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The practices, knowledge, and attitudes about common hereditary cancers: Survey of General Practitioners in Johannesburg



Chantel van Wyk

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Masters of Science in Medicine in Genetic Counselling.

Johannesburg, South Africa, 2008

DECLARATION

I, Chantel van Wyk, hereby declare that this research report is my own work. It is being submitted for the degree of Masters of Science in Medicine at the University of the Witwatersrand, Johannesburg. It is the first time this report will be submitted for a degree and has not been submitted before at any other University.

……

Chantel van Wyk

…… day of……. 2008.

I dedicate this research report to all those who have survived cancer, and in memory of those who lost their lives and loved ones because of this disease.

In particular: to Christel van Wyk, Thomien Brits, Nancy Rudolf, Dreyer Bester, 'Klein' Hannes du Toit, and Donnald Dey, with love

Also, to my beloved family, friends and boyfriend, Jaco Brand who have supported me always throughout my studies.

ABSTRACT

INTRODUCTION: Cancer is one of the most common diseases in the developed world and both genetic and environmental factors play a role in the development of cancer. About 5-10% of all cancers are due to predisposing genes. Some of the more common inherited cancer syndromes are hereditary breast and ovarian cancer (HBOC) and two colorectal cancer syndromes, familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). Recognition of cancer susceptibility can allow "at risk" individuals and families to participate in cancer risk assessment, genetic testing, and various cancer prevention strategies. As the public is becoming more aware of inherited cancers, it is expected that there will be an increasing demand for genetic services and testing. For this reason more GP involvement is required to assess patients and families at risk and refer them appropriately. Since the Clinical and Counselling Section, Division of Human Genetics, National Health Laboratory Service and University of the Witwatersrand, Johannesburg is establishing a cancer genetics service it woud be of great value to assess the GPs' practice, knowledge and attitudes with regards to cancer genetics and this was therefore the aim of this study.

METHODOLOGY: A quantitative, exploratory research design was chosen and GPs in the Johannesburg area were selected as subjects. After the completion of a pilot study a research package was mailed to 196 GPs. This package was sent out twice and both times the GPs were asked to respond within 3-4 weeks. The final sample consisted of 61 GPs and the data were analysed using descriptive statistics.

RESULTS: Of the 61 participants more male GPs (42, 69%) than female GPs (19, 31%) responded and there were about an equal number of GPs practicing alone (29, 48) and in a multiple practice (32, 52%). Twenty two (33%) of the GPs had never had personal experience of cancer. **Practices:** The GPs made use of several cancer screening procedures but obtained limited information on cancer history from their patients particularly from second degree relatives and about age of onset. Very few subjects (15, 25%) reported that they assess patients' risk for inherited cancer susceptibility and only 22 (36%) reported that they refer patients to other facilities for risk assessment and genetic testing. **Knowledge:** Only 32 (52%) of the GPs were aware of genetic testing facilities and 54 (86%) reported never having

received advertising material to promote genetic testing for cancer susceptibility services. They also are not aware of genetic counselling facilities but do feel patients should have genetic counselling by a genetic counselor, clinical geneticist or oncologist before genetic testing. Even though genetic testing for inherited cancer susceptibility is only available at some academic institutions, mostly on a research basis, the GPs seem to be unaware of the availability of genetic testing in South Africa for colorectal cancer genes (8, 13% and 9, 15%) but 28 (46%) knew about breast cancer genes. They were not aware of the autosomal dominant inheritance of hereditary breast cancer and the percentage of individuals with breast cancer who carry the *BRCA1/2* gene nor did they know the penetrance of HNPCC genes. **Attitudes:** The subjects' attitudes to genetic testing for inherited cancer susceptibility were positive although they reported that they were unaware of several general factors regarding cancer genetic testing. The GPs had limited knowledge about inherited cancers and do not take an active part in cancer genetic management. However, 53 (87%) of the GPs reported interest in learning about these services and expected to play a role in cancer genetics in the future.

CONCLUSION: The findings of this study suggest that there is a need to educate GPs about the basic cancer genetic concepts so that they can identify patients at risk for an inherited cancer syndrome. They need to be informed about the genetic tests currently available for the inherited cancer syndromes, and about genetic counselling and testing facilities.

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GLOSSARY

The terms in the glossary are adapted from Dorland's Illustrated Medical Dictionary (2003).

Autosomal dominant inheritance: The expression of a trait in the heterozygous state, which is located on an autosome.

Colonoscopy: An examination in which the doctor looks at the colon through a flexible, lighted instrument called a colonoscope.

DNA: The primary carrier of genetic information. It is a macromolecule usually consisting of a polynucleotide chain, phosphate and deoxyribose sugar.

Exon: The DNA base sequences of a gene that encode amino acids. Exons are interspersed with non-coding regions called introns.

Gene: A sequence of DNA that codes for a particular protein.

Mastectomy: Excision of the breast.

Microsatellite: A small run of tandem repeats of nucleotides (usually less than 0.1kb) of a simple DNA sequence, usually 1-4 base pairs in length.

Mutation: Alterations in the DNA sequence or chromosome structure that may alter the function of a gene and may cause disease.

Oncogene: A gene capable under certain conditions of causing the initial and continuing conversion of normal cells into cancer cells.

Oophorectomy: The removal of an ovary or ovaries.

Polyp: A mass of tissue that projects into the colon.

Prophylactic surgery: Surgery performed before a particular phenotype manifests itself in an individual.

Salpingo-oophorectomy: (Salpingo) – surgical removal of a uterine tube and ovary.

Sigmoidoscopy: A procedure in which the doctor looks inside the rectum and the lower part of the colon (sigmoid colon) through a lighted tube.

Tumour: An abnormal mass of tissue that results from excessive cell division. They may either be benign (not cancerous) or malignant (cancerous).

LIST OF ABBREVIATIONS

AD	Autosomal dominant
AAPC	Attentuated adenomatous polyposis coli
APC	Adenomatous polyposis coli gene
BRCA	Breast cancer
BRCA1	Breast cancer susceptibility gene 1
BRCA2	Breast cancer susceptibility gene 2
BSE	Breast self examinations
CA-125	Cancer antigen 125
CANSA	Cancer Registry of South Africa
CBE `	Clinical breast examinations
CHRPE	Congenital hypertrophy of the retinal pigment epithelium
CRC	Colorectal cancer
DA	Diploma in anaesthesia
DCH	Diploma in child health
DFM	Department of family medicine
DNA	Deoxyribonucleic acid
DTMH	Diploma in tropical medicine and hygiene
FAP	Familial Adenomatous Polyposis
FDR	First degree relative
FOBT	Fecal occult blood test
GP	General practitioner
HBOC	Hereditary breast and ovarian cancer
HER2	Human epidermal growth factor receptor 2
HNPCC	Hereditary Nonpolyposis Colorectal Cancer
HRT	Hormone replacement therapy
hMLH1	human MutL homologue 1
hMSH2	human MutS homologue 2
hMSH6	human MutS homologue 6
MEN	Multiple endocrine neoplasia

MMR	Mismatch repair genes
MSI	Microsatellite instability
MYH	Mut Y human homolog
NCR	National Cancer Registry
NHLS	National Health Laboratory Service
NF	Neurofibromatosis
OC	Ovarian cancer
PARP	Poly (ADP-ribose) polymerase
SA	South Africa
SAIMR	South African Institute for Medical Research
SDR	Second degree relative
sDNA	Stool DNA testing
TS	Tumour suppressor gene
USA	United States of America

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

This chapter provides a brief overview of cancer, and two hereditary cancer syndromes, namely hereditary breast and ovarian cancer (HBOC) and colorectal cancer (CRC). Genetic counselling, in particular, cancer counselling is discussed. An overview of previous research, regarding GPs' practices and their understanding of hereditary cancers is also presented.

1. LITERATURE REVIEW

1.1. CANCER

Cancer is one of the most common diseases in the developed world. Approximately 1 in 3 individuals will develop cancer in their lifetime (Futreal, Kasprzyk, Birney et al., 2001). In South Africa, the national cancer registry (NCR), which was established in 1986 by the South African Institute for Medical Research (SAIMR), now the National Health Laboratory Service (NHLS), keeps an updated registry of cancers diagnosed by all the pathology laboratories in South Africa. The latest available results reported a total of 59 592 and 59 908 new histologically diagnosed cancer cases in 1998 and 1999 respectively (Mqoqi, Kellett, Sitas et al., 2004).

Cancer develops from a multi-step process and both genetic and environmental factors play a role; therefore cancer can occur as a sporadic event, or can be due to predisposing genes which can be inherited. Identification of these genetic and environmental influences are central aims of cancer research.

Cells function in response to various biochemical signals and are programmed to divide, differentiate into mature cells, and die by means of programmed cell death (apoptosis). Changes in the cell signalling pathways, that occur as a result of various genetic and environmental insults, affect normal cell function and could eventually lead to cancer development in various cells and tissues. Several genes in these cells are known to play a role in cancer development. These genes, contributing to cancer, are known as proto-oncogenes, tumour suppressor genes, and mismatch repair genes, and are discussed in more detail later in this chapter.

Environmental factors that play a role in cancer development include sunlight (ultra violet radiation), chronic electromagnetic field exposure, ionising radiation, parasites, viruses, cellular oxygen deficiency, pesticide and herbicide residues, dioxins, unhealthy diet and free radicals (Wogan, Hecht and Felton et al., 2004; Emdin, 2004; Miller, Keku, Satia et al., 2007; Rudel, Attfield, Schifano et al., 2007).

Any individual is at risk for developing cancer during his/her lifetime. Ultimately all cancers are the result of genetic changes which damage or mutate deoxyribonucleic acid (DNA) (Futreal et al., 2001). When a mutation in an individual's genes occurs at a somatic level, cancer is "acquired". These mutations are present in 90-95% of all cancers (Harper, 2004). The remaining 5-10% of cancers are due to mutations that occur in the germline, thereby predisposing an individual to develop cancer (Harper, 2004). This is important because these mutations in the germline can be passed on, and thus will not only have serious consequences for an individual but also for subsequent generations (Turnpenny and Ellard, 2005). These germline mutations can cause a range of hereditary cancer syndromes.

1.1.1. Cancer genes

Proto-oncogenes, tumour suppressor genes, and DNA repair genes are known to play a role in cancer development. Each of these groups of genes plays a role in the control of various cell regulation pathways and/or cell functions. Currently, it is estimated that about 1% of the total human genome is involved in cancer pathogenesis, and as cancer research progresses more genes are being identified. For example, currently there are 368 genes known which, if functioning abnormally, are involved in cancer pathogenesis, compared to the 291 reported in 2004 (Futreal, Coin, Marchall, et al., 2004; Cancer Genome project, Jan 2008). The majority of these genes are tumour supressor genes. Of the 291 genes involved in cancer pathogenesis described by Futreal et al (2004) about 80% show somatic mutations, 10% demonstrate germline mutations and 10% show a combination of both germline and somatic mutations.

Proto-oncogenes are known to play a role in signal transduction, a complex stepwise signalling pathway that controls cell proliferation and differentiation through transporting messages to and from the cell membrane through the cytoplasm into the nucleus (Turnpenny and Ellard, 2005). Point mutations and chromosome translocations can cause a disruption of the normal cell function and lead to over-activity of the signalling pathways and over-production of proteins and thus transform the proto-oncogene into an oncogene. By 2005,

approximately 100 oncogenes had been identified (Futreal et al., 2001; Turnpenny and Ellard, 2005).

Tumour suppressor genes are known as protective genes, regulators or inhibitors. These genes suppress and regulate cell growth and death, and control cell division by encoding various proteins. Mutations in these genes cause a loss of control of cell growth. Tumour suppressor genes act recessively at a cellular level and obey the Knudson's two hit hypothesis (Knudson, 1971). This theory suggests that genes on both of an individual's chromosomes need to be mutated to lead to cancer. If an individual inherits a mutated gene on one chromosome they will need another "hit" (mutation) in their second gene in order to develop cancer. Examples of these genes include *BRCA1*-, *BRCA2*- (causing breast and ovarian cancer) and *APC*-[causing familial adenomatous polyposis (FAP)].

DNA repair genes function mainly in correcting errors that have occurred when DNA replicates. If the DNA repair gene fails to repair the errors, mutations may accumulate in many genes, resulting in dysfunction and cancer development. Examples of DNA repair genes include the mismatch repair genes, *hMLH1*, *hMSH2* and *hMSH6*, mutated in hereditary non polyposis colorectal cancer (HNPCC) and the *MYH* gene mutated in autosomal recessive FAP (Firth and Hurst, 2006).

1.1.2. Diagnosis of hereditary cancers

Many cancers show familial clustering, and seem to be due to inherited predisposing genetic factors (Lindor, Greene, Mayo et al., 1998). Some of these so-called cancer syndromes are Hereditary breast/ovarian cancer syndrome (HBOC), Hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, Li-Fraumeni syndrome, Multiple endocrine neoplasia (MEN) syndrome types 1 and 2, Neurofibromatosis (NF) types 1 and 2, von Hippel-Lindau disease, Bloom syndrome and familial pancreatic cancer. For the purposes of this study, HBOC and colorectal cancer (CRC) syndromes will be discussed in detail.

There are several diagnostic clues that can indicate if an individual or family is at risk for a hereditary cancer (Lynch, Lynch, Casey et al., 1997; Lindor et al., 1998; Harper, 2004; Lalloo, Kerr, Friedman et al., 2006). These include:

(1) Two or more first and/or second degree relatives with the same common cancer
(2) Several first and/or second degree relatives who have a related type of cancer
(3) Two members in the family with the same rare cancer
(4) Two members in the family with related rare cancers
(5) Early age of onset for the specific cancer type
(6) Bilateral cancer
(7) Multi-focal tumours
(8) More than one type of associated cancer in one individual

This information is essential to determine whether an individual or family is at risk of developing a hereditary cancer syndrome. Recognition of cancer susceptibility can allow "at risk" individuals and families to participate in cancer risk assessment, genetic testing, and various cancer prevention strategies like intensive surveillance, prophylactic surgery and cancer prevention therapy (Kausmeyer, Lengerich, Kluhsman et al., 2006). Diagnosis of a hereditary cancer syndrome usually depends on gathering detailed information about critical family members. Critical family members do not only include the affected individual, but also all the 1st degree relatives (siblings, offspring and parents), second degree relatives (aunts, uncles and grandparents), and cousins. Cancer details such as the type of cancer, primary site of tumour, if metastasis occurred, bilateral tumours, the age of onset, and the cause and age of death are important to assess. Tumour histology should also be fully documented (Hoskins, Stopfer, Calzone et al., 1995).

Risk assessment can divide individuals or families with a cancer history into three risk categories namely: average, moderate and high. Cancers in average risk families are not usually considered to be a result of a predisposing inherited cancer gene and these individuals should follow screening protocols as set for the general population. Moderate risk families have a family history of cancer and include some affected individuals; the age of onset is older and the cancer cause is usually multi-factorial. High risk families have a more striking family history including multiple affected members. They show a clear autosomal dominant (AD) inheritance pattern, and early age of cancer onset (Lalloo et al., 2006). The offspring of a mutation positive individual for an autosomal dominant hereditary cancer has a 1 in 2 or 50% chance of inheriting the predisposition to cancer. For these high risk individuals genetic testing is offered (if available), and stricter surveillance procedures are available. Once an

individual is found to be a mutation carrier for a hereditary cancer syndrome they might consider the option of prophylactic surgery.

1.2. SPORADIC AND HEREDITARY BREAST AND OVARIAN CANCER

1.2.1. Sporadic breast and ovarian cancer

Breast cancer (BRCA) and ovarian cancer (OC) are two of the most common cancers that occur in females. About 90-95% of these cancers are sporadic (Harper, 2004).

1.2.1.1. Incidence

According to the NCR, a total of 5901 new histologically diagnosed cases of BRCA were reported in 1998-1999 in SA, making this the commonest type of cancer amongst women. Over these two years about 1 in 27 females were estimated to be at risk of developing BRCA in their life time (Mqoqi et al., 2004). The lifetime risk is highest in white females, followed by coloured and Asian females sharing a similar incidence, and black females having the lowest incidence rate (Sitas, Madhoo, Wessie et al., 1998; Mqoqi et al., 2004) (See Table 1.1).

Ovarian cancer has been described as the seventh most common cancer among women and the lifetime risk of developing this cancer is 1/180 (Mqoqi et al., 2004). In SA it is estimated that the lifetime risk in the white population of developing ovarian cancer is higher than that of the black, coloured and Asian populations (See Table 1.1). No data on BRCA and OC occurring together in the SA population have been documented.

Table 1.1: Lifetime risks for breast and ovarian cancer by population group in SA in 1999 (Mqoqi, 2004).

	Breast cancer LR[1]	**Ovarian cancer LR[1]**
White	1/12	1/82
Black	1/49	1/313
Coloured	1/18	1/159
Asian	1/18	1/121

[1] LR: Lifetime risk suggesting that every 1 in X number of individuals will develop cancer between the ages of 0 and 74 years.

1.2.1.2. Risk factors

Every woman is at risk of developing breast and/or ovarian cancer in her lifetime. The majority of sporadic cases are reported in post-menopausal women (55 years and older) (Philips, Glendon and Knight, 1999; Norman, Bradshaw, Groenewald et al., 2006). Breast and ovarian cancer have a multifactorial aetiology and it is therefore suggested that reproductive, hormonal, environmental, as well as genetic factors play a role in cancer development. The risk factors that increase the risk of developing breast cancer are summarized in Table 1.2.

Table 1.2: Factors increasing the risk of developing breast cancer (Adapted from Hsieh, Trichopoulos, Katsouyanni et al., 1990; Kelsey, Gammon, and John, 1993; Lipworth, 1995; Lim, Hearle, Shah et al., 2003; Reeves, Yawitch, van der Merwe et al., 2004; Brody et al., 2007; Rudel et al., 2007).

	Risk factors
Reproductive factors	• **Early menstruation** (before age 12) • **Late menopause** (after age 54) • Nulliparous woman • First child at a later age, over age 30 years
Hormonal factors	• Combined oral contraceptive pill • **Hormone replacement therapy** (HRT)
Environmental factors	• Obesity • **Alcohol consumption, and smoking** • Exposure to estrogen-like chemicals in pesticides and other industrial products • **Radiation**
Genetic factors	• Breast cancer predisposing genes, *BRCA1* and *BRCA2* genes • Strong family history of breast and/or ovarian cancer with AD inheritance pattern • High risk population groups such as Afrikaners and Ashkenazi Jewish • Presence of other rare cancer causing syndromes such as Fanconi anaemia, Peutz-Jeghers syndrome.

Pregnancy (before the age of 30 years), breast feeding, healthy diet and exercise are protective risk factors and therefore decrease the risk of developing breast cancer (Brody, Rudel, Michels, et al., 2007).

1.2.1.3. Detection and management

The Cancer Registry of South Africa's (CANSA) recommendations for healthy breast care include: monthly breast self examinations (BSE) for all women, thorough clinical breast examinations (CBE) done by a health professional every 1-2 years and mammography screening annually after the age of 50 years.

Breast and ovarian cancer can be treated surgically and in addition treatments such as chemotherapy, radiation therapy and the use of chemoprevention drugs such as tamoxifen® are available. The type of treatment will be based on the site and stage of the cancer. There are various oncology centres across SA that manages cancer patients.

1.2.2. HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

Lynch and Krush (1971) studied three families which included members with both breast and ovarian cancer, where they described hereditary breast-ovarian cancer syndrome (HBOC). Since then, research has focused on finding genetic as well as environmental factors for this hereditary cancer syndrome.

Approximately 5-10% of all breast and/or ovarian cancer cases are caused by predisposing genetic factors, HBOC is inherited in an autosomal dominant manner with incomplete penetrance (Harper, 2004). Thus, if an individual carries an inherited mutated gene, he/she is predisposed to develop the cancer syndrome. However, with incomplete penetrance it does not necessarily mean they will develop cancer in their lifetime. Individuals at risk of carrying a cancer predisposing mutation can be identified by using basic cancer risk criteria and assessing their family history.

The genes responsible for causing HBOC syndrome are two tumour suppressor genes, Breast cancer susceptibility gene 1 (*BRCA1)* and Breast cancer susceptibility gene 2 (*BRCA2).* These two genes were found to be responsible for about 84% of HBOCs (Easton, Bishop, Ford et al., 1993; Ford, Easton and Stratton, 1998). Both of these genes are large with many exons (Miki, Swensen, Shattuck-Eidens et al., 1994; Wooster, Bignell, Lancaster et al., 1995)

and mutations may occur at any site throughout these genes. Certain characteristics in tumour pathology and hormonal constitution can be used as clues to distinguish between *BRCA1* and *BRCA2* mutations (Hedenfalk, Duggan, Chen et al., 2001).

1.2.2.1. Breast cancer susceptibility gene 1 (*BRCA1*)

The *BRCA1* gene was mapped to chromosome 17q21 in 1990 (Hall et al., 1990) and identified in 1994 (Miki et al., 1994) as a susceptibility gene for breast and ovarian cancer. The gene consists of 24 coding exons and encodes a 220-kd protein of 1863 amino acids and frameshift or nonsense mutations are mostly present (Minki et al., 1994; Deng, 2006). To date approximately 800 *BRCA1* mutations have been identified of which most are unique to a family (Petrucelli, Daly, Culver et al., 2007).

BRCA1 germline mutation carriers have an estimated 44 - 78% lifetime risk to age 70 years for developing breast cancer, and an 18 - 54% lifetime risk for developing ovarian cancer (Firth and Hurst, 2006). There is also a 48% risk of developing contralateral breast cancer by the age of 50 years, and 64% by the age of 70 years (Haites et al., 2002). Such individuals are also at further risk for developing pancreatic, colon, prostate, endometrial, and cervical cancer (Ford, Easton, Bishop et al., 1994; Firth and Hurst, 2006).

Histologically, *BRCA1* tumours were mostly found to be estrogen, progesterone and epidermal growth factor 2 (HER-2) receptor negative (Lakhani, van de Vijver, Jacquemier et al., 2002; Reis-Filho and Tutt, 2008).

1.2.2.2. Breast cancer susceptibility gene 2 (*BRCA2*)

The *BRCA2* gene was mapped in 1995 to chromosome 13q12-q13 (Collins, McManus, Wooster et al., 1995). This gene consists of 27 exons and encodes a 380-kd protein consisting of 3418 amino acids (Wooster et al., 1995; Petrucelli, Daly, Culver et al., 2007). Similar to *BRCA1,* about 800 *BRCA2* mutations have been identified and again only a small number of these mutations have been identified repeatedly in unrelated families (Petrucelli et al., 2007).

Female carriers of a *BRCA2* mutation have a 31 - 56% risk of developing breast cancer and a 2.4 - 19% risk of developing ovarian cancer by 70 years of age. Male *BRCA2* mutation carriers have an estimated risk of 6% by age 70 years of developing male breast cancer (Firth and Hurst, 2006). Individuals are also at risk for developing prostate and pancreatic

cancers (Hahn, Greenhalf and Ellis, 2003), gall bladder/bile duct, larynx, oesophagus, colon, stomach cancer and malignant melanomas (Easton, Steele, Fields et al., 1997; Firth and Hurst, 2006).

Unlike *BRCA1* related tumours, *BRCA2* tumours seem to test positive for both hormone receptors (oestrogen and progesterone*)* (Loman, Johannson, Bendahl et al., 1998).

1.2.2.3. Founder mutations

A founder mutation can be described as a mutation that is commonly found in a specific population group as a result of having a common ancestor. A founder effect may arise when a population become isolated and inbred.

Founder mutations for HBOC syndrome have been reported in German, Polish, Scandinavian, Icelandic, and the Finnish population groups (Haites et al, 2002). In the Ashkenazi Jewish population, three founder mutations have been identified- 185delAG and 5382insC in the *BRCA1* gene, and 6174delT in the *BRCA2* gene (Streuwing, Abeliovich, Peretz et al., 1995; Streuwing, Hartge, Wacholder et al., 1997). Founder mutations have also been identified in the Afrikaner population. Five Afrikaner families were found to have an *E881X* mutation (Reeves, et al., 2004). To date, there are three mutations routinely tested for in Afrikaners namely E881X and 1493delC in the *BRCA1* gene, and 8162delG in the *BRCA2* gene (van der Merwe and van Rensburg, 2007; van Rensburg, van der Merwe, Sluiter et al., 2007). Van Rensburg et al (2007) determined that these unique Afrikaner mutations are found in 93% of HBOC families.

1.2.2.4. Surveillance, treatment and management options for *BRCA1/2* carriers

Several prevention and detection strategies are available to *BRCA1/2* carriers (see Table 1.3). Surveillance tests are used to identify and diagnose breast cancer and/or ovarian cancer early. Screening should commence at about 25-35 years of age or a few years before the earliest diagnosis of breast and/or ovarian cancer, or any other related cancer, in a family (Horsman, Wilson, Avard et al., 2007). Since *BRCA1/2* carriers are also at risk of developing other cancers, the individual and medical professionals should be alerted.

Prophylactic options include bilateral mastectomy and/or salpingo-oophorectomy (see glossary). Bilateral prophylactic mastectomy reduces the risk of developing breast cancer by

about 91%, and bilateral oophorectomy (see glossary) reduces breast cancer risk by approximately 50% and ovarian cancer risk by 80-95% (van Sprundel, Schmidt, Rookus et al., 2005; Domcheck and Rebbeck, 2007).

Table 1.3: Proposed management strategies for female *BRCA* 1/2 mutation carriers (adapted from Fasouliotis and Schenker, 2000; Warner, Plewes, Hill, et al., 2004; Horsman et al., 2007).

Disease	Surveillance options	Prophylactic options
Breast cancer	Monthly breast self examinations from 18 years of age Six monthly or yearly clinical breast examination* Annual Mammography scans* or Annual breast ultrasound scans* or Annual breast magnetic resonance imaging*	Prophylactic mastectomy Chemoprevention drugs Oophorectomy
Ovarian cancer	Annual cancer antigen 125 (CA-125) screening* Annual ovarian ultrasound scans* Use of oral contraceptives	Salpingo-oophorectomy

*** From about age 25-35 years**

Chemoprevention drugs such as Tamoxifen®, Raloxifen®, Aromatase® inhibition and Fenretinide® can be used as treatment or prophylaxis for breast cancer and are known to reduce the incidence of further breast cancer (Newman and Vogel, 2007; Richardson, Johnston, and Pater et al., 2007). Another prophylactic method, which shows promise in actively playing a role in repairing DNA single-strand breaks, is Poly (ADP-ribose) polymerase (PARP). It is used as a therapeutic intervention as it targets the DNA repair defects in breast cancer mutant cells (Farmer, McCarbe, Lord, et al., 2005; De Soto and Deng, 2006). This drug is currently not available in SA.

1.3. SPORADIC AND HEREDITARY COLORECTAL CANCER

1.3.1. SPORADIC COLORECTAL CANCER

Colorectal cancer (CRC), also called colon cancer or bowel cancer is a common cancer affecting both males and females. Cancer commonly arises from benign adenomatous polyps in the colon. Both genetic and environmental influences play a role in the development of

CRC Burt (1996) found that potentially definable genetic components exist in 15-35% of CRCs and the remaining 65- 85% are sporadic.

1.3.1.1. Incidence

In SA, CRC affects all ethnic groups. The NCR's report on the incidence of CRC between 1998 and 1999 showed significant differences between the various ethnic groups in SA (White, Black, Asian, and Coloured). Differences between genders were also noted (Mqoqi et al., 2004). White males and females have a greater lifetime risk for CRC compared to the other population groups, and black males and females have the lowest risk for developing CRC in their lifetime (see Table 1.4). In 1999, CRC was found to be the fourth leading cancer in males (lifetime risk of 1 in 83) and the third leading cancer in females (lifetime risk of 1 in 131) in SA (Albrecht, 2006; Mqoqi et al., 2004).

Table 1.4: The lifetime risk of developing CRC for males and females in different SA population groups (statistics of CRC incidence in 1999, adapted from Mqoqi et al., 2004).

	Females LR[1] for CRC	**Males LR[1] for CRC**
White	1/48	1/31
Black	1/385	1/286
Asian	1/99	1/51
Coloured	1/89	1/56

[1]LR: Lifetime risk suggesting that every 1 in X number of individuals will develop cancer between the ages of 0-74 years.

1.3.1.2. Risk factors

Various factors can increase an individual's risk of developing CRC. This cancer is more common in older individuals (older that 60 years of age). It is also known that certain types of polyps in the colorectum are more prone to cancer development that others. Other risk factors can be seen in Table 1.5. Protective factors include a healthy diet and a healthy lifestyle (Potter, 1999).

Table 1.5: Factors increasing an individual's risk for colorectal cancer (Reviewed in Mqoqi et al., 2004; Wogan et al., 2004; Chao, Thun, Connell et al., 2005; Park, Hunter, Spiegelman et al., 2005).

	Risk factors
Age	• Risk of CRC increase with increasing age. Most common in individuals older that 60 years
Genetic factors	• Strong family history of CRC with a AD inheritance pattern • FAP and HNPCC mutation carriers
Environmental factors	• Alcohol consumption and smoking • Physical inactivity • High calorie diets with the intake of lots of animal fats including consuming over done red meat products • Virus exposure in particular human papilloma virus

1.3.1.3. Detection and management

CRC can be detected by making use of fecal occult blood test (FOBT), endoscopy, sigmoidoscopy, colonoscopy and stool DNA testing (sDNA) (Järvinen, Aarino, Mustonen, et al., 2000). Individuals in the general population should initiate screening modalities at 50 years of age and every five years thereafter (CANSA, 2007).

1.3.2. HEREDITARY COLORECTAL CANCER SYNDROMES

Hereditary forms of CRC are due to the inheritance of a single altered gene which predisposes an individual to develop cancer. Two of the most common forms of hereditary CRC include familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC) which account for <1% and 1-7% of all inherited CRC respectively (Burk, Petersen, Lynch, et al., 1997; Jo and Chung, 2005). Others include Gardner syndrome, Turcot syndrome, attentuated adenomatous polyposis coli (AAPC), and hereditary flat-adenoma syndrome (Lindor et al., 1998).

1.3.2.1. Familial adenomatous polyposis

Familial adenomatous polyposis (FAP) was one of the first inherited conditions identified that predisposes individuals to develop colorectal cancer (Kinzler, Nilbert, Su et al., 1991).

The disease affects the colon as well as the stomach, duodenum, jejunum and ileum (Goldberg, 1997). FAP is defined as the presence of more than 100 polyps (see glossary) in an individual's colorectum. The polyps appear in puberty and lead to clinical manifestations including diarrhoea, rectal bleeding and features of anaemia (Groden, Thliveris, Samowitz et al., 1991; reviewed in Järvinen, 2004). Approximately 66% of individuals carrying a FAP gene mutation will have cancer by a mean age of 39 years (Coleman and Tsongalis, 2002). Several other features such as congenital hypertrophy of the retinal pigment epithelium (CHRPE), dentiginous cysts and fundic gland polyposis of the stomach, periampullary carcinomas, osteomas, epidermoid cysts, thyroid cancer, brain tumours, and rarely hepatoblastomas are associated with FAP and can be indicative of this diagnosis (Coleman and Tsongalis, 2002; Lalloo et al., 2006).

FAP follows an autosomal dominant inheritance pattern and is predominantly due to mutations in the adenomatous polyposis coli (*APC)* gene, a tumour suppressor gene situated on chromosome 5q21 (Kinzler et al., 1991). This gene encodes a 312 kDa protein with multiple domains binding with several proteins i.e. beta-catenin, axin, CtBP, Asefs, IQGAP1, EB1 and microtubules, to ensure normal cellular functioning (Aoki and Taketo, 2007). The mutations in this gene are predominantly due to premature truncation of the APC protein (Powell, Petersen, Krush et al., 1993). Individuals carrying this gene mutation have about a 99% risk of carcinogenesis (Goldberg, 1997; Rozen and Macrae, 2006) and their offspring have a 1 in 2 or 50% risk of inheriting the gene. Over 826 germline mutations in the *APC* gene have been identified in FAP families and the mutation detection rate is estimated at 90% (Beroud, Collod-Beroud, Boileau et al., 2000; Solomon and Burt, 2007). The mutation most frequently found in FAP families in most population groups is a 5 base pair deletion in codon 1309 of the *APC* gene. It is associated with an earlier age of presentation of colonic adenomas and a higher number of adenomas present in the colon (Bertario, Russo, Sala et al., 2003; De Rosa, Scarano, Panariello et al., 2003). The above mutation and a 5 base pair deletion in codon 1061 have also been described in two African families (Xhosa and Zulu) although CRC incidence is lower in these individuals (Grobbelaar, Wilken, de Ravel et al., 2002).

Mutations in the Mut Y human homolog (*MYH)* gene on chromosome 1p34.1 are associated with a FAP like condition (attenuated form of FAP), affecting mostly Caucasian individuals, and presenting with a smaller number of adenomas (Baglioni and Genuardi, 2004). Disease

due to mutations in the *MYH* gene seems to follow an autosomal recessive inheritance pattern and therefore siblings of an individual carrying a *MYH* mutation are at 25% risk of also carrying this mutation (Baglioni and Genuardi, 2004).

1.3.2.1.1. Surveillance and management for FAP mutation carriers

Surveillance for at risk family members includes annual sigmoidoscopy from age 11 years and colonoscopy every 3-5 years (Lalloo et al., 2006). Screening should also include a gastroduodenoscopy (Coleman and Tsongalis, 2002; Chen, Phillips, Grist, et al., 2006). If any of the symptoms appear before the age of 10 years, screening and appropriate management should commence immediately.

In the case of a FAP mutation carrier, prophylactic colectomy or protocolectomy with ileal pouch-anal anastomosis is recommended at age 20-25 years or 5 years earlier than the youngest affected family member (Coleman and Tsongalis, 2002).

1.3.2.2. Hereditary non-polyposis colorectal cancer

Hereditary non-polyposis colorectal cancer, also known as Lynch syndrome (Lynch, Shaw, Magnuson et al., 1966; Lynch, Smyrk and Lynch, 1997) is the most common hereditary form of CRC (Hadley, Jenkins, Diamond et al., 2004). Unlike FAP, HNPCC is not defined by multiple polyps, although some polyps may be present. With this condition, tumours mainly arise from a single colorectal lesion and occur more frequently in the proximal colon (Rijcken, Hollema, Kleibeuker et al., 2002). This condition occurs in approximately 1 in 3000 individuals (Firth and Hurst, 2006). Diagnosis of HNPCC can be clinically suspected if one of two standardised set of criteria are met: Amsterdam 1 (Vasen, Mecklin, Khan et al., 1991) revised to Amsterdam 2 (Vasen, Watson, Mecklin et al., 1999), and Bethesda criteria (Rodriguez-Bigas, Boland, Hamilton et al., 1997) (See Table 1.6.)

Table 1.6: Amsterdam I, II and Bethesda criteria for clinical diagnosis of HNPCC.

Amsterdam I criteria: (Vasen et al., 1991).

- Colorectal cancer confirmed histologically in at least three relatives, one being a first degree relative (FDR) of the other two
- Disease occurrence in at least two successive generations
- Age of diagnosis earlier than 50 years in at least one individual
- Exclusion of FAP

Amsterdam II criteria: (Vasen et al., 1999).

At least three relatives diagnosed with a HNPCC-associated cancer (colorectal, endometrial, ovary, stomach, hepatobiliary, small bowel, brain, ureter or renal pelvis and skin), tumours histologically verified where possible.

Including the presence of the following criteria:

- One case a FDR of the other two
- At least two successive generations affected
- At least one case diagnosed before the age of 50
- Exclusion of FAP

Bethesda criteria: (Rodriguez-Bigas et al., 1997).

- Amsterdam criteria must be met in family

Or

- Two HNPCC related malignancies, including synchronous and meta-chronous colorectal cancers or associated extra-colonic cancers

Or

- Individuals with colorectal cancer and one FDR with colorectal cancer and/or HNPCC related extra-colonic cancers and/or a colorectal adenoma
  Cancer diagnosed < 45 years and adenoma < 40 years.

Or

- Individuals in the family with:
  Colorectal and endometrial cancer at age < 45 years
  Cancer in proximal colon with an undifferentiated pattern < 45 years
  Adenomas diagnosed at < 40 Years.

HNPCC follows an autosomal dominant inheritance pattern and genes causing this particular syndrome include *hMLH1*, *hMSH2* (Nicolaides, Papadopolous, Liu et al., 1994), *hMSH6* and other rarer genes *hMLH3*, *hPMS1* and *hPMS2* (Kolodner, Hall, Lipford et al., 1995). These genes are all considered to be mismatch repair genes (MMR). Mutations in both the *hMSH2*

gene (on chromosome 2p22-p21) and the *hMLH1* gene (on chromosome 3p21.3) account for more than 90% of HNPCC cases, whereas mutations in the *hMSH6* gene account for about 1-7% of HNPCC cases (Peltomaki, Lothe and Aaltonin, 2003). About 5% of mutations in *hMLH1* and 20% of mutations in the *hMSH2* gene are large deletions or genetic rearrangements (Wagner, Barrows, Wijnen et al., 2003). By sequencing the *hMLH1* and *hMSH2* genes, mutation detection rates are 90-95% and 50-80% respectively (Wagner et al., 2003; Pistorius, Gorgens, Plaschke et al., 2006). Tumours of these mutation positive individuals seem to show microsatelite instability (MSI) meaning that DNA replication is error-prone (Peltomaki et al., 1993; Coleman and Tsongalis, 2002).

Individuals that test positive for a HNPCC mutation are also at risk for extra-colonic malignancies such as endometrium, ovary, small intestine, biliary tract, ureter, renal pelvis, stomach and pancreas (Möslein, Krause-Paulus Hegger et al., 2000). Those individuals that test positive for the *hMLH1* and *hMSH2* specifically will have a risk of about 80% for males and 40-60% for females of developing CRC by 70 years of age (Mitchell, Farrington, Dunlop et al., 2002).

1.3.2.2.1. Surveillance and management for HNPCC mutation carriers

HNPCC mutation carriers are advised to have colonoscopies every 2-3 years from the age of 20-25 years, a modality which in turn will half their risk for CRC and reduce the chance of death due to cancer by 65% (Lalloo et al., 2006). Since adenomas in the colorectum are known to grow rapidly and are usually the reason for cancer, surveillance is important as they can be removed early (Vasen, Nagengast and Khan, 1995). Women should also have annual gynaecologic examinations (endometrial and ovarian) from the age of 30 years. Finally prophylactic colectomy, hysterectomy and oophorectomy are measures available to reduce the risk of cancer in mutation positive individuals.

Screening of other sites such as, small intestine, biliary tract, ureter, renal pelvis, stomach and pancreas should also be considered if indicated in a specific family (Coleman and Tsongalis, 2002).

1.4. GENETIC COUNSELLING

The genetic counselling process is defined as: "the process of helping people understand and adapt to the medical, psychological, and familial implications of the genetic contributions to disease. The process integrates:

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence
- Education about inheritance, testing, management, prevention, resources and research
- Counselling to promote informed choices and adaptation to the risk or condition" (Resta, Biesecker, Bennett et al., 2006, pp 79)

Genetic counselling is provided by appropriately trained professionals including genetic counsellors, clinical geneticists and genetic nurse counsellors. Patients with a variety of genetic conditions, including several cancer syndromes, are expected to benefit from this service.

1.4.1. Cancer genetic counselling

Over the last couple of years the demand for cancer risk assessment and predictive testing for individuals with a personal and/or family history of cancer has increased rapidly (Kausmeyer et al., 2006). Therefore, cancer genetics programmes have been established to provide patients at risk with a genetic counselling service. Kelly (1991) and Schneider and Marnane (1997) described these cancer services using the term cancer risk counselling. Cancer risk counselling can be defined as a "communication process regarding an individual's possible increased risk of developing specific forms of cancer and includes obtaining detailed family, medical, and lifestyle histories, documentation of cancer-related diagnoses, pedigree construction and analysis, risk assessment and counselling, and discussion of options for early detection and prevention" (Schneider and Marnane, 1997, pp 98). Once all the information is obtained and documented, the patient's risk can be assessed by using various risk calculation guidelines, e.g. Gail, Claus, Ford or Tyrer models for BRCA and Amsterdam I/II and Bethesda criteria for CRC (Gail, Brinton, Byar et al., 1989; Claus, Risch and Thompson, 1994; Vasen et al., 1999; Laloo et al., 2005).

1.4.2. Genetic testing procedures for cancer susceptibility genes

Cancer genetic counselling services also include the option of facilitating genetic testing for various cancer susceptibility genes. Individuals and families in the moderate and high risk categories may be offered genetic testing. However, testing should only be offered after a complete pre-test counselling session, which includes a discussion about the benefits and limitations, ethics and implications, as well as medico-legal issues of genetic testing (Coleman and Tsongalis, 2002). Once the patient gives informed consent and is emotionally able to cope with any result, testing can proceed.

At present in SA testing for HBOC is available for the three founder Ashkenazi Jewish and the three founder Afrikaner mutations at the Cancer Genetics Group, Human Genetics Section, University of Pretoria. Families and individuals without this ancestry can also get tested by means of sequencing both the *BRCA1* and *BRCA2* genes for disease causing mutations. However, this service is currently only offered on a research basis (Personal communication, L van Rensburg, Cancer Genetics Group, Human Genetics Section, University of Pretoria). Another SA laboratory which offer *BRCA* founder mutation testing is the Division of Human Genetics, University of Free State. If individuals are found to test negative for the three common Ashkenazi Jewish or three Afrikaner mutations they can be offered further screening which includes the screening of exon 11 in the *BRCA1* gene and exons 10-11 in the *BRCA2* gene. They can also have screening of the complete *BRCA1* and *BRCA2* genes (Personal communication, N.C. van der Merwe, Division of Human Genetics, University of Free State). Blood samples can also be sent overseas to several laboratories for complete *BRCA1* and *BRCA2* sequencing.

Since the 1980's, Ramesar, Madden, Felix et al (2000) have studied 500 HNPCC probands from the coloured population of the Northern Cape. Molecular studies on these individuals revealed a founder mutation, C1528T in the *hMLH1* gene. This particular predisposing mutation was extensively researched and is also found to be associated with an increased risk of extracolonic cancers in female carriers (Felix, Bodmer, Fearnhead et al., 2006; Blokhuis, Goldberg, Pietersen et al., 2007). Testing for HNPCC (including the three common genes: *hMLH1*, *hMSH2* and *hMSH6)* is done on a research basis at the Human Genetics Research Unit, University of Cape Town; but has been promised as a diagnostic service in the near future (Human genetics research unit, colorectal cancer project, 2008) The *APC* gene causing

FAP is analysed at the Division of Human Genetics, University of Stellenbosch on a research basis.

Genetic testing can be complicated by variable expression of the gene, heterogeneity, polymorphisms, and penetrance of mutations. The tests are expensive, and can have various psychological, legal, and social consequences (Nakamura, Grody and Wu et al., 2004), and therefore it is important for each of these issues to be considered during a predictive genetic test consultation. Once test results are available a post-test genetic counselling session is arranged and it is recommended that a patient bring a support person to this session. At this appointment the test results, consequences of the results, and options available regarding management are discussed in detail. Emotional support is provided during the entire process and patients are referred to psychologists and various cancer support groups for further support if indicated. Insurance discrimination, coverage, and stigmatisation of genetic testing for inherited cancer susceptibility is misperceived, and more research is needed to fully understand this topic (Kausmeyer et al., 2006).

1.4.3. Current status of cancer genetic counselling services in SA

Medical genetic services in SA were established in the 1950's, when individual physicians with an interest in medical genetics provided genetic counselling (Jenkins, 1990). Currently genetic counselling services are provided in the major cities of SA including Cape Town, Bloemfontein, Pretoria, Durban and Johannesburg with outreach services to other cities, smaller towns and rural areas. The Division of Human Genetics, University of the Witwatersrand and NHLS is currently providing genetic counselling services at three academic hospitals (Johannesburg Hospital, Chris Hani Baragwanath Hospital and Coronation Women and Children's Hospital) and a private hospital (The Donald Gordon Medical Centre) in Johannesburg and at various outreach clinics (Port Elizabeth, East London, Polokwane). Between January 2001 and December 2007, approximately 66 referrals for breast cancer, 41 for colorectal cancer and 33 for cases of cancer in the family have been documented at the Clinical and Counselling Section, in the Division of Human Genetics, University of the Witwatersrand and NHLS in Johannesburg and the numbers are increasing rapidly (Database of the Clinical and Counselling Section of the Division Human Genetics, University of the Witwatersrand and the NHLS, Johannesburg).

1.5. GENERAL PRACTITIONERS AND HEREDITARY CANCERS

General practitioners are considered to be the primary health care facilitators providing a service to the community. They are easily accessed and tend to be the 'middle man' between patients and specialists. GPs are involved in long term care of patients and their families and deal with many complex conditions, and therefore they seem to be ideally placed to play an active role in the "new genetics" by detecting at risk individuals and families and referring them appropriately (Mann, 2001; Brownson, Davis, Simms, et al., 1993).

1.5.1. Knowledge, attitudes and practice of GPs regarding cancer genetics

Several studies have explored the knowledge and attitudes of GPs regarding genetics and genetic testing and found that GPs have limited knowledge of genetic conditions and practices but accept that they have an escalating role to play in participating in "new genetics" (Emery, Watson, Rose et al., 1999; Fry, Campell and Gudmunsdottir et al., 1999; Bathurst and Huang, 2006). Other studies specifically related to cancer genetics, more specifically breast cancer and ovarian cancer, revealed that GPs referred low risk individuals to genetic services and seem to have unrealistic expectations of what happens at cancer genetic clinics (Watson, Clements and Yudkin et al., 2001; Pichert, Dietrich, Moosemann et al., 2003).

Widerhoff, Vadaparampil, Greene et al (2005) suggested that basic knowledge of cancer genetics is vital for efficient assessment and management of risk for the appropriate health care of patients. They added that doctors should decide when it would be suitable to refer patients to other specialities like genetic counsellors and medical geneticists.

A detailed family history is considered to be an essential tool to identify individuals and families at risk for a hereditary cancer and to separate them into the three risk categories (average, moderate, high risk). Several protocols exist to assist GPs in assessing cancer risks. These protocols also include recommended management options (Lalloo et al., 2006). Once individuals are recognised as being at high risk they should be referred to a cancer genetic counsellor for a further detailed family, medical and cancer history assessment, as well as counselling and possible testing. A study reviewing patients' files and doctors' notes, determined that nearly all patient records studied documented a presence or absence of a

family history of cancer. The information did not contain enough detail to permit cancer risk assessment (Tyler and Snyder, 2006).

Bathurst et al (2006) suggested that public awareness about rapid advances in cancer genetics and inherited cancer syndromes will increase the demand for genetic services and testing. For this reason more GP involvement is warranted in order to assess patients and families at risk and refer them appropriately. It is expected that GPs will directly order genetic tests for cancer susceptibility in the future (Escher and Sappino, 2000). No research on the topic has been found in the SA context.

1.6. MOTIVATION FOR THE STUDY

In SA, when someone is ill or has any medical enquiries e.g. cancer in the family, the first and most likely medical professional they will consult is their GP. Bearing this in mind, it is important to know how much GPs know about cancer genetics, and whether they offer referral for cancer risk counselling and cancer susceptibility testing. The literature revealed that a clear understanding of general principles that apply to hereditary cancers is important (Widerhoff et al., 2005). It is important to be able to identify at risk individuals and families, refer them, and manage them appropriately.

Since the Clinical and Counselling Section, Division of Human Genetics, NHLS and University of the Witwatersrand is establishing a cancer genetics service it will be of great value to assess the GPs' understanding and practices with regards to cancer genetics. This research project was therefore designed to assess the practice, knowledge and attitudes of GPs in Johannesburg regarding hereditary cancers to establish whether there is need for further research and/or educational programs for GPs and whether GPs showed an interest in learning more about hereditary cancer and cancer susceptibility testing.

1.7. AIMS AND OBJECTIVES OF THE STUDY

Objective: To determine practices, knowledge, and attitudes of GPs in Johannesburg regarding common hereditary cancers using a questionnaire.

Aims:

- To explore the **practices** of GPs regarding cancer screening, inherited cancer susceptibility testing and referral of patients to other specialities.
- To assess the **knowledge** of GPs regarding inherited cancer, genetic counselling and genetic testing for specific hereditary cancer genes and concepts.
- To explore the **attitudes** of GPs regarding hereditary cancer susceptibility testing recommendations.
- To assess if there are **differences** between male and female GPs as well as those in single and multiple practices regarding their practices, knowledge, and attitudes concerning hereditary cancer.

CHAPTER 2

METHODOLOGY

This chapter describes the materials and methods used to conduct this research. It includes the research design, research tool, ascertainment and selection of the study subjects, data collection and data analysis.

2.1. RESEARCH DESIGN

A quantitative, exploratory research design was chosen, as the study was aimed at determining the practices, knowledge, and attitudes of GPs in the Johannesburg area, regarding common hereditary cancers.

Quantitative research is focussed on the collection of numerical data (Brink, 1999). In a quantitative survey a formally structured questionnaire is used as a research tool to gather specific information from a research population (Brink, 1999).

The objectives of an exploratory study include exploration of the dimensions of a phenomenon and the way it manifests, thus providing more insight (Brink, 1999). An exploratory research design was best suited to address the aims of this study e.g. to explore the subject's practices, knowledge and attitudes regarding cancer genetic screening procedures, cancer genetic susceptibility risk assessments and cancer genetic susceptibility testing.

2.2. RESEARCH TOOL

The research tool was a modified structured self-administered questionnaire (see appendix A). A questionnaire, designed and used by Widerhoff et al (2005) was modified for the purpose of this research. Widerhoff et al's (2005) questionnaire assessed knowledge about hereditary breast/ovarian and colorectal cancer amongst physicians in the United States of America. Their questionnaire was 12 pages long and consisted of 35 questions, divided into three parts: cancer susceptibility screening practices, attitudes regarding inherited cancer

susceptibility testing, and background and practice characteristics. Through electronic mail communication with Prof L Widerhoff (see Appendix B) authorisation was obtained to modify and use their questionnaire for this research project.

The questionnaire was adapted to suit this particular study. Widerhoff et al (2005) conducted their research in the United States of America, thus demographic questions needed to be changed to suit the local context e.g. they asked if their participants were Latino or Hispanic, both ethnic groups that are not common in SA. Terminology relating to the professional designations, medical aid and practices were also changed in keeping with local practices e.g. Americans make use of the term health insurance plans whereas South Africans use the term medical aid plans. Finally the questions were re-organized into four sections to assess the participant's demographics (Part I), practices (Part II), knowledge (Part III) and attitudes (Part IV).

The final questionnaire was seven pages long and had a total of 31 questions. Twenty-five of the questions were multiple choice questions and subjects were required to choose answers from a selection of options. Of these 25 multiple choice questions seven had additional space for the subjects to specify or elaborate on the answers they selected. The remaining 6 of the 31 questions in the questionnaire, were open-ended.

Part I: Your background and practice characteristics (Questions 1 to 8)
This part included eight demographic questions about age, sex, qualifications, practice information, number of patients seen per week, and time spent in practice. The second last question in this section was to establish if the participant had had any family members diagnosed with cancer. The researcher asked this question to determine if there was a personal interest in familial cancer. The last question enquired as to whether the subjects had received any advertising materials regarding genetic testing for inherited cancer susceptibility in the past twelve months. The researcher wanted to know this information to test whether there was a correlation between increased knowledge regarding such services and having received advertising material.

Part II: Practices in cancer susceptibility screening (Questions 1 to 11)
This section consisted of eleven questions which assessed the subjects' practices regarding several cancer susceptibility screening procedures (Fecal occult blood test, Prostate-specific

antigen, Pap smear, clinical breast examination, mammography, CA-125 and abdominal ultrasound), family history information for new patients (self medical and cancer history, first and second degree relatives as well as ages of cancer onset), the number of patients interested in inherited cancer risk assessment and genetic testing as well as the subjects ordering and referring of cancer genetic tests, and finally their expectations of future usage of inherited cancer practices.

Part III: Knowledge of genetic counselling and testing for inherited cancer. (Questions 1 to 6). This section assessed the subjects' awareness of the availability and location of genetic testing and counselling facilities for several inherited cancer susceptibility genes, *BRCA1/2, hMLH1, hMSH2, APC*. The subjects' knowledge about several cancer genetic concepts was assessed by asking them about their knowledge of the inheritance of BRCA genes, the percentage of breast cancer cases accounted for by BRCA genes and the penetrance of HNPCC.

Part IV: Attitudes on inherited cancer susceptibility testing (Questions 1 to 6).
Six multiple choice questions were posed to assess the attitudes of the participants regarding their interest in providing genetic counselling, assess which factors influence their decisions to use genetic tests for inherited cancer susceptibility and about which basic genetic tests for inherited cancer concepts they are aware.

2.3. PILOT STUDY

After the research tool was adapted, a pilot study was conducted to test the questionnaire. A pilot study according to Last (2002) is "a small-scale methodological test intended to ensure that proposed methods and procedures will work in practice before being applied…" The purpose of the pilot study in this project was to improve the research tool, to establish whether the questions posed were understandable and unambiguous. The pilot study also helped to establish the time it would take the participants to complete the questionnaire. The researcher also wanted to establish if the tool would provide enough relevant information to answer all the research questions and if the proposed method to collect the data was appropriate.

A medical practice in Johannesburg with 7 GPs was approached where 5 GPs agreed to participate in this pilot study. The participants reported that they understood all the questions in the questionnaire and thus no major corrections were required. In part IV of the questionnaire, question 1 was changed slightly. This was a question with 3 response choices (Yes, No and Don't know) The last mentioned option was removed because of ambiguity. The participants reported that the questionnaire took approximately 15 minutes to complete and no other suggestions were made.

2.4. ASCERTAINMENT AND SELECTION OF STUDY SAMPLE

The subjects selected were general practitioners (GPs) all of whom are part of a mailing list of the Department of Family Medicine (DFM), School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand (WITS), Johannesburg. These GPs are all in a private practice setting and involved in teaching post-graduate medical graduates.

The researcher contacted the Head of Department of Family Medicine Prof B. Sparks, who facilitated the process. The contact list was made available to the researcher. It consisted of 212 GPs and included postal and physical practice addresses. The subjects' offices were contacted in order to confirm their postal or physical addresses, before a research package was mailed. The final study sample comprised 196 GPs because some GPs had emigrated, relocated or retired. A research package was posted that included a research cover letter from the Head of Family Medicine, an information sheet, a response sheet, 2 self addressed envelopes and the seven-page questionnaire (Appendix A and C1-3)

2.5. DATA COLLECTION

In this research project, the postal service was used as a distribution method and the research package was mailed to the 196 subjects. They were initially given four weeks to complete the questionnaire and response sheet, and return the provided self-addressed envelopes to the researcher. Separate envelopes were provided to maintain the subjects' anonymity so that their answers could not be linked to their personal information, but the researcher could keep track of who had responded so that they were not contacted again.

The first completed questionnaires were returned approximately a week after they were sent out and by the due date 26 (13%) of the questionnaires had been returned. As postal surveys tend to have a poor response rate of 10-50% (Neuman, 1997), the researcher devised strategies to increase the response rate. These included mailing a second research package containing a new positively worded cover letter (Appendix C2), the questionnaire and two self-addressed envelopes. The subjects were then given three weeks to respond. This strategy was successful as an additional 35 questionnaires were received within 6 weeks. Thus a total of 61 (31%) completed questionnaires were received. Only one questionnaire was returned blank and seven research packages were returned by the post office because of post boxes being closed, wrong addresses or for other reasons not provided. The total time period over which data were collected was approximately three months.

Once the completed questionnaires were received, they were given a unique identification number. The data from each of the questionnaires were then entered into an Excel database for analysis.

2.6. ANALYSIS OF DATA

Data from all 61 questionnaires were entered into the database and analysed using descriptive statistics, i.e. tables and cross tables, graphs and figures to facilitate an understanding of the research project's data (Brink, 1999). Frequency distributions, central tendency statistics associations and inference were also employed to gain an understanding of the study data. The subjects were divided into groups, namely males and females, and multiple and single practices, and the variables of these two groups were compared by using chi-squared and Fisher's exact tests (Fisher, 1935). The sample size was considered too small for further stratified analysis of age and personal experience/family history of cancer. The data were depicted graphically in graphs, histograms and tables.

2.7. ETHICAL CONSIDERATIONS

The research protocol was submitted and ethics approval was granted by the Human Research Ethics Committee (Medical), Faculty of Health Sciences, the University of the Witwatersrand, reference number: M070219 (Appendix D).

Anonymity of the GPs was maintained by not having any form of identification on the questionnaire and confidentiality was maintained as a separate response sheet obtaining the subjects' personal details as well as an opportunity to receive feedback on the research findings was provided. The subjects had to send the completed questionnaire and response sheet back in the two separate provided envelopes. Only the researcher had access to the completed questionnaires.

CHAPTER 3

RESULTS

3.1 INTRODUCTION

In this chapter the results of the data collected from the 61 questionnaires are discussed. The data were analysed using descriptive statistics depicted in tables, cross tables, graphs and figures. This chapter consists of four parts namely demographics, practice, knowledge and attitudes. Comparisons were also made between the practice, knowledge and attitudes of GPs in single and multiple practices and between males and females as well as between subjects with personal experience of cancer and those with none. Although the sample size was small, a few significant differences between GPs in single and multiple practices and between males and females were found, and only these are presented in this chapter. The sample size was too small for further stratified analysis of age and personal experience/family history of cancer.

From a sample of 196 subjects, 62 responded and only 61 (31%) of the completed questionnaires were used for analysis. This is considered a reasonable response rate for a postal survey (Neuman, 1997). The researcher excluded incomplete questionnaires and those that were returned to the researcher by the post office due to wrong address or closed post boxes. These data are summarized in Table 3.1.

Table 3.1: Summary of the sample

Total number of subjects surveyed	**196**
Completed research packages received 1st round	26
Completed research packages received 2nd round	35
Incomplete research packages received	1
Research packages returned to sender	8
TOTAL research packages returned	70
Excluded from research	9
Final sample completed questionnaires useful for analysis	**61**

3.2. PART I: GPs' BACKGROUND AND PRACTICE CHARACTERISTICS AND ADDITIONAL INFORMATION

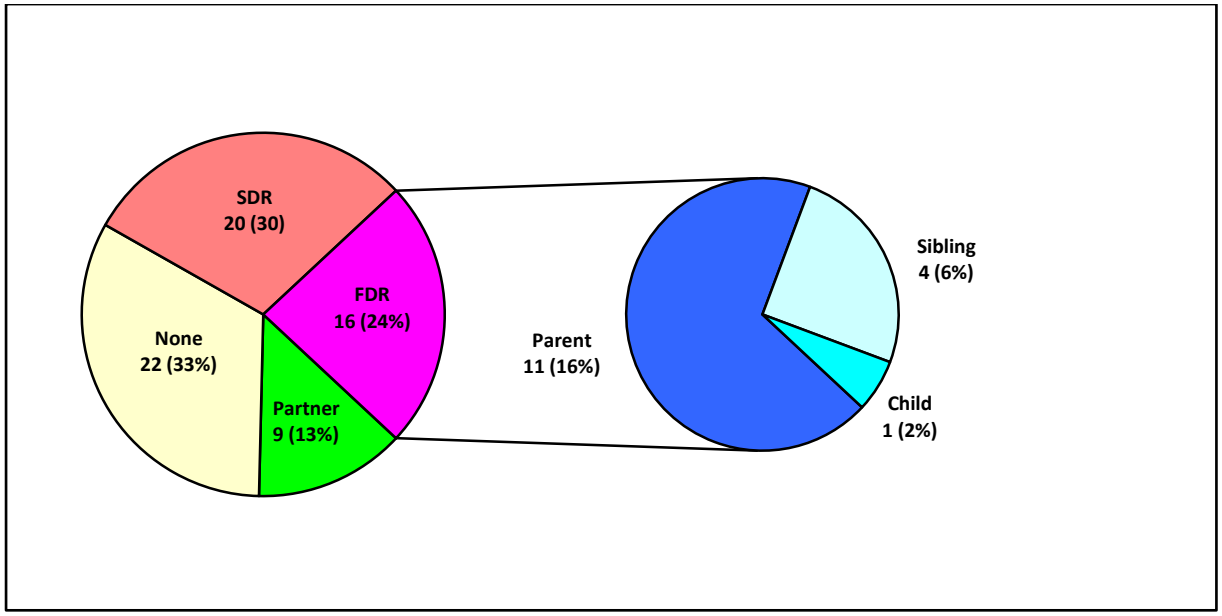
3.2.1 Questions 1-6: Demographics. This section describes the study subjects' ages, gender, qualifications, number of patients seen and the total amount of hours spent in the practice.

The respondents included 19 (31%) female subjects and 42 (69%) male subjects. The subjects ages ranged from 35 to 69 years of age with a mean age of 49 years and a standard deviation of 10. The average age of male GPs is 51 years old compared to the average age of female GPs being 47 years old (p= 0.12).All of the subjects have a Bachelor of Medicine and Surgery degree and 24 (39%) subjects reported having additional degrees (BSc, BPharm) or diplomas (DA, DCH, DTMH).

About an equal number of subjects reported practising in a single (29, 48%) and a multiple (32, 52%) practice setting. The 61 subjects saw a median of 110 patients a week (range: 60-400), of which a total of 50 were male and 60 female patients. This result shows that one GP saw 400 patients a week which means 80 patients a day. This GP reported practising in a multiple practice alongside four colleagues, this subject could have interpreted this question as the total number of patients seen in the practice and if so each would see about 20 patients a day. They spent on average 45 hours per week (range: 7-72) in their practice.

3.2.2 Questions 7-8: Additional information. This section also obtained information on whether there were any cases of cancer in the subjects' families and if they had ever receive advertising material promoting cancer susceptibility testing.

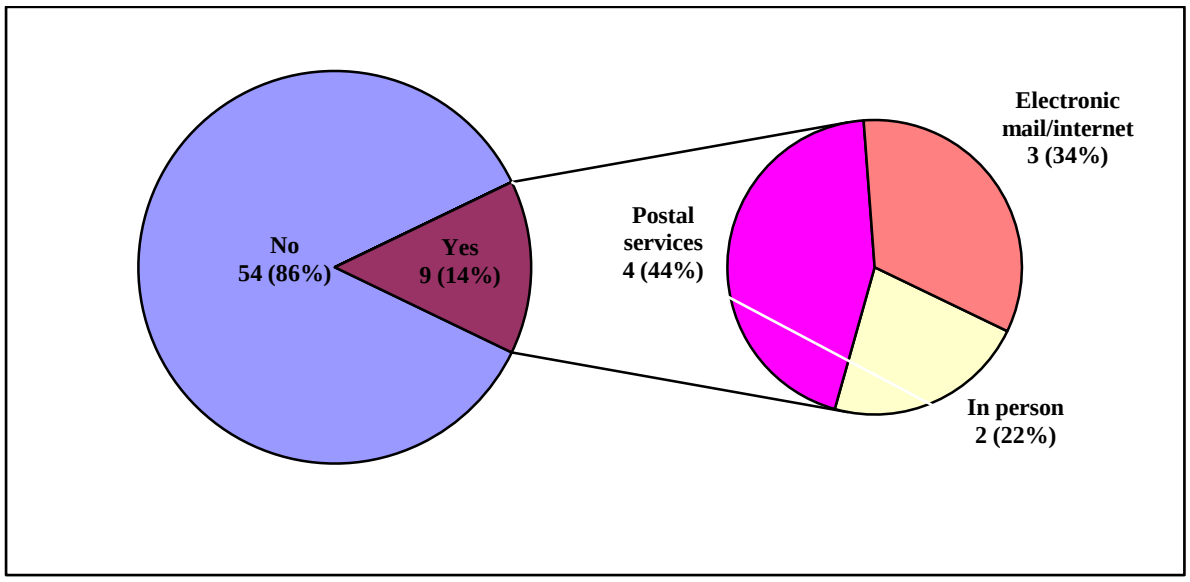
The subjects had to choose between 7 options. Three subjects chose more than one option, therefore in this particular question there were 67 responses. This question was posed to determine whether a personal experience of cancer would result in increasing interest in familial cancer. As can be seen in Figure 3.1, 22 (33%) of the subjects did not have any relatives with cancer, 16 (24%) had a first degree relative with cancer and 20 (30%) reported having affected second degree relatives. Therefore a total of 54% of subjects had a family member affected with cancer. None of the subjects reported that they had cancer themselves and 9 (13%) had partners affected with cancer.



n= 67: Some subjects chose more than one option, therefore 67 responses.
FDR: First degree relative, SDR: Second degree relative

Figure 3.1: Responses of subjects with regards to whether any of their family members were diagnosed with cancer.

Figure 3.2 indicates that the majority of subjects (54, 86%) had never received any advertising material and very few (9, 14%) subjects have received any advertising material marketing genetic tests for inherited cancer susceptibility testing. Advertising material could have been obtained in person, by telephone, by mail, by electronic mail (internet).



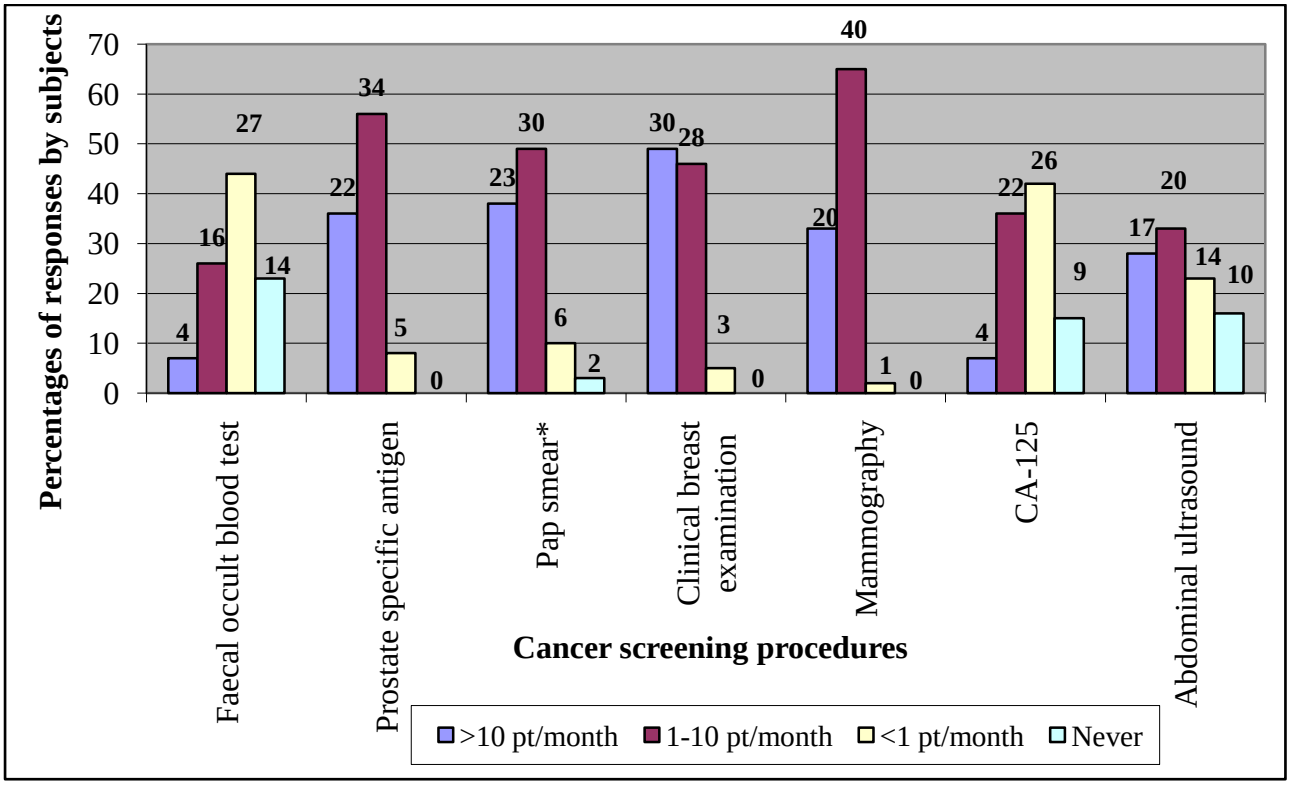
n= 63: Some subjects chose more than one option, therefore 63 responses.

Figure 3.2: The number of subjects who received advertising material marketing genetic testing for inherited cancer susceptibility.

3.3. PART II: PRACTICES ON CANCER SUSCEPTIBILITY SCREENING

3.3.1. Question 1: Cancer screening procedures used by the subjects.

Population screening strategies are the most important tools for the early detection and diagnosis of cancer. The results regarding which screening tests the subjects in this study used are presented in Figure 3.3. The majority of the subjects reported that they mostly make use of the following screening modalities for 1 to 10 patients per month: prostate specific antigen (PSA) (56, 92%), Pap smear (53, 87%), clinical breast examination (58, 95%) and mammography (60, 98%). An abdominal ultrasound examination is used by 37 (61%) of subjects. The tests used in at least 1 patient per month or never by most subjects are faecal occult blood tests (FOBT) (41, 67%) and CA-125 (35, 57%).



*** Significant difference between subjects in single and multiple practices (p= 0.002)**

The numbers (n) of responses by subjects are shown on the bars

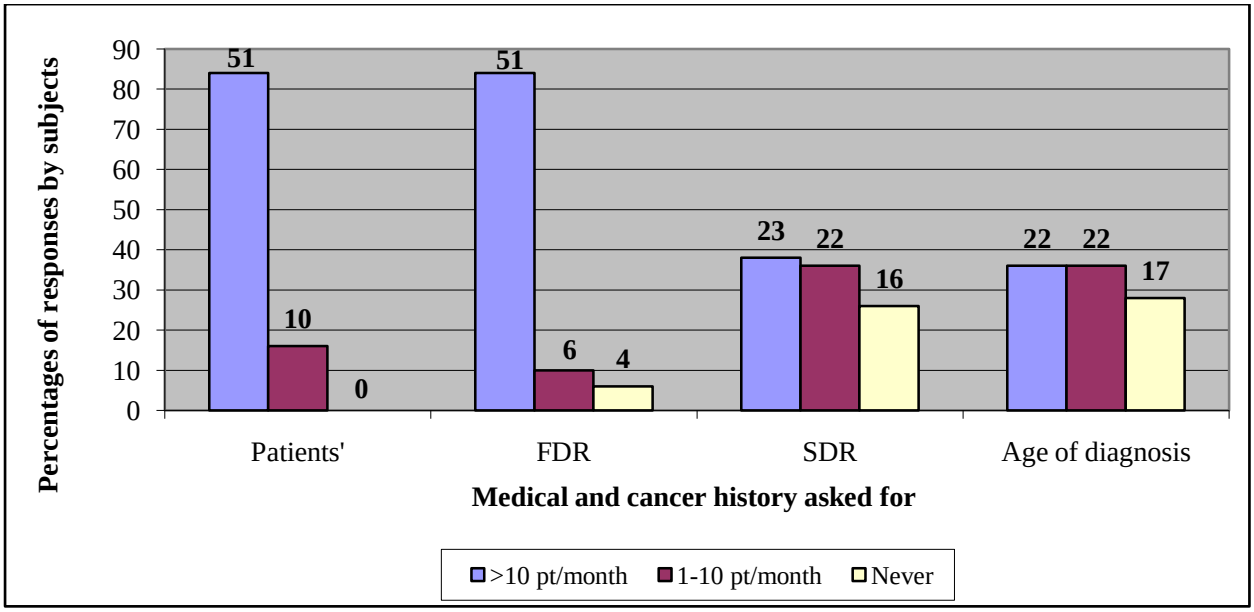
Figure 3.3: Subjects' monthly usage of cancer screening procedures.

The responses of subjects regarding their practices of cancer screening procedures in single and multiple practices were compared. Only one significant difference between the use of

cancer screening procedures was found in this category. This result showed that 79% (n=23/29) of subjects in a single practice use a Pap smear for >10 pt/month compared to the 41% (n=13/32) of subjects in a multiple practice that use this test for > 10 pt/month (χ^2 = 12.69, df = 3, p = 0.002).

3.3.2. Question 2: Information that the subjects gather from their new patients.

As can be seen in Figure 3.4, 84% (n= 51) of subjects ask >10 'new' pt/month for medical and cancer history information. An equal number of subjects reported also asking for medical and cancer history information on their patients' first degree relatives (FDR). The results show that the subjects are less likely to enquire about their patients' second degree relatives' (SDR) medical and cancer history information and the ages at diagnosis of cancer for both FDR and SDR.



The numbers (n) of responses by subjects are shown on the bars

FDR= First degree relatives, SDR= Second degree relatives

Figure 3.4: The number of new patients who are asked medical and family cancer history per month.

3.3.3. Question 3-5: Patients' interest in cancer risk assessment and testing.

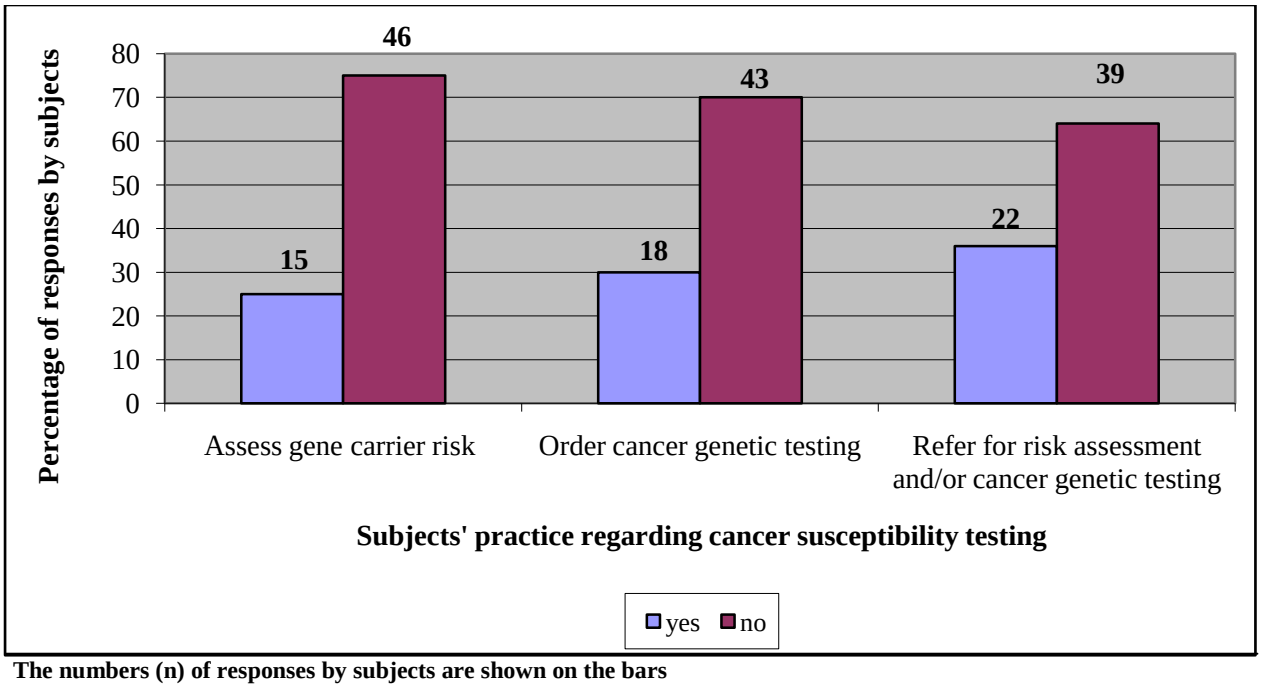
Patients see GPs for several health reasons. Thirty four (56%) of the subjects reported that between 1 to 10 patients per month asks them if they have an increased risk for cancer,

because of their family history. Only 2 (3%) subjects reported that they had never been asked the question. The subjects were asked how frequently during the last 12 months their patients asked them about their hereditary cancer risks compared to previously and interestingly 70% (n= 43) of the subjects selected the "remained the same" response.

Fifty one percent (n= 31) of the subjects reported that they had patients who asked them if they could or should get tested for an inherited cancer susceptibility.

3.3.4. Question 6-9: The subjects' use of cancer genetic testing.

The majority of subjects (46, 75%) reported not assessing whether their patients were candidates for cancer genetic testing. The remaining 15 (25%) subjects, who did assess their patients' risks, assessed on average about 10 patients risks per year. Thirty percent (n= 18) of the subjects ordered genetic tests for inherited cancer susceptibility compared to the 70% (n= 43) that did not. The research assessed what proportion of the subjects refer patients elsewhere for cancer genetic testing and/or risk assessment and 36% (n= 22) have referred 91 patients. The above results are all displayed in Figure 3.5.



The numbers (n) of responses by subjects are shown on the bars

Figure 3.5: Subjects practices regarding cancer genetic testing.

Responses can be seen in Figure 3.6 as to where subjects refer their patients for further risk assessment and genetic testing for inherited cancer susceptibility. The category "other" includes Breast Cancer Clinics, Oncology Clinics and various specialists e.g. gastroenterologists. Half (32, 52%) of the subjects did not respond when asked to name a facility.

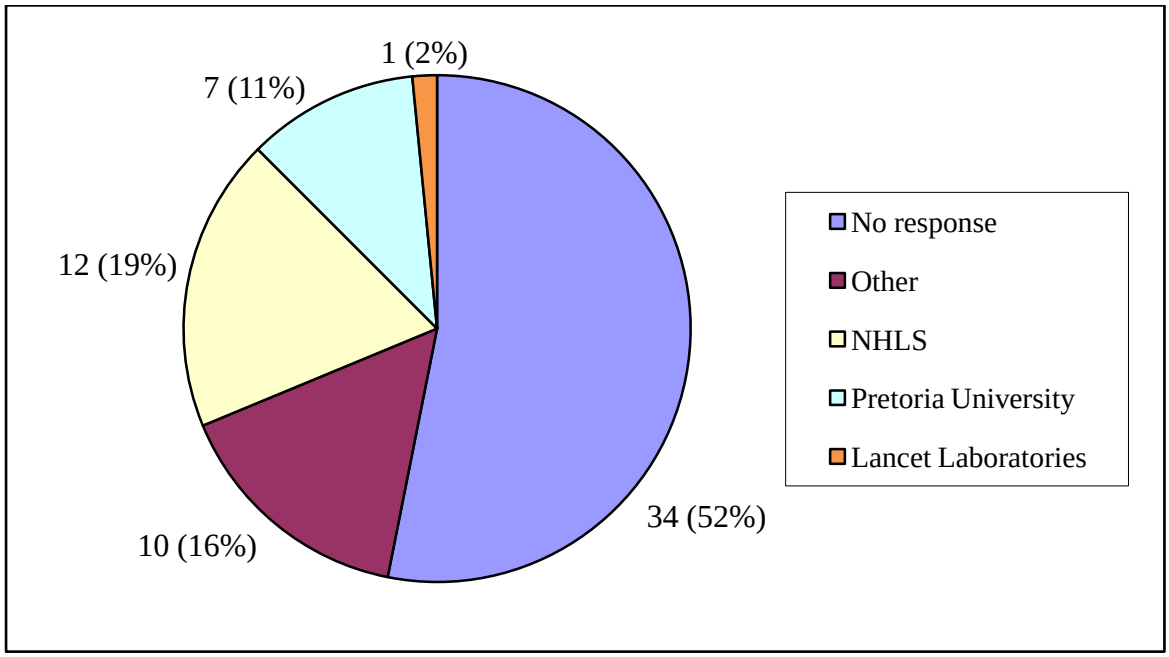
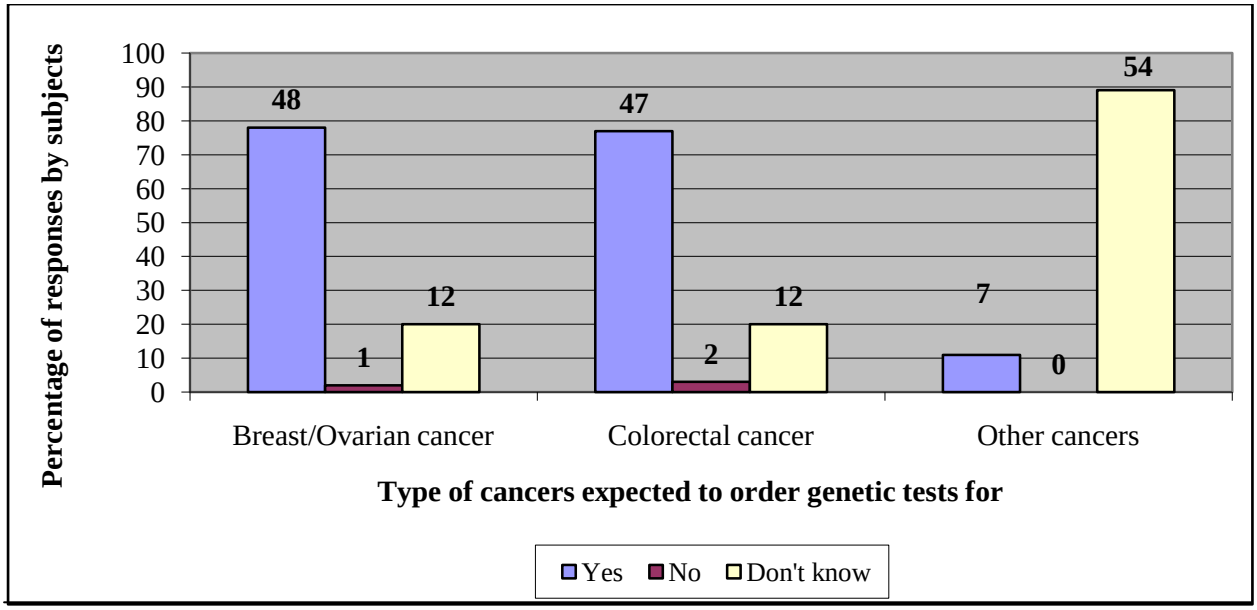


Figure 3.6: Response of the subjects as to where they refer patients for inherited cancer susceptibility services.

3.3.5. Question 10-11: Subjects' expectations for future research.

The majority, 39 (64%) of the subjects expect that the number of patients who will undergo genetic testing for inherited cancer susceptibility will increase within the next 5 years, compared to 11 (18%) who predict that it will remain the same, and 22 (36%) that indicated they are unsure what will happen.

The subjects also reported that they expect to be directly involved in the ordering of genetic tests for breast and ovarian cancer (48, 79%) and CRC (47, 77%) in the future, and 7 (11%) expect to request genetic testing for other cancers such as lung cancer and prostate cancer (see Figure 3.7).



The numbers (n) of responses by subjects are shown on the bars

Figure 3.7: Subjects responses to the types of cancers for which they expect to be ordering genetic susceptibility testing.

3.4. PART III: KNOWLEDGE ON GENETIC COUNSELLING AND GENETIC TESTING FOR INHERITED CANCER

3.4.1. Questions 1-3: Participants' knowledge of genetic counselling, of genetic testing facilities and tests for cancer genes.

The results from these questions are summarized in Table 3.2. The Division of Human Genetics, University of the Witwatersrand and NHLS is currently the only facility in Johannesburg that provides genetic counselling services specifically for inherited cancer susceptibility. Thirty eight percent (n= 23) of the subjects were aware of the availability of genetic counselling facilities and 27% (n= 17) correctly named the NHLS. The other subjects (10, 16%) named other facilities (Lancet Laboratory, Pretoria Academic and Cancer clinics or Specialist clinics) and 58% (n= 37) did not respond.

In Gauteng, genetic testing for some inherited cancer syndromes is available at the Cancer Genetics Group, Human Genetics Section, University of Pretoria. Only after genetic counselling does the Division of Human Genetics, University of the Witwatersrand and NHLS provide a testing service through the Cancer Genetics Group, Human Genetics

Section, University of Pretoria. This testing has not been on a commercial basis but rather through a research institution.

Table 3.2: Knowledge of genetic counselling and testing facilities and cancer susceptibility genes.

	Subjects N	%
1. Availability of genetic counselling facilities n=61		
Yes	23	38
No	24	39
Don't know	14	23
Sites of counselling facilities* n=64		
0. No answer	37	58
1. Other #	4	6
2. NHLS (SAIMR)	17	26
3. PTA academic	3	5
4. Lancet laboratories	3	5
2. Availability of genetic testing facilities n-61		
Yes	32	52
No	16	26
Don't know	13	21
Sites of genetic testing facilities* n=68		
0. No answer	29	42
1. Other #	8	12
2. NHLS (SAIMR)	17	25
3. PTA academic	4	6
4. Lancet laboratories	10	15
3. Availability of commercial testing for cancer susceptibility genes n=61		
a. *BRCA1* and *BRCA2* genes	28	46
Yes	0	0
No	33	54
Don't know		
b. *hMSH2* and *hMLH1* genes	8	13
Yes	0	0
No	53	87
Don't know		
c. *APC* gene	9	15
Yes	0	0
No	52	85
Don't know		

***Some subjects' reported more than one genetic counselling and genetic testing facility**

 # Other includes: breast cancer clinics, support groups and specialist physicians (gastro-enterologists, oncologists)

The researcher found that approximately half of the subjects (32, 52%) knew about the availability of these genetic testing facilities. Only 6% (n= 4) of the subjects were aware of Pretoria's genetic testing facilities and 25% (n= 17) reported the NHLS. A large group of the subjects (29, 43%) did not respond when asked to name the site of a genetic testing facility; 15% (n= 10) and 12% (n= 8) selected incorrectly Lancet Laboratory and others (Breast Cancer Clinics, Oncology Clinics and various specialist clinics e.g. Gastroenterology Clinics) respectively. In SA limited genetic tests are available for both the *BRCA* genes in HBOC, as well as for the *hMLH1* and *hMSH2* genes in HNPCC and for the *APC* gene in FAP and none are commercially available. Testing the knowledge of the subjects regarding the availability of testing for these 5 genes most of the subjects, (28, 46%) were aware that there are genetic tests available for the *BRCA1/2* genes. The majority of the subjects were unaware of genetic testing for *hMLH1*, *hMSH2* (53, 87%) and the *APC* (52, 85%) gene.

3.4.2. Questions 4: Inheritance of *BRCA* genes

About the same number of subjects responded "yes" (27, 44%) correctly and "don't know" (33, 54%) and 1 (2%) responded "no" to the question: "Suppose you have a female patient whose aunt or grandmother on her father's side carries the *BRCA1* gene mutation for HBOC, in your opinion could your patient also be a carrier of this mutation?" This suggests that nearly half of the subjects knew that individuals can inherit BRCA gene mutations from their fathers, as these are autosomal dominant mutations.

3.4.3. Questions 5: Percentage of BRCA mutations in breast cancer

About 5-10% of breast and ovarian cancers are due to the genetic predisposing genes, *BRCA1* and *BRCA2*. Eighteen (30%) subjects accurately responded that less than 10% of females with breast cancer are at risk of carrying a *BRCA1* or *BRCA2* mutation, compared to 31 (50%) that did not know. The other subjects responded inaccurately.

3.4.4. Question 6: Penetrance of HNPPC genes

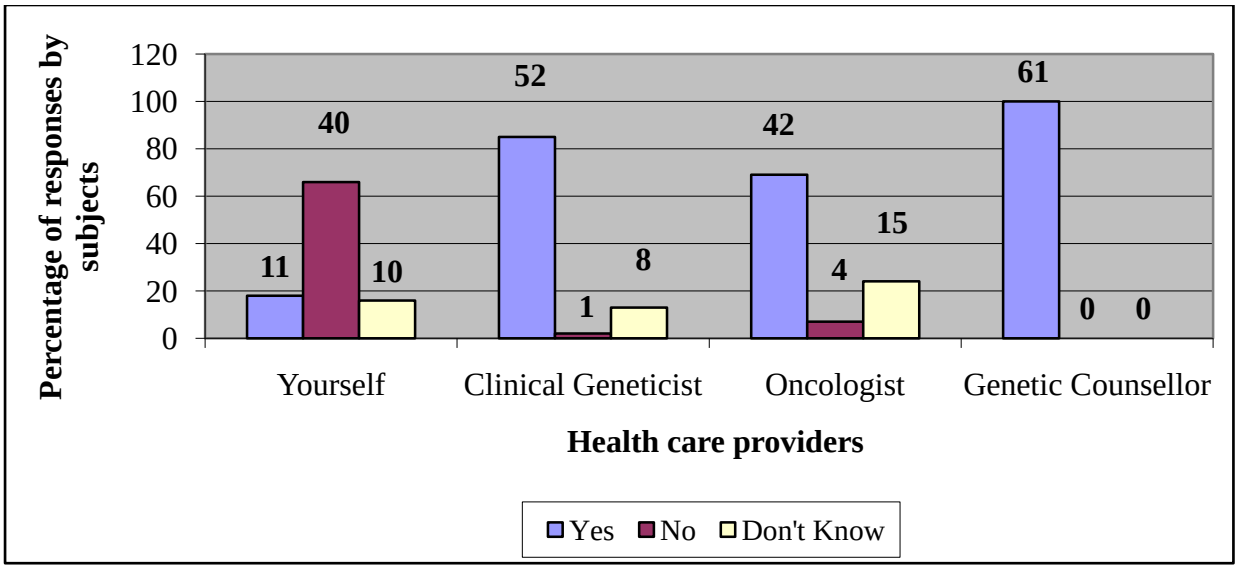
The majority of the subjects (46, 75%) did not know what the penetrance of the HNPCC genes are. Only 3 (5%) selected the correct 50-100% response.

3.5. PART IV: ATTITUDES ON INHERITED CANCER SUSCEPTIBILITY TESTING RECOMMENDATIONS

This section explored the subject's attitudes regarding inherited cancer susceptibility testing recommendations.

3.5.1. Question 1: Providers of genetic counselling

Genetic counselling is a service that provides patients with information on genetic testing and their risks for inherited cancer. The subjects were asked to indicate which health care providers they feel can provide a genetic counselling service (see Figure 3.8). All 61 (100%) of the subjects reported that registered genetic counsellors are qualified to provide genetic counselling. They also thought that clinical geneticists and oncologists could provide this service, possibly suggesting that the oncologist will provide genetic counselling equivalent to the clinical geneticist who has training in genetic counselling. Interestingly most of the subjects (40, 65%) indicated that they did not see themselves as competent to provide genetic counselling.



The numbers (n) of responses by subjects are shown on the bars

Figure 3.8: Subjects' responses regarding health care professionals thought to be qualified to provide genetic counselling.

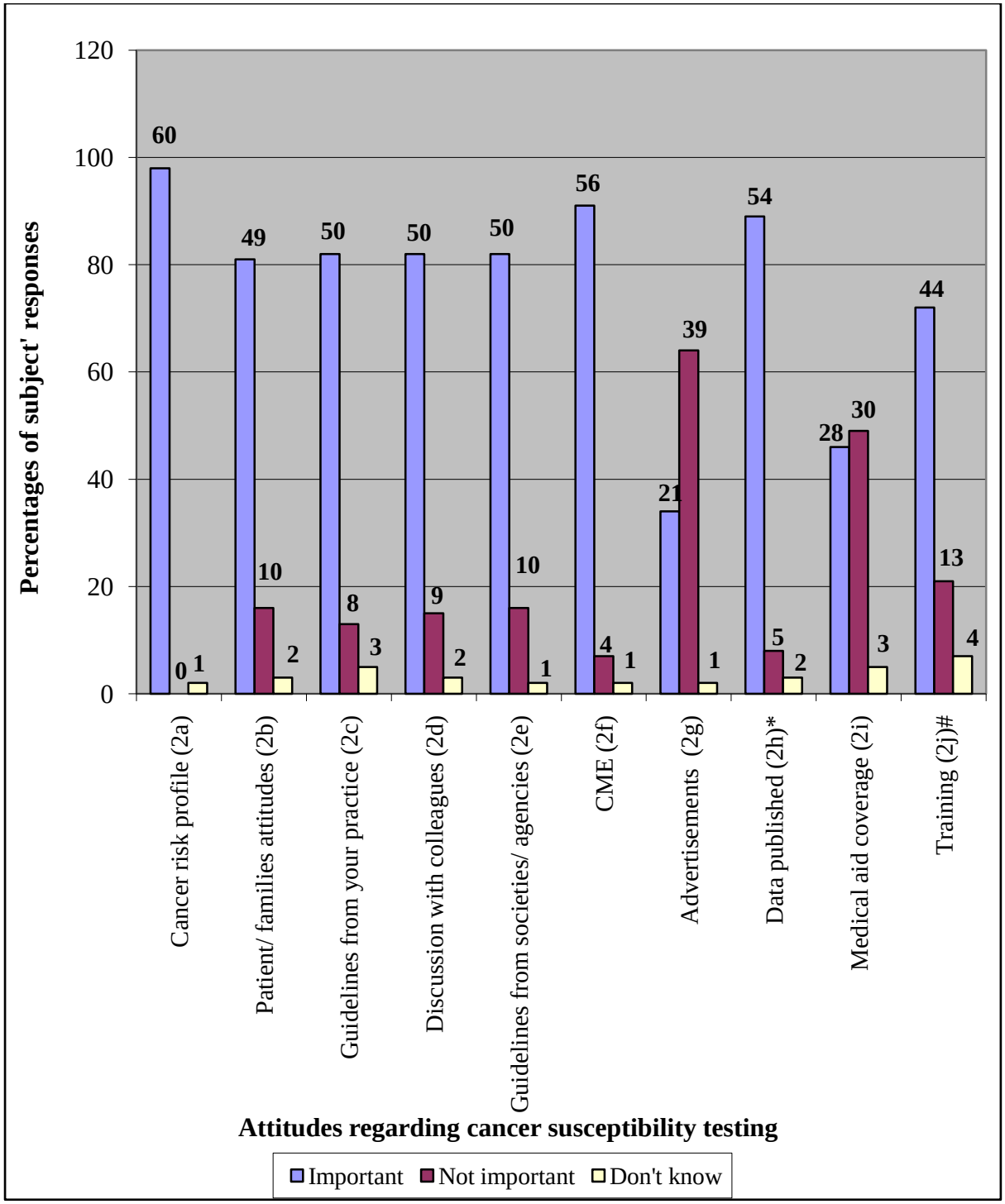
3.5.2. Question 2: Factors that play a role in deciding the use of genetic tests for inherited cancer susceptibility

The subjects were given 10 factors regarding genetic tests for inherited cancer susceptibility and asked to indicate which ones influence their decision. The data were collapsed into three groups namely important (very important and somewhat important), not important (not very important and not important at all) and don't know, and the results are presented in Figure 3.9.

Ninety eight percent (n= 60) of the subjects reported that a patient's cancer risk profile is important (2a). Eighty percent (n=49) reported that they take a patient and their family's attitudes towards genetic testing for inherited cancer susceptibility into consideration when deciding to offer them cancer genetic testing (2b). The other factors which seem to play an important role in the subjects' decision to use genetic testing for inherited cancer susceptibility were information resources including guidelines in their practice, discussions of cases between colleagues and guidelines from medical societies (each equal responses of 50, 82%), continuing medical education (56, 92%), clinical data from medical literature (54, 88%) and lastly training in medical schools and their internship years (44, 72%) (2c-f, h,j).

What is notable in question 2g, was that the majority (39, 64%) of the subjects thought that commercial advertisements and promotions were not important. This factor does not influence their decision to use genetic testing for inherited cancer susceptibility. In question 2i asking about the importance or not of coverage of genetic tests by their patient's medical aid plans, equal numbers of the subjects thought medical aid coverage was important and not important.

Furthermore the researcher also looked to see if there were any differences between the attitudes of the subjects in two categories: male and female and single and multiple practices. Significant results were found in question 2j and 2h. In question 2j, males thought that cancer genetic training in medical school or during residency (internship) was important as opposed to the females who indicated it to be less important ($\chi^2 = 5.22$; df = 2, p = 0.047). In 2h with regard to single and multiple practices, the researcher found that more subjects in a multiple practice felt that clinical data in the medical literature is important compared to those in a single practice ($\chi^2 = 8.075$, df = 3, p = 0.037).



 # Significant difference between the attitudes of male and female subjects (p = 0.047)
*** Significant difference between the attitudes of subjects in single and multiple practices (p = 0.037)**
The numbers (n) of responses by subjects are showed on the bars

Figure 3.9: Subjects' attitudes regarding the role various factors, concerning genetic tests for genetic cancer susceptibility, play in their decision-making process to use cancer susceptibility testing.

3.5.3. Question 3: Statements regarding genetic tests for inherited cancer susceptibility

This question asked the importance of several statements regarding genetic tests for inherited cancer susceptibility and a likert scale was used to gather the information. The results can be seen in Table 3.3.

Table 3.3: Subjects' attitudes regarding the role various inherited cancer susceptibility testing statements play in their practice.

Numbers and percentage (%) of GP's

	Agree		**Disagree**		**Don't know**	
	n	**%**	**n**	**%**	**n**	**%**
Clear guidelines (3a)	21	34%	18	30%	22	36%
Testing availability (3b)	27	45%	13	21%	21	34%
Testing cost-effective (3c)	10	16%	16	26%	35	58%
Risks are clear (3d)	26	42%	18	30%	17	28%
Genetic testing ambiguous (3e)*	7	12%	13	21%	41	67%
Medical aid cover (3f)	0	0%	24	41%	36	59%
Confidentiality (3g)	15	25%	36	59%	10	16%
Insurance discrimination (3h)	43	70%	7	12%	11	18%
Genetic counselling before testing (3i)	57	93%	3	5%	1	2%

*** Significant difference between the attitudes of male and female subjects (p = 0.031)**

Fifty seven percent (n= 35) of the subjects responded that they did not know if genetic testing of patients with a family history of cancer is cost-effective because inherited mutations are rare (3c). Sixty seven percent (n= 41) and 59% (n= 36) of the subjects were unsure whether genetic tests for inherited cancer susceptibility have too many false positive, false negative, or ambiguous (3e) results and whether medical aid coverage is available for these tests (3f).

The statement, 3h, that patients with positive test results are at risk for insurance discrimination (43, 70%), and 3i, that patients should not have genetic tests without having

had genetic counselling (57, 93%) were those that the subjects mostly agreed with. Thirty three percent (n= 21), 44% (n= 27) and 43% (n=26) of subjects agreed with statements 3a, 3b and 3d respectively. In question 3g, 70% (n= 43) disagreed with the statement: "It is difficult to ensure that patients test results will remain confidential.

The attitudes between male and female subjects in this section were compared, and a significant difference was found only in question 3e; more male than female subjects reported that genetic tests for inherited cancer susceptibility have too many false positive, false negative, or ambiguous results ($\chi^2 = 6.71$, df = 2, p = 0.031).

3.5.4. Question 4: GPs' qualifications to recommend genetic testing

The subjects were asked whether they considered themselves qualified to recommend genetic testing for inherited cancer susceptibility to their patients. The majority of subjects (46, 75%) felt that they were not qualified compared to 15 (24%) subjects that reported feeling that they are somewhat qualified.

3.5.5. Questions 5-6: GPs' interest in continuing medical education in cancer genetics

Most (53, 87%) subjects indicated that they are very/somewhat interested in receiving continuing medical education in genetic risk assessment and testing for cancer susceptibility (Figure 3.10). One subject who responded 'not very interested' stated that he would be retiring soon but thought that the field of cancer genetics was "fascinating".

With regards to guidelines, almost all of the subjects, (60, 98%) indicated that they feel that there is a need for guidelines on cancer genetics for general practitioners.

Finally the subjects were given a separate response sheet where they had to indicate whether they wanted a summary of the results after completion of the project and 84% (n= 51) responded that they did. This suggests that the majority of subjects are interested in gaining more information about this project and cancer genetics.

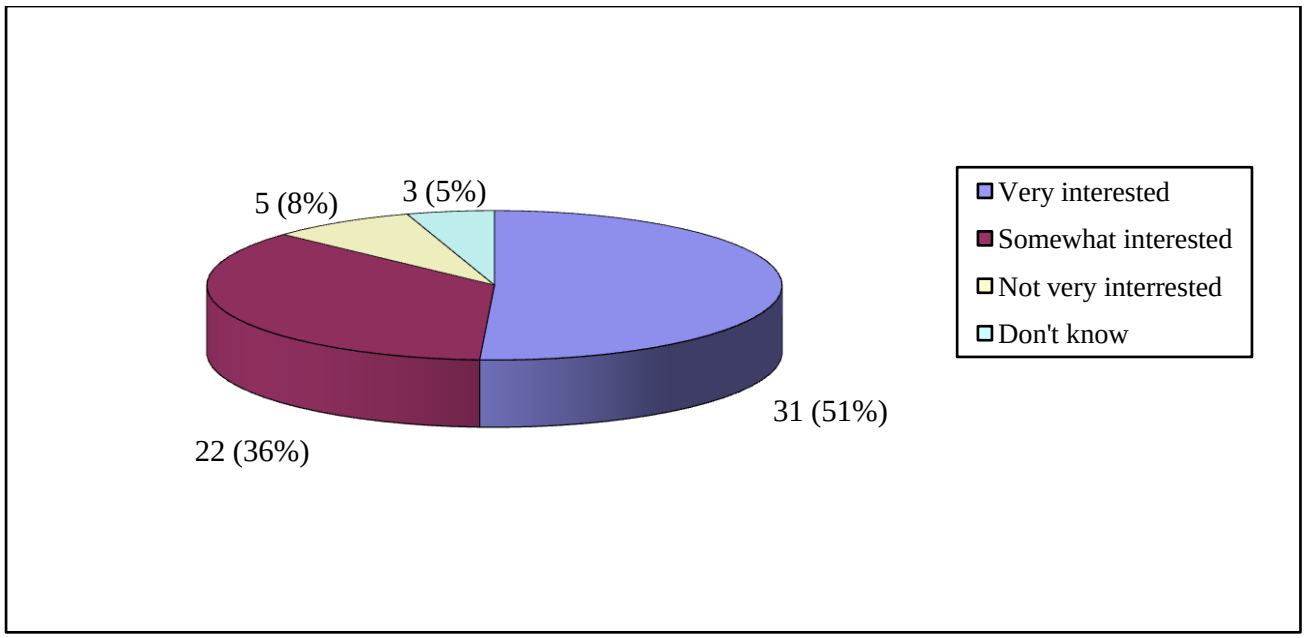


Figure 3.10: Subjects interest in receiving continuing medical education in genetic risk assessment and testing for inherited cancer susceptibility (Question 5).

3.6. SUMMARY

The data from 61 completed questionnaires were analysed and the results showed that more male than female subjects participated in the research and about equal numbers of subjects practiced in single or multiple practices. Sixty eight percent of the subjects reported that they have never received advertising material about cancer genetic testing and the majority of subjects were not aware of genetic testing and counselling facilities in their geographic area.

The results also showed that the subjects seem to obtain limited information on cancer history in their patients' for SDRs and age of onset. Only a few subjects assessed their patients' risk for inherited cancer susceptibility and even less refer their patients to other facilities for risk assessment and genetic testing.

In the section, on knowledge, the results showed that subjects seemed to be more aware of BRCA genes than of CRC genes and concepts. The subjects' attitudes to genetic testing for inherited cancer susceptibility were assessed. Several factors, such as patient history and family attitudes to testing, as well as information from several medical facilities, played an important role in the subjects' decision to make use of genetic testing for inherited cancer susceptibility. Information from commercial advertisements did not play an important role in their decision making process. The majority of the subjects were unsure about the costs of

cancer genetic tests and about interpretation of the results. Many thought positive test results would lead to insurance discrimination, and that all individuals who want testing must have genetic counselling. With respect to the subjects' practice of their use of cancer screening procedures and attitudes about genetic tests for inherited cancer susceptibility, a few significant differences between the attitudes of male and female subjects as well as between the groups single and multiple practices were found and reported on. Finally the subjects reported that they mostly do not see themselves as suitably qualified to recommend genetic tests for inherited cancer susceptibility. They also indicated a need for general practitioner guidelines about cancer genetics.

CHAPTER 4

DISCUSSION

The results of this study show that amongst GPs in Johannesburg genetic counselling and testing facilities are not well known. The GPs are unfamiliar with the cancer genetic concepts tested such as the inheritance of *BRCA1/2* genes, the percentages of breast cancer cases with either *BRCA1* or *BRCA2* genes and the penetrance of HNPCC genes. They also rarely make use of cancer genetic services. However, the GPs reported interest in receiving guidelines to assist them in cancer risk assessment and referral practices.

4.1. PART 1: DEMOGRAPHICS OF THE SAMPLE

More males than female GPs participated in the project (2:1 ratio). Since the male: female ratio in GPs in Johannesburg was unknown the researcher cannot comment on why this occurred. Because more male than female GPs were qualified before the year 2000, it might have been expected that more male GPs would participate in this study (Breier and Wildschut, 2006).

The subjects' ages ranged from 35 to 69 years, suggesting that the youngest participant could have completed her medical school training in 1998 and the oldest his training in 1964. This strengthens the above statement that it is more likely that older male GPs would have participated in the study compared to the female GPs.

This study also looked at the categories single versus multiple GP practices to determine if there are any differences between the practice, knowledge and attitudes of these GPs. The results showed that about the same numbers of GPs practiced alone (29, 48%) and together with colleagues (32, 52%). There seem to be no information in the literature about GPs practicing alone and in multiple practices in SA.

4.2. PART II: CANCER SUSCEPTIBILITY SCREENING PRACTICES

4.2.1. Use of cancer screening procedures

Cancer screening procedures are used to allow early detection of cancer leading to early intervention and management. An encouraging finding in this study was that GPs are involved in cancer prevention practices as they commonly make use of several cancer screening modalities by either performing screening tests themselves e.g. clinical breast examinations, or by referring patients elsewhere for cancer screening tests. This finding subsequently demonstrates that GPs are willing to take part in cancer-prevention.

The subjects were asked on how many asymptomatic patients per month they performed specific cancer screening tests on, or referred elsewhere. The results showed that GPs use CBEs (58, 95%), mammography (60, 98%), Pap smears (53, 87%) and abdominal ultrasound examination (37, 61%) for 1-10 patients per month and they reported using CA-125 for at least 1 patient per month or never. The cancer screening test more commonly used for males seems to be a PSA test, which 92% (n= 56) of GPs use for 1 – 10 patients per month.

For both males and females FOBT is used to detect CRC and it seems that the GPs do not use this test as commonly as the other cancer screening tests (see Figure 3.3). As a FOBT is proposed to be a cost-effective, noninvasive screening method, and has been shown to reduce CRC mortality by about 16% (Walker, 2007), it is uncertain as to why the subjects do not make use of this test as readily as other screening methods. One reason could be because this test shows low sensitivity and specificity and high false positive and negative results (Bond, 2002). Walsh and Terdiman (2003) showed that GPs make use of sigmoidoscopies or colonoscopies since both of these tests show improved detection of both small and large colorectal lesions. As these two mentioned tests were not included as options in this study, the subjects' use of these could not be evaluated.

4.2.2. Information gathering

This study found that 84% (n= 51) of subjects ask medical and family cancer history of the individual patient and their first degree relatives, but less often obtain this information on second degree relatives and also seems to rarely document the ages of cancer onset in the

family (22, 36%). In order to calculate an individual's risk for cancer susceptibility, a complete three generation family history needs to be obtained. A history needs to include information about cancer types and diagnosis in every affected individual as well as the ages of cancer onset, as there is a strong association with inherited cancers and multiple affected family members, as well as earlier ages of onset. The majority of GPs from this study do not seem to obtain enough information and thus would not necessarily be able to assess their patient's risks for inherited cancer susceptibility accurately. However, it should be noted that 38% (n= 23) of GPs do seem to gather appropriate family histories as they document cancer history in multiple generations as well as the ages of cancer onset in affected individuals.

Tyler et al (2006) found that information in patient records from several medical practices was not enough for correct cancer risk assessments, correlating with this study's findings. These results are of concern as at risk patients may not be identified and therefore not appropriately referred. The researcher feels that there is a need to educate GPs about the importance of obtaining a complete family history, which could be done by providing them with cancer risk assessment tools using cancer pamphlets as guidelines.

4.2.3. Interest of GPs' patients in hereditary cancer

Watson et al (2001) studied GP referrals to the Oxford Regional Genetic Service. In one question they enquired as to who initiated discussions about familial cancer and the results showed that in most of the cases it was the patient who usually initiated a discussion on familial cancer and also requested referral for risk assessment and testing. This study found that 56% (n= 34) of the GPs reported that between 1 -10 patients per month asked about their individual cancer risk, as they had a family history of cancer. The GPs reported that currently, compared to previously, there is no increase in the number of patients asking about familial cancer risks. This suggests that the general population does not seem to have an increasing interest in or awareness of hereditary cancers. The researcher anticipates increasing interest of the general public in hereditary cancers with time and awareness. The literature anticipates an increasing interest and demand for genetic services and testing as the public are becoming more aware and knowledgeable about hereditary diseases, including cancers (Kirk and Kefford, 2000; Watson et al., 2001; Sanderson, Wardle, Jarvis, et al., 2004).

4.2.4. Use of genetic tests for inherited cancer susceptibility

Considering that 51% (n= 31) of GPs have been asked by their patients if they could get tested for inherited cancer susceptibility, it would be expected that more GPs would have assessed their patients' risks. However, it was found that only 25% (n= 15) of the GPs determined whether their patients were candidates for cancer genetic testing, compared to the 75% (n= 46) that did not assess risks. It is probable that the GPs are unfamiliar with cancer risk assessment methods and therefore do not assess risk for inherited cancer susceptibility.

Widerhoff, Freedman, Olson et al., (2003) investigated primary and secondary care physicians' use of cancer susceptibility testing. They explored whether their subjects ordered cancer susceptibility testing or referred patients for testing and/or risk assessment. Their study found that only 33% of their subjects made use of cancer susceptibility tests. Similarly, this study found that 30% (n= 18) and 36% (n= 22) of the GPs reported that they order genetic tests for cancer susceptibility and refer patients elsewhere for testing or assessment respectively. As direct cancer susceptibility tests are generally not available to the GPs in SA, it is not unexpected that the majority of subjects (43, 70%) did not order any cancer susceptibility tests during the past 12 months prior to completing this survey. A concern is what GPs regard as a genetic test for inherited cancer susceptibility, as they could have confused a genetic test for cancer susceptibility with a cancer screening tests such as mammography or colonoscopy.

There are facilities available for assessment of patient risks for inherited cancer susceptibility, which include the Division of Human Genetics, NHLS and the University of the Witwatersrand. In the case of genetic testing for inherited cancer susceptibility, testing is mostly available on a research basis rather than diagnostically as a service through academic institutions for example the Human Genetics Division, University of Pretoria and the Division of Human Genetics, NHLS and the University of Free State. This is not entirely surprising as it is not a commercially available service. **Lucassen, Watson, Harcourt et al (2001) examined the influence that referral guidelines have on GPs and their practices, and found that** these increase the number of appropriate referrals to genetic clinics. This suggests that if referral guidelines are distributed to the subjects from this research they may refer at risk patients to genetics clinics.

4.2.5. Expectations for future use of cancer genetic tests

The majority of the subjects (39, 64%) predicted that the number of their patients who will make use of cancer genetic tests will increase in the next 5 years and they expect to be requesting cancer susceptibility tests for BRCA, OC, CRC, prostate and lung cancer, suggesting that GPs expect to be more active in ordering genetic testing for inherited cancer susceptibility. Several other studies found that the general public is becoming more aware of the availability of cancer susceptibility tests and an increase in demand for testing is predicted (Fry et al., 1999; Escher et al, 2000; Pichert et al, 2003).

4.3. PART III: GPs' KNOWLEDGE

Widerhoff et al., (2005) proposed that basic knowledge regarding cancer genetics is essential to accurately assess and manage individuals and families at risk for a hereditary cancer. Based on the results of this study it seems that many GPs are unfamiliar with several cancer genetic concepts and did not know about the availability of genetic counselling and testing facilities.

4.3.1. Location of counselling and testing facilities and testing for inherited cancer genes.

Patients with inherited cancer syndromes were seen occasionally at the Division of Human Genetics, NHLS and the University of the Witwatersrand, Johannesburg prior to 2001. Numbers however have increased since 2001 probably due to an increasing knowledge of inherited cancers in both the public and the medical profession. According to this study, GPs were more aware of genetic testing services (32, 52%) than genetic counselling services (23, 38%) that are available in their area. Few GPs (9, 14%) reported ever having received any advertising material promoting genetic tests for inherited cancer susceptibility (see Figure 3.2) and therefore it was not surprising that they are not aware of genetic testing facilities. Also, genetic testing for inherited cancer is currently not readily available in SA. These results suggest that GPs have limited knowledge of genetic counselling services in their area and it could also suggest limited knowledge of the role genetic counselling plays in other genetic disorders.

Fifty eight and 43% of GPs did not respond when asked to provide a name of a genetic counselling and testing facility respectively, or they named an incorrect facility. Only 27% were aware that the Division of Human Genetics, University of the Witwatersrand and National Health Laboratory Service is the only facility in Johannesburg that provides genetic counselling for inherited cancer susceptibility. Six (10%) of the subjects still referred to the Division of Human Genetics, University of the Witwatersrand, NHLS as the South African Institute of Medical Research which indicates that they are not familiar with the name change of this institution in the year 2000. The Division of Human Genetics, University of the Witwatersrand, NHLS provides a service for genetic testing for inherited cancer susceptibility using the Human Genetics Division, University of Pretoria. Only 25% (n= 17) and 6% (n= 4) of GPs knew about these services in Johannesburg and Pretoria respectively. As so few GPs knew about the correct counselling and testing facilities it is suggests that they are unaware of these services. It could also suggest limited knowledge regarding the role of genetic counselling services not only for inherited cancers but also for other genetic disorders. This implies a need for the Division of Human Genetics, University of the Witwatersrand and NHLS to promote their genetic services in JHB, Gauteng and ideally throughout the whole of SA. Also there is a need for diagnostic genetic testing services for inherited cancer susceptibility.

Overall, the GPs were more aware of the availability of genetic testing for HBOC cancer susceptibility genes, *BRCA1/2* (28, 46%) than for HNPCC, *hMLH1* and *hMSH2* (8, 13%) and FAP, *APC* (9, 15%). They may be more aware of HBOC testing than CRC testing, because breast cancer receives more coverage in the media; the South African Government, Department of Health declared the month of October the official breast cancer awareness month. These services are also more available. Also in the past a private testing facility proactively promoted their genetic testing services for breast cancer by giving lectures on inherited breast cancer testing to health professionals. With increasing public awareness in BRCA, patients are enquiring more about their risks and testing options.

4.3.2. BRCA1/2 inheritance, hereditary breast cancer population risk and HNPCC penetrance

Of concern is that only 27 (44%) GPs in this study were aware that *BRCA1/2* mutations can be inherited through the paternal as well as the maternal line, 18 (30%) understood that these

mutations occur in <10% of breast cancer cases, and 31 (50%) of the subjects were uncertain of the percentage of the *BRCA1/2* mutations in breast cancer patients. Only 3 (5%) identified penetrance of HNPCC mutations correctly as being > 50%, and 46 (75%) of the subjects were unaware of the penetrance.

The results show that the GPs participating in this study, seem to have limited knowledge of both the HBOC syndrome and CRC genetic concepts tested. These findings were comparable to those of Widerhoff et al's., (2005) who assessed the knowledge of USA physicians regarding basic cancer concepts. Widerhoff et al (2005) suggested that the reason for this could be that cancer susceptibility genes were only discovered relatively recently and it is thus expected that the GPs are unfamiliar with cancer genetic concepts. Also, most of the GPs surveyed would not have been taught about hereditary cancer genes and concepts during their training in medical school. Other studies also noted limited knowledge of GPs regarding hereditary cancers (Escher et al, 2000; Watson et al., 2001; Rose, Watson, Yudkin, et al., 2001). This in turn would influence the GPs role in identifying individuals at risk for an inherited cancer, initiating risk assessment, referral and management.

4.4. PART IV: GPs ATTITUDES ABOUT INHERITED CANCER SUSCEPTIBILITY TESTING

4.4.1. Genetic counselling.

It is encouraging to note that all of the GPs (61, 100%) responded in this section that they felt a genetic counsellor is the most qualified to provide genetic counselling; followed by a clinical geneticist (52, 85%) and oncologist (42, 69%). It is possible that the use of the term genetic counselling in the question was leading and thus contributed to so many doctors (100%) providing genetic counsellors as one of their answers. However, they also thought that clinical geneticists and oncologists were suitable health care professionals to provide genetic counselling, which remains encouraging. This result could be somewhat in conflict with the fact that only a few GPs were aware of the availability of genetic counselling facilities (see Table 3.2). Just because GPs are knowledgeable about who can provide genetic counselling does not mean that they know where genetic counselling services are available.

Elwyn and Gray (2000) reported that GPs are not interested in providing genetic counselling. In their study 65% (n= 40) of the GPs stated that they do not feel equipped to provide genetic counselling. Fry et al (1999) also found that GPs did not want to counsel patients about cancer risks. Several studies looked at possible reasons why GPs do not want to counsel patients about inherited cancers and consistently found that they reported that they do not have time to provide a medical as well as a counseling session during a consultation (Fry et al., 1999; Escher et al., 2000; Bathurst et al., 2006). This study confirmed that the subjects have time limitations with each consult, since they reported spending ±45 hours per week in practice seeing a median of 110 patients weekly. If GPs work a 5 day week, they would spend about 9 hours per day seeing ±22 patients a day for ±25 minutes each. If this is compared to the duration of a genetic counselling session, (where a session is approximately 60 minutes, where ±20 minutes of the session is allocated to obtain a family history and draw a complete 3 generation family tree), it can be acknowledged that the subjects do not have enough time to spend with each patient in order to do a complete family history, genetic risk assessment and genetic counselling.

4.4.2. Factors influencing GPs decision to use cancer susceptibility testing.

With respect to which factors influence the GPs' decisions to use genetic tests for inherited cancer susceptibility they acknowledged most of the factors as being important. Firstly, the GPs responded that an individual patient's cancer risk profile (60, 98%) and attitudes towards genetic testing (49, 80%) are important. Secondly, the GPs felt that information and guidelines from several institutions: their practices (50, 82%), government societies/agencies (50, 82%), published data in medical literature (54, 88%), continuing medical education (56, 92%) and training in medical school (44, 72%) are important.

In contrast, 64% (n= 39) of the subjects responded that commercial advertisements and promotions are not important. Since advertising for hereditary cancers has been relatively limited this finding was not surprising. However, as testing for genetic susceptibility becomes more available diagnostically or predictively the use of commercial advertisements may become a key factor to publicity awareness. Vadaparampil, Widerhoff, Olsen et al (2005) referred to commercial advertisements as additional sources of information and found that their subjects thought of such information sources as important. It would therefore be valuable for the Division of Human Genetics, University of the Witwatersrand and NHLS to

note that when setting up an awareness campaign to advertise their genetic testing and counselling services for inherited cancer susceptibility, that more than one way of advertisement and awareness should be used to approach GPs e.g. personal contact with the GPs should be made, as well as the implementation of commercial advertisements and promotions.

With regards to the role that training in medical school plays it was significant that male subjects thought it was more important than did the female subjects (p= 0.047). Since cancer susceptibility genes were only discovered relatively recently, this information has only been incorporated into medical school training since then. Today even only the basic information about genetics, in particular cancer genetics, is taught in medical schools in SA. Therefore the older GPs participating in this study would not have been taught about inherited cancer genes and the availability of testing and counselling for at risk individuals during their training in medical schools. Since in this study male GPs were on average older (although this was not significant) it was surprising that the male GPs reported their training in medical school to be an important factor which would assist them to recommend genetic tests for cancer susceptibility.

There was also a significant difference in responses between GPs practicing alone and those practicing in a multiple practice. It seems that clinical data from medical literature was more important to those subjects in a multiple practice, whereas subjects in a single practice reported it to be not important (p= 0.037). It could be that GPs in a single practice have their own guidelines and patient management protocols, in contrast to the GPs in a multiple practice that make use of guidelines from medical literature. Also GPs in a multiple practice are more open to discuss new medical findings with their colleagues.

4.4.3. Subjects' statements regarding genetic tests for inherited cancer susceptibility.

It is recommended that patients have genetic counselling prior to any genetic testing (Harper, 2005). A genetic counsellor will empower the counselee with information regarding the testing procedures, discuss the advantages and limitations of the tests as well as provide emotional support throughout the whole process. Ninety three percent (n= 57) of the GPs agreed with the statement that suggested that patients should not have genetic tests without having genetic counselling.

Dickens, Pei, and Taylor (1996) suggested that those individuals who test positive for genetic susceptibility may be at increased risk for disability, life insurance and employment discrimination. This study determined that the majority of the subjects (43, 70%) strongly agreed that patients with positive test results for inherited cancer susceptibility are at risk for insurance discrimination. In a study done by Freedman, Wideroff, Olson, et al (2003) which also explored physicians' attitudes towards genetic testing for cancer susceptibility, it was found that 81% of their subjects responded that positive test results lead to insurance discrimination. The World Health Organisation's (WHO) Guidelines on Bioethics (1999) stated that: "Genetic information should not be used as the basis for refusing employment or insurance". The above is also similar to UK guidelines (Williams, Skirton and Masny, 2006). No evidence of insurance discrimination with regards to inherited cancer susceptibility has been found in SA. Discrimination has been observed in other chronic conditions e.g. HIV positive status (Aids Law Project, 2008).

About equal numbers of GPs agreed (21, 34%) and did not know (22, 36%) that there are guidelines available for managing positive cancer susceptibility patients. Similarly, 43% (n= 26) agreed that risks for a patient who tested positive for an inherited cancer susceptibility gene are clear. This suggest that GPs seem to have some idea of interpreting and managing genetic test for inherited cancer susceptibility results. Again it is concerning as to what their understanding is about genetic tests, as they could be understanding it to be cancer screening tests rather then genetic tests. Forty four percent (n= 27) of GPs agreed that genetic testing services are readily available. In response to a different question noted in this study 52% (n= 32) reported that they are aware of genetic testing facilities available.

Forty one (67%) of the GPs were unsure whether a genetic test for inherited cancer susceptibility has inaccurate or ambiguous results. It is significant that more male subjects were unsure about the statement that "genetic tests for inherited cancer susceptibility has too many false positive, false negative or ambiguous results" compared to the female subjects who (p= 0.031). This finding could suggest that many GPs do not understand the interpretation of genetic test results.

Fifty seven percent (n= 35) and 67% (n= 41) of GPs were also unsure about the costs and coverage of genetic tests by medical aid schemes. Some medical aid schemes are known to

cover patient's genetic tests but it is not well known which ones and it is thus the patient's responsibility to consult with their medical aids before genetic testing is to be performed.

Thirty six (59%) GPs disagreed with the statement "it is difficult to ensure that patients test results will remain confidential". This suggests that the majority of GPs feel they can ensure confidentiality of their patients' medical information. In a similar study, Freedman et al (2003) found that 47% of their subjects agreed that patient confidentiality could be ensured compared to the 53% that thought it was difficult to ensure confidentiality of patient test results.

4.4.4. Attitudes about and interest in cancer susceptibility testing

Zielinski (2005) found that about 60% of primary care physicians in the United States of America don't feel qualified to recommend testing themselves. The current study found that 75% (n= 46) of GPs do not feel qualified to recommend cancer genetic testing. This may be due to limited knowledge, limited training or lack of awareness of the facilities which offer testing. It could also be seen as a reason why the subjects in this study rarely make use of cancer genetic testing (see figure 3.5).

GPs accept that they have an increasing role to play in cancer genetic services. They are prepared to participate in family history taking, deciding which patients to refer for genetic testing and to manage cancer predisposed patients. However, they were found to be unfamiliar with cancer risks calculations and cancer genetic counselling (Fry et al., 1999). In this study 87% (n= 53) of GPs expressed interest in learning more about specific areas of inherited cancer genetics, including genetic risk assessment and testing for inherited cancer susceptibility but as seen previously they do not see themselves fit to provide genetic counselling.

It was encouraging to find that 98% (n= 60) of the GPs felt a need for guidelines and 84% (n= 51) requested a report of the research findings, indicating that GPs in Johannesburg are interested in receiving education about cancer genetics and are interested in playing a role in such services in the future. An educational program, providing GPs with informational booklets, cancer genetic pamphlets and educational lectures could thus be designed.

CHAPTER 5

SUMMARY AND CONCLUSIONS

This chapter covers the summary of the research with reference to the aims and objectives of this study, limitations in this study and recommendations for future research as well a conclusion.

5.1. SUMMARY

With reference to the first aim of this study which was to explore the **practices** of GPs regarding cancer screening, inherited cancer susceptibility testing and referral of patients to other specialities this study found the following:

- GPs seem to use several cancer screening procedures frequently e.g. clinical breast examinations, mammograms, PSA and Pap smear. They seem to use CA-125 and FOBT less often.
- They do not obtain enough family history information from their patients and thus would not necessarily be able to assess cancer risks accurately.
- Although many of the GPs patients were found to be interested in cancer risk assessment and genetic testing for inherited cancer, GPs were found to assess their patients risks rarely and also rarely refer patients to have genetic testing for inherited cancer susceptibility.
- Most GPs expect to be directly involved in the ordering of genetic testing for inherited cancer susceptibility for breast cancer, colorectal cancer, prostate cancer and lung cancer in the future.

The second aim was to assess the **knowledge** of GPs regarding inherited cancer, genetic counselling and genetic testing for specific hereditary cancer genes and concepts. With regards to this aim the research found:

- Many GPs are not aware of the availability of genetic counselling and testing facilities.

- The majority of GPs know that genetic tests for HBOC are available but the minority know about the available genetic tests for HNPCC and FAP. These tests are not available diagnostically in SA, but only on a research basis.
- Nearly 50% of the GPs were unaware of the transmission of *BRCA1* gene through the paternal as well as the maternal line and also were uncertain of the percentage of female patients with breast cancer who will have *BRCA1/2* mutations.
- Many GPs were unaware of the penetrance of HNPCC mutations.

With reference to the third aim of this study which was to explore the **attitudes** of GPs regarding hereditary cancer susceptibility testing recommendations the following were found:

- Although the question was posed in a leading manner all of the GPs felt that a genetic counsellor is the most qualified to provide genetic counselling followed by a clinical geneticist and oncologist but not themselves.
- The majority of GPs reported the following factors to be important:
    - an individual patient's cancer risk profile
    - patients' and families' attitudes towards genetic testing
    - information and guidelines from several institutions: their practices, government societies/agencies, published data in medical literature, continuing medical education, and training in medical school
- Most GPs responded that commercial advertisements and promotions are not important and they were unsure about the involvement of patients medical aid plans when it comes to coverage of such tests.
- Nearly all of the GPs indicated that all patients should have genetic counselling before they have any genetic testing.
- Most GPs agreed with the statements that:
    - genetic testing services are readily available
    - risks for patients who test positive are clear
    - individuals who test positive for genetic susceptibility may be at increased risk for insurance discrimination
- The majority of GPs are unsure about whether:
    - a genetic test for inherited cancer susceptibility has inaccurate or ambiguous results
    - genetic testing is cost effective

  - medical aids cover genetic tests for inherited cancer susceptibility
  - clear guidelines are available to manage patients with positive test results
- Only about half of the GPs feel they can guarantee confidentiality of their patients' medical information.
- Only one quarter of the GPs feel qualified to recommend genetic tests for inherited cancer susceptibility but they feel there is a need for guidelines and furthering their training.
- The majority of the GPs wanted a summary of this research report.

The final aim was to assess if there are **differences** between male and female GPs as well as those in a single and multiple practices regarding their practices, knowledge, and attitudes in hereditary cancer:

- Significantly more male GPs consider the information about inherited cancers which they learn in medical school training as important compared to the female GPs.
- Clinical data from medical literature was more important to those subjects in a multiple practice, whereas subjects in a single practice reported it to be not important.
- It was significant that more male subjects were unsure whether a genetic test for inherited cancer susceptibility has inaccurate or ambiguous results compared to the female subjects who seemed to understand the interpretation of genetic test results better.

5.2. LIMITATIONS

During the course of this study certain limitations became evident and are listed below:

- As the GPs were affiliated with an academic institution and thus motivated, the sample could have been biased. Therefore their practice, knowledge and attitudes may not be representative of other GPs who are not affiliated with an academic institution.
- The sample size was small and only 61 GPs participated in the project which made statistical analysis limiting.
- The study was conducted in the Johannesburg area and therefore the findings cannot be generalised to other parts of SA.
- The study was conducted in English and in a multilingual society the language barrier may influence the accuracy of some of the answers.

- The GPs might have answered the survey in a way of social desirability and thus this may have caused bias.
- The subjects were not asked to give reasons for the answers they provided and the discussion of the results in this section is therefore mostly speculation.
- When the subjects were asked about their practice in cancer genetic procedures, colonoscopy was not included and this limited the researcher's ability to assess their use of surveillance for CRC.
- The subjects were asked about commercial genetic testing. It is difficult to judge their answers as no real commercial testing is available, although some testing is available on a limited service basis.

5.3. RECOMMENDATIONS

- Since this study showed that GPs thought continuing medical education is a valuable resource to learn more about inherited cancer, an educational and awareness program should be initiated to educate GPs on cancer genetic risk assessment (taking a three generation family history, age of cancer diagnosis and type of cancer including histology information) and the availability of genetic testing and counselling facilities for inherited cancer susceptibility. The educational program can take place by providing GPs with informational letters, pamphlets and talks and the information addressed should include appropriate family history. Ultimately this may improve the management of "at risk" individuals and increase referral rates to the correct genetic counselling and testing facilities.

5.4. FUTURE RESEARCH

- The literature mostly compares the knowledge and attitudes regarding hereditary cancers between different specialists and GPs. Future research could therefore focus on the practice, knowledge and attitudes of different health care providers especially specialist doctors and compare the findings with the findings of this study. Including in this, cancer risk assessment could be further explored.
- Once the Division of Human Genetics, University of the Witwatersrand and NHLS has initiated educational interventions and guidelines to assist GPs with risk

assessment and referral for inherited cancer patients, it would be valuable to test their knowledge of genetic tests for inherited cancer susceptibility and to re-assess whether referral rates increase and what impact this would have on testing and counselling services. Specialists e.g. oncologists, gastroenterologists could also be educated about risk assessment and referral for inherited cancer susceptibility.

- It would also be interesting to establish what the general public's awareness and needs are with regards to inherited cancers, by assessing their understanding of hereditary cancer, their interest in receiving more information and also their attitudes regarding genetic testing for inherited cancer susceptibility.
- The Division of Human Genetics, University of the Witwatersrand and NHLS could conduct an audit on the records of patients seen for genetic counselling regarding inherited cancer to establish what is currently happening in this service and where improvements can be made.
- A larger sample could be used and this research can be conducted in other areas of Gauteng or the greater SA.

5.5. CONCLUSIONS

In conclusion, it seems that many GPs have limited knowledge of both genetic testing for inherited cancer and the availability of facilities to provide genetic testing and counselling, however they reported interest in learning about these services and expect to play a role in cancer genetic services in the future.

The findings suggest that there is a need to educate GPs about the basic concepts in cancer susceptibility screening and testing. This enable them to identify those at risk for inherited cancer syndromes, provide information about the genetic tests currently available for inherited cancer susceptibility and available genetic counselling and testing facilities. Awareness and educational programs could be done by distributing cancer genetic information pamphlets, referral guidelines and/or with informational lectures to the GP. Future research could be focused on assessing the use of these educational interventions.

REFERENCES

AOKI, K. & TAKETO, M.M. (2007) Adenamatous polyposis coli (APC): a multi-functional tumour suppressor gene. *J Cell Sci*, 120(Pt19): 3327-3335.

BAGLIONI, S. & GENUARDI, M. (2004) Simple and complex genetics of colorectal cancer susceptibility. *Am J Med Genet C Semin Med Genet*, 129(1): 35-43.

BATHURST, L. & HUANG, Q.R. (2006) A qualitative study of GPs' views on modern genetics. *Aust Fam Physician,* 35(6): 462-464.

BEROUD, C., COLLOD-BEROUD, G., BOILEAU, C., SOUSSI, T., JUNIEN, C. (2000) UMD (Universal mutation database): a generic software to build and analyze locus-specific databases. *Hum Mutat,* 15: 86-94.

BERTARIO, L., RUSSO, A., SALA, P., VARESCO, L., GIAROLA, M., MONDINI, P., PIEROTTI, M., SPINELLI, P., RADICE, P. (2003) Multiple approach to the exploration of genotype-phenotype correlations in familial adenomatous polyposis. *J Clin Oncol*, 21: 1698-707.

BOND, J.H. (2002) Fecal occult blood test screening for colorectal cancer. *Gastrointest Endosc Clin N Am*, 12(1): 11-21.

BREIER, M. & WILDSCHUT, A. (2006) The feminisation of medical schools in South Africa. *HSRC Review*, 4(4): 10-12.

BRINK, H.I. (1999). *Fundamentals of Research Methodology for Health Care Professionals.* Juta & Co., Cape Town

BRODY, J.G., RUDEL, R.A., MICHELS, K.B., MOYSICH, K.B., BERNSTEIN, L., ATTFIELD, K.R. & GRAY, S. (2007) Environmental pollutants, diet, physical activity, body size, and breast cancer: where do we stand in research to identify opportunities for prevention? *Cancer*, 109(12 Suppl): 2627-34.

BROWNSON, R.C., DAVIS, J.R., SIMMS, S.G., KERN, T.G. & HARMON, R.G. (1993) Cancer control knowledge and priorities among primary care physicians. *J Cancer Educ*, 8(1): 35-41.

BURK, W., PETERSEN, G., LYNCH, P., BOTKIN, J., DALY, M., GABER, J., et al., (1997) Recommendations for follow-up care of individuals with inherited predisposition to cancer: hereditary nonpolyposis colon cancer. Cancer Genetic Study Consortium. *J Am Med Assoc*, 277: 915-919.

BURT, R.W. (1996) *Prevention and Early Detection of CRC*. WB Saunders Co, London.

CHAO, A., THUN,M.J., CONNELL, C.J., MCCULLOUGH, M.L., JACOBS, E.J., FLANDERS,W.D., RODRIGUEZ,C., SINHA, R., CALLE, E.E. (2005) Meat consumption and risk of colorectal cancer. *JAMA*, 293: 172-82

CHEN, C.S., PHILLIPS, K.D., GRIST, S., BENNET, G., CRAIG, J.E. MUECKE, J.S. & SUTHERS, G.K. (2006) Congenital hypertrophy of the retinal pigment epithelium (CHRPE) in familial colorectal cancer. *Fam Cancer,* 5(4): 397-404.

CLAUS, E.B., RISCH, N. & THOMPSON, W.D. (1994) Autosomal dominant inheritance of early onset breast cancer. *Cancer,* 73: 643-651.

COLEMAN, W.B. & TSONGALIS, G.J. (2002) *The Molecular Basis of Human Cancer. Humana Press*, Totowa, New Jersey. pp 134.

COLLINS, N., MCMANUS, R., WOOSTER, R., MANGION, J., SEAL, S., LAKHANI, S.R., ORMISTON, W., DALY, P.A., FORD, D. & EASTON, D.F., et al. (1995) Consistent loss of the wild type allele in breast cancer from a family linked to the BRCA2 gene on chromosome 13q12-13. *Oncogene,* 10(8): 1673-1675.

DENG, C.X. (2006) BRCA1: cell cycle checkpoint, genetic instability, DNA damage response and cancer evolution. *Nucleic Acids Research,* 34: 1416-26

DE ROSA, M., SCARANO, M.I., PANARIELLO, L., MORELLI, G., RIEGIER, G., ROSSI, G.B., TEMNESTA, A. & ROMANO, G., et al. (2003) The mutation spectrum of the APC gene in FAP patients from Southern Italy: detection of known and four novel mutations. *Hum Mutat,* 21(6): 655-656.

DE SOTO, J.A. & DENG, C. (2006) PARP-1 inhibitors: are they the long-sought genetica drugs for BRCA1/2-associated breast cancers? *Int J Med Sci*, 3(4): 117-123.

DICKENS, B.M., PEI, N. & TAYLOR, K.M. (1996) Legal and ethical issues in genetic testing and counselling for susceptibility to breast, ovarian and colon cancer, *Can Med Assoc J.* 154(6): 813- 818.

DOMCHECK, S.M. & REBBECK, T.R. (2007) Prophylactic oophorectomy in women at increased cancer risk. *Curr Opin Obstet Gynecol*, 19(1): 27-30.

DORLAND'S ILLUSTRATED MEDICAL DICTIONARY. (2003) 30th edition. Saunders.

EASON, D.F., BISHOP, D.T., FORD, D. & CROCKFORD, G.P. (1993) Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. The Breast Cancer Linkage Consortium. *Am J Hum Genet,* 52(4): 678-701.

EASTON, D.F., STEELE, L., FIELDS, P., ORMISTON, W., AVERILL, D., DALY, P.A., MCMANUS, R., NEUHAUSEN, S.L., FORD, D., WOOSTER, R., CANNON-ALBRIGHT, L.A., STRATTON, M.R. & GOLDGAR, D.E. (1997) Cancer risks in two large breast cancer families linked to BRCA2 on chromosome 13q12-13. *Am J Hum Genet,* 61: 120-128.

ELWYN, G., GRAY, J. & IREDALE, R. (2000) Tensions in implementing the new genetics. General practitioners in south Wales are unconvinced of their role in genetics services. *BMJ*, 321(7255): 240-242.

EMERY, J., WATSON, E., ROSE, P. & ANDERMANN, A. (1999) A systematic review of the literature exploring the role of primary care in genetic services. *Fam Pract*, 16(4): 426-445.

ESCHER, M. & SAPPINO, A.P. (2000) Primary physicians' knowledge and attitudes towards genetic testing for breast-ovarian cancer predisposition. *Fam Pract*, 11(9): 1131-1135.

FARMER, H., MCCABE, N., LORD, C.J., TUTT, A.N.J., JHONSON, D.A., RICHARDSON, T.B., SANTAROSA, M., DILLON, K.J., ET AL. (2005) Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*, 434: 917-921.

FASOULIOTIS, S.J. & SCHENKER, J.G. (2000) BRCA1 and BRCA2 mutations: decision-making dilemmas concerning testing and management. *Obstet and Gynecol survey*, 55 (6): 373-384.

FELIX, R., BODMER, W., FEARNHEAD, N.S., VAN DER MERWE, L. GOLDBERG, P. & RAMESAR, R.S. (2006) GSTM1 and GSTT1 polymorphisms as modifiers of age at diagnosis of hereditary nonpolyposis colorectal cancer (HNPCC) in a homogeneous cohort of individuals carrying a single predisposing mutation. *Mutat Res*, 602 (1-2): 175-181.

FIRTH, H.V. & HURST, J.A. (2006) *Oxford desk reference clinical genetics.* Edited by Hall JG. Oxford university press, United States of America.

FISHER, Sir, R.A. (1935) The designs of experiments. New York. Hafner.

FORD, D., EASTON, D.F., BISHOP, D.T., NAROD, S.A. & GOLDGAR, D.E. (1994) Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Lancet* 343: 692-5.

FORD, D., EASTON, D.F., STRATTON, M., et al. (1998) Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet*, 62(3): 676-689.

FREEDMAN, A.N., WIDEROFF, L., OLSON, L., DAVIS, W., KLABUNDE, C., SRINATH, K.P., REEVE, B.B., CROYLE, R.T. & BALLARD-BARBASH, R. (2003) US physicians' attitudes toward genetic testing for cancer susceptibility. *Am J Med Genet*, 120(1): 63-71.

FRY, A., CAMPBELL, H., GUDMUNSDOTTIR, H., RUSH, R., PORTEOUS, M., GORMAN, D. & CULL, A. (1999) GPs' views on their role in cancer genetics services and current practice. *Fam Pract*, 16(5): 468-474.

FUTREAL, P.A., COIN, L., MARSHALL, M., DOWN, T., HUBBARD, T., WOOSTER, R., RAHMAN, N. & STRATTON, M.R. (2004) A census of human cancer genes. *Nature Rev Can*, 4: 177-183.

FUTREAL, P.A., KASPRZYK, A., BIRNEY, E., MULLIKIN, J.C., WOOSTER, R. & STRATTOHN, M.R. (2001) Cancer and Genomics. *Nature*, 409: 850-852.

GAIL, H.M., BRINTON, L.A., BYAR, D.P., CORLE, D.K., GREEN, S.B., SCHAIRER, C., ET AL. (1989) Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst*, 81: 1897-1886.

GOLDBERG, B. (1997) *Altenative Medicine: Definitive Guide to Cancer.* Tiburon, Future Medicine Inc, California.

GROBBELAAR, J.J., WILKEN, E., DE RAVEL, T.J., NICHOLSON, D.L. & KOTZA, M.J. (2002) Familial adenomatous polyposis in two Black South African families. *Clin Genet,* 61(3): 214-217.

GRODEN, J., THLIVERIS, A., SAMOWITZ, W., CARLSON, M., GELBERT, L., ALBERTSEN, H., JOSLYN, G. & STEVENS, J., et al. (1991) Identification and characterization of the familial adenomatous polyposis coli gene. *Cell*, 66: 589-600.

HADLEY, D.W., JENKINS, J.F., DIMOND, E., DE CARVALHO, M., KIRSCH, I. & PALMER, C.G. (2004) Colon cancer screening practices after genetic counseling and testing for hereditary nonpolyposis colorectal cancer. *J Clin Oncol*, 22(1): 39-44.

HAITES, N. & GREGORY, H. (2002) *Overview of the clinical genetics of breast cancer in Familial Breast and Ovarian Cancer: Genetics, screening and management* edited by Morrison PJ, Hodgson SV and Haites NE. Cambridge University Press, United Kingdom.

HALL, J.M., LEE, M.K., NEWMAN, B. ET AL (1990) Linkage of early onset breast cancer to chromosome 17q21. *Science,* 250: 1684-1689.

HAHN, S.A., GREENHALF, B., ELLIS, I., SINA-FREY, M., RIEDER, H., KORTE, B., GERDES, B., KRESS, R., ZIEGLER, A., RAEBURN, J.A., CAMPRA, D., GRUTZMANN, R., REHDER, H., ROTHMUND, M., SCHMIEGEL, W., NEOPTOLEMOS, J.P. & BARTSCH, D.K. (2003) BRCA germline mutations in familial pancreatic carcinoma. *J Natl Cancer Inst,* 95: 214-21.

HARPER, P.S. (2004) *Practical Genetic Counseling*. Hodder Arnold Publishers, New York.

HEDENFALK, I., DUGGAN, D., CHEN, Y., RADMACHER, M., BITTNER, M., SIMON, R., MELTZER, P. & GUSTERSON, B., et al. (2001) Gene-expression profiles in hereditary breast cancer. *N Engl J Med,* 334(8): 539-548.

HORSMAN, D., WILSON, B.J., AVARD, D., MESCHINO, W.S., KIM, S.C., PLANTE, M., EISEN, A., HOWLEY, H.E., SIMARD, J. & NATIONAL HEREDITARY CANCER TASK FORCE (2007). Clinical management recommendations for surveillance and risk-reduction strategies for hereditary breast and ovarian cancer among individuals carrying a deleterious BRCA1 or BRCA2 mutation. *J Obstet Gynaecol Can*, 29(1): 45-60.

HOSKINS, K.F., STOPFER, J.E., CALZONE, K.A., MERAJVER, S.D., REBBECK, T.R., GARBER, J.E. & WEBER, B.L. (1995) Assessment and counseling for women with a family history of breast cancer: a guide for clinicians. *JAMA*, 273(7): 577-585.

HSIEH, C.C., TRICHOPOULOS, D., KATSOUYANNI, K. & YUASA, S. (1990) Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: associations and interactions in an international case-control study. *Int J Cancer*, 46: 769-800.

JÄRVINEN, H.J., AARNIO, M., MUSTONEN, H., AKTAN-COLLAN, K., AALTONEN, L.A., PELTOMÄKI, P., DE LA CHAPELLE, A. & MECKLIN, J.P. (2000) Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology*, 118(5): 829-34.

JENKINS, T. (1990) Medical genetics around the world: Medical genetics in South Africa. *J Med Genet*, 27: 760-779.

JO, W.S. & CHUNG, D.C. (2005) Genetics of Hereditary Colorectal Cancer. *Semin Oncol*, 32: 11-23.

KAUSMEYER, D.T., LENGERICH, E.J., KLUHSMAN, B.C., MORRONE, D., HARPER, G.R. & BAKER, M.J. (2006) A survey of patients' experiences with the cancer genetic counseling process: recommendations for cancer genetics programs. *J Genet Couns*, 15(6): 409-431.

KELLY, P.T. (1991) *Understanding breast cancer risk.* Temple University Press, Pennsylvania.

KELSEY, J.L., GAMMO, M.D. & JOHN, E.M. (1993) Reproductive factors and breast cancer. *Epidemiol rev*, 15: 36-47.

KINZLER, K.W., NILBERT, M.C., SU, L.K., VOGELSTEIN, B., BRYAN, T.M., LEVY, D.B., SMITH, K.J. & PREISINGER, A.C., el al. (1991) Identification of FAP locus genes from chromosome 5q21. *Science*, 253: 661-665.

KIRK, J. & KEFFORD, R. (2000) Cancer in the family: risks and management. *Med J Aust*, 172(11): 529-530.

KNUDSON, A.G. (1971) Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci*, 68: 820-823.

KOLODNER, R.D., HALL, N.R., LIPFORD, J., KANE, M.F., MORRISON, P.T., FINAN, P.J., BURN, J. & CHAPMAN, P., et al. (1995) Structure of the human MLH1 locus and analysis of a large hereditary nonpolyposis colorectal carcinoma kindred for mlh1 mutations. *Cancer Res*, 55(2): 242-248.

LAKHANI, S.R., VAN DE VIJVER, M.J., JACQUEMIER, J., ANDERSON, T.J., OSIN, P.P., MCGUFFOG, L. & EASTON, D.F. (2002) The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. *J Clin Oncol*, 20(9): 2310-2318.

LALLOO, F., KERR, B., FRIEDMAN, J.M. & EVANS, D.G.R. (2006) *Risk assessment and management in cancer genetics.* Oxford university press, New York.

LIM, W., HEARLE, N., SHAH, B., MURDAY, V., HODGSON, S.V., LUCASSEN, A., ECCLES, D., TALBOT, I. et al (2003) Further observations on LKB1/STK11 status and cancer risk in Peutz-Jeghers syndrome. *Br J Cancer*, 89: 308-13.

LINDOR, N.M., GREENE, M.H. & MAYO FAMILIAL CANCER PROGRAM. (1998) Special article: The concise handbook of family cancer syndromes. *Journal of National Cancer Institute*, 9(14): 1039-1071.

LIPWORTH, L. (1995) Epidemiology of breast cancer. *Eur J Cancer Prev*, 4: 7-30.

LOMAN, N., JOHANNSON, O., BENDAHL, P.O., BORG, A., FERNO, M. & OLSSON, H. (1998) Steroid receptors in hereditary breast carcinomas associated with BRCA1 or BRCA2 mutations or unknown susceptibility genes. *Cancer*, 83: 310-319.

LUCASSEN, A., WATSON, E., HARCOURT, J. ROSE, P. & O'GRADY, J. (2001) Guidelines for referral to regional genetics service: GPs respond by referring more appropriate cases. *Fam Pract*, 18: 135-140.

LYNCH, H. & KRUSH, A. (1971) Carcinoma of the breast and ovary in three families. *Surg Gynecol Obstet*, 133: 644

LYNCH, H.T., SHAW, M.W., MAGNUSON, C.W., LARSEN, A.L. & KRUSH, A.J. (1966) Hereditary factors in two large midwestern kindreds. *Arch Intern Med*, 117: 206-212.

LYNCH, H.T., SMYRK, T. & LYNCH, J.F. (1997) An update of HNPCC (Lynch syndrome). *Cancer Genet Cytogenet*, 93: 84-99.

LYNCH, H.T., LYNCH, J.F., CASEY, M.J., BEWTRA, C. & NAROD, S. (1997) *Genetics and Gynecologic Cancer in: Principles and practice of gynaecologic oncology*, 2nd ed by Hoskins WJ, Perez CA, and Young RC. Lippincott-Raven Publishers. P 31-59.

MANN, L. (2003) The general practitioner and the "new genetics". *Med J Aust*, 179(2): 109-111.

MIKI, Y., SWENSEN, J., SHATTUCK-EIDENS, D., FUTREAL, P.A., HARSHMAN, K., TAVTIGIAN, S., LIU, Q. & COCHRAN, C., et al. (1994) A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science,* 226: 66-71.

MILLER, E.A., KEKU, T.O., SATIA, J.A., MARTIN, C.F., GALANKO, J.A. & SANDLER, R.S. (2007) Calsium, dietary, and lifestyle factors in the prevention of colorectal adenomas. *Cancer*, 109(3): 510-517.

MITCHELL, R.J., FARRINGTON, S.M., DUNLOP, M.G. & CAMPBELL, H. (2002) Mismatch repair genes hMLH1 and hMSH2 and colorectal cancer, A HuGE Review. *Am J Epidemiol,* 156: 885-902.

MÖSLEIN, G., KRAUSE-PAULUS, R., HEGGER, R., PETERSCHULTE, G. & VOGEL, T. (2000) Clinical aspects of hereditary nonpolyposis colorectal cancer. *Ann N Y Acad Sci,* 910: 75-83.

MQOQI, N., KELLETT, P., SITAS, F. & JULA, M. (2004) Incidence of histologically diagnosed cancer in South Africa, 1998-1999. National Cancer registry of South Africa, National Health Laboratory Service, Johannesburg.

NAKAMURA, R.M., GRODY, W.W., WU, J.T. & NAGLE, R.B. (2004) *Cancer diagnostics: current and future trends.* Humana Press, Totowa, New Jersey.

NEUMAN, W.L. (1997) *Social research methods: Qualitative and quantitative approaches*. 3rd ed. Allyn & Bacon.

NEWMAN, L.A. & VOGEL, V.G. (2007) Breast cancer risk assessment and risk Reduction. *Surg Clin North Am*, 87(2): 307-316.

NICOLAIDES, N.C., PAPADOPOLOUS, N. & LIU, B.O., et al. (1994) Mutations of two PMS homologues in hereditary non-polyposis colon cancer. *Nature,* 371: 75-80.

NORMAN, R., BRADSHAW, D., GROENEWALD, P., SCHNEIDER, M. & PIETERSE, D. (2006) Revised burden of disease estimates for the Comparative Risk Factor Assessment, South Africa 2000. Cape Town. South African Medical Research Counsel.

PARK, Y., HUNTER, D.J., SPIEGELMAN, D., BERGKVIST, L., BERRINO, F. et al. (2005) Dietary fibre intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. *JAMA,* 295: 2849-2857.

PELTOMAKI, P., LOTHE, R.A., AALTONEN, L.A., et al. (1993) Microsatellite instability is associated with tumours that characterize the hereditary non-polyposis colorectal carcinoma syndrome. *Cancer Res*, 553: 5853-5856.

PHILIPS, K.A., GLENDON, G. & KNIGHT, J.A. (1999) Putting the risk of breast cancer into perspective. *N Engl J Med,* 340: 141-144.

PICHERT, G., DIETRICH, D., MOOSMANN, P., ZWAHLEN, M., STAHEL, R.A. & SAPPINO, A.P. (2003) Swiss primary care physicians' knowledge, attitudes and perceptions towards genetic testing for hereditary breast cancer. *Fam Cancer,* 2(3-4): 153-158.

PISTORIUS, S., GORGENS, H., PLASCHKE, J., HOEHL, R., KRUGER, S., ENGEL, C., SAEGER, H.D., SCHACKERT, H.K. (2006) Genomic rearrangements in MSH2, MLH1 or MSH6 are rare in HNPCC patients carrying point mutations. *Cancer Lett*, 248(1): 89-95.

POTTER, J.D. (1999) Colorectal cancer: Molecules and populations. *J Natl Cancer Inst*, 91(11): 916-932

POWELL, S.M., PETERSEN, G.M., KRUSH, A.J., BOOKER, S., JEN, J., GIARDIELLO, F.M., HAMILTON, S.R., VOGELSTEIN, B., KINZLER, K.W. (1993) Molecular diagnosis of familial adenomatous polyposis. *N Engl J Med*, 329: 1982-7

RAMESAR, R.S., MADDEN, M.V., FELIX, R., HAROCOPOS, C.J., WESTBROOK, C.A., JONES, G., CRUSE, J.P. & GOLDBERG, P.A. (2000) Molecular genetics improves the management of hereditary non-polyposis colorectal cancer. *S Afr Med J*, 90: 709-714.

REEVES, M.D., YAWITCH, T.M., VAN DER MERWE, N.C., VAN DEN BERG, H.J., DREYER, G. & VAN RENSBURG, F.J. (2004) BRCA1 mutations in South African breast and/or ovarian cancer families: evidence of a novel founder mutation in Afrikaner families. *Int J Cancer*, 110(5): 677-682.

REIS-FILHO, J.S. & TUTT, A.N. (2008) Triple negative tumours: a critical review. *Histopathology*, 52(1): 108-118.

RESTA, R., BIESECKER, B.B., BENNETT, R.L., BLUM, S., HAHN, S.E., STRECKER, M.N. & WILLIAMS, J.L.: THE NATIONAL SOCIETY OF GENETIC COUNSELORS' DEFINITION TASK FORCE. (2006) A new definition of genetic counseling: national society of genetic counselors' task force report. *J Genet Couns*, 15(2): 77-83.

RIJCKEN, F.E., HOLLEMA, H. & KLEIBEUKER, J.H. (2002) Proximal adenomas in hereditary non-polyposis colorectal cancer are prone to rapid malignant transformation. *Gut*, 50(3): 382-6.

RITCHARDSON, H., JOHNSON, D., PATER, J. & GOSS, P. (2007) The National Cancer Institute of Canada Clinical Trials Group MAP.3 trial: an international breast cancer prevention trial. *Curr Oncol*, 14(3): 89-96.

RODRIGUEZ-BIGAS, M.A., BOLAND, C.R., HAMILTON, S.R., HENSON, D.E., JASS, J.R., KHAN, P.M., et al. (1997) A national cancer institute workshop on hereditary nonpolyposis colorectal cancer syndrome: meeting highlights and Bethesda guidelines. *J Natl Cancer Inst*, 89: 1758-1762.

ROSE, P.W., WATSON, E., YUDKIN, P. et al., (2001) Referral of patients with a family history of breast/ovarian cancer- general practitioners' knowledge and expectations. *Fam Pract*, 18: 487–490.

ROZEN, P. & MACRAE, E. (2006) Familial adenomatous polyposis: the practical applications of clinical and molecular screening. *Fam Cancer,* 5(3): 227-235.

RUDEL, R.A., ATTFIELD, K.R., SCHIFANO, J.N. & BRODY, J.G. (2007) Chemicals causing mammary gland tumors in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer prevention. *Cancer,* 109(12 Suppl): 2635-66.

SANDERSON, S.C., WARDLE, J., JARVIS, M.J. & HUMPHRIES, S.E. (2004) Public interest in genetic testing for susceptibility to heart disease and cancer: a population-based survey in the UK. *Prev Med,* 39(3): 458-464.

SCHNEIDER, K.A. & MARNANE, D. (1997) Cancer risk counselling: how is it different? *J Genet Couns*, 6(2): 97-109.

SITAS, F., MADHOO, J. & WESSIE, J. (1998) Cancer in South Africa, 1993-1995. National Cancer Registry of South Africa, South African Institute for Medical Research, Johannesburg.

STREUWING, J.P., ABELIOVICH, D., PERETZ, T., AVISHI, N., KABACK, M.M., COLLINS, F.S., et al. (1995) The carrier frequency of the BRCA1 185delAG mutation in approximately 1% of Ashkenazi Jewish individuals. *Nat Genet,* 11: 198-200.

STREUWING, J.P., HARTGE, P., WACHOLDER, S., BAKER, S.M. & BERLIN, M. et al. (1997) The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jewish. *N Engl J Med,* 336: 1401-1407.

TURNPENNY, P. & ELLARD, S. (2005) *Emery's Elements of Medical Genetics.* 12th Edition. Elsevier Churchill livingstone, China.

TYLER, C.V. & SNYDER, C.W. (2006) Cancer risk assessment: examining the family physician's role. *J Am Board Fam Med,* 19(5): 468-477.

VADAPARAMPIL, S.T., WIDERHOFF, L., OLSON, L., VISWANATH, K. & FREEDMAN, A.N. (2005) Physician exposure to and attitudes toward advertisements for genetic tests for inherited cancer susceptibility. *Am J Med Genet A,* 135(1):41-6

VAN DER MERWE, N.C. & VAN RENSBURG, E.J. (2007) Genealogical identification of founding couples for the E881X and the 1493delC *BRCA1* founder mutations unique to South Africa. ABSTRACT: SASHG Congress, sentinel genetics, Golden Gate, South Africa, 1-3 March 2007.

VAN RENSBURG, E.J., VAN DER MERWE, N.C., SLUITER, M.D. SCHLEBUCH, C.M., YAWITCH, T.M., DAJEE, B.K. & DELPORT, B. (2007) The impact of the BRCA-genes on the burden of familial breast and/or ovarian cancer in South Africa. ABSTRACT: SASHG Congress, sentinel genetics, Golden Gate, South Africa, 1-3 March 2007.

VAN SPRUNDEL, T.C., SCHMIDT, M.K., ROOKUS, M.A., BROHET, R., VAN ASPEREN, C.J., RUTGERS, E.J., VAN'T VEER, L.J. & TOLLENAAR, R.A. (2005) Risk reduction of contralateral breast cancer and survival after contralateral prophylactic mastectomy in BRCA1 or BRCA2 mutation carriers. *Br J Cancer*, 93(3): 287-292.

VASEN, H.F.A., MECKLIN, J.P.L., MEERA KHAN, P. & LYNCH, H.T., et al. (1991) The international collaborative group on hereditary non-polyposis colorectal cancer. *Dis Colon Rectum*, 34: 424-425.

VASEN, H.F., NAGENGAST, F.M., KHAN, P.M. (1995) Interval cancers in hereditary non-polyposis colorectal cancer (Lynch syndrome). *Lancet*, 345: 1183-1184.

VASEN, H.F., WATSON, P., MECKLIN, J.P. & LYNCH, H.T., et al. (1999) New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. *Gastroenterology*, 116: 1453-1456.

WAGNER, A., BARROWS, A., WIJNEN, J.T., VAN DER KLIFT, H., FRANKEN, P.F., VERKUIJLEN, P., NAKAGAWA, H., GEUGIEN, M. et al (2003) Molecular analysis of hereditary nonpolyposis colorectal cancer in the United States: high mutation detection rate among clinically selected families and characterization of an American founder genomic deletion of the MSH2 gene. *Am J Hum Genet*, 72: 1088-100.

WALKER, C.W. (2007) Fecal occult blood tests reduce colorectal cancer mortality, *Am Fam Physician*, 75(11): 1652-1653.

WALSH, J.M.E. & TERDIMAN, J.P. (2003) Colorectal cancer screening. *JAMA*, 289: 1297-1302.

WARNER, E., PLEWES, D.B, HILL, K.A., CAUSER, P.A., ZUBOVITZ, J.T., JONG, R.A., CUTRARA, M.R., DEBOER, G., et al. (2004) Surveillance of BRCA1 and BRCA2 Mutation carriers with magnetic resonance imaging, ultrasound, mammography, and Clinical breast examination. *JAMA*, 292(11): 1317-1325

WATSON, E., CLEMENTS, A., YUDKIN, P., ROSE, P., BUKACH, C., MACKAY, J., LUCASSEN, A. & AUSTOKER, J. (2001) Evaluation of the impact of two educational interventions on GP management of familial breast/ovarian cancer cases: a cluster randomized controlled trial, *Br J Gen Pract*, 51(471): 817-821.

WIDERHOFF, L., FREEDMAN, A.N., OLSON, L., KLABUNDE, C.N., DAVIS, W., SRINATH, K.P., CROYLE, R.T. & BALLARD-BARBASH, R. (2003) Physician use of genetic testing for cancer susceptibility: results of a national survey. *Cancer Epidemiol Biomarkers Prev*, 12(4): 295-303.

WIDERHOFF, L., VADAPARAMPIL, S.T., GREENE, M.H., TAPLIN, S., OLSON, L. & FREEDMAN, A.N. (2005) Hereditary breast/ovarian and colorectal cancer genetics knowledge in a national sample of US physicians. *J Med Genet*, 42: 749-755.

WILLIAMS, J.K., SKIRTON, H. & MASNY, A. (2006) Ethics, policy, and educational issues in genetic testing. *J Nurs Scholarsh*, 38(2): 119-125

WOGEN, G.N., HECHT, S.S., FELTON, J.S., CONNEY, A.H. & LOEB, L.A. (2004) Environmental and chemical carcinogenesis. *Semin Cancer Biol*, 14(6): 473-486.

WOOSTER, R., BIGNELL, G., LANCASTER, J., SWIFT, S., SEAL, S. MANGION, J., COLLINS, N., GREGORY, S., GUMBS, C. & MICKLEM, G. (1995) Identification of the breast cancer susceptibility gene *BRCA2*. *Nature*, 378: 789-791.

ZIELINSKI. S.L. (2005) As genetic tests move into the mainstream, challenges await for doctors and patients. *JNCI*, 97(5): 334-336.

ELECTRONIC REFERENCES

ALBRECHT, C. (2006) Overview of the South African cancer research environment as a basis for discussions concerning the activation of CARISA (Cancer Research Initiative of South Africa). http://www.sahealthinfo.org/cancer/overviewdocument.pdf [accessed June 2007]

AIDS LAW PROJECT 'EQUALITY AND JUSTICE FOR ALL' http://www.hri.ca/partners/alp/about/index.shtml

BLOKHUIS, M.M., GOLDBERG, P.A., PIETERSEN, G.E., ALGAR, U., VORSTER, A.A., GOVENDER, D. & RAMESAR, R.S. (2007) The extracolonic cancer spectrum in females with the common 'South African' hMLH1 c.C1528T mutation. *Fam Cancer*. http://www.springerlink.com/content/c18v422311v84117/

CANCER ASSOCIATION OF SOUTH AFRICA (CANSA) http://www.cansa.org.za/

CANCER GENOME PROJECT http://www.sanger.ac.uk/genetics/CGP/ http://www.sanger.ac.uk/genetics/CGP/Census/Table_1_full_2007-02-13.xls

HUMAN GENETICS RESEARCH UNIT, COLORECTAL CANCER PROJECT, 2008 Retrieved April, 2008, from http://www.iidmm.uct.ac.za/ramesar/research.htm

LAST, J.M. (2002) The Gale Group Inc., Macmillan Reference USA, New York, Gale Encyclopedia of Public Health. http://www.healthline.com/galecontent/pilot-study. [accessed 24 July 2007]

EMDIN, L. (2004) The environmental causes of cancers. *The SA J of Natural Medicine*. http://www.naturalmedicine.co.za/sajnm_main/article.php?story=20040108150329575 [accessed July 2007]

PETRUCELLI, N., DALY, M.B., CULVER, J.O.B. & FELDMAN, G.L. (2007) BRCA1 and BRCA2 Hereditary Breast/Ovarian Cancer, GENE REVIEWS. http://www.genetests.org/ http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=qTes6SDkkedqj&gry=&fcn=y&fw=ghaj&filename=/profiles/brca1/index.html

SOLOMON, C. & BURT, R.W. (2007) *APC*-Associated Polyposis Conditions, GENE REVIEWS. http://www.genetests.org/ http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=Y9MXs1G8Jgm4n&gry=&fcn=y&fw=RYFi&filename=/profiles/fap/index.html

WORLD HEALTH ORGANIZATION (WHO) GUIDELINES ON BIOETHICS (1999), online*:* Nature: International Weekly Journal of Science http://helix.nature.com/wcs/b23a.html [accessed: October 2007]

Appendix A: Questionnaire

NATIONAL HEALTH LABORATORY SERVICE

University of the Witwatersrand, School of Pathology
Division of Human Genetics

GENETIC COUNSELLING CLINIC

Hospital Street, Johannesburg, 2001
Telephone: +27-11-489-9224/9223/9211

PO Box 1038, Johannesburg, 2000
Fax: +27-11-489-9226/9209/9286

Professor D Viljoen 489-9239 • Prof A Krause 489-9219 • Prof A Christianson 489-9212 • Ms T Wessels 489-9243

GENERAL PRACTITIONERS SURVEY ON CANCER SUSCEPTIBILITY TESTING

PART I. YOUR BACKGROUND AND PRACTICE CHARACTERISTICS

1. What is your date of birth? _____

2. What is your sex? ☐ Male ☐ Female

3. What are your qualifications?

_____

4. Including yourself, how many practitioners are in your practice setting? _____

5. On average, how many male patients and how many female patients do you see each week?
_____male patients _____female patients

6. On average how many hours per week do you spend in practice: _____hrs/week.

7. Have any of the following people in your family ever been diagnosed with cancer? **(CHECK ALL THAT APPLY)**
☐ A parent ☐ A brother or sister ☐ A spouse or partner
☐ A son or daughter ☐ Yourself ☐ None of the above
☐ Other **Specify:** _____

8. During the past 12 months, did you receive advertising materials from a company marketing genetic tests for inherited cancer susceptibility? **(CHECK ALL THAT APPLY)**
☐ Yes, in person ☐ Yes, by telephone ☐ Yes, by mail ☐ Yes, by email (Internet)
☐ No, I have not received any materials ☐ Don't know

PART II. PRACTICES ON CANCER SUSCEPTIBILITY SCREENING

1. For asymptomatic patients of the appropriate age and sex, on how many patients per month do you perform or refer elsewhere each month for the following cancer screening procedures? Less than 1 patient each month, one to ten patients each month, more than ten patients each month, or never? **(CHECK "NOT APPLICABLE" IF THE TEST IS NOT APPROPRIATE IN YOUR PATIENT POPULATION.)**

	>10 pt/month	**1-10 pt/month**	**<1 pt/month**	**Never**
a. Fecal occult blood test (FOBT)	☐	☐	☐	☐
b. Prostate-specific antigen (PSA)	☐	☐	☐	☐
c. Pap smear	☐	☐	☐	☐
d. Clinical breast examination (CBE)	☐	☐	☐	☐
e. Mammography	☐	☐	☐	☐
f. CA-125	☐	☐	☐	☐
g. Abdominal ultrasound	☐	☐	☐	☐

2. How many new patients per month do you ask to provide the following information: **(CHECK ONE BOX ON EACH LINE)**

	>10 pt/month	**1-10 pt/month**	**<1 pt/month**	**Never**
a. A medical history?	☐	☐	☐	☐
b. A family history of cancer among first degree relatives, such as parents, siblings, and children?	☐	☐	☐	☐
c. A family history of cancer among second degree relatives, such as grandparents, aunts, and uncles?	☐	☐	☐	☐
d. Age of diagnosis of relatives with cancer?	☐	☐	☐	☐

3. How many patients per month ask you if they have an increased risk of cancer because of their family history of cancer?

☐ >10 pt/month ☐ 1-10 pt/month ☐ <1 pt/month ☐ never

4. During the past 12 months, have they asked you the above question more frequently, less frequently, or the same as in previous years?

☐ More frequently ☐ less frequently ☐ remained the same ☐ don't know

5. During the past 12 months, have any of your patients asked you if they can or should get tested for an inherited cancer susceptibility gene?

☐ Yes Approximately how many patients? _____ ☐ No

6. During the past 12 months, have you assessed any of your patients' personal and family medical history to determine if they are candidates for genetic testing for inherited cancer susceptibility? (Do not include patients whom you referred to another health care provider for this assessment.)

☐ Yes Approximately how many patients? _____ ☐ No

7. During the past 12 months, have you ordered a genetic test for inherited cancer susceptibility?

☐ Yes ☐ No

8. During the past 12 months, have you referred any of your patients to another health care provider for a genetic test for inherited cancer susceptibility, or for an assessment of whether or not they are candidates for genetic testing?

☐ Yes Approximately how many patients? _____ ☐ No

9. To what kind of healthcare facility or provider did you refer them?

_____

_____

10. During the next five years, do you expect the number of your patients who undergo genetic testing for inherited cancer susceptibility to: **(CHECK ONE BOX)**

☐ Increase substantially ☐ Increase somewhat ☐ Remain the same
☐ Decrease somewhat ☐ Decrease substantially ☐ Don't know

For the next question, please respond Yes, No, or Not Sure

11. In the next 5 years, do you expect to directly order, or refer patients elsewhere for, a genetic test for inherited cancer susceptibility for: **(CHECK ONE BOX ON EACH LINE)**

	Yes	**No**	**Not Sure**
a. Breast or ovarian cancer	☐	☐	☐
b. Colon cancer	☐	☐	☐

c. Other (Specify) _____

PARTIII. KNOWLEDGE ON GENETIC COUNSELLING AND GENETIC TESTING FOR INHERITED CANCER.

1. Are there any facilities that can do genetic counselling for inherited cancer susceptibility in the geographic area from which you draw your patients?

☐ Yes ☐ No ☐ Don't know

If you answered yes please name these facilities _____

2. Are there any facilities that can do genetic testing for inherited cancer susceptibility in the geographic area from which you draw your patients?

☐ Yes ☐ No ☐ Don't know

If you answered yes please name these facilities _____

3. Based on your current knowledge, are tests for the following inherited cancer susceptibility genes commercially available in South Africa?

	Yes	**No**	**Don't know**
a. BRCA1 and BRCA2 genes for hereditary breast/ovarian syndrome.	☐	☐	☐
b. MLH1 and MSH2 genes for hereditary non-polyposis colorectal cancer (HNPCC).	☐	☐	☐
c. APC gene for familial adenomatous polyposis (FAP).	☐	☐	☐

4. Suppose you have a female patient whose aunt or grandmother on her father's side carries the BRCA1 gene mutation for breast/ovarian cancer syndrome. In your opinion, could your patient also be a carrier of this mutation? **(CHECK ONE BOX)**

☐ Yes ☐ No ☐ Don't know

5. In your opinion, what percentage of female breast cancer patients have a BRCA1 or BRCA2 gene mutation?

☐ Less than 10% ☐ 10 to 19% ☐ 20 to 49% ☐ 50 to 100% ☐ Don't know

6. In your opinion, what percentage of patients who carry a gene for hereditary non-polyposis colorectal cancer will actually go on to develop colorectal cancer?

☐ Less than 10% ☐ 10 to 19% ☐ 20 to 49% ☐ 50 to 100% ☐ Don't know

PART IV. ATTITUDES ON INHERITED CANCER SUSCEPTIBILITY TESTING RECOMENDATIONS

For the next question, please respond Yes, No, or Don't know

1. Genetic counselling provides patients with information on genetic testing and their risk for inherited cancer. Who of the following health care provider(s) would you consider qualified to provide genetic counselling to your patients? **(CHECK ONE BOX ON EACH LINE)**

	Yes	No	Don't know
a. Yourself	☐	☐	☐
b. Clinical geneticist	☐	☐	☐
c. Oncologist	☐	☐	☐
d. Registered genetic counsellor	☐	☐	☐

Give a reason for your answer_____

2. If you were to use genetic tests for inherited cancer susceptibility, what role would each of the following factors play in your decisions whether or not to recommend testing? Would they be very important, somewhat important, not very important, not important at all, or don't you know? **(CHECK ONE BOX ON EACH LINE)**

	Very Important	Somewhat Important	Not Very Important	Not Important at All	Don't know
a. The individual patient's cancer risk profile	☐	☐	☐	☐	☐
b. The individual patient's or their family's attitudes toward genetic testing	☐	☐	☐	☐	☐
c. Recommendations and guidelines from your institution or practice	☐	☐	☐	☐	☐
d. Discussions with your colleagues	☐	☐	☐	☐	☐
e. Recommendations and guidelines from medical societies or government agencies	☐	☐	☐	☐	☐
f. Information you obtained through continuing medical education	☐	☐	☐	☐	☐
g. Commercial advertisements and promotions	☐	☐	☐	☐	☐
h. Clinical data published in the medical literature	☐	☐	☐	☐	☐
i. Coverage of genetic tests by your patients' medical insurance plans	☐	☐	☐	☐	☐
j. Your training in medical school, residency	☐	☐	☐	☐	☐

3. For each of the following statements concerning genetic tests for inherited cancer susceptibility, indicate whether you strongly agree, somewhat agree, somewhat disagree, strongly disagree, or don't you know? **(CHECK ONE BOX ON EACH LINE)**

	Strongly Agree	Somewhat Agree	Somewhat Disagree	Strongly Disagree	Don't know
a. Clear guidelines or strategies are available for managing patients with positive test results	☐	☐	☐	☐	☐
b. Genetic testing services are readily available	☐	☐	☐	☐	☐
c. Genetic testing of patients with a family history is cost effective because inherited mutations are rare	☐	☐	☐	☐	☐
d. The risk of cancer in patients who have a positive genetic test is clear	☐	☐	☐	☐	☐
e. Genetic tests for inherited cancer susceptibility have too many false positive, false negative, or ambiguous results	☐	☐	☐	☐	☐
f. Genetic tests for inherited cancer susceptibility are usually covered by your patients' medical aid plans	☐	☐	☐	☐	☐
g. It is difficult to ensure that patients' test results will remain confidential	☐	☐	☐	☐	☐
h. Patients with positive test results are at risk for insurance discrimination	☐	☐	☐	☐	☐
i. Patients should not undergo genetic testing unless they get genetic counseling about the risks, benefits and consequences of the test.	☐	☐	☐	☐	☐

4. How qualified or unqualified do you consider yourself to recommend genetic testing for inherited cancer susceptibility to your patients? **(CHECK ONE BOX)**

☐ Very well qualified ☐ Somewhat qualified ☐ Not very well qualified
☐ Not qualified at all ☐ Don't know

5. How interested would you be in receiving continuing medical education credits for training in genetic risk assessment and testing for inherited cancer susceptibility? **(CHECK ONE BOX)**

☐ Very interested ☐ Somewhat interested ☐ Not very interested
☐ Not interested at all ☐ Don't know

6. In your opinion, is there a need for general practitioner guidelines for genetic testing for inherited cancer susceptibility?

☐ Yes ☐ No ☐ Don't know

Thank you very much for your participation in this survey.

If you would like to receive a summary report of the findings from this survey? Please remember to complete and return the postal card provided.

Appendix B: Permission to use Widerhoff et al (2005) questionnaire in this study

Chantel van Wyk

From: Wideroff, Louise (NIH/NCI) [E] [widerofl@mail.nih.gov]
Sent: Thursday, July 06, 2006 3:17 PM
To: Chantel van Wyk
Cc: Freedman, Andrew (NIH/NCI) [E]
Subject: RE: Physician survey

Dear Ms. Van Wyk,

The questionnaire is available for public use at http://riskfactor.cancer.gov/studies/physician/psqtquest.pdf so please feel free to access and use it. Good luck with your project.

Best regards,

Louise Wideroff, PhD, M.S.P.H.
Risk Factor Monitoring and Methods Branch
Applied Research Program
Division of Cancer Control and Population Sciences
National Cancer Institute
EPN 4005 MSC 7344
6130 Executive Blvd.
Bethesda, MD 20892-7344

tel: 301-435-6823
fax: 301-435-3710
wideroff@nih.gov

-----Original Message-----
From: Chantel van Wyk [mailto:chantel.vanwyk@nhls.ac.za]
Sent: Thursday, July 06, 2006 7:36 AM
To: Wideroff, Louise (NIH/NCI) [E]
Subject: Physician survey

****

The views expressed in this email are, unless otherwise stated, those of the author and not those of the National Health Laboratory Services or its management. The information in this e-mail is confidential and is intended solely for the addressee.

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****

Internal Virus Database is out-of-date.
Checked by AVG Free Edition.
Version: 7.5.467 / Virus Database: 269.6.1/776 - Release Date: 2007/04/25 12:19 PM

Appendix C1: Information sheet from Head of Family Medicine

DEPARTMENT OF FAMILY MEDICINE
UNIVERSITY OF THE WITWATERSRAND

23 May 2007

Dear Colleague

Attached is information on a research project being conducted by a Wits student, Chantel van Wyk, who is currently doing her MSc (Med) Genetic counselling degree. The project will examine "Practices, knowledge and attitude of GPs about inherited cancers", and has the total support of the Department of Family Medicine.

This project is **vital to our understanding** of how family practitioners manage inherited cancers. We would really appreciate your contribution to this research and urge you to complete the attached questionnaire.

Kind regards,

Prof. Bruce L W Sparks
Head, Department of Family Medicine

10th Floor, Medical School. Faculty of Health Sciences, York Rd, Parktown, 2193, South Africa
☎ Work: +27-(0)11-717.2041, Fax: +27-(0)11-717.2558
EMail: brucespa@global.co.za

Appendix C2: Research information sheets

NATIONAL HEALTH LABORATORY SERVICE

University of the Witwatersrand, School of Pathology
Division of Human Genetics

GENETIC COUNSELLING CLINIC

Hospital Street, Johannesburg, 2001
Telephone: +27-11-489-9224/9223/9211

PO Box 1038, Johannesburg, 2000
Fax: +27-11-489-9226/9209/9286

Professor A Christianson 489-9239 • Prof A Krause 489-9219 • Ms T Wessels 489-9243

Dear Doctor

23 May 2007

I am Chantel van Wyk, a genetic counselling student in the Division of Human Genetics of the National Health Laboratory Service and the University of the Witwatersrand.

I am conducting a study, for my Masters degree, looking at **"Practices, knowledge and attitude of GPs about inherited cancers"**. I would like to invite you to participate in this research. Participation involves completing the attached questionnaire and response sheet, and sending it back to the researcher in the separate envelopes provided. It will take approximately **10-15 min** of your time to complete. Please **complete and return** this **by 22 June 2007.**

The information obtained from the questionnaire will be kept confidential and anonymous. The results of the study will be written up as a research report and published in a scientific journal. The survey is anonymous. Your name will not be linked to your answers and will not be made public. I would appreciate it if you could complete and post the separate response sheet (where you specify whether you would like to receive a summary of the research) back to me. This will assist me with follow up and record keeping.

If you do not participate in the research this will not disadvantage you in any way.

For more information please feel free to contact me or my supervisors.

Thank you for your participation

Ms Chantel van Wyk (011) 489 9362

Supervisor 1: Ms Tina-Marie Wessels (011) 489 9243
Supervisor 2: Prof Amanda Krause (011) 489 9219

NATIONAL HEALTH LABORATORY SERVICE

University of the Witwatersrand, School of Pathology
Division Of Human Genetics

GENETIC COUNSELLING CLINIC

Hospital Street, Johannesburg, 2001
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PO Box 1038, Johannesburg, 2000
Fax: +27-11-489-9226/9209

Prof A Christianson 489-9212 • Prof A Krause 489-9219 • Ms T Wessels 489-9243

09 July 2007

Dear Doctor

I am Chantel van Wyk, a genetic counselling student in the Division of Human Genetics of the National Health Laboratory Service and the University of the Witwatersrand.

I am conducting a study for my Masters degree, looking at **"Practice, knowledge, and attitudes of GPs about inherited cancers"**. To date, only 15% of questionnaires have been returned completed. Therefore, I would like to encourage you to participate in this study.

Participation involves completing the attached questionnaire and responce sheet, and returning it to the researcher in the separate envelopes provided. It should take approximitaly **10-15 min** of your time to complete.

Please **complete and return** these **by 27 July 2007**. If you have already completed and returned the questionnaire, thank you.

For more information please feel free to contact me or my supervisors.

Thank you for your participation

Chantel van Wyk (011) 4899362

Supervisor 1: Ms Tina-Marié Wessels (011) 489 9243
Supervisor 2: Prof Amanda Krause (011) 489 9291

Appendix C3: Response sheet

NATIONAL HEALTH LABORATORY SERVICE

University of the Witwatersrand, School of Pathology

DIVISION OF HUMAN GENETICS

Hospital Street, Johannesburg, 2001
Telephone: +27-11-489-9224/9223/9211

PO Box 1038, Johannesburg, 2000
Fax: +27-11-489-9226/9209/9286

Professor D Viljoen 489-9239 • Prof A Krause 489-9219 • Prof A Christianson 489-9212 • Prof M Ramsay 489-9214
Dr H Soodyall 489-9208 • Dr AB Lane 489-9221 • Ms T Wessels 489-9243

If you would like to receive a summary of the research. Please complete and return to the researcher.

Full name: _____

Postal address: _____

_____

_____

Code: _____

Contact Tel: _____

Fax: _____

Cell: _____

e-mail address: _____

Preference: Mail ☐

e-mail ☐

Appendix D: Ethics approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 van Wyk

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M070219**
PROJECT	The Practices, Knowledge, and Attitudes about Common Hereditary Cancers: Survey of General Practitioners in Johannesburg
INVESTIGATORS	C van Wyk
DEPARTMENT	Dept of Human Genetics
DATE CONSIDERED	07.03.02
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 07.03.05 **CHAIRPERSON** .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Mrs TM Wessels

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