Risk Factors for Endometrial Cancer among Black South African Women; a Case Control Study

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DECLARATION

I, Aus Tariq Ali, declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine (Epidemiology and Biostatistics) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree at this University or any other University.

Aus T. Ali

DEDICATION

I dedicate this work to my Father Tariq Ali Al-Ani

ABSTRACT

Introduction: Endometrial cancer is a gynaecological cancer that mostly affects women in their sixth and seventh decades of life. It is the fourth most common malignancy in women and ranks eighth among all causes of female cancer in terms of age-adjusted mortality. In developed and numerous developing countries endometrial cancer, as well as other types of cancer in women, is an ever-increasing threat that may be explained, among other reasons, by increased life expectancy and a reduction in fertility or birth rates. Conversely, in South Africa and most other African countries, the previous reasons do not exist, because there is a decline in life expectancy due to increased HIV, low income, and a high fertility rate. International epidemiological studies have established significant relationships between endometrial cancer and risk factors such as the woman's age, race, early menarche and late menopause, parity, a history of breast or ovarian cancer, the use of endogenous estrogens, concomitant diabetes, family history of breast and ovarian cancer, estrogen therapy, obesity, and the use of tamoxifen. The aim of the study was to identify risk factors associated with endometrial cancer among black South African women.

Method: The present case control study comprised black South African women diagnosed with a cancer in Johannesburg, between 1995 and 2005. The study included 592 women aged 27 to 90 years who were admitted to three main public hospitals in the city of Johannesburg with histologically confirmed cancers. 148 cases with endometrial cancer and 444 women with other forms of cancer were analysed. Only newly occurring cases (incident) were included. Women in the control group consisted of those with

cancers not associated with reproductive or hormonal factors, i.e. not cancers of the breast or the female reproductive system. Data handling, cleaning and analysis were done using Stata 9 (STATA).

Results: Univariate analysis showed that the risk for endometrial cancer was significantly (P<0.05) affected by: miscarriages, the place of former residence, place of current residence, the use of snuff, wine consumption, age of the youngest child, diabetes, age of menarche, age of menopause, and menstrual status. Smoking was found to be a protective factor for endometrial cancer compared to other cancers. After multivariate adjustment, endometrial cancer risk was significantly (P<0, 05) associated with miscarriages, age at menarche, and earlier completion of childbearing. Smoking remained a protective factor against endometrial cancer.

Conclusion: The current study reports similar results to those observed in other international investigations. The risk of endometrial cancer was higher among women who were older, women who experienced miscarriages, and those who fell pregnant early in their reproductive lives. Smoking was a protective factor against endometrial cancer compared to other cancers. However, comparing the cases of endometrial cancer with smoking-associated cancer controls (i.e. lung cancer, oesophageal cancer, and mouth cancer) might have distorted the results. A more appropriate control group for confirming the relationship between smoking and endometrial cancer would be subjects with no cancer. Also, it will be important to evaluate the risk factors for cancer among the other race groups in South Africa.

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Chapter One

Introduction

1.1. Introduction

Endometrial cancer is a cancer that starts in the endometrium, the inner lining of the uterus. It is one of the most common cancers in women; ranking fourth among incident cancers in women, and eighth in terms of age-adjusted mortality (1). Although it has a comparatively low mortality rate compared with other gynaecological cancers, it is capable of aggressive behaviour. Despite the previous facts, endometrial cancer is a disease in which 85% of patients can be cured. It has been estimated that the prevalence of endometrial cancer is about 0.01% in most developed countries (1). It is primarily a disease of postmenopausal women, and affected women typically present with postmenopausal vaginal bleeding, resulting in earlier diagnosis than for most other gynecologic malignancies (2). Because of this fact, there is no support for the screening of asymptomatic women, and some evidence against the benefit of screening (3). The disease manifests at an average age of 55, a full decade later than cervical cancer, and is traditionally considered a disease of the sixth and seventh decades of life (4).

Endometrial cancer develops when the cells that make up the inner lining of the uterus (the endometrium) become abnormal and grow uncontrollably (5, 6). Endometrial cancer represents more than 95% of the uterine cancer. The most common type of uterine cancer is adenocarcinoma (7). It arises from an abnormal multiplication of endometrial cells (atypical adenomatous hyperplasia) and is made up of mature, specialized cells (well-differentiated). It is very rare

that endometrial cancer occurs without a preceding hyperplasia and is made up of poorly differentiated cells. The more common of these types are the papillary serous and clear cell carcinomas. Poorly differentiated endometrial cancers are often associated with a less promising prognosis (2).

Endometrial cancer remains the gynecologic malignant disease with the highest annual prevalence in the Northern America and part of Europe. The causes of endometrial cancer are unknown, but some factors like; early menarche and late menopause, miscarriages, nullparity, history of breast or ovarian cancer, the use of endogenous estrogens, concomitant diabetes, hypertension, and obesity have been found to increase endometrial cancer risk. The study question, for the current study, is what are the risk factors related to endometrial cancer in Black South African women. Specifically, whether early menarche, late menopause, nulliparity, miscarriages, age at first and last birth, the use of endogenous estrogens, diabetes, hypertension, HIV-AIDS, and other socioeconomic factors are risk factors for endometrial cancer in Black South African women

1.2. Problem statement

The Black population represents the majority of South African society (more than 75% of the total population) and like other races was marginilised during the apartheid regime. This marginilisation has created gaps in the existing information regarding many public health issues with endometrial cancer being one of them. In 1994, an extensive case control study was started to look at

different types of cancer in the Black population in the city of Johannesburg. Increasing prevalence of endometrial cancer in westernised countries, has led researchers in these countries to identify risk factors for the development of this cancer. Changing lifestyles in the South African society generally and in the black population specifically could create new risk factors that may increase the prevalence of diseases like endometrial cancer. Thus endometrial cancer is clearly an important health problem in the Black population that needs to be dealt with appropriately to sustain public health advances that have already been achieved.

1.3. Significance of the study

This study will enable us to highlight the risk factors associated with endometrial cancer in black women in South Africa. Understanding these risk factors will give us an idea as to which of these are preventable, and thus reduce the risk of black women getting endometrial cancer. By classifying the women with endometrial cancer according to age, we will be able to identify at which age black women get diagnosed most often with endometrial cancer. This may help the country to develop programme that would create awareness of endometrial cancer in different age groups, thereby resulting in possible earlier diagnosis and the increase in survival. Also this may increase the survival among black women specifically and women who belong to other races generally. This study may increase awareness of the disease in the black population. Finally, it will be also a good opportunity for the country to monitor cancers by population groups.

Chapter Two

Literature Review

2.1. Incidence of Endometrial Cancer

Endometrial cancer is the most common gynaecological cancer usually affecting women in the post-menopausal age group. The average age at diagnosis differs from country to country but is usually 55-65 years in most countries. Similarly, the peak endometrial cancer incidence also fluctuated between countries, but the limit is between the ages of 70 and 74. Endometrial cancer comes fourth among incident cancers in women, and eighth in terms of age-adjusted mortality. Although 90% of women with endometrial cancer present with abnormal uterine bleeding and nearly 75% of women present with early stage disease, the death rate due to this cancer has increased over 100% during the past 20 years (8). Endometrial cancer represents almost 2% of all cancer incidence (around 4% in women), and accounts for approximately 1% of all cancer deaths (nearly 2% in women) (9).

The incidence of endometrial cancer increases after menopause and continues to increase with increasing age especially when there is an exposure to unopposed oestrogen including hormone replacement therapy. It has been reported that approximately 85% of cases are diagnosed in postmenopausal patients (10). The average age at diagnosis differs from country to country but is about 60 years or older in most countries (6). Endometrial cancer is mainly a disease of high-income countries, where overall rates are nearly five times higher than rates in middle to low income countries. The incidence of endometrial cancer is about 10 times higher in developed countries than in Asia and Africa

(11). Age adjusted rates of endometrial cancer are increasing in countries undergoing transition from low-to high income economies, although there is no clear, overall trend in high-income countries (12,13).

In South Africa, the incidences rates of uterine cancer are two fold lower compared to incidence rates reported in developed countries (figure 2-1) and, are two fold higher than in developing countries (14). Endometrial cancer ranks 14th and considered to be the most prevalent of all cancers in the total population. According to the South African cancer registry reports, 1996-1997 and 1998-99, Asian females had the highest incidence rate of endometrial cancer. Endometrial cancer was the third and the fourth leading cancer among Asian females in 1996 and 1997 respectively, and a similar trend has been found in 1998-1999. In Black females, it is ranked the fourth leading cancer (figure 2-2). The lifetime risk of developing this cancer in Asian females was about 1 in 87 in 1997, while in black women it was 1 in 189 (15). Unfortunately, there is no other information describing the distribution of incidence rate of endometrial cancer with age in Black South African women, nor there similar data regarding other races.

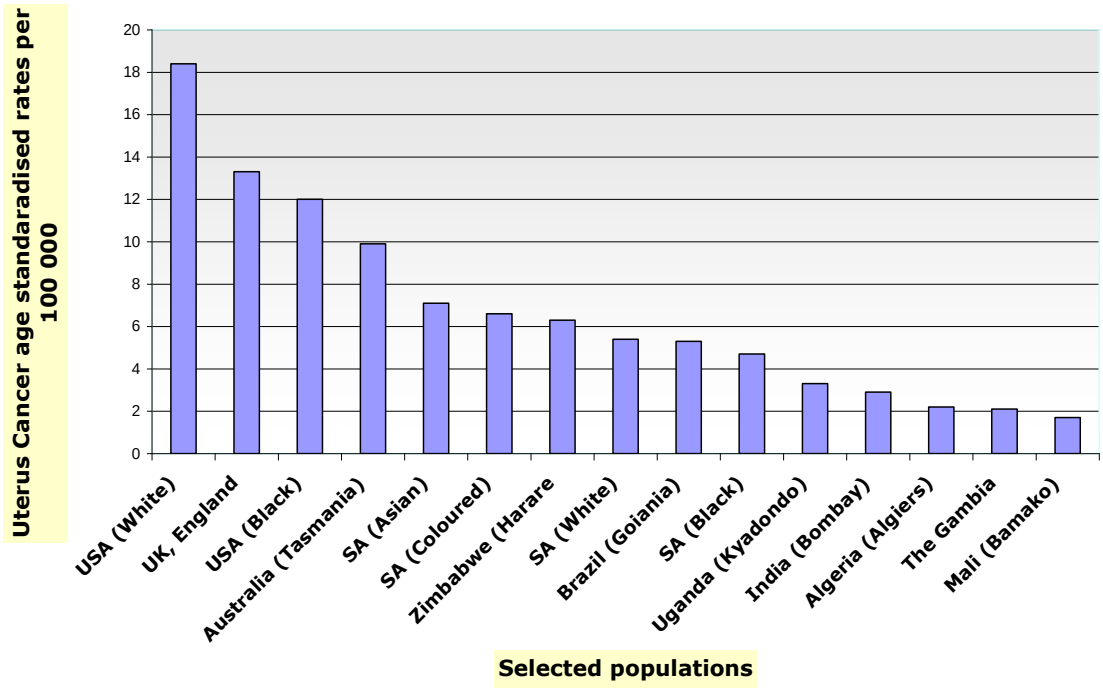


Figure (2-1) Age standardized incidence rate for uterus cancer per 100 000 for selected countries from 1995-2000. (14)

Endometrial cancer is considered to be the most common invasive gynaecological cancer in Northern America, and part of Europe. The range of the incidence of the disease (after adjusting for age) fluctuates from 15 per 100 000 women in North America and Northern Europe to less than 5 per 100 000 in most of Africa and Asia. However, the risk of the disease has been shown to increase in Asian and African emigrants to developed countries, possibly due to changes in environmental risk factors (14). The wide difference in the incidence of endometrial cancer across the world (figure 2-1) may be explained by differences in the distribution of known and unknown risk factors of the disease.

It has been estimated that in a country like the USA there were, 40.100 new cases of endometrial cancer diagnosed in 2008 and 7470 women had died from the disease in that year(16). According to the National Cancer Institute, in the USA, the death rate from endometrial cancer fell more than 50% from 1950-1970 and has continued to decline, due in large part to earlier diagnosis and more effective treatment. Though the incidence of endometrial cancer rose rapidly briefly in the 1970s, presumably due to the increased use of menopausal oestrogen therapy, it has since stabilised (17).

Studies in the USA have consistently shown that black women have a lower overall incidence (51%) of endometrial cancer than white women (75%) (13), but are diagnosed with later-stage disease, have shorter survival, and have the highest mortality from endometrial cancer of all ethnic groups in the USA. These observations may not necessarily be indicative of differences in ethnicity only rather late detection and advanced staging of endometrial cancer in black women led to the observed higher mortality rates (18, 19, 20).

Lower socioeconomic status and greater clinical co-morbidity have also been found to contribute to poor outcomes among African-American women in some studies (21, 22). These factors lead to delayed diagnosis, differential treatment and ultimately may contribute to racial differences in endometrial cancer survival. During the nineteenth century, the chances of 5-years survival for African American women with endometrial cancer were 58.9%, 66.67% for Hawaiian and 85.8% for white women (23). The overall 5-years survival rate was found to be

lower in middle- than in high-income countries (67% compared with 82%) (24, 25). The lower survival rate among African American and Hawaiian women with endometrial cancer as compared to Caucasian women suggests that access to health care may be an issue. It is very likely that endometrial cancer in white women is diagnosed at an earlier stage and is thus easier to treat (26). Death rate may increase due to the treatment of other types of cancers, like use of surgical resection for early-stage lung cancer, radical prostatectomy for localised prostate cancer, and radiation therapy for localised breast cancer (26, 27).

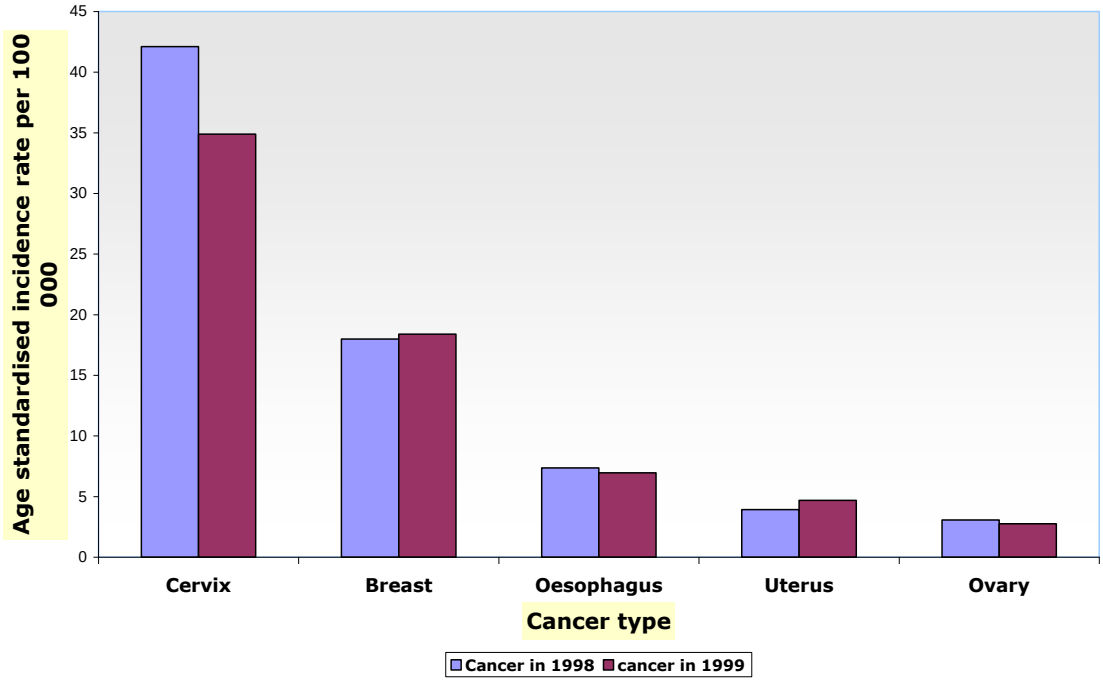


Figure (2-2) Leading cancers in Black South African females (15)

2.2. Anatomy of the Uterus

The uterus is a muscular hollow organ, upside-down, pear-shaped, that is located in a woman's pelvis behind the bladder and in front of the rectum, and has two main parts. The lower end of the uterus, which extends into the vagina, is called the cervix. The upper part is the body of the uterus, also known as the corpus (figure 2-3). The body of the uterus has two layers the outer which is a thick muscular wall called the myometrium and helps the mother to push the baby out during birth and an inner lining which is very sensitive to hormones and it changes daily during the menstrual cycle and called the endometrium. The inner layer is designed to provide an ideal environment for implantation and growing of the fertilized egg. If pregnancy does not occur, the endometrium is shed causing the menstrual period (28).

The changing thickness of the endometrial is highly dependent on the secretion of estrogen and progesterone. Estrogen causes cellular growth and is an important component of the rebuilding, follicular phase of the menstrual cycle. Progesterone is secreted during the later, thick-walled luteal phase, and it balances out the effects of the estrogen. Abnormal growth of endometrial cells (whether cancerous or not) and endometrial cancer are believed to be due to chronic exposure to too much estrogen without the balancing effect (28).

Table 6 in the appendix displays FIGO Surgical Stages for Endometrial Cancer, which considered world widely in identifying the stage of the disease

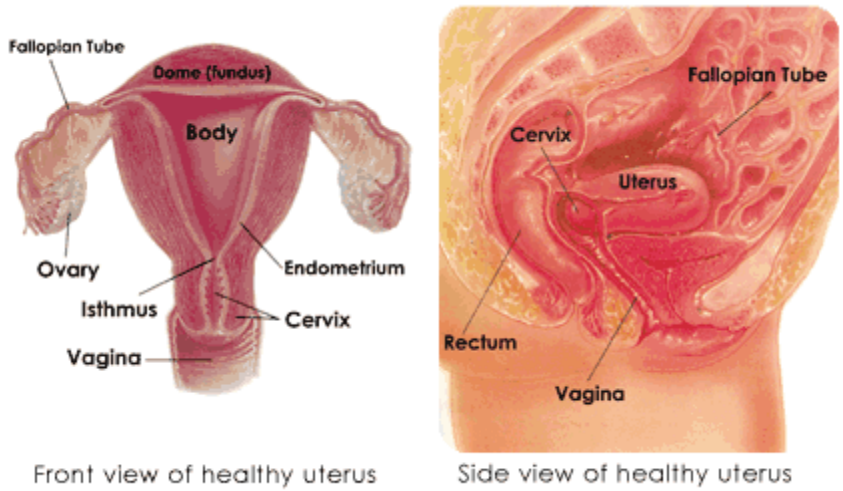
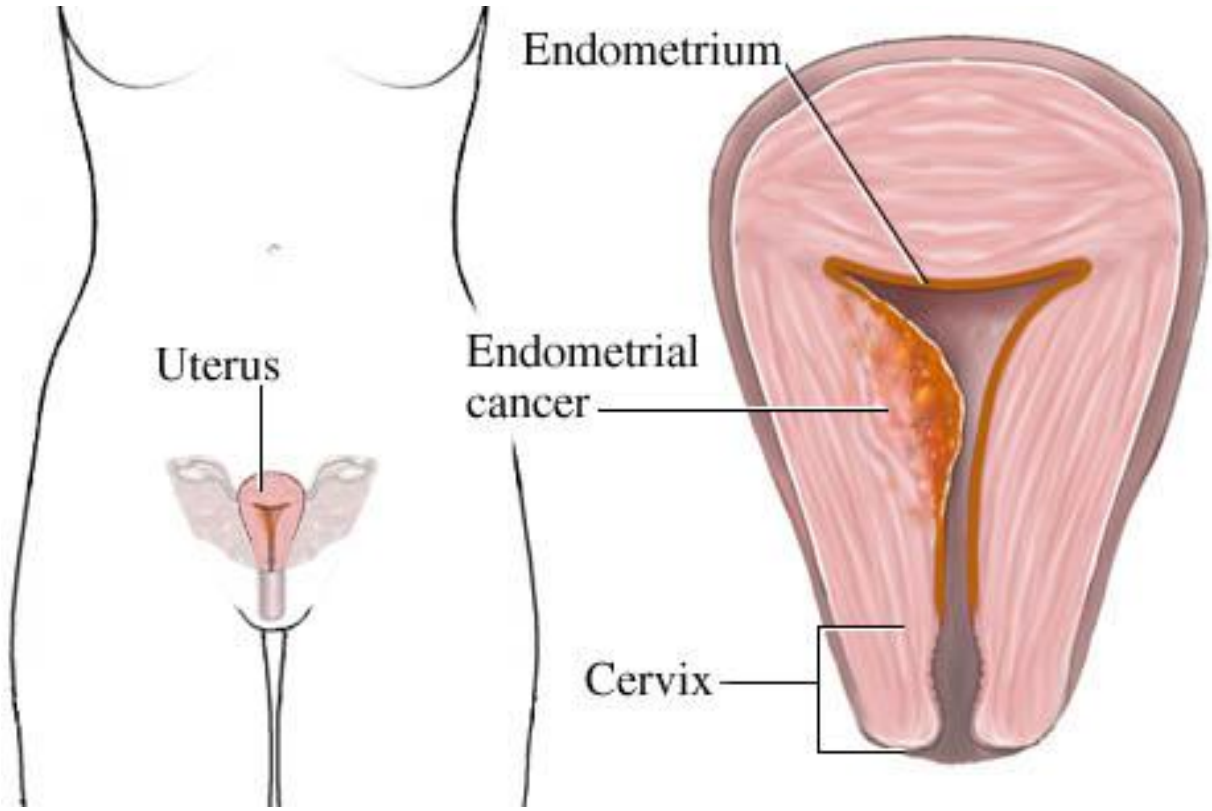


Figure 2-3 Comparison in female reproductive system between healthy women – up- and woman with endometrial cancer-down- (28).



2.3. Risk Factors for Endometrial Cancer

Risk factors for endometrial cancer have been well defined in western countries. The risk of the disease increases with age and family history of endometrial cancer, particularly among close relatives. Infertility is highly associated with endometrial carcinoma, particularly in the presence of polycystic ovarian syndrome, which is linked with the development of premenopausal endometrial cancer (2). Long-term use of unopposed oestrogens for hormone replacement therapy also increases the risk of endometrial cancer. Although prescribing oestrogens alone is now uncommon, women with an intact uterus can still be prescribed unopposed oestrogens, increasing their risk of developing endometrial cancer six fold (2).

Despite the fact that certain risk factors are more common in women who get endometrial cancer, researchers in this field found that the impact of these factors differs in various populations. Almost 70% of endometrial cancers are reported in women who have no documented risk factors-such as those that might disorder endocrine processes (29). International epidemiological studies have established the following risk factors to be related with endometrial cancer:

2.3.1. Age

Increasing age plays an important role in endometrial cancer, as well as with other female-specific cancers, such as breast, cervical, and vaginal cancer. Endometrial cancer is more common in menopausal women than in

premenopausal women (30) and the lifetime risk of the disease increased with age reaching 40% at age 70 (31).

2.3.2. Race

Studies have shown that white women have a higher risk of developing endometrial cancer than women of other racial groups. Setiawan and colleagues showed that the risk of endometrial cancer in white Americans far exceeded that in African Americans, Native Hawaiians, Japanese Americans, and Latinas (32). Nevertheless, the mortality rate from endometrial cancer among black women in the USA is 79% higher than the mortality rate in white women (33). These differences in mortality rate can be partially explained due to the stage at diagnosis, where 40% of the survival difference is attributable to African American women presenting with more advanced-stage disease.

2.3.3. Geographical and Socioeconomic factors

In general, the incidence of cancer may significantly differ from country to country or from area to another area in the same country, or state. Differences in lifestyle and socioeconomic are exist not only among countries but also among races (11, 12, 13). The socioeconomic gradient in cancer risk generally tends to affect women in different ways. It found to be positive (richer women are more affected than their poorer counterpart) for skin melanoma and cancers of the colon, breast, and ovaries, whereas negative association has been observed (i.e., poorer women are more affected than their richer counterpart) for lung, stomach, esophagus, and cervical cancer (34)

2.3.3.1. Place of birth & Place of residence

As people moving from place to another during their life time, this may underestimate the previous risk factors. However, most other studies, found no significant relationship between place where a woman was born or place of residence and the risk of endometrial cancer (35).

2.3.3.2. Education level

Although, education is found to be inversely associated with the incidence of most cancers, especially those related to smoking (36, 37), however it is relation with endometrial cancer still controversial. Educated women are usually cautious about the risk factors of diseases, but some risk factors of disease like female cancer are found in epidemiological to have a positive correlation. Educated women get an excess to oestrogen replacement, which related to the development of endometrial cancer. Also, educated women get better access to medical care and therefore, they early diagnosed, while uneducated women, even though they get the disease, they may died with out seeking medical care (38).

2.3.3.3. Smoking

Although smoking is consider to be a risk factor for many kinds of cancers, the case with endometrial cancer seems different. Many studies have reported, that smoking is a protective factor against endometrial cancer in premenopausal and post menopausal women (39, 40, 41). The risk of endometrial cancer had declined dramatically, with increased duration of smoking (39, 41, 96, 98). Smoking considers having anti-estrogenic effect (42, 43). Many studies have

shown that the risk of endometrial cancer has decreased significantly in women who smoke (41) and the risk continued to decrease with increased duration of smoking (39, 41). However, the latter relationship was only found to exist in postmenopausal women (39, 41).

The association between smoking and endometrial cancer risk may be attributed to anti- estrogenic effect of smoking (42, 43). Thus, Smokers have lower endogenous estrogen levels compared to nonsmokers (44, 45), and because estrogen promotes the progress of endometrial cancer, their chances of developing the disease decreased compared to non-smokers (44, 45). Smoking also reduced the effect of oestrogen by reducing the age of menopause, so that smokers has less menstrual cycles compared non-smokers (46).

2.3.4. Early Menarche & Late Menopause

Women who start menstruating early in life or who have a late menopause have an increased risk of developing endometrial cancer (47, 48). Similarly, an increased number of menstrual cycles during a woman's lifetime raise her risk of endometrial cancer, due to the high exposure to estrogen. Women whose menopause occurred after the age of 50 years had a 67% elevated risk of endometrial cancer compared with women whose menopause occurred before the age of 45 years. This risk increased to 79% when menopause occurred after the age of 55 years (33).

2.3.5. Family history

Studies reported a small increase in the risk of endometrial cancer (5%) associated with a family history of the disease (49), especially among first degree relatives (50, 51). Studies have found that family history of endometrial cancer is associated with a higher risk of the disease in premenopausal women (51, 52). Some of these families also have an inherited tendency to develop a type of colon cancer called hereditary non-polyposis colon cancer (HNPCC) (53). Family history of cancer is another independent risk factor for endometrial cancer (51). Studies have reported an increase in the number of young women with endometrial cancer who have a family history of cancer (not necessarily endometrial cancer), suggesting a genetic link (54, 55).

2.3.6. History of breast or ovarian cancer

Women who have had breast or ovarian cancer may have an increased risk of developing endometrial cancer. Some of the dietary, hormonal, and reproductive risk factors for breast and ovarian cancer also increase the endometrial cancer risk. Beiner and colleagues (56) found a 5.3-fold elevated risk of endometrial cancer in women carrying a deleterious mutation in the BRCA1 gene that were treated with tamoxifen for previous breast cancer. In another study carried out on mutation-positive families in Western Europe and North America, the Breast Cancer Linkage Consortium found a 2.7-fold increase in relative risk of endometrial cancer in BRCA1 mutation carriers (57) but no increased risk for BRCA2 mutation carriers (58).

2.3.7. History of Infertility

Early loss of ovarian function is not only associated with loss of fertility but also puts the patients at risk for endometrial cancer at a very young age. In recent years there has been an exponential rise in the number of endometrial cancer patients, as well as a decrease in the age of onset. The majority of these cases are associated with chronic anovulation (5, 6). Anovulation is found to be associated with elevated estrogen level in the blood, and this increase woman risks to develop endometrial cancer. Studies showed that women with Poly Cystic Ovary Syndrome (PCOS) and women with estrogen-secreting ovarian tumors are more prone to have endometrial cancer especially in their reproductive life (59, 60). A study performed on young women showed, that almost third the cases with endometrial cancer have PCOS (5, 61). It was also shown that woman with irregular menstrual cycles were at a higher risk for endometrial cancer than woman with normal cycles. Some other studies have shown that PCOS, and insulin resistance, which are both components of metabolic syndrome, may play a pivotal role in the pathogenesis of endometrial cancer, perhaps through disruption of hormonal processes (62). On the other hand, ovulation-stimulating drugs such as clomiphene widely used by infertile women, has recently been reported to be risk factor for uterine cancer by increasing estradiol levels (63).

2.3.8. Nulliparity

Nulliparous women are at increased risk for endometrial cancer compared to parous women, and high parity was found to be negatively associated with

endometrial cancer (64, 65). During pregnancy, the hormonal balance shifts toward more progesterone, which plays as a protective factor against endometrial cancer. Therefore, multiple pregnancies were observed to reduce endometrial cancer risk compared to higher risk of endometrial cancer of multi-parous (64). Maternal age at first birth and parity seems to interact (65). Parity might be a sign of different levels of oestrogens because oestrogen is some how higher in the first than in the second pregnancy (66). Increasing maternal age at first birth is associated with an increasing relative risk of endometrial cancer (65). Nulliparity is not only associated with increased endometrial cancer but also with decreased survival rate among patients with endometrial cancer. Studies found that 55% of endometrial cancer patients were nulliparous, with an approximate incidence of 71% in women aged 40 years or younger (47).

2.3.9. Age at first and last live birth

Age when mother delivered her baby is important, as it found to be significantly related with the increase risk of endometrial cancer (47, 49, 67, 68, 69). Age at first pregnancy does not appear to have any significant relationship with endometrial cancer in most studies. The risk of endometrial cancer decreased when women delay the birth of last child later on in comparison with women who complete their reproductive life earlier (69, 70).

2.3.10. Numbers of miscarriages

Although early ending of pregnancy as well as miscarriage have shown to be correlated positively with increasing risk of breast cancer, epidemiological studies either reported no relationship (47, 71, 72), or considered early end of pregnancy

as protective factor (64, 73,74,75) for endometrial cancer. Significant relationship between endometrial cancer and number miscarriages can be existed in univariate analysis, but after adjusting for other factor this relationship may disappear (76).

2.3.11. Estrogen therapy (ET)

Estrogen Therapy (ET) is the use of estrogen to offset the symptoms of menopause. Estrogen is used to be prescribed alone to treat symptoms of menopause such as hot flushes (77, 78). Epidemiological and clinical studies have shown that endometrial cancer as a disease is connected with high level of exposure to estrogen, and the use of estrogen alone increases the risk of endometrial cancer by five times, as it causes delay in the age of menopause. This finding has resulted in a huge reduction in the use of unopposed estrogen by postmenopausal women without hysterectomy since 1980 (79**)**. However, a diverse combination of estrogen plus progestin regimens soon became available for women without hysterectomy (80). Controversy among researchers regarding the relation between the sequential estrogen plus progestin regimens and endometrial cancer are continuous. Many studies reported a significant increase in endometrial cancer risk with the use of estrogen plus progestin regimens, although not as much as unopposed estrogen does (81-84). In a study performed in the UK and based on a huge number of postmenopausal women without hysterectomy, no association of endometrial cancer with sequential estrogen plus progestin use were reported (85). Studies have reported a positive relation between combined estrogen and progestin regimens and the risk of developing

breast cancer (81, 83). It has been suggested that if woman chose to use the new therapy, it is better to use it at the lowest possible dose and for the shortest possible time, and to have a yearly check up (81).

Most of the evidence regarding estrogens and cancer risk deals with exogenous estrogens and suggests an increased risk of (fatal) breast and endometrial cancer among hormone replacement therapy users (86, 87). However, several studies indirectly provide support for an association between exposure to endogenous estrogens and an increased risk of breast cancer, endometrial cancer, and ovarian cancer (88, 89).

2.3.12. High fat diet

Environmental factors, including those related to diet, are believed to contribute significantly to the etiology of many forms of cancer (90). Studies have shown a positive relation between endometrial cancer and high-fat diet (91, 92, 93). This can be explained in two ways. Firstly, a high level of fat in daily food can lead to the development of obesity that, in turn is considered to be a risk factor for endometrial cancer. The second explanation is that a fatty diet affects estrogen metabolism, which increases the risk of endometrial cancer (94, 95).

2.3.13. Obesity

The relation between obesity and endometrial cancer risk has been the subject of many studies. Numerous of these investigations have shown that increasing body weight is recognized as determinant of endometrial cancer especially in

developed countries (96). Obese women have a 3-fold higher risk compared with under weight or normal weight women (49, 97). Although most of a woman's estrogen is produced by her ovaries, fat tissue in obese women can change some other hormones into estrogens. Having more fat tissue can increase a woman's estrogen levels and therefore increase her endometrial cancer risk. To the contrary, the risk of endometrial cancer in obese premenopausal women is due to progesterone deficiency rather than an excess of oestrogen (98). In comparison with women who maintain a healthy weight, endometrial cancer is twice as common in overweight women, and more than three times as common in obese women. The strong interaction between BMI and endometrial cancer, supports the hypothesis that, hyperinsulinaemia is an etiologic factor for endometrial cancer (35). Insulin may be an important factor in explaining the strong relations between the risk of endometrial cancer and adiposity (99). Furthermore, obesity may affect endometrial cancer through increase the risk of diabetes and hypertension, which both shown to increase the risk of endometrial cancer risk (96, 97).

2.3.14. Diabetes

Studies have found a positive correlation between diabetes and endometrial cancer; however it is unclear whether this relationship is due to the diabetes itself, or due to complications with weight (47, 100, 101). As most people with type 2 diabetes are overweight or obese, the chances of having endometrial cancer in woman with type 2 diabetes are two to four times higher than non-diabetic woman (47, 100). However, some studies found that endometrial cancer

risk is higher in women who are overweight and diabetic than in women who are overweight but not diabetic. Some studies have shown that women with type 1 diabetes tend to have high risk of endometrial cancer despite not being obese, while other studies show no relation with type 1 diabetes (47, 101).

2.3.15. HIV/AIDS

Infection by human retroviruses, particularly HIV-1/2, is a major public health problem worldwide, especially in Africa. The previous, beside new HIV-AIDS, defining cancers (102, 103, 104), have put the epidemiologists under new challenges, first to find the exact kind of cancers that related to HIV, and second to find the mechanism/s the connected these diseases with each other. So far, no study reported a relationship between endometrial cancer and HIV.

2.3.16. Hypertension

Hypertension is a disease usually associated with heavy weight, and older age. Patients with endometrial cancer may suffer from hypertension, because either they are aged, or obese or both (47, 105). Despite the previous facts, at least one study had suggested link between hypertension and endometrial cancer (106).

2.3.17. Tamoxifen

Women who used Tamoxifen to treat metastatic breast cancer or to prevent recurrence of breast cancer are under risk of developing endometrial cancer (107, 108). Tamoxifen acts like estrogen in the uterus causing the uterine lining to grow, and as the duration of treatment increases the thickness of the uterine

lining increases (109). The risk of endometrial cancer and the severity of the diseases which usually associated with poorer survival rate found to be increased with duration of use Tamoxifen (108). It has been estimated that 20 of each 1000 women used Tamoxifen for at least 10 years will develop endometrial cancer later on (110, 111).

2.3.18. Prior pelvic radiation therapy

Endometrial cancer risk may increase after the surrounding areas have been exposed to radiation. Treating other sorts of cancers with radiation can cause damage to the DNA of cells, which may increase the risk of a second type of cancer such as endometrial cancer (112).

2.4. Study question

What are the risk factors associated with endometrial cancer in black South African women.

2.5. The Aim/Aims of this study

2.5.1 General

To investigate the relationship between certain risk factors and endometrial cancer in Black South African women who were admitted at Johannesburg tertiary hospitals.

2.5.2 Specific

To determine the association between geographical, socioeconomic factors, reproductive factors, diseases like HIV-AIDS, diabetes, hypertension, and endometrial cancer in Black South African women at Johannesburg tertiary hospitals.

Chapter Three

Materials and Methods

3.1 Study Design

This an age matched case control study is based on data collected from 1995 to 2004 by the Cancer Epidemiology Research Group, which has interviewed black South African women with newly diagnosed cancer, at Johannesburg's tertiary hospitals. The present study examines the role of a variety of possible risk factors as well as the use of exogenous estrogens in the epidemiology of endometrial cancer.

3.2. Study population

The study population comprised 592 female Black South Africans admitted to three hospitals located in the city of Johannesburg; Chris Hani Baragwaneth Hospital, Hillbrow Hospital, and Johannesburg General Hospital. All admitted cases agreed to participate in the study (100% participation rate). Participation rate in the control group was 90%. Control group participants were cancer patients as well so that their attendance to the interview depended on their ability to speak (i.e. some cancer like oesophageal cancer, mouth, cancer, and tongue cancer was not able to speak).

One hundred and forty eight black women aged 27-90 years with endometrial cancer, diagnosed and histological confirmed during the period 1995-2004 constitute the case population. Every endometrial cancer case was matched with 3 control subjects of similar age (either exactly the same age or ±1 year), as this ratio (1case: 3 controls) ensures the required statistical power to answer the study objectives (table 1 in the appendix). Control subjects comprised women

admitted to the main hospitals in the city of Johannesburg with other types of cancers unrelated to gynaecological cancers, such as cancers of the colon, brain, kidney, and lung. The Cancer Epidemiology Research Group previously established using other cancers as controls to be a valid method in papers published in international journals, arising from this case control study (113).

3.3. Diagnosis and confirmation of the cases

Women usually visit the clinic when they have unusual vaginal bleeding, or any other symptoms that suggest a possibility of endometrial cancer or any female cancer. In the current study, confirmation of the cases was done in two different ways either by endometrial biopsy, which is the usual way that a pathologist confirms cancer or by assessing the thickness of the endometrium by using transvaginal ultrasound probe. Indeed this technique can help differentiate benign from malignant causes of bleeding, because only around 8–10% of women who experience postmenopausal bleeding have endometrial cancer (114). According to this technique a woman does not need to undergo a biopsy, when the endometrial tissue thickness measures less than 5 mm, which has negative predictive value of 99%. However, in premenopausal women, it is more difficult to find out if the thickening is due to cancer as they normally have a thicker endometrial stripe. Therefore, we here suggest to use another newly type of ultrasound known as a sonohysterography involving placing fluid in the uterus to get a better view of the endometrial stripe in future studies. In order to avoid any mistake in diagnosis in future studies, it is however important to establish a

'one-step' rapid access clinic, which combines clinical evaluation, ultrasound, and if necessary, an endometrial biopsy (114).

3.4. Premenopausal and Postmenopausal women

Menopause means the permanent physiological or natural, cessation of menstrual cycles. In other words, menopause means the natural and permanent stopping of the monthly female reproductive cycles, and in humans this is usually indicated by a permanent absence of monthly periods or menstruation. Technically it refers to the final period, but because it is a gradual process no sudden events, a period of time equal 24 months after the last period, had been taken into account when we considered a woman as postmenopausal. Any women reporting a period within 3 months period, was considered as premenopausal, even if the period was absent the last 21 months before

3.5. Inclusion and exclusion criteria

Study participation was restricted to women admitted to the previously mentioned hospitals located in Johannesburg. Only newly occurring cases (incident) were included. Generally, the definition of case assumes that, for any disease people are divided into two discrete classes the affected (diseased) and non- affected (not having the exact disease). In the current study cases were diagnosed by biopsy/ultrasound, so that we are relatively certain that endometrial cancer cases are cases. According to diagnosis criteria, cases were Black South African women clinically diagnosed and confirmed recently with endometrial cancer, at previously mentioned main public hospitals.

Cases were premenopausal women and postmenopausal women, have been diagnosed with endometrial cancer not before six months (as average time), when they were interviewed in this study. Women in the control group consisted of those with cancers not associated with reproductive or hormonal factors, i.e. cancers of the breast or the female reproductive system. We have excluded from the control group any women who previously had a hysterectomy. Women who were admitted to a different hospital were excluded from both the case and control groups. Control subjects without an intact uterus were replaced with another eligible subject.

3.6. Data collection

A structured interview, on average 60 minutes in length, was administered to obtain information about hypothesized risk factors, including demography, pregnancy history, menstrual history, contraceptive use, diet, alcohol intake, place of cooking, smoking and residence (see index). Nurses trained in interviewing, questioned cases and controls of this study at Chris Hani Baragwaneth, Hillbrow, and Johannesburg Hospitals using a structured two page questionnaire. As mentioned before, women were considered to be postmenopausal if they said they had not had a period within two years of the date of the interview, whereas women who had a menstrual period within three months of the time of interview were considered to be premenopausal.

All subjects were questioned to determine hysterectomy status, while HIV status was ascertained though laboratory test. Serum specimens were stored at -20 to -30º prior to being batched for HIV testing. HIV testing was done using the Abbott Axysm HIV1/2 gO Microparticle Enzyme Immunoassay. Thereafter the Vironostika (HIV Uni-Form II plus O) microELISA has been used (102). Less than 1% of the patients refused testing.

The interviews for both cases and control groups were conducted in the preferred language of the patient (usually Sesotho or Zulu) following written or verbal (if illiterate) consent to participate. The questionnaires were anonymous and included questions on smoking, frequency of alcohol consumption, birthplace, residence, education, reproductive, contraceptive and lifetime sexual history. Information on exposure to established and proposed risk factors and on other relevant variables has been obtained by means of a structured questionnaire administered by trained interviewers.

3.7. Data analysis

3.7.1. Data extraction and cleaning

Data handling, cleaning and analysis was done using Stata 9 (STATA). Data cleaning was started by listing all variables then checking if any of the figures related to these variables were missing.

3.7.2. Descriptive analysis

To determine at which age-categories black women get diagnosed most often with endometrial cancer, five year age intervals were chosen to see the distribution of cases, and also to compare the distribution of the cases and the controls. Three tables have been constructed to display the frequency of the variables of interest. Before comparing cases and controls according to their age group, a full description of each control regarding the kind of cancer that the patient has, number of patients for each type, age at disease diagnosis, have been given. To compare characteristics of cases and controls, we used Chi-square test for categorical variables, while for continuous variables we used t-test, ANOVA, and Mann Whitney.

3.7.3. Analytic analysis

Conditional logistic regression analysis was used to investigate the association between each risk factor and endometrial cancer in univariate models. Odds ratios and corresponding 95% confidence intervals were estimated and *p*-values were calculated to test the significance at 5% significance level. Confounding factors were taken into account in multiple logistic regression and models

including diabetes and HIV status. The variables that demonstrated a significant association with endometrial cancer in univariate models were entered into multiple logistic regression models. All variables significantly related to endometrial cancer risk were initially included in a full multiple logistic elimination. Factors that were significant at 5% were returned in the final model. We then systematically built a multiple logistic regression model by removing the factors with the largest Wald-stattistic *p*-value, and compared the subsequent log likelihood ratio chi-squares. If the removal of the factor did not significantly change the log-likelihood, then the factor was dropped. The process was repeated until we could not drop factors any further. Interactions between variables were assessed by inclusion of interaction terms in the logistic regression models. In order to detect any changes in the significance of the variables we stratified by HIV, Diabetes, and hypertension.

3.8. Ethical approval

This study has been approved by the University of Witwatersrand human ethic committee (ethics clearance number: M981119). A letter of permission from the Head of the Cancer Epidemiology Research Group and a copy of the ethical approval letter have been attached in the appendix of this report. The participants gave signed informed consent.

Chapter Four

Results

4.1. Results

This study was designed to explore risk factors for endometrial cancer in Black South African women in the city of Johannesburg. In this chapter, results from the data analysis using Chi-square analysis comparing demographic, reproductive and lifestyle factor for cases of endometrial cancer and controls are presented. All variables significantly related to endometrial cancer risk were initially included in a full multiple logistic elimination.

After adjusting for other variables , the significant variables that I got in my multivariate analysis were; number of miscarriages, age at menarche, age of youngest child which represented the of mother at last birth, while smoking was significantly protective against endometrial cancer. Stratification by HIV, Diabetes, and hypertension did not show any changes in the significance of the variables. I have also looked at the interaction between variables and was found none.

4.2. Descriptive statistics

Data was analysed using Stata 9 software comparing characteristics of cases with controls. Chi square analysis results have been divided in to three tables, according to the relation among the variables in each table. Tables; 4-1, 4-2, 4-3 compare demographic, reproductive and lifestyle factors for cases of endometrial cancer and controls. Table 4-4 displays univariate and multivariate analysis results. While, tables, 3, 4, and 5 in the appendix compare demographic,

reproductive and lifestyle factors for cases of endometrial cancer and controls as percentages.

4.3. Description of data set

The study population comprised 592 patients. The youngest participant was 27 years old, while the oldest was 90 years old, and the average age was 60.3, with an S.D. of 13.61. All participants were black patients admitted to previously mentioned hospitals in the city of Johannesburg, South Africa. The relationship between age and cancer diagnosis was studied by dividing the participants in this study into 13 groups according to their age, starting from age group 25-29, to age group 85-90. The majority of the participants fell within the 55-75 age group (table 1 in the appendix). These patients represented 57.4% of the total study participants.

One hundred and forty eight patients with endometrial cancer were recruited as cases and 444 patients with different types of cancer (excluding gynaecological cancer) were recruited as controls (table 2 in the appendix). As seen in table 4-2, more cases had miscarriages than did controls. More controls than cases reported that their oldest child was less than 56 years old, while more cases than controls reported that their child was over 56 when they were interviewed. Similarly, more controls reported that their youngest child was less than 43, whilst more cases reported that their youngest child was over the age of 43. A higher percentage of the cases reported that their monthly cycle had started when their ages were between 11 and 14 years when compared with the control

group. Most of the controls reported that their monthly cycle had started after the age of 15 years.

Although similar percentages of cases and controls reported that their period ended before 39 years old, the percentage of cases who reported that their period had ended after the age of 50 years was greater than the controls.

Out of the total number of cases and controls, cases were less likely to report that they smoked, at the time of the interview when compared to the controls. Finally, more cases than controls reported that they were HIV positive at the time of the interview. Tables 4-1, 4-2, and 4-3 provide a detailed description of the cases and controls of the current study.

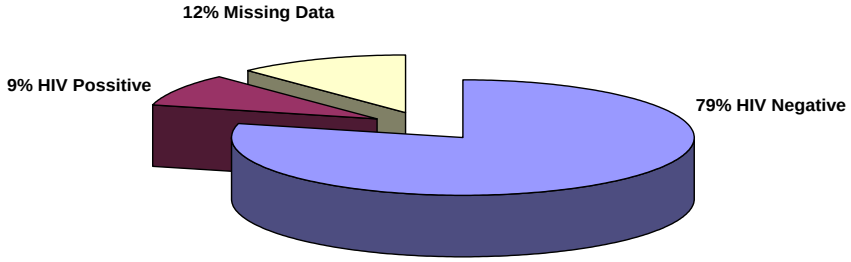


Figure 4-1 HIV status among Black South African women (cases and controls).

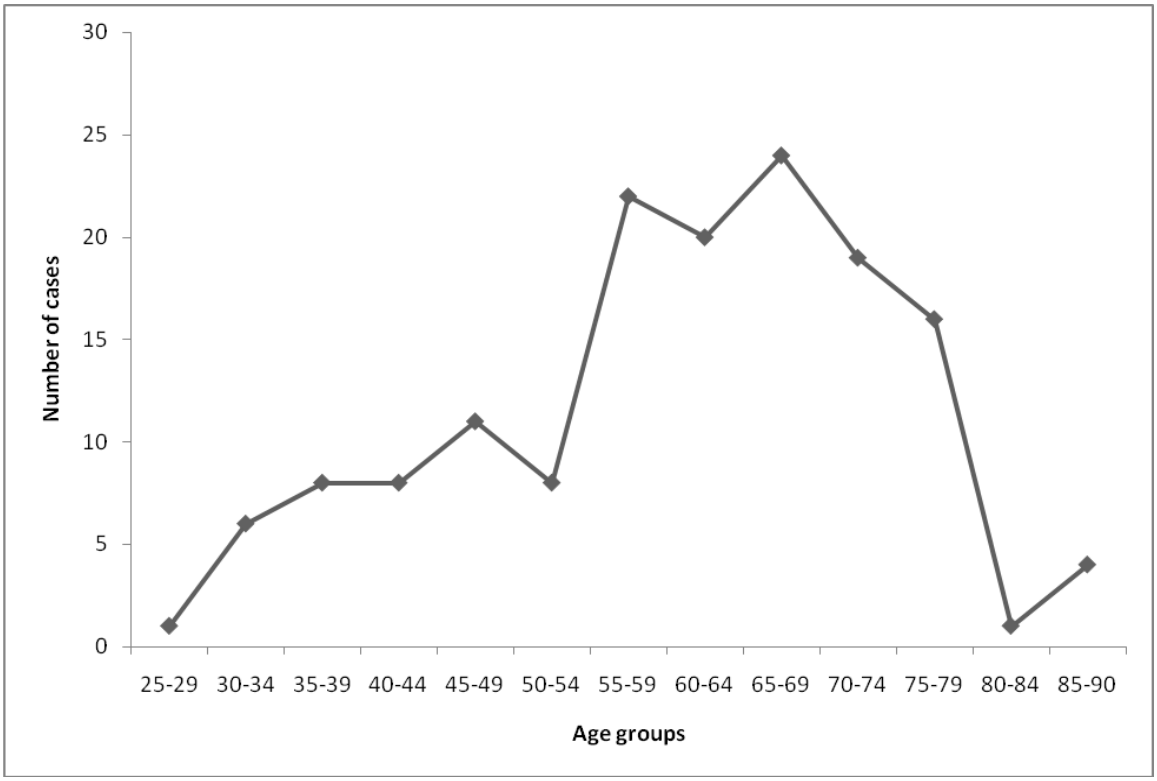


Figure 4-2 Relationship between age and endometrial cancer among Black South African women (cases).

4.4. Univariate and multivariate analysis of factors associated with endometrial cancer

4.4.1. Socioeconomic Factors

4.4.1.1. Educational level

University education seemed to be associated with increased odds of developing endometrial cancer in this study whilst other levels of education, lower than the university level, tended to be protective. These associations were however statistically insignificant (Table 4-4).

4.4.1.2. Place of former residence

Compared to women who had resided in Soweto for a long period, long residence in Gauteng, Northern Cape, Mpumalanga and North West Provinces were significantly associated with increased risk for endometrial cancer (Table 4-4). However, the highest risk was associated with residence in the Mpumalanga (OR; 4.03, 95% CI: 1.64-9.89) and North West Province (OR; 5.03, 95% CI: 2.11-12.01).

4.4.2. Lifestyle factors

4.4.2.1. Snuff use

Compared to non-snuffer, current snuffer were almost twice as likely to have endometrial cancer (OR; 1.91, 95% CI: 1.17-3.13), while snuff use found to have a protective effect in former snuffer (OR; 0.66, 95% CI: 0.34 -1.28).

4.4.2.2. Smoking

Compared to non-smokers, current smokers (OR; 0.34, 95%CI: 0.16-0.75) and former smokers (OR; 0.39, 95% CI: 0.20-0.77) in this study were less likely to have endometrial cancer. Moreover, the protective effect of current or past smoking remained significant after adjusting for confounders in the multivariate model (Table 4-4). Hence, women in the former smokers' category were about 0.64 times less likely to have endometrial cancer whilst those in the current smokers' category were 0.73 times less likely to have endometrial cancer.

4.4.2.3. Wine consumption

Women who reported drinking wine more than once a week were more likely to have endometrial cancer by almost 12 fold compared to those who did not drink wine. On the other hand, those who drank wine less than once a week were less likely to have endometrial cancer compared to those who reported that they never drink wine, despite the fact that this relation was not significant (OR; 0.50,95% CI :0.08-3.25). No such relationship was found in multivariate analysis.

4.4.3. Reproductive Factors

4.4.3.1. Age at menarche

Women who had their first menstruation between ages 15-18 years (R; 0.49, 95% CI: 0.33-0.74) were less likely to have endometrial cancer compared to those who had their first menstruation between ages 11-14 years. These results were consistent with Chi-square analysis (table 4-2), univariate analysis and

multivariate analysis (table 4-4). Hence for every one year delay in the age of menarche, women in the 15-18 years category were at reduced risk of endometrial cancer by about 0.51.

4.4.3.2. Age at menopause

Women who had their menopause between the ages 51-60 years (OR; 2.66, 95% CI: 0.96-7.33) were more likely to have endometrial cancer compared to those who had ended their menstruation between the ages (30-39 years).

4.4.3.3. Number of miscarriages

Compared to women with no history of miscarriage, those with a history of three or more miscarriages were almost four times as likely to have endometrial cancer (OR; 3.98, 95% CI:2.06-7.70). Though the effect of multiple miscarriages on endometrial cancer attenuated after adjusting for potential confounders in the multivariate model, it remained significant (OR; 3.17, 95% CI: 1.52-6.58).

4.4.3.4. Menstrual period (The duration from menarche to menopause)

Menstrual period (reproductive span) was generated by subtracting the age of menarche from the age at menopause. In univariate analysis, the effect of menstrual period on endometrial cancer was statistically insignificant for women who had menstruated for a period of 25-34 years (OR; 1.19, 95% CI: 0.50-2.85), and women who had menstruated for a period of 35-46 years (OR; 2.41, 95% CI: 0.98-5.91).

4.4.3.5. The age of youngest child or age at last live birth

Age of the youngest child refers to the women ages' at the last successful delivery (age at last live birth), and can also refer to their ages at the last successful pregnancy. Compared to women who had children aged between 1-14 years, those who had older children had more chance to develop endometrial cancer. In another word women who had their last birth at earlier age had increased odds of developing endometrial cancer, the risk increased with increasing age of the youngest child (table 4-4).The effect of age at time of last live birth remained significant in the multivariate model for women in the 29-42 years category (OR; 3.67, 95% CI: 1.37-12.69) and 43-65 years category (OR; 8.78, 95% CI: 2.73-40.87).

4.4.4. Other risk factors and endometrial cancer

Further risk factors examined were diabetes, hypertension and HIV status. Due to considerable numbers of missing data especially for diabetes and HIV these variables were investigated separately in the multivariate model to assess their association with endometrial cancer in the subpopulation whom on diabetes, hypertension and HIV status was available.

4.4.4.1. Diabetes

In univariate analysis, the relationship between diabetes and endometrial risk was significant (OR; 2.70, 95% CI: 1.19-6.11), while this relation was non-significant in multivariate analysis (OR= 2.23, 95% CI: 0.93- 5.34).

4.4.5.2. HIV

There was an inverse significant relationship between HIV and endometrial risk in the univariate analysis (OR= 0.42, 95% CI: 0.18-0.97). No significant relationship found in the multivariate analysis (OR= 0.43, 95%: CI: 0.17- 1.10).

4.4.5.3. Hypertension

The relation between hypertension and endometrial risk was significant in the univariate analysis (OR=2.94, 95% CI: 1.67- 5.17). A significant relationship has been detected between hypertension and endometrial cancer risk in multivariate (OR= 3.16, 95% CI: 1.68- 5.92).

Table 4-1 Comparison in demographical factors between cases and controls among Black South African women, at Johannesburg tertiary hospitals between 1995 and 2004

Variables	**Controls**	**No.**	**Cases**	**No.**	***P*-value**
Total Number	**444**		**148**		
Age (mean)	60.30		60.30		
Highest age (years)	90		90		
Youngest age (years)	27		27		
Standard deviation	13.63		13.63		
Education level		**444**		**148**	***P*= 0.514**
No schooling	25.7**%**	114	31.1**%**	46	
Grade 1 to grade 4	9.2**%**	41	9.5**%**	14	
Grade 5 to grade 7	20.5**%**	91	18.2**%**	27	
Grade 8 to grade 10	26.4**%**	117	20.3**%**	30	
Grade 11 to grade 12	16.0**%**	71	18.2**%**	27	
University level	1.6**%**	7	2.7**%**	4	
Missing data	0.7**%**	3	----------		
Pension status		**444**		**148**	***P*= 0.052**
Yes	23.0**%**	102	22.3**%**	33	
No	16.2**%**	72	25.0**%**	37	
Missing data	60.81**%**	270	52.7**%**	78	
Place of residence (Urban/Rural)		**444**		**148**	***P*= 0.546**
Urban areas	82.9**%**	368	79.7**%**	118	
Rural areas	16.0**%**	71	19.6**%**	29	
Missing data	1.1**%**	5	0.7**%**	1	
Place of birth		**444**		**148**	***P*= 0.181**
Soweto	7.5**%**	33	4.7**%**	7	
Johannesburg	9.1**%**	40	5.4**%**	8	
Gauteng	22.9**%**	101	32.4**%**	48	
North Province	13.1**%**	58	15.5**%**	23	
Kwazulu Natal	16.7**%**	74	13.5**%**	20	
Free State	13.4**%**	59	15.5**%**	23	
North West	9.7**%**	43	6.8**%**	10	
Mpumalanga	7.7**%**	34	6.1**%**	9	
Missing data	0.45	2	------	----	
Place of current residence		**444**		**148**	***P*= 0.081**
Soweto	38.1**%**	169	27.0**%**	40	
Johannesburg	13.5**%**	60	10.8**%**	16	
Gauteng	28.4**%**	126	36.5**%**	54	
Kwazulu Natal	5.0**%**	22	6.8**%**	10	
Northern province	6.1**%**	27	10.8**%**	16	
Free State	2.9**%**	13	3.4**%**	5	
North West	5.9**%**	26	4.7**%**	7	
Missing data	0.23**%**	1	0.0000	-----	

Table 4-2 Comparison in reproductive factors between cases and controls among Black South African women, at Johannesburg tertiary hospitals between 1995 and 2004

Variables	Controls%	NO	Cases%	NO	P-value
Age at Menarche		**444**		**148**	***P*= 0.003**
Age 11-14 years	28.6%	**127**	45.3%	**67**	
Age 15-18 years	61.3%	**272**	47.3%	**70**	
Age 19-22 years	6.1%	**27**	4.7%	**7**	
Missing data	4.1%	**18**	2.7%	**4**	
Age at Menopause		**444**		**148**	***P*= 0.001**
Age 30-39 years	5.0%	**22**	6.8%	**10**	
Age 40-45 years	15.3%	**68**	12.2%	**18**	
Age 46-50 years	36.7%	**163**	35.8%	**53**	
Age 51-60 years	19.1%	**85**	33.1%	**49**	
Missing data	23.9%	**106**	12.2%	**18**	
Ever pregnant		**444**		**148**	***P*= 0.154**
Yes	95.0%	422	92.6%	**137**	
No	5.0%	22	6.8%	**10**	
Missing data	----------	-----	0.7%	**1**	
Full term pregnancies		**444**		**148**	***P*= 0.111**
Once	8.1%	**36**	9.5%	**14**	
Twice	13.3%	**59**	17.6%	**26**	
Three times	11.7%	**52**	14.2%	**21**	
Four times	15.5%	**69**	10.1%	**15**	
Five times or more	46.2%	**205**	39.2%	**58**	
Missing data	5.2 %	**23**	9.5%	**14**	
Age of the Child					
1. Oldest child		**444**		**148**	***P*= 0.000**
Age 2-19 years	8.8%	**39**	4.7%	**7**	
Age 20-37 years	27.3%	**121**	19.6%	**29**	
Age 38-55 years	47.5%	**211**	44.6%	**66**	
Age 56-76 years	6.5%	**29**	7.4%	**11**	
Missing data	9.9%	**44**	23.7%	**35**	
2. Youngest child		**444**		**148**	***P*= 0.000**
Age 1-14 years	15.3%	**68**	4.7%	**7**	
Age 15-28 years	26.1%	**116**	18.2%	**27**	
Age 29-42 years	33.1%	**147**	28.4%	**42**	
Age 43-65 years	5.9%	**26**	9.5%	**14**	
Missing data	19.6 %	**87**	39.2%	**58**	
Miscarriages		**444**		**148**	***P*= 0.000**
Never had miscarriage	36.3%	**161**	25.7%	**38**	
One miscarriage	19.1%	**85**	22.3%	**33**	
Two miscarriages	8.3%	**37**	11.5%	**17**	
Three or more miscarriages	5.6%	**25**	16.2%	**24**	
Missing data	30.6%	**136**	24.3%	**36**	
Oral contraceptives		**444**		**148**	***P*= 0.711**
Yes	13.7%	**61**	14.2%	**21**	
No	85.8%	**381**	85.8%	**127**	
Missing data	0.5%	**2**	--------	**-----**	
Injectable contraceptives		**444**		**148**	***P*= 0.225**
Yes	12.8%	**57**	9.5%	**14**	
No	86.0%	**382**	90.5%	**134**	
Missing data	1.1%	**5**	---------	**-----**	

Table 4-3 Comparison in lifestyle factors between cases and controls among Black South African women, at Johannesburg tertiary hospitals between 1995 and 2004

Variables	Controls%	No	Cases%	No	P-value
Snuff use		**444**		**148**	***P*= 0.018**
Current	13.3%	**59**	23.0%	**34**	
Former	13.1%	**58**	8.1%	**12**	
Never	73.4%	**326**	68.2%	**101**	
Missing data	0.2%	**1**	0.7%	**1**	
Snuffing frequency		**444**		**148**	***P*= 0.325**
1-4 times daily	12.39%	**55**	18.2%	**27**	
5-9 times daily	7.88%	**35**	6.8%	**10**	
10-20 times daily	5.41%	**24**	6.1%	**9**	
Missing data	74.32%	**330**	68.9%	**102**	
Smoking status		**444**		**148**	***P*= 0.002**
Current	12.4%	**55**	5.4%	**8**	
Former	15.5%	**69**	7.4 %	**11**	
Never	71.6%	**318**	87.2%	**129**	
Missing data	0.5%	**2**	---------	------	
Age when start smoking		**444**		**148**	***P*= 0.001**
Age 10-16	7.0 %	**31**	2.70%	**4**	
Age 17-24	13.7%	**61**	5.41%	**8**	
Age 25-50	5.6%	**25**	2.70%	**4**	
Missing data	73.7%	**327**	89.19%	**132**	
Age of stop smoking		**444**		**148**	***P*= 0.174**
Age 15-30	1.8%	**8**	2.0%	**3**	
Age 31-46	2.5%	**11**	2.7%	**4**	
Age 47-62	5.2%	**23**	0.7%	**1**	
Age 63-76	2.3%	**10**	1.4%	**2**	
Missing data	88.3%	**392**	93.2%	**138**	
Wine consumption		**444**		**148**	***P*= 0.010**
Most days	2.7%	**12**	2.7%	**4**	
More than once a week	0.2%	**1**	2.7%	**4**	
Less than once a week	2.7%	**12**	1.4%	**2**	
Never	40.3%	**179**	49.3%	**73**	
Missing data	54.1%	**240**	43.9%	**65**	
Maize Beer consumption		**444**		**148**	***P*= 0.063**
Most days	2.9%	**13**	3.4%	**5**	
More than once a week	3.8%	**17**	3.4%	**5**	
Less than once a week	6.5%	**29**	12.8%	**19**	
Never	32.4%	**144**	37.2%	**55**	
Missing data	54.3%	**241**	43.2%	**64**	
Diabetes		**444**		**148**	***P*= 0.003**
Yes	3.8%	**17**	7.4%	**11**	
No	50.9%	**226**	35.8%	**53**	
Missing data	45.3%	**201**	56.8%	**84**	
Hypertension		**444**		**148**	***P*= 0.000**
Yes	23.0%	**102**	30.4%	**45**	
No	36.3%	**161**	16.2%	**24**	
During pregnancy	0.2%	**1**	00.00	**00**	
Missing data	40.5%	**180**	53.4%	**79**	
HIV		**444**		**148**	***P= 0.014***
Yes	10.6%	**47**	4.7%	**7**	
No	78.8%	**350**	77.7%	**115**	
Missing data	10.6%	**47**	17.6%	**26**	

Table 4-4 Association between demographical, reproductive, life style factors and endometrial cancer among Black South African women, at Johannesburg tertiary hospitals between 1995 and 2004 (Univariate analysis)

	Univariate Analysis		
Variables	**Odds Ratio**	**p-value**	**95% CI***
Education			
No schooling	1		
School (Grade 2/4)	0.55	0.472	0.11 - 2.80
School (Grade 5/7)	0.73	0.651	0.19 - 2.81
School (Grade 8/10)	0.29	0.085	0.07 - 1.19
School (Grade 11/12)	0.83	0.827	0.15 - 4.63
University	1.33	0.665	0.36 - 4.88
Miscarriages			
No miscarriage	1		
One miscarriage	1.63	0.075	0.95 - 2.80
Two miscarriage	1.90	0.061	0.97 - 3.72
Three or more miscarriages	3.98	0.000	2.06 - 7.70
Place of former residence			
Soweto	1		
Johannesburg	1.88	0.273	0.61 - 5.78
Gauteng	3.33	0.018	1.23 - 9.04
N. Province	2.75	0.024	1.14 - 6.64
Mpumalanga	4.03	0.002	1.64 - 9.89
N. West Province	5.03	0.000	2.11 -12.01
Place of current residence			
Soweto	1		
Gauteng	1.92	0.008	1.18 - 3.12
N Province	2.52	0.010	1.24 -5.11
KwaZulu Natal	4.90	0.002	1.76 -13.68
Use of Snuff			
Never snuff	1		
Former snuffer	0.66	0.217	0.34 -1.28
Current snuffer	1.91	0.010	1.17 -3.13
Wine consumption			
Non-drinkers	1		
Drinking wine more than once a week	11.72	0.049	1.01 - 136.18
Drinking wine less than once a week	0.50	0.468	0.08 - 3.25
Ever smoke			
Never	1		
Former	0.39	0.006	0.20 - 0 .77
Current	0.34	0.007	0.16 - 0 .75
Age of youngest child+			
Age youngest child (1/14 years)	1		
Age youngest child (15/28 years)	2.64	0.051	1.00 - 6.98
Age young child (29/42 years)	3.82	0.009	1.40 - 10.46
Age youngest child (43/65 years)	8.98	0.000	2.68 - 30.04
Age of oldest child++			
Age oldest child (2/19 years)	1		
Age oldest child (20/37 years)	1.41	0.536	0.48 - 4.15
Age oldest child (38/55 years)	2.15	0.190	0.68 - 6.76
Age oldest child (56/76 years)	3.33	0.109	0.76 -14.48

Variables	Odds Ratio	p-value	95% CI*
Diabetes			
No	1		
Yes	2.70	0.017	1.19 - 6.11
Hypertension			
No	1		
Yes	2.94	0.000	1.67- 5.17
HIV			
No	1		
Yes	0.42	0.042	0.18 – 0.97
Age of menarche			
Period begins at age 11/14 years	1		
Period begins at age 15/18 years	0.49	0.001	0.33 - 0.74
Period begins at age 19/22 years	0.47	0.098	0.19 -1.14
Age at Menopause			
Period ended at age 30/39 years			
Period ended at age 40-45 years	1		
Period ended at age 46-50 years	0.91	0.85	0.32-2.55
Period ended at age 51-60 years	1.49	0.42	0.55-4.02
	2.66	0.05	0.96-7.33
Menstrual period **			
period Length(15/24 years)	1		
period Length(25/34 years)	1.19	0.696	0.50 - 2.85
period Length(35/46 years)	2.41	0.055	0.98 - 5.91
Menstrual status			
Period ended (menopausal woman)	1		
Period not ended (not menopausal)	0.23	0.001	0.10 - 0.54

*CI: Confidence Interval; **Menstrual period is a new variable generated by subtracting the age of menarche from the age at menopause; + also represent the age of woman at the time of the last birth; ++ also represent the age of woman at the time of first birth.

Table 4-5 Association between demographical, reproductive, life style factors and endometrial cancer among Black South African women, at Johannesburg tertiary hospitals between 1995 and 2004 (Multivariate analysis).

	Multivariate Analysis $		
Variables	**Odds Ratio**	**p-values**	**95% CI**
Miscarriages			
No miscarriage	1		
One miscarriage	1.61	0.11	0.90 2.89
Two miscarriage	1.80	0.10	0.88 - 3.65
Three or more miscarriages	3.17	**0.002**	1.52 - 6.58
Ever smoke			
Never	1		
Former	0.34	**0.004**	0.17 - 0.71
Current	0.27	**0.002**	0.12 - 0.62
Age of youngest child+			
Age youngest child (1/14 years)	1		
Age youngest child (15/28 years)	2.48	0.099	0.84- 7.30
Age young child (29/42 years)	3.67	**0.012**	1.37 - 12.69
Age youngest child (43/65 years)	8.78	**0.001**	2.73 – 40.87
Age of menarche			
Period begins at age 11/14 years	1		
Period begins at age 15/18 years	0.63	**0.043**	0.40 - 0.98
Period begins at age 19/22 years	0.56	0.239	0.22 - 1.45

*CI: Confidence Interval; **Menstrual period is a new variable generated by subtracting the age of menarche from the age at menopause;
+ also represent the age of woman at the time of the last birth
++ also represent the age of woman at the time of first birth.
^ All variables had been adjusted for each others

Chapter Five

Discussion

5. Discussion

The present case-control study in Black South African women evaluates risk factors and their relationship with endometrial cancer. To our knowledge, this is the first study in South Africa that aims to investigate the risk factors for endometrial cancer. To simplify the discussion of the results, this section has been divided into five major parts, and these include; the study design, the relationship between endometrial cancer and age, the relationship between endometrial cancer and social factors, the relationship between endometrial cancer and reproductive factors and the relationship between endometrial cancer and diseases like diabetes, HIV and hypertension.

5.1. Discussion of the study design

Studies and their results differ with regard to their quality as well as with their respective contribution to the evidence base. The success or failure of any type of epidemiological study depends on the design of an epidemiological study In addition, with statistical analysis, the generation of confidence intervals (CI) is useful because it tells the reviewer how precise the estimate is, or in the case of endometrial cancer treatment, how precise the percentage survival estimate actually is. A larger study size gives the study more solidity in terms of the results obtained. Another important issue is the study duration and time intervals, for example when reviewer compare studies it is important that they compare similar time periods and time intervals. Also, if a study began many years before a second study, it is clearly possible that the results of the two studies may vary simply because of changes in the standards of practice occurring during the time

period covered by the two studies. When two studies are conducted in two distinctly different time periods, even if the duration of the studies is similar, a difference in results obtained is possible. Materials, devices, techniques used in 1970 to confirm diagnosis of a disease may not even be available for use a decade later (115).

A case control study entails comparing the frequency of exposure in a group of subjects having the disease (the cases) in comparison to another group (the controls) who resemble them in as many relevant aspects as possible, but who do not have the disease or condition of interest. The measured variable, unknown at the onset, is exposure status to a factor that has preceded the occurrence of disease and possibly caused it (116). Thus, the groups in case control studies are indentified on the basis of the outcome. Case control studies are an excellent design to study rare diseases and for diseases with long latent and or incubation periods (117).

Before discussing the results, it is important to consider the significance of methodological issues. In the present case control study, we studied endometrial cancer, a common cancer in females. Case control design has the logistic benefits that it may be based entirely in health facilities and that it is relatively quick and easy to carry out. In the current study age matched controls were randomly selected from the same hospitals using other types of cancers. Controls were also cancerous but comprised cancers unrelated to endometrial

cancer. Selecting patients with cancer as controls has several advantages; first, it enabled us to obtain a similar quality of information. Second, it enabled us to recruit controls whose referral pattern was similar to those of the cases and who presumably came from the same study base, and were clearly identified. Third, in this way, we minimised recall or reporting bias and interviewer bias as much as possible as people with diseases may remember past events clearly or on the other hand may deny certain past behaviours. Lastly, choosing cancer patients as controls made the study easier with regard to the feasibility, and more economical but not perfect in term of its results (117, 118).

The disadvantages of the current design include; firstly, problems associated with selecting cases and controls. Theoretically, illegibility criteria for cases define the source population in case control studies, from which controls should be selected. That is if hospitalised cancer cases are biased sampling of the general population, controls would also be biased in the same way (119). In case control studies it is usually difficult to find a suitable control group. In the present study, we selected the control from patients admitted to same the hospitals as cases but with different types of cancers, although in some other studies controls have been selected from patients visiting cancer screening centres (119).

Secondly, it may have been possible that inclusion of other types of cancers in the control group might have distorted the results since the patients with other types of cancers may have a background similar to the patients with endometrial

cancer (117, 118). To minimise this problem as much as possible, patients with female cancers were excluded from the control group (e.g. cervical, vaginal or breast cancer). In the current study, however we did not compare our cases with healthy controls but with cases (cases vs. cases). Over estimating and/or under estimating of risk factor in relation to disease under study may happen. For example smoking is a well known risk factor for lung cancer, and using controls with lung cancer can result in a potential effect of smoking on endometrial cancer cases even when it is not. Studies like this should be repeated using different population as controls and by using different study designs.

Thirdly, case-control studies often cannot determine whether exposure preceded the outcome (temporal sequence). Although the definition of cases was strict in this study, it is possible however, that some of the cases might be uterus cancer rather then endometrial cancer, which means that not all the cases represented cases. Lastly, researchers consider cohort studies superior to case control studies. However, the cohort design is not suited to studying rare diseases like gynaecological cancer because the time between exposure and disease manifestation is very long. It is also possible that exposure patterns may change any time, for example the composition of oral contraceptives, may change during the course of the study and make the results inappropriate; or women can switch from oral contraceptive to injectable contraceptive; or women who smoke may give up on smoking and the opposite is possible. Furthermore, cohort studies are not ideal to cover incident cases of gynaecological cancer, as there are many

incidents cases of gynaecological cancer that are relatively young compared with cancer of other sites (120). On the other hand, case control studies can identify younger cases as well as at older cases. Finally, baseline data may be sparse because the large number of subjects does not allow for long interviews. Thus, case control studies are regarded as a more efficient method for investigating risk factors for endometrial cancer (120).

In African countries, however, feasibility to run cohort studies is controversially difficult due to many reasons and these include; financial difficulties, loss of follow up, difficulties in recruiting people, lack of expertise, time, etc.

5.2. The relationship between age and endometrial cancer

The mean age of cases in this study (60.3 years) is well in line with international studies that previously considered 61 years old is the mean age for endometrial cancer. There were 23 cases (15.5%) under the age of 45 years, and this is consistent with international studies that had shown that 5-30% of the endometrial cancer population is found to be premenopausal (14, 121). The mean age of menopause in our study was 49.23 years for the cases and 48.24 years for the controls and 48.51 years for the total population. The median age was 50 with a standard deviation of 5.58. The mean age at menopause differs between countries, races and populations. For example the mean age of menopause in the United States is 51 years, (Menarche: Mean 15.19; SD 1.89; Median 15, youngest 11, and oldest 21). Premenopausal women of the control group less than the mean age numbered 51 out of a total of 154 cases.

Not surprisingly, we have found a positive correlation between increasing age and the occurrence of endometrial cancer (figure 4-2), which has been widely reported by other studies (122). Age is also an important prognostic factor for survival in endometrial cancer as studies have shown that younger patients have a better survival than older patients (10, 16). In the present study we found two peaks (at ages 55-59 years, and 65-69 years), when we created age intervals of five years, and this was not paralleled with other studies which found only one peak for the cases. There are two explanations for this fluctuation, first this is possibly due to incomplete collecting of data, and second is the possibility that

women in this age group already died of other diseases. Ultimately, the total number of our cases in this study may be too low. Our expectation, in a bigger study for the same area will be one peak at the age interval 60-65.

5.3. Geographical and Socioeconomic factors

It is widely accepted that the risk of endometrial cancer differs markedly from country to country, but this is mainly due to differences in socioeconomic levels, lifestyle, or differences among races. However, the literature has not yet shown significant differences within the same race living in separate areas.

5.3.1. Place of birth & Place of residence

Like most other studies, we found no significant relationship between place where a woman was born or place of residence and the risk of endometrial cancer (35).

5.3.2. Education level

Although, the relationship between education and endometrial cancer is still controversial, it has found to have an inverse relationship with other cancers especially those related to smoking (36, 37). In the present study, education level was protective when women had a level of education (represented by school) between grade 8-10, however the *P*- value was not significant (*P* >0.05). The effect of education then started again to be less effective for those who had education between grade 10 and before joining the university (those who already finished metric), with odd ratio close to 1 (Odd for this group = 0.912). At university level, the odd ratio crossed 1 (Odd= 1.33), but again the *P*- value was not significant (*P*=

0.665). This means that endometrial risk has increased for those who joined the university about 0.33 times compared to those who have no education at all. The difference may have been partly explained by a greater use of oestrogen replacement among more educated women in earlier studies or by better access to medical care and therefore more complete diagnosis.

On the other hand low education has been shown to be associated with high mortality rate in other types of cancer. Albano and colleagues have reported that mortality rates for lung cancer were conspicuously higher in less educated men than in more educated men, irrespective of race, however the differences were less extreme in women (38). Educated women are most probably early diagnosed, firstly because, they are aware of the disease, and second their economic levels are higher than non educated women. These reasons at the end may increase the survival rate significantly, not only in women with endometrial cancer but for all kinds of cancer (123).

5.3.3. Smoking

The present study appears to show that smoking is a protective factor against endometrial cancer (*P<0.05*). The results of the present study are consistent with previously reported studies (39, 40, 41). Parazzini and colleagues have reported that smoking is a protective factor against endometrial cancer in postmenopausal women (40). Many studies have shown that the risk of endometrial cancer has decreased significantly in women who are currently smoker (41, 124, 125) and the risk continued to decrease with increased duration of smoking (39, 41,125).

The highest inverse relationship between smoking and endometrial risk found was a 40% reduction in disease risk among women currently smoking and among women who reported to smoke for 20 years or longer. However, the latter relationship was found to exist only among postmenopausal women (125). Newcomer and colleagues (2001) showed that among postmenopausal women, the risk linked with current use of postmenopausal hormones appeared to be greater among non-smokers than among current smokers (126).

However, in our study we do believe that part of the protective effect of smoking could be potentially due to the high numbers of smoking associated cancers within the control group (table 2 in the appendix). For example, in our study cases of oesophageal cancer represented 25% of the total number of participants within the control group. Oesophageal cancer is one of the most aggressive malignancies found to be significantly associated with smoking (127). Similarly other cancers in the control group like lung cancer (128, 129), mouth cancer and tongue cancer (130) that have been associated with smoking, were present in 6.98%, 2.25% and 3.15% participants respectively in the control group. This may have influenced the effect size and the direction of the smoking-endometrial cancer risk association.

The association between smoking and endometrial cancer risk may be attributed to anti- estrogenic effect of smoking (42, 43). Estrogen can promote the development of endometrial cancer by initiating mutations and promoting cellular proliferation in endometrial glands. Androgens and progestins reduce estrogen-induced cellular

proliferation in endometrial glands and work against the development of endometrial cancer. Smokers have lower endogenous estrogen and/or higher androgen levels compared to nonsmokers (44, 45). It has been shown that smoking reduced the age at menopause, thereby dropping the number of menstrual cycles that women may have in their life, which ultimately minimizes the effect of oestrogen in these women ultimately reducing the risk of endometrial cancer (46). Stockwell and Lyman have shown a protective effect of smoking cigarettes against endometrial cancer in women aged 50 years or older. Risks were significantly reduced among moderate smokers (OR = 0.6, CI= 95%), heavy smokers (OR = 0.4, CI=95%), and former smokers (OR = 0.6, CI=95%). However, this relationship was not detected among women under age 50 years (39).

The largest and most recent cohort study (43) also showed a significant decrease of endometrial cancer risk among current and former smoker compared to non smoker. There was also an inverse association between smoking intensity and duration with endometrial cancer risk, although the trend was not statistically significant (43). To the opposite from previously reported studies, other case-control studies showed weak to moderate inverse association between cigarette smoking and endometrial cancer risk (42). As a conclusion statement, most studies agreed that, smoking reduced the risk associated with endometrial cancer among women at greatest risk, especially obese women or those who use postmenopausal hormones (124, 125, 126). However, due to the high number of

smoking associated cancers in our study, we do believe that the protective effect of was exaggerated.

5.4. Reproductive factors

There is considerable evidence that the reproductive factors play pivotal roles not only in the aetiology of endometrial cancer, but most female cancers. This is because most of these factors may directly or indirectly affect the balance of estrogen/progesterone levels, and this can lead to a change in an organ's exposure to the hormones. The menstrual cycle, number of pregnancies, number of miscarriages, age of menarche and age at menopause, and contraceptives use are all associated with fluctuating levels of estrogen and progesterone (47, 76, 131, 132). The following reproductive factors were the focus of our study:

5.4.1. Age at menarche

The age of women at menarche and age at menopause is the most frequently studied and the most controversial characteristic, not only in relation to endometrial cancer, but also with all types of gynaecological cancers (133). In the current study we found a significant relationship between age at menarche and endometrial cancer ($P<0.05$). Our results were paralleling with results from Fujita and colleagues who found significant relationship between age at menarche and endometrial cancer (133). Similarly, prospective studies indicate that there is a reduction in risk of endometrial cancer when menarche takes place at a later age (48,76), and this is due to reduction in the overall number of cycles, resulting in

less estrogen that may affect the body. Previous case control studies regarding the effect of age at menarche on endometrial cancer have been equivocal, with some studies showing no definite relationship (134), and others showing a 2-fold increased risk of endometrial cancer when menarche occurs at later age (47).

It has been hypothesised that high energy intake in general could result in an increased risk of endometrial cancer, both by producing obesity, lowering the age at menarche, and lowering the age maturation (131). Evidence for the latter mechanism include the observation that the age of menarche is delayed by protein-calorie malnutrition, and tend to occur earlier in better nourished western industrialised countries and relatively high socioeconomic groups than in more poorly nourished and underdeveloped countries and lower socioeconomic groups.

5.4.2. Age at menopause

In the present study, evaluation of the relationship between age at menopause and the risk of endometrial cancer showed a significant association only in univariate analyses (4-4), while no such relation existed in multivariate analyses (table 4-4) despite the fact that there was a strong association in Chi square tests ($P<0.01$) (table 4-2). These results parallel a previous study, where Brinton and colleagues found no association between endometrial risk and age at menopause (47).

Indeed most recent studies observed a positive relationship between endometrial cancer and age at menopause (47, 70, 76). The later age at menopause, the

higher risk of endometrial cancer, because higher age means more cycles, that is, more exposure to estrogens. In our study the only explanation for our results may be due to the fact that our controls also have cancers, and these cancers may directly or indirectly affect the menstrual cycle. The cancers may have an indirect effect as they occurred mostly around the age of menopause, therefore it might have disturbed their menstrual cycles, as menses are affected strongly by the psychological status of the woman, and no doubt having cancer lead to deterioration in the psychological status. While the direct effect is due the high levels of cytokines that is common in cancer patients and thus affect the oestrogen/progesterone levels (76).

5.4.3. Age at first and last live birth

The present study has detected a significant relationship in the univariate analysis (table 4-4) between the risk of endometrial cancer and the age youngest child (age of women at last live birth), thus the older the age of youngest child the higher risk of endometrial cancer. This relation was consistent in the multivariate analysis, while no significant relationship has been noticed between the age of oldest child (age of the women at first live birth) and the risk of endometrial cancer in both univariate analysis and multivariate analysis. The relationship between the ages of oldest and/or youngest child and endometrial cancer may reflect the age of the mother at first and last successful delivery and its relation with endometrial cancer. Age at first pregnancy does not appear to have any significant relationship with endometrial cancer in most studies (47, 49, 67, 68, 69). On the contrary women

who give births relatively late in their reproductive lives have been shown to be at lower risk for endometrial cancer than are those who complete their childbearing early (70, 69).

Lesko and colleagues found that delivery after age 40 years was associated with as much as a 60 percent reduction in endometrial cancer risk (135). Anovulatory cycles are common at both the beginning and the end of reproductive life; their occurrence late in reproductive life and the effect on the risk of endometrial cancer is of interest here. Because pregnancy is indicative of normal ovulatory function, women who deliver late in life can be assumed to be ovulatory late in reproductive life (at least up to the time of conception), while women who do not become pregnant late may or may not be ovulatory during this period of life. Thus, women who have delivered a child late in life are at a lower risk of having anovulatory cycles late in reproductive life compared with women who have not had a late pregnancy, and therefore may be at lower risk of endometrial cancer. Alternatively, late pregnancy itself may confer a direct protective effect on the endometrium (69).

5.4.4. Number of pregnancies

Nulliparity is associated with a two- to threefold increased incidence of endometrial cancer. Nulliparity is believed to be related to infertility rather than intentional prevention of pregnancy. Infertility related to anovulation and progesterone deficiency increases the risk of endometrial cancer, whereas infertility related to tubal factors does not (8). In the present study and unlike other studies, we did not

find a significant relation between endometrial risk and nulliparity (*P*>0.05), nor have we found any significant differences between having up to seven pregnancies and/or not having any pregnancy and the risk of endometrial cancer (8). The small number of nulliparous women in our study could be one of the reasons that caused the non significant association with endometrial cancer.

5.4.5. Numbers of miscarriages

The present study has detected a significant relationship between the occurrence of miscarriage and the risk endometrial cancer. Our results were consistent in Chi square analysis, univariate analysis, as well as multivariate analysis. The relationship between endometrial cancer and miscarriage is still unclear as most studies did not find any association (47, 71, 72), although some others suggested a protective factor (64, 73, 74, 75). McPherson and colleagues have shown a significant relationship between endometrial cancer and numbers of miscarriages, but after adjusting for other factors this association no longer exists (76).

Ending the pregnancy before the age of 22 weeks or miscarriage has been reported in some studies to be more related to risk of breast cancer. In early pregnancy the level of oestrogens elevates, provoking breast cells to grow in preparation for lactation. It has been hypothesised that if this process is interrupted with an abortion – before full differentiation in the third trimester then more relatively vulnerable undifferentiated cells could be left than there were prior to the pregnancy, resulting in a greater potential risk of breast cancer. However, no

explanation has been proposed in the literature why miscarriage might increase the risk of endometrial cancer (74, 75).

5.4.6. The use of Contraceptives

No significant relationship has been found in the present study between the use of oral and/or injectable contraceptives and endometrial cancer risk. Other studies have reported that contraceptives have a protective effect against endometrial cancer, and the use of the combined oral contraceptive pill which contains oestrogen and progestogen had reduced the risk of endometrial cancer significantly (136, 137, 138). In a study performed in Sweden, Weiderpass et al. reported that long-term use of combined oral contraceptives appears to decrease the risk more, and the protective effect may continue for 20 years after the woman stopped treatment (136).

5.5. Other risk factors and endometrial cancer

5.5.1. Diabetes

The relationship between diabetes and endometrial cancer risk was significant in univariate analysis ($P>$ 0.05). However, due to considerable number of missing data (45.27% of the controls and 56.76% of the cases) this variable has been excluded from the multivariate analysis. Brinton and colleagues (1992), have found a positive association between being diabetic and the risk of endometrial cancer (relative risk 2.0), even after adjusting for weight and other related factors (47). In most other studies, no significant relationship has been detected between diabetes and endometrial cancer (70, 105, 139, 140, 141, 142).

Diabetes is assumed to be a risk factor for endometrial cancer, although epidemiological studies data are controversial as most of the results are not consistent. When studies adjusted for body weight, the relationship between diabetes either becomes weaker (69, 70) or disappeared (139,140). This is because most of type 2 diabetes patients are often obese (131), and studies consistently show strong positive associations between body weight and endometrial cancer (70). Some other studies demonstrated that this relation is due the hyperinsulinaemia, as high levels of insulin may have an etiologic role in endometrial cancer independent of body weight and not only with endometrial cancer but with other kind of cancer as has been hypothesised for colorectal (143, 144) and breast (145,146) cancer. Unfortunately, we do not have any information regarding the weight of the participants; neither have we had any information to state whether or not some of the participants are hyperinsulinemic.

5.5.2. HIV/AIDS

The inverse significant relationship detected with endometrial cancer, could be due the high number of control patients who might have HIV related cancer. The percentage of controls that were HIV-positive was more than double to this within the cases (table 2 in the appendix). Unlike any other disease HIV-AIDS has been associated with extraordinary level of fear, shame, denial and discrimination since it was identified. This negative stigma with HIV-AIDS has not only created a drawback in any study rely on self report, but also created a barrier in fighting the disease. The status of being HIV positive has been reported in several studies to

be associated with other kinds of cancer. In addition to the AIDS-defining cancers such as non-Hodgkin's lymphoma, Kaposi's sarcoma, and cervical cancer, rates of Hodgkin's disease and anal cancer have been reported consistently to be associated with HIV/AIDS patients (102, 103, 104).

5.5.3. Hypertension

The current study showed a significant association between endometrial cancer and the history of having hypertension in the univariate analysis (OR=2.94, 95% CI: 1.67-5.17). However, due to the considerable number of missing data (40.54 of the controls and 53.38% of the cases), this variable has been excluded from the multivariate analysis. Hypertension is common in women with endometrial cancer, suggesting that it may play some role in the development of the disease (47).

It has been reported that hypertension may increase the risk of cancer by blocking and subsequently modifying apoptosis, thereby affecting the regulation of cell differentiation and determination (139, 140). Although hypertension is related to being overweight, which in turn is associated with elevated oestrogen levels, hyperinsulenimia and high levels of cytokines (106), most studies failed to find independent relation between hypertension and endometrial cancer (105). Again missing data regarding hypertension in the current study might affect the power of the analysis.

Brinton and colleagues 1992 have found a significant relation between hypertension and endometrial cancer, but this relation has disappeared after

adjusting for weight, suggesting no sole relation between endometrial cancer and hypertension (47). Unfortunately, we do not have any information regarding the weight of the study participants in order to judge whether or not the significant relation between hypertension and endometrial cancer is due to weight or solely related to the disease.

Postmenopausal status, hypertension and obesity could all be considered as risk factors for carcinomatous transformation within endometrial polyps in women without a history of breast carcinoma with Tamoxifen treatment (147). However, our series is small (only six cases considered) and further studies are necessary to confirm this hypothesis.

Conclusion

1. Endometrial cancer was more frequent among women who were older, especially after menopause. Women who experienced miscarriages were also at higher risk for endometrial cancer.

2. The risk of endometrial cancer was higher in women who complete their childbearing earlier in their reproductive lives compared with those who completed their child bearing late while no relationship has been found in women with a history of infertility.

3. It appears that the amount of oestrogen that a woman is exposed to in her lifetime influences her chances of contracting endometrial cancer. Women who are exposed to more estrogen, either naturally or from outside sources, are more likely to develop endometrial cancer. Thus any factor that causes a woman to have high levels of estrogen is also a risk factor for endometrial cancer. The more menstrual cycles a woman has in her lifetime, the more oestrogen her endometrium is exposed to. Women who started menstruating early, and go through menopause late are applicable in this case.

4. There was significant relationship between number of miscarriages and endometrial cancer risk, and this relationship was significantly high when miscarriages were three times or more.

5. This study showed an inverse relationship between smoking and the risk of endometrial cancer, and this was not surprising as most studies had showed smoking to have a protective effect against endometrial cancer. However, comparing the cases of endometrial cancer with smoking-associated cancer controls (i.e. lung cancer, oesophageal cancer, and mouth cancer) might have an effect. Our suggestion is to compare the cases in such studies with controls that had no cancers to finalise the relation between smoking and endometrial cancer.

6. The conflict between our study and some previous study results may be due to population differences across studies or the way that the study been designed. (i.e. the way that the information was collected from the cases and controls, source of controls, etc).

7. Because the incidence of endometrial cancer escalates with increasing age, this may continue to be future problem as most societies tend to be elderly (increasing old people due to low fertility rate). This issue could be less clear in the South African black population, but may play a pivotal role in changing the incidence of the disease in other races in the future.

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Appendix

Appendix 1.1

Table-1- The distribution of endometrial cancer cases and controls, by age group among Black South African women, at Johannesburg tertiary hospitals between 1995 and 2004

Age (years)	**Endometrial cancer cases**		**Controls**	
	No	**%**	**No**	**%**
25-29	1	0.675	3	0.675
30-34	6	4.054	18	4.054
35-39	8	5.405	24	5.405
40-44	8	5.405	24	5.405
45-49	11	7.432	33	7.432
50-54	8	5.405	24	5.405
55-59	22	14.864	66	14.864
60-64	20	13.513	60	13.513
65-69	24	16.216	72	16.216
70-74	19	12.837	57	12.837
75-79	16	10.81	48	10.81
80-84	1	0.675	3	0.675
85-90	4	2.702	12	2.702
Total	**148**	**100.0**	**444**	**100.0**

Table-2-The contribution of each cancer in the study among Black South African women, at Johannesburg tertiary hospitals between 1995 and 2004

Type of cancer	**Freq.**	**Percent out of the controls**	**% out of the total number**
Tongue cancer	14	3.15	2.36
Mouth cancer	10	2.25	1.69
Parotid cancer	4	0.9	0.68
Esophagus	111	25.00	18.75
Stomach	21	4.73	3.55
Colon	14	3.15	2.36
Rectum	21	4.73	3.55
Liver	11	4.47	1.86
Pancreas	5	1.12	0.84
Maxillary sinus	8	1.80	1.35
Lung	31	6.98	5.24
Bone of Skull	7	1.57	1.18
Bone marrow	63	14.18	10.64
Skin	44	9.91	7.43
Sub. tissue	8	1.80	1.35
Kidney	5	1.12	0.84
Bladder	6	1.35	1.01
Thyroid gland	9	2.03	1.52
Limbs	6	1.35	1.01
Lymph nodes	33	7.43	5.57
Other primary sites	13	2.93	2.20
Endometrial cancer	148	----------	25.00
Total	**592**	**100.00**	**100.00**

Table-3- Comparison of demographical factors between cases and controls among Black South African women, at Johannesburg tertiary hospitals between 1995 and 2004

Variables	Controls	No.	Cases	No.	*P*-value
Total Number	**444**		**148**		
Age (mean)	60.30		60.30		
Highest age (years)	90		90		
Youngest age (years)	27		27		
Standard deviation	13.63		13.63		
Education level		**444**		**148**	
No schooling	% 71.3	114	% 28.8	46	
Grade 1 to grade 4	% 74.6	41	% 25.5	14	
Grade 5 to grade 7	% 77.1	91	% 22.9	27	***P*= 0.514**
Grade 8 to grade 10	% 79.6	117	% 20.4	30	
Grade 11 to grade 12	% 72.5	71	% 27.6	27	
University level	% 63.6	7	% 36.4	4	
Missing data	% 0.7	3	----------		
Pension status		**444**		**148**	
Yes	% 75.6	102	% 24.4	33	***P*= 0.052**
No	% 66.1	72	% 33.9	37	
Missing data	% 77.6	270	% 22.4	78	
Residence status (Urban/Rural)		**444**		**148**	
Urban areas	% 75.7	368	% 24.28	118	***P*= 0.546**
Rural areas	% 71.0	71	% 29.00	29	
Missing data					
Place of birth		**444**		**148**	
Soweto	% 82.5	33	% 17.5	7	
Johannesburg	% 83.3	40	% 16.7	8	
Gauteng	% 67.8	101	% 32.2	48	
North Province	% 71.6	58	% 28.4	23	
Kwazulu Natal	% 78.7	74	% 21.3	20	
Free State	% 72.0	59	% 28.1	23	***P*= 0.181**
North West	% 81.1	43	% 18.9	10	
Mpumalanga	% 79.1	34	% 20.9	9	
Missing data	%100.00	2	------	----	
Place current residence		**444**		**148**	
Soweto	% 80.9	169	% 19.1	40	
Johannesburg	% 79.0	60	% 21.1	16	
Gauteng	% 70	126	% 30	54	
Kwazulu Natal	% 68.8	22	% 31.3	10	
Northern province	% 62.8	27	% 37.2	16	***P*= 0.081**
Free State	% 72.2	13	% 27.8	5	
North West	% 78.8	26	% 21.2	7	
Missing data	% 100	1	0.0000	-----	

Table -4- Comparison of reproductive factors between cases and controls among Black South African women, at Johannesburg tertiary hospitals between 1995 and 2004

Variables	%Controls	NO	%Cases	NO	P-value
Age at Menarche		**444**		**148**	
Age 11-14 years	% 65.5	127	% 34.5	67	
Age 15-18 years	% 79.5	272	% 20.5	70	***P*= 0.003**
Age 19-22 years	% 79.4	27	% 20.6	7	
Missing data	% 81.8	18	% 18.2	4	
Age at Menopause		**444**		**148**	
Age 30-39 years	% 68.8	22	% 31.3	10	
Age 40-45 years	% 79.1	68	% 20.9	18	***P*= 0.001**
Age 46-50 years	% 75.5	163	% 24.5	53	
Age 51-60 years	% 63.4	85	% 36.6	49	
Missing data	% 85.5	106	% 14.5	18	
Pregnancies		**444**		**148**	
Yes	% 75.5	422	% 24.5	137	***P*= 0.154**
No	% 68.8	22	% 31.3	10	
Missing data	----------	-----	% 100.00	1	
No of full term pregnancies		**444**		**148**	
Once	% 72.0	36	% 28.0	14	
Twice	% 69.4	59	% 30.6	26	
Three times	% 71.2	52	% 28.8	21	***P*= 0.111**
Four times	% 82.1	69	% 17.9	15	
Five times or more	% 78.0	205	% 22.1	58	
Missing data	% 62.2	23	% 37.8	14	
Age of the Child					
1. oldest child		**444**		**148**	
Age 2-19 years	% 84.8	39	% 15.2	7	
Age 20-37 years	% 80.7	121	% 19.3	29	***P*= 0.000**
Age 38-55 years	% 76.2	211	% 23.8	66	
Age 56-76 years	% 72.5	29	% 27.5	11	
Missing data	% 55.7	44	% 44.3	35	
2. Youngest child		**444**		**148**	
Age 1-14 years	% 90.7	68	% 9.3	7	
Age 15-28 years	% 81.1	116	% 18.9	27	***P*= 0.000**
Age 29-42 years	% 77.8	147	% 22.2	42	
Age 43-65 years	% 65.0	26	% 35.0	14	
Missing data	% 60.0	87	% 40.0	58	
Miscarriages		**444**		**148**	
No miscarriage	% 80.9	161	% 19.1	38	
One miscarriage	% 72.0	85	% 28.0	33	
Two miscarriages	% 68.5	37	% 31.5	17	***P*= 0.000**
Three or more miscarriages	% 51.0	25	% 49.0	24	
Missing data	% 79.1	136	% 20.9	36	
Use of contraceptives		**444**		**148**	
Yes	% 74.4	61	% 25.6	21	***P*= 0.711**
No	% 75.0	381	% 25.0	127	
Missing data	% 100	2	--------	**-----**	
Use inject-able contraceptive		**444**		**148**	
Yes	% 80.3	57	% 19.7	14	***P*= 0.225**
No	% 74.0	382	% 26.0	134	
Missing data	% 100	5	---------	**-----**	

Table- 5- Comparison of lifestyle factors between cases and controls among Black South African women, at Johannesburg tertiary hospitals between 1995 and 2004

Variables	%Controls	No	%Cases	No	P-value
Snuff use		**444**		**148**	
Current snuffer	% 63.4	59	% 36.6	34	
Former snuffer	% 82.9	58	% 17.1	12	***P*= 0.018**
Never snuff	% 76.4	326	% 23.7	101	
Missing data	% 50.0	1	% 50.0	1	
Snuffing frequency		**444**		**148**	
Snuff 1-4 times daily	% 67.1	55	% 32.9	27	
Snuff 5-9 times daily	% 77.8	35	% 22.2	10	***P*= 0.325**
Snuff 10-20 times daily	% 72.7	24	% 27.3	9	
Missing data	% 76.4	330	% 23.6	102	
Smoking		**444**		**148**	
Current smoker	% 87.3	55	% 12.7	8	
Former smoker	% 86.3	69	% 13.8	11	***P*= 0.002**
Never smoke	% 71.1	318	% 28.9	129	
Missing data	% 100.00	2	---------	------	
Age of start smoking		**444**		**148**	
Age 10-16	% 88.6	31	% 11.4	4	
Age 17-24	% 88.4	61	% 11.6	8	***P*= 0.001**
Age 25-50	% 86.2	25	% 13.8	4	
Missing data	% 71.2	327	% 28.8	132	
Age of stop smoking		**444**		**148**	
Age 15-30	% 72.7	8	% 27.3	3	
Age 31-46	% 73.3	11	% 26.7	4	***P*= 0.174**
Age 47-62	% 95.8	23	% 4.2	1	
Age 63-76	% 83.3	10	% 16.7	2	
Missing data	% 74.0	392	% 26.0	138	
Wine consumption		**444**		**148**	
Most days	% 75.0	12	% 25.0	4	
More than once a week	% 20.0	1	% 80.0	4	***P*= 0.010**
Less than once a week	% 85.7	12	% 14.3	2	
Never drink	% 71.0	179	% 29.0	73	
Missing data	% 78.7	240	% 21.3	65	
Maize Beer consumption		**444**		**148**	
Most days	% 72.2	13	% 27.8	5	
More than once a week	% 77.3	17	% 22.7	5	***P*= 0.063**
Less than once a week	% 60.4	29	% 39.6	19	
Never drink	% 72.4	144	% 27.6	55	
Missing data	% 79.0	241	% 21.0	64	
Diabetes					
Yes	% 81.0	**226**	**%** 19.0	**53**	***P= 0.003***
No	% 60.7	**17**	% 39.3	**11**	
Missing data	% 70.5	**201**	% 29.5	**84**	
HIV				**148**	***P= 0.014***
Yes	% 87.0	**47**	%12.9	**7**	
No	% 75.3	**350**	% 24.7	**115**	
Missing data	% 64.3	**47**	% 35.6	**26**	
Hypertension					
Yes	**% 69.4**	**102**	**% 30.6**	**45**	***P= 0.000***
No	**% 87.0**	**161**	**% 13.0**	**24**	
Only during pregnancy	**% 100.0**	**1**	**----------**	**0**	
Missing data	**% 69.5**	**180**	**30.5**	**79**	

1. 2. Staging of endometrial cancer

Most endometrial cancers are staged according to a surgical system approved in 1988 by the International Federation of Gynecology and Obstetrics. Factors used to stage the disease include the depth of the tumor, whether the tumor has spread to the cervix and other nearby organs, the cytology of the cancer (cellular make-up and activity), whether it has metastasized to the lymph nodes, and the extent to which it has spread to other parts of the body. Endometrial cancer in patients, who are unable to undergo surgical evaluation, is staged using an older, clinical staging system.

Table -6- FIGO's Surgical Stages for Endometrial Cancer (147).

Stage I	The tumor is confined to the uterine fundus (the body of the uterus). **Survival rate is about 90% to 95%.**
Stage IA	The tumor is limited to the endometrium (the lining of the uterus), and no myometrial invasion.
Stage IB	The tumor invades less than one-half of the myometrial thickness (the myometrium is the muscular tissue that is found just beneath the endometrium), %50 myometrial invasion.
Stage IC	The tumor invades more than one-half of the myometrial thickness.
Stage II	The tumor extends to the lower part of the uterus (the corpus and the cervix). **Survival rate is about 75%.**
Stage IIA	Cervical extension is limited to the endocervical glands; glands in the inner lining of the uterus, where the cervix meets the uterus (endocrine glandular involvement).
Stage IIB	Tumor invades the cervical stroma (the supporting connective tissue of the cervix). Cervical stromal involvement.
Stage III	There is regional tumor spread. **Survival rate is about 60%.**
Stage IIIA	The tumor invades the uterine serosa (the layer of tissue that surrounds the outside of the uterus), or adnexa (tissues on either side of the uterus), or cells in the peritoneum (the member surrounding the abdominal cavity) show signs of cancer.
Stage IIIB	Vaginal metastases are present.
Stage IIIC	The tumor has spread to lymph nodes near the uterus.
Stage IV	There is bulky pelvic disease or distant spread (intraabdomenal metastasis, extra abdominal metastasis, and/ or involvement of the lamph nodes). **Survival rate is about 15% to 26%.**
Stage IVA	Tumor has spread to the bladder or rectum.
Stage IVB	Distant metastases are present.

MRC/NHLS/CANSA/Wits CANCER EPIDEMIOLOGY RESEARCH GROUP (CERG)
JOHANNESBURG STUDY QUESTIONNAIRE FOR PATIENTS

Date of Birth OR Age Study No:

Day Month Year 1 9 Years

Sex *(please tick)* 1 M F 2

Diagnosis(Clinical) Path No ICD

Histology result, if available Hospital No. M

Initials of Interviewer

Date of Interview Day Month Year 2 0 0

BLOODS:

RED TOP yes no

PURPLE TOP yes no

Where were you born? *(please tick)*

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

Where do you normally live? *(please tick)*

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

How long have you lived there? Years

What is the highest standard you passed at school? *(please tick)*

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

Gr10 Gr11 Gr12

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

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

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

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

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

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

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

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

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

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

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

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

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

1 Yes, more than 5 years | No 2

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

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

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

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

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

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

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

Before you became ill, did you ever have your blood pressure measured? *(Please tick)*

1. Yes | 2. No | 3. Yes only during pregnancy

If yes, were you told it was high? *(Please tick)*

1. Yes | 2. No | 3. Yes only during pregnancy

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

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

BEER				SPIRITS		WINE	OTHER
Maize	Sorghum "Cartoon"	Other homemade	Commercial	Homemade (gavini)	Commercial		

a: 2l wine bottle
b: 1l bottle 7.50 ✓
c: 1l carton
d: 750ml wine bottle
e: 500ml beer glass
f: 375ml half jack/pint
g: 340ml beer can/dumpy
h: 250ml glass
i 200ml wine glass/nip
j : 100ml (small glass)
k 50ml miniature airplane bottle
l 25ml tot
mother (please specify)

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

How many husbands/wives have you had?

FOR WOMEN ONLY: Have you ever been pregnant? *(please tick)* 1 Yes No 2

If yes, how many times have you been pregnant? ☐☐

If yes, how many times have you had a miscarriage? ☐☐

If yes, how many of your children were born alive? ☐☐

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

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

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

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

ALL: How many boyfriends/girlfriends have you had?

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

Age now
(from previous page) _____

Age at first birth _____

Age at last birth _____

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

If Yes, did your periods stop: ☑

1. naturally	2. due to surgery	3. due to medical treatment	4. due to IC use	5. other	6. unknown

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

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

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

Have you ever had a 'pap' smear?☑

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

L: Describe your usual or past occupation (eg. Driver, machine operator)..... ☐☐☐

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

What language do you speak most at home? ☐

What language does/did your father speak? ☐

What language does/did your mother speak? ☐

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

Study number: _____

Cancer Epidemiology Research Group **Case-Control Study**

Antiretroviral Drug Usage

*Please ask **ALL PATIENTS** the following questions AFTER you have completed the standard questionnaire. Make sure that you emphasize that the information is voluntary and confidential.*

Have you ever been tested for HIV (before current test)? **Yes** **No** (circle one)

If YES, proceed: Were you tested: **before this illness / at time of current illness only** (circle one)

Were you given the test results? **Yes** **No** (circle one)

If YES, proceed: Are you willing to disclose your status? **Yes** **No** (circle one)

If YES, proceed: Are you HIV: **positive** **negative** (circle one)

Date of last/current test (mm/yyyy): __________

If POSITIVE, proceed:
Have you ever taken anti-Retroviral medicines for your HIV infection? **Yes** **No** (circle one)

(Be careful to explain to the patient that we mean "Western" medicine/pills/capsules specifically for the HIV itself, NOT for opportunistic infections.)

If YES, Proceed:

From: _____ (start date) To: _____ (end date)

From: _____ (start date) To: _____ (end date)

From: _____ (start date) To: _____ (end date)

The ARV drugs were provided by (tick all that apply):

- ☐ Private practitioner
- ☐ Public hospital/clinic
- ☐ NGO
- ☐ Study/ clinical trial

Thank the patient for answering these extra questions even if they only answered the first one.

JOHANNESBURG HOSPITALS NHLS/ CERG CANCER EPIDEMIOLOGY STUDY

Interviewer check list and patient CONSENT FORM

Note to the Interviewer: **study no:**_____

This is a checklist for you and a Consent Form for the patient.
Please ask the questions in your own words.
Tick ☑ the boxes and fill in the blanks ***as you complete that task.***

My name is _____*(name of interviewer)*

I work at the National Health Laboratory Service and would like to ask you some questions.
Please ask:

1. *Has the patient ever been diagnosed with a* ***cancer prior to this cancer?*** *yes ☐ no ☐ not known ☐*
   If yes, thank the patient for their time but DO NOT proceed with the interview.
2. *When was the patient was* ***diagnosed with the PRESENT CANCER?:*** ☐ *more than 6 months ago*
   ☐ *less than 6 months ago*
   ☐ *has not yet received diagnosis.*

If the patient was diagnosed ***more than 6 months ago****, thank the patient but DO NOT INTERVIEW THE PATIENT.*
If the patient was diagnosed less than 6 months ago, make sure that:

- *the patient has* ***NOT had any chemotherapy or radiotherapy;***
- *the patient has* ***NOT been interviewed for this study before***

.....*Tick the box once you have done this.* ☐

A: We would like you to take part in a study to find out if your exposure to substances in the environment, your circumstances and habits, your occupation, previous illnesses, and/or inherited factors play a role in the illness you have developed.

We have chosen a group of patients from this ward / clinic because of their current illness so that we can make comparisons between illnesses. We are asking you to spend 20 – 30 minutes answering questions about yourself, your family, and your work. *Do you have any questions so far?*

You may refuse to answer any questions if you choose. All answers will be treated confidentially. If you decline to participate or if you decline to answer some questions this will not affect your treatment in any way.

This is a consent form. It says in writing what I have just told you. Please sign and date it here to show that you have understood what I have told you and that you willingly agree to answer questions.

Signature_____ Date _____

B: We would also like to take 3 – 4 teaspoons of blood from you for future research into the causes of your illness. No names will be attached to the sample tubes.

The blood we take for this study will not be tested immediately; it will be frozen. There is no time limit to how long it will be stored. It may be tested for evidence of various infections including HIV; it may be tested for substances (cells, proteins, other body chemicals) which might make it easier for you to have become ill. It may also be tested for inherited factors which might make it more likely for you to have gotten the illness you now have. These tests will help us to understand your and other patients' illness better and, perhaps, prevent others from getting it. We only need to take blood from you once.

This is a consent form. It says in writing what I have just told you. Please sign and date it here to show that you have understood what I have told you and that you willingly agree to have your blood collected.

Signature_____ Date _____

Signature of witness _____Date _____
(in case verbal consent given)

For enquiries telephone: Dr. Lara Stein 011 489 9170 lara.stein@nhls.ac.za
Margaret Urban 011 489 9713 margaret.urban@nhls.ac.za

NATIONAL HEALTH
LABORATORY SERVICE

MRC/NHLS/WITS
Cancer Epidemiology Research Group

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30 October 2007

Prof. P.E. Cleaton-Jones
Chairperson
Committee for Research on Human Subjects (Medical)
University of the Witwatersrand Medical School

RE: PERMISSION FOR AUS T. ALI TO USE JOHANNESBURG CASE CONTROL STUDY DATA

Dear Professor Cleaton-Jones

As Acting Director of the Cancer Epidemiology Research Group, I herewith give permission for Aus T. Ali (student number: 0102620J) to analyze and report on limited data from the Johannesburg case control study (ethics clearance number: M981119) for the completion of his MSc (Biostatistics and Epidemiology) in the School of Public Health. He will only be given access to data specific to his MSc project, entitled 'Risk Factors for Endometrial Cancer among Black South African women in Johannesburg'. He has signed a confidentiality agreement with regard to the use of this data.

I am currently on maternity leave, and can be contacted on 011-7841379 or 082-8964657 if necessary.

Yours sincerely,

Lara Stein.

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Stein

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER 40445**
PROJECT	Cancer Case-Control Study (was M981119)
INVESTIGATORS	Dr L Stein
DEPARTMENT	MRC/NHL/CANSA/WITS
DATE CONSIDERED	04.04.30
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 04.04.30 **CHAIRPERSON** .....

(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor :

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

THE END