN RELATION TO EXPOSURE TO HORMONAL CONTRACEPTIVES

Hormonal Contraceptive Use Related Characteristics	Univariate (Unadjusted)		Multivariate (Adjusted)	
	Odds Ratio (95%C.I)	P value	Odds Ratio (95% C.I)	P value
Contraceptive use				
Never	1		1	
Exclusively OC use	2.26 (1.64 , 3.12)	< 0.0001	1.92 (1.45 , 2.80)	<0.0001
Exclusively IC use	1.65 (1.25, 2.18)	<0.0001	1.51 (1.14, 2.01)	0.008
Combined OC&IC	1.92 (1.39,2.64)	<0.0001	1.68 (1.21, 2.33)	0.004
Age at last use of OC				
14-19	1		1	
20-29	0.60 (0.28,1,28)	0.192	0.56(0.25,1.23)	0.151
30-39	1.5 (0.56,3.98)	0.427	1.15(0.38,3.42)	0.800
40-50	1 (0.83,11.93)	1.000	0.87(0.06,10.92)	0.914
Time since first use of OC				
≤4	1		1	
5-9	1.11(0.38,3.34)	0.851	0.42(0.06,2.98)	0.390
≥10	2.14(0.87,5.26)	0.095	1.13(0.21,6.1)	0.883
Age at first use of IC				
14-19	1		1	
20-29	1.85(1.14,3.01)	0.012	1.37(0.74,2.53)	0.308
30-39	1.61(0.91,2.86)	0.100	1.47(0.65,3.31)	0.348
40-50	4.24(1.44,12.48)	0.009	4.38(0.84,22.83)	0.079
Age at last use of IC				
14-19	1		1	
20-29	1.06(0.44,2.54)	0.890	0.39(0.12,1.27)	0.121
30-39	2.04(0.84,4.95)	0.111	1.18(0.37,3.75)	0.778
40-50	1.75(0.68, 4.48)	0.243	0.78(0.21,2.79)	0.705
Age				
15-19	1		1	
20-29	1.07(0.10,10.59)	0.952	0.86(0.08,9.30)	0.907
30-39	4.04(0.44,36.87)	0.215	3.44(0.34,34.13)	0.291
40-49	6.46(0.71,58.34)	0.097	6.99(0.70,69.13)	0.096
50-59	3.37(0.37,30.4)	0.278	4.24(0.43,42.44)	0.214
60-69	2.51(0.27,22.70)	0.412	3.60(0.36,35.97)	0.274
70-75	2.18(0.23,20.15)	0.492	3.21(0.31,32.82)	0.325
Years of education				
≤ 7	1		1	
8-11	1.38(1.08,1.76)	0.008	1.3(0.97,2.80)	0.076
≥ 12	1.96(1.50,2.55)	<0.0001	1.6(1.20,2.10)	0.001
				<0.0001*
Smoking status				
Never	1		1	
Past smoker	0.85(0.52,1.28)	0.396	0.83(0.53,1.31)	0.439
Current smoker	1.30(0.90,1.86)	0.154	1.14(0.78,1.66)	0.476
Place of birth				
Rural	1		1	
Urban	1.30(1.06,1.58)	0.009	1.18(0.96,1.46)	0.112

OR and 95% confidence interval unadjusted and adjusted for age (continuous), level of education, smoking status, area of birth

* The p value of a non-parametric test for trend

CHAPTER FIVE: DISCUSSION

Injectable hormonal contraceptives, especially DMPA (trade name Depo-Provera) and to a greater extent, combined estrogen/progestogen oral contraceptives have been subjected to repeated epidemiologic assessment of breast cancer risk since sex hormones as contraceptives began in 1960.[6,8,27,28,29,30,31,32,33] In contrast to many published studies relating hormone replacement therapy to increased risk of breast cancer in post-menopausal women, the association between contraceptive hormones and breast cancer has not yet been resolved.[6,8,34,35,36,37] On the African continent, epidemiological investigations to assess the role of hormonal contraceptives in the increasing incidence of breast cancer among African women are rare. A case control study, in which cases of breast cancer (n=419) and controls (n=1,625), was carried out in the Western Cape from 1994 to 1997.[6] The findings suggested a non significant relative risk associated with injectable progestogen contraceptives: RR: 0.9 (95%CI 0.7, 1.2, including the null value:1), while an overall increased risk was found in association with oral contraceptive use (relative risk 1.2, 95% CI 1.1, 1.5).

The present research report is based on an ongoing case control study undertaken by the MRC/Wits/NHLS Cancer Epidemiology Research Group at tertiary hospitals in Gauteng. The study includes 753 women diagnosed with breast cancer and 855 controls. Cases and controls did not show any significant difference with regard to characteristics that are normally associated with the risk of developing breast cancer. The mean age of cases and controls were 51.5 and 53.3 respectively while the median age of cases and controls were 51 and 55 years, respectively. Our study participants were older than those described in a study aimed at describing hormonal contraceptive

use patterns among black and coloured South African women. The investigation that was carried out in the Western Cape reported median age of cases and controls of 43 and 42 years, respectively.[8] The older age among participants in this study is due to the fact that they were all cancer patients. Surprisingly, in our study, reproductive characteristics such as age at menarche, age at first birth, parity and age at menopause did not show any significant difference among cases and controls. Similarly, socio-demographic factors normally associated with breast cancer in other studies, such as area of residence (urban/rural) and smoking status showed no significant difference between cases and controls. In the comparison of means/proportions, the only sociodemographic characteristics that appeared to be significantly different between cases and controls were age and education level.

With regard to hormonal contraceptive use characteristics, proportions of cases and controls that used oral pills were significantly different. The trend was also observed among cases and controls who used either injectable contraception alone or both hormonal methods. On the contrary, there was no significant difference in the distribution between cases and controls in the following characteristics that are related to either hormonal contraceptive method: age at starting use, age at last use, time since first use, time since last use and duration of use.

The bivariate analysis conducted in this study shows that at the 5% significance level, breast cancer is statistically significantly associated with the following reproductive and socio-demographic characteristics: age, education level, smoking status and place of birth. In our dataset, contrary to findings in the medical literature, age at menarche was not associated with breast cancer. Similarly, age at first child birth was also not

found to be associated with breast cancer, in contrast to other studies. Finally, in contrast to the breast cancer literature, parity was also not found to be associated with breast cancer in our investigation, and was therefore not considered for further analysis.

In this investigation, the non-existence of association between well-known risk factors and breast cancer may be due to selection, information and/or measurement bias in the study design and conduct. Cases and controls were selected from the same hospitals because it was easier to access and recruit study participants. However, one must bear in mind that these controls may not be representative of the population (socioeconomic groups of black South African women) that produced the cases with regard to risk factors normally associated with breast cancer. For instance, a nun diagnosed with cancer other than gynaecological at these tertiary hospitals would not be an appropriate control for a multiparous domestic worker presenting with breast cancer at the same institutions. Therefore, it would have been better to use population-based controls.

The analysis revealed that malignant breast cancer is associated with the use of oral contraception, injectable contraception, both oral and injectable contraceptive use, age at first use of IC and age at last use of IC. In contrast, age at first use of OC variable was not associated with breast cancer. Age at last use of OC variable showed a p value ($p=0.050$) that is at the borderline of 5% significance level and therefore was subsequently assessed in multivariate analysis. Time since first use and time since last use of each contraceptive method were not associated with breast cancer. The most likely reason for these results is that it is probably unlikely that women accurately

remember, and therefore accurately report, each time that they start and stop different methods of contraception. Thus there is likely to be some kind of reporting error. In the Apartheid era, women were sometimes injected with ICs at clinics without even being told or consulted about it. In addition, it is also possible that the microscopic/histological diagnosis of breast cancer among black South African women may have occurred at an advanced stage of the disease and therefore, its actual onset did not correspond with the time of confirmation by clinicians and pathologists. Thus, except for the time since first use of OC variable, that showed a slightly higher p value (p=0.060) than the significance level, other features of hormonal contraceptive use such as time since first use and time since last use of either oral or injectable contraceptives were not included in their respective multivariate regression models. Similarly, because duration of use of either hormonal contraceptive method was not available, age at first use subtracted from age at last use was used as a proxy measure, without taking into account possible interruptions and pregnancies. The fact that no association was found between duration of use of OC and IC and breast cancer may be a result of this being an inaccurate reflection of actual use. However, given that the relationship between duration of use of IC and breast cancer showed a p value slightly higher than the 5% significance level (p=0.060), the variable was included in multivariate logistic regression model for further analysis.

5.1 Risk of breast cancer in relation to the use of hormonal contraceptives

Based on analysis at the 5% level of significance in univariate and multivariate logistic regression models, this study indicates that there is an increased risk for developing breast cancer associated with oral contraceptives. After adjusting for

independent risk factors, the strength of the association was OR: 2.0 (95%CI 1.45, 2.80, p<0.0001). This finding shows a measure of effect that is much higher than an overall 1.2 fold increase associated with oral contraceptive use in a case control study conducted in greater Cape Town.[6] However, the result in the current study is supported by the fact that both case control studies found an increased risk associated with oral contraceptive use. No other contraceptive use features were found to have statistically significant risk associated with breast cancer in multivariate regression analysis. This seems to be incompatible with the overall risk increase associated with oral contraceptive use, and contrasts with the findings of a world-wide meta-analysis that reported an increased risk of breast cancer among women using oral contraceptives for a longer duration.[39, 40] Even age at last use of OC and time since first use of OC, included in the model because of their borderline significance level in the bivariate analysis, were not associated with breast cancer before and after adjusting for independent risk factors. This may be attributable to many reasons such as inappropriate selection of controls, poor recall of interruption in use of hormonal contraception (information bias) or a poor proxy measurement of certain variables. Information bias could have occurred if the cases recalled their contraceptive exposures better than the controls. It is likely that hormonal contraceptive users may be more aware of the possible role of the contraceptive method in the development of breast cancer. However, our results corroborate the findings of the greater Cape Town study. The latter also showed non- significant relative risks (RR) associated with interval since first use, interval since last use and duration of use of oral contraceptives.[6] These results were found in the Cape Town study despite a much more detailed questionnaire than the current study with regard to patterns of usage, e.g. interruptions in use (L Stein, personal communication).

There is evidence derived from experiments on beagle dogs that unopposed progesterones, and more specifically Depo-Provera, may increase breast cancer risk.[41] However, many investigators believe that there is no risk in humans of developing breast malignant neoplasm that is associated with that contraceptive method.[41, 42] In contrast, the present findings suggest that injectable contraceptive use increases the overall risk of developing breast cancer. Indeed, after adjusting for all confounders and other risk factors as identified in the bivariate analysis, the odds ratio was 1.51 (95%CI: 1.14, 2.01, p=0.008). These results differ significantly from the findings of the greater Cape Town study that found a non-significant relative risk associated with IC use (OR 0.9 95%CI:0.7, 1.2: the confidence interval includes 1; the null value). Similarly, the results are not consistent with the findings of two epidemiological studies conducted in USA and in which no overall increase in the risk was found.[43,44]

Our findings show that the injectable progestogens do not protect against breast cancer malignancy as has been suggested by their anti-oestrogenic activity. After adjusting for independent risk factors and excluding women who used, in addition, oral contraceptives, there were no other statistically significant results associated with IC use characteristics. These findings differ from the results of the greater Cape Town study that demonstrated an increased risk associated with the time since last use and the duration of use.[6] However, the fact that there was no evidence of statistically significant findings associated with the time since last use and the duration of injectable contraceptives use may be the result of incorrect proxy measure used, or measurement bias related to these variables. For instance, the measurement of the duration of hormonal contraceptive use did not take into account possible

interruptions of hormonal contraceptive use due to pregnancies, possible change of contraceptive method or to absence of permanent sexual partners.

In our investigation, the combined use of both injectable and oral contraceptives increase the risk of breast cancer (OR: 1.68. 95%CI: 1.21, 2.33, p=0.002). In addition, there was strong effect modification between oral and injectable contraceptive use in the development of breast cancer. This finding was the reason for which either contraceptive method was examined separately in multivariate analysis in order to precisely measure its associated risk. The fact that the risk associated with the use of both oral and injectable contraceptives does not show any multiplicative or additive pattern, as it would be statistically expected, may be attributable to the biological process underlying the role of oestrogen and progesterone in the development of breast malignancy. Indeed, there is no simple causal relationship between hormonal contraceptives and the development of breast cancer. Rather, the pathogenesis of breast malignancy is the result of complex interaction of multiple factors; sex hormones (endogenous or exogenous), environment (socio-demographic characteristics) and genes (BRCA1 or BRCA2 mutations). All those factors are involved at different levels in the molecular pathways leading to malignant breast tumours.[1, 9]

Education level was associated with hormonal contraceptive use in the unadjusted bivariate analysis and was significantly associated with an increased risk for breast cancer. Therefore, education level was a confounding factor in the association between hormonal contraceptive use and breast cancer. South Africa is a society in transformation, particularly for the black South African population in general and

women in particular.[38] The latter are indeed becoming more and more urban dwellers and more educated than before. This could mean that more women would be exposed as result of their high education attainment. However, the fact that education level is significantly associated with an increased risk for breast cancer does not imply a causal relationship. It may have merely occurred as a result of increased breast cancer awareness among black South African women who are more educated, or greater access to health care among the better educated. There may be other socio-economic factors such as diet, body mass index and obesity, related to socioeconomic status and education level that could shed light on the role of different socio-economic factors in the development of breast cancer.

In our investigation, active smoking did not appear to be a risk factor for breast cancer. This finding corroborates the results of the Million Women Study.[45]

5.2 Limitations

The data for the present analysis was taken from an ongoing case control study, which was set up to look at the importance of suspected risk factors for all types of cancer. Therefore, the study was not specific to breast cancer. As a result, neither oral nor injectable contraceptive doses were accurately determined, and their composition as well as the duration and regularity of use were not clearly ascertained. In addition, information on some of the well known or suspected risk factors for breast cancer such as, duration of breastfeeding, family history and body mass index was not collected because data on these variables were not available.

Information on the type and dose of oestrogen and of progestagen in the hormonal contraceptive that our study participants have used was not ascertained.

The investigation was based on a case control study that is prone to information (recall and measurement) bias and selection bias. Even though the study was hospital-based covering a wide catchment area, the selection of controls among other women suffering from cancers other than of gynaecological origin may be problematic, because cases and controls might have well-known as well as unidentified similar environmental and genetic risk factors: socio-economic factors and genetic mutations.

Lastly, the study did not focus on current hormonal contraceptive users because there was not enough data in the group.

CHAPTER SIX: CONCLUSIONS AND RECOMMENDATIONS

This research report has provided strong evidence for three main conclusions applicable to Black South African women attending public hospitals:

First, there is an overall increase in the risk of developing breast cancer for women who used oral contraceptives. The strength of the association between oral contraception and breast cancer appears to be real and not due to confounding or other independent risk factors because the latter were adjusted for. No other oral contraceptive use pattern was significantly associated with the risk of developing breast malignancy.

Secondly, the use of injectable contraceptives increases the overall risk of developing breast malignant tumours. However, there was no evidence to suggest that the risk increased with injectable contraceptives use characteristics such as age at starting and stopping use, time since first and last use, and duration of use.

Third, there was strong interaction between oral contraceptive use and injectable contraception in the development of breast cancer.

Fourth, based on the bivariate and multivariate analyses, there was strong evidence that education level was associated with the exposure and was independently significantly associated with the risk of developing breast cancer. Therefore, education level was confounding the association between hormonal contraceptive use

and breast cancer. Whether this finding reflect the reality or is a result of bias may be a subject of further investigations, however the overall increased risk associated with hormonal contraceptives use in our findings suggests that more attention be paid in choosing contraceptive method.

In general, the findings of this study can be used as basis for a number of policy recommendation related to existing prevention and control strategy of breast cancer among black South African women. Firstly, of the findings should form part of public health education awareness campaigns about all potential risk factors for breast cancer. Secondly, given the increased risks, black South African women who use hormonal contraceptives and oral contraceptives in particular, should undergo regular mammography screening for breast cancer.

Finally, considering the fact that the study design was not specific to breast cancer and consequently some relevant information was not collected or was measured by poor proxy, I would recommend that another more specific case control study that would include even black South African women using private health care facilities, be undertaken in the Johannesburg area. Similarly, the role of well known breast cancer risk factors such as parity, breast-feeding and body mass index in the development of breast cancer among black south African women should be considered for further research.[8,40]

REFERENCES

1. Hartge P. Genes, Hormones, and Pathways to Breast cancer. N Eng J Med 2003 June; 348(23):2352-2354

2. Clemons M, Goss P. Etrogen and the Risk of Breast Cancer. N Eng J Med 2001Jan; 344(4):276-285

3. Pia KV, Hollie VT, Paul NA, Gwyneth KD, Timothy JK. Circulating levels of sex hormones and their relation to risk factors for breast cancer: a cross-sectional study in 1092 pre-and postmenopausal women (United Kingdom), Cancer Cases Controls 2001; 12:47-59

4. Henderson BE, Ross R, Bernstein L.Estrogens as a cause of human cancer: the Richard and Hinda Rosenthal foundation award lecture. Cancer Res., 48:246-253

5. Polly A M, Jill AM, Hoyt GW, Suzanne GF, Michele GM, Janet RD et al.Oral Contraceptives and the Risk of Breast Cancer. N Eng J Med.2002 June, 346(26):2025-2032

6. Shapiro S, Rosenberg L, Hoffman M, Truter H, Cooper D, Rao S et al . Risk of Breast Cancer in Relation to the Use of Injectable Progestogen Contraceptives and Combined Estrogen, Progestogen Contraceptives. American Journal of Epidemiology.2000; 151(4):396-403

7. Rosenberg L, Judith PK, Shapiro S, Hoffman M, Cooper D

Risk Factors for Breast Cancer in South African Women. SAMJ, 2002 June; 92(6):447-448

8. Baillie R, Katznellenbogen J, Hoffman M, Schierhout G, Truter H, Dent D “et al”. A Case Control Study of Breast Cancer Risk and Exposure to Injectable Progestogen Contraceptives. South Africa Med. Journal 1997; 87:302-305

9. Susan CL, Ramzi SC.The Breast. in: Ramzi SC, Vinay K, Tucker C, 6th edition. Robbins Pathologic Basis of Disease. Philadelphia: Saunders, 1999:1102-15

10. Stevens A, James S.Lowe, Young B: Wheater's Basic Histopathology. Philadelphia: Churchill Livingstone, 2002; 219-223

11. Parkin DM .Breast Cancer. In: Cancer in Africa. World Bank. In press

12. National Cancer Registry. Incidence of Histologically Diagnosed Cancer in South Africa, 1996-1997.Johannesburg, National Health Laboratory Service, 2003

13. National Cancer Registry. Incidence of Histologically diagnosed Cancer in South Africa, 1998-1999.Johannesburg, National Health Laboratory Service, 2004

14. Parkin DM,Vizcaino AP, Skinner MEC, Ndhlovu A. Cancer patterns and risk factors in the African Population of South-western Zimbabwe,1963-1977.Cancer Epidemiol.Biomarkers and Prevention 1994,3:537-547

15. Sitas F, Madhoo J, Wessie J. Incidence of histologically diagnosed cancer in South Africa, 1993-1995. National Cancer Registry, South African Institute for Medical Research, Johannesburg 1998

16. Skinner MEG, Parkin DM, Vizcaino AP, Ndhlovu. Cancer in the African Population of Bulawayo, Zimbabwe, 1963-1977.IARC Technical Report No.15, International Agency for Research on Cancer, Lyon, 1993

17. Beaghole R, Bonita R, Kjellstrom T. Basic epidemiology. World Health Organisation, Geneva.1998 46-49

18. Katzenellenbogen JM, Joubert G, Abdool Karim SS. Epidemiology. A manual for South Africa. Cape Town, Oxford University press Southern Africa.1997; 120-12

19. Betty R, Kirkwood, Jonathan AC Sterne. 2nd edition. Essential Medical Statistics, Massachusetts, Blackwell Science, 2003:205-213

20. Walker A.R.P, Walker B.F, Funani S., Walkers A.J: Characteristics of black women with breast cancer in Soweto, South Africa; The cancer journal 1989;2(10) 316-318

21.Lambe M, Hsieh C, Tsaih SW, Ekbom A, Adami H O, Trichopoulos D; Maternal risk of breast cancer following multiple births: a nationwide study in Sweden. Cancer Causes and Control, 1996 7; 533-538

22. Palmer Julie R, Rosenberg L, Aileen Clarke Stolley Paul D, Warshauer M. Ellen, Zauber Ann G., Shapiro S. Breast cancer and Cigarette smoking: A hypothesis. American Journal of epidemiology 1991; 134:1-13

23. Hoffman M,D, de Pinho H, Cooper D, Sayed R, Dent DM, Gudgeon A, van Zyl J,Rosenberg L, Shapiro S. Breast Cancer incidence and determinants of cancer stage in the Western Cape; South Africa Med. Journal; Dec 2000,90(12) 1213-1215

24. Kelsey JL, Gammon MD John EM. Reproductive factors and breast cancer. Epidemiol.Rev, 1993; 15:36-47

25. Chang S, Parker SL, Tuan Pham, Buzdar AU, Stephen DH. Inflammatory breast cancer and body mass index. J.Clin.Oncol. 16:3731-3735

26. Haupt A. Thomas T. Kane; Population Handbook.5th edition. Population Reference Bureau Washington DC 2004:13-14

27. Stata corp. Stata statistical software. Release 8.0 College Station, Tx: stata Corporation.2003

28. Weinstein AL, Mahoney MC, Nasca PC, Leske MC, Varma AO. Breast cancer risk and oral contraceptive use: results from a large case control study. Epidemiology 1991; 2:353-58

29. Ewetrz M. Oral contraceptives and breast cancer risk in Denmark. Eur J Cancer 1992; 28A:1176-81

30. White E, Malone KE, Weiss NS, Darling JR. Breast cancer among young US women in relation to oral contraceptive use. J Natl Cancer Inst 1994; 86:505-14

31. Brinton LA, Darling JR, Liff JM, et al. Oral contraceptives and cancer risk among younger women. J Natl Cancer Inst 1995; 87:827-35

32. Rosenberg L, Palmer JR, Rao RS, et al. Case-control study of oral contraceptive use and risk of breast cancer. Am J Epidemiol 1996; 143:25-37

33. Harris NV, Weiss NS, Francis AM, Polissar L. Breast cancer in relation to patterns of oral contraceptive use. Am J Epidemiol 1982; 116:643-51

34.Tworoger S, Missmer A, Barbieri L, Willet C, Coldtz A, Hankinson H. Plasma sex Hormone Concentrations and Subsequent risk of Breast Cancer among Women using postmenopausal Hormones. J.of the Nat. Canc. Institute. April 2005, 8:595-602

35. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from epidemiological studies of 52705 women with breast cancer and 108411 women without breast cancer. Lancet 1997:1047-59

36.Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal Estrogen and Estrogen-progestin Replacement Therapy and Breast Cancer Risk. JAMA, Jan 2000, 283(4):485-491

37. Olsson H, Moller TR, Ranstam J. Early oral contraceptive use and cancer among premenopausal women: final report from a study in southern Sweden. J Natl Cancer Inst 1988; 81:173-80

38.Pacella-Norman R, Urban MI, Sitas F, Carrara H, Sur R, Hale M, Ruff P, Patel M et al. Risk factors for oesophageal, lung, oral and laryngeal cancers in black South Africans. Br j cancer 2002; 86; 1751-1707

39. Collaborative Group on Hormonal Factors on Breast Cancer. Breast Cancer and hormonal contraceptives (1996a); Lancet 347: 1713-27

40. Collaborative Group on Hormonal Factors on Breast Cancer. Breast Cancer and Hormonal Contraceptives: further results (1996b) Contraception 54:1S-106S

41. Weisz J, Ross GT, Sotley PD. Report of the Public Board of inquiry on Depo-Provera. Rockville, Maryland: United States Food and Drug Administration, 1984

42. World Health Organisation. Facts about injectable contraceptives: memorandum from a WHO meeting. Bull World Health Organ 1982; 199-210

43. Paul C, Skegg DCG, Spears GFS. Depot medroyprogesterone (Depo-Provera) and risk of breast cancer. BMJ 1989; 299:759-762.

44. WHO collaborative Study of Neoplasia and steroid Contraceptives. Breast cancer and depot- medroxyprogesterone acetate; a multinational study. Lancet 1991; 338:833-838

45**.** The Million Women Study Collaborative Group. The Million Women Study: design and characteristics of the study population. Breast Cancer Res. 1999; 1(1): 73–80.