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INHERITED BREAST AND OVARIAN CANCER:

A REVIEW OF THE AVAILABLE GENETIC COUNSELLING AND TESTING SERVICES IN JOHANNESBURG

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

Johannesburg, 2013

DECLARATION

I, Marianne Jefferies, declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine in the branch of Genetic Counselling, in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

……...….

……..…...day of ……..…, 2013

DEDICATION

I dedicate this work to my husband, Rui, and my son, Cristian, for giving me happiness, laughter, hope, faith and love.

ABSTRACT

Five to ten percent of both breast and ovarian cancer cases are attributable to dominantly inherited mutations in genes that predispose to cancer, with a large proportion caused by mutations in the breast and ovarian cancer predisposing genes *BRCA1* and *BRCA2*. Testing for these inherited cancers is indicated for individuals identified as being at high risk, or moderate to high risk, of having a cancer syndrome based on their family history of breast and/or ovarian cancer. Screening for high-risk individuals through services such as genetic counselling, has the potential to improve outcomes for these individuals and lower mortality rates. This study focused on individuals who attended genetic counselling for breast and/or ovarian cancer at the Genetic Counselling Clinics of the Division of Human Genetics, University of the Witwatersrand and the National Health Laboratory Service, Johannesburg from 2001 to 2010. The study was divided into a file review on 218 counsellees and a telephonic interview of 50 counsellees. Focusing on breast and/or ovarian cancer, the study aimed to review who attends genetic counselling and why; who is offered genetic testing; what testing is offered and performed and; who pays for the testing, as well as gain a better understanding of how the service is received by counsellees. The study found that the majority of counsellees are white females, at a high risk of inherited breast and/or ovarian cancer, attend the genetic counselling session alone and are self-referred. There is an under representation of the black and coloured populations and an over representation of the Ashkenazi Jewish population in the cohort. The study's findings showed that a main motivator for individuals attending genetic counselling was for *BRCA* mutation testing, with the majority of testing offered being nationally based testing. The study also demonstrated that the service is generally well received and counsellees reported having a positive experience. Overall, the study pointed to the general lack of understanding and public awareness of genetic counselling, with suggestions to market to both the general population and to other medical professionals in order to reach more high risk individuals. On a practical level, a follow up service was suggested to ensure counsellees adhered to screening measures, informing counsellees on changes to testing protocols and identifying family members who may be at an increased risk of inherited breast and/or ovarian cancer.

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TABLE OF CONTENTS

DECLARATION ..... **II**

DEDICATION ..... **III**

ABSTRACT ..... **IV**

ACKNOWLEDGEMENTS ..... **V**

LIST OF FIGURES ..... **X**

LIST OF TABLES ..... **XI**

LIST OF ABBREVIATIONS ..... **XII**

CHAPTER 1 INTRODUCTION **1**

1.1 BREAST CANCER 1

1.1.1 Breast cancer classification *2*

1.1.2 Risk factors for breast cancer *3*

1.1.3 Screening and risk reducing surgery for breast cancer *3*

1.2 OVARIAN CANCER 4

1.2.1 Ovarian cancer classification *5*

1.2.2 Risk factors for ovarian cancer *5*

1.2.3 Screening and risk reducing surgery for ovarian cancer *5*

1.3 INCIDENCE OF BREAST AND OVARIAN CANCER 6

1.3.1 South African incidence of breast and ovarian cancer *6*

1.4 GENETICS OF HEREDITARY BREAST AND OVARIAN CANCER 7

1.4.1 BRCA1 and BRCA2 ..... *8*

1.4.2 Penetrance of breast and ovarian cancer in BRCA mutation carriers *10*

1.5 *BRCA1/2* MUTATION TESTING 10

1.5.1 Targeted mutation analysis *11*

1.5.2 Other testing methods *13*

1.5.3 Cost of BRCA mutation testing *15*

1.6 GENETIC COUNSELLING 15

1.6.1 Reasons for attending genetic counselling for breast and/or ovarian cancer *16*

1.6.2 Genetic counselling for hereditary breast and/or ovarian cancer in Johannesburg 17
1.6.3 Pedigree analysis 18
1.6.4 Risk assessment 19
1.6.5 Psychosocial aspects of being at risk for hereditary breast and ovarian cancer 22
1.7 MOTIVATION FOR RESEARCH 23
1.8 AIM 24
1.9 OBJECTIVES 24
CHAPTER 2 SUBJECTS AND METHODS 25
SECTION A: FILE REVIEW 25
2.1 SUBJECTS 25
2.1.1 File collection 26
2.2 METHODS 27
2.2.1 Data collection 27
2.2.2 Classification of "counsellee" 28
2.2.3 Data analysis 29
SECTION B: TELEPHONIC QUESTIONNAIRE 29
2.3 PILOT STUDY 30
2.4 SUBJECTS 31
2.5 METHODS 31
2.5.1 Data collection 31
2.5.2 Data analysis 31
CHAPTER 3 RESULTS 32
SECTION A: FILE REVIEW 32
3.1 SESSION INDICATORS 32
3.1.1 Yearly counsellee attendance numbers 32
3.1.2 Number of individuals in attendance per genetic counselling session 33
3.1.3 Reason for attending a genetic counselling session 33
3.2 DEMOGRAPHICS 33
3.2.1 Descent 34

3.2.2 Genetic risk classification *34*
3.3 *BRCA* MUTATION TESTING 35
3.3.1 BRCA mutation testing offered *35*
3.3.2 BRCA mutation testing performed *36*
3.3.3 Number of BRCA mutation tests performed *36*
3.3.4 Cost of BRCA mutation testing *37*
3.3.5 BRCA disease-causing mutations identified *37*
3.4 PEDIGREE ANALYSIS 38
3.4.1 Other cancers in the family of the counsellee *39*
SECTION B: TELEPHONIC QUESTIONNAIRE 40
3.5 THE RESPONDENTS 40
3.5.1 Reason for attending genetic counselling *41*
3.5.2 Initial expectation of genetic counselling *42*
3.6 INFORMATION CONVEYED DURING GENETIC COUNSELLING 42
3.6.1 Genetics of breast and/or ovarian cancer *42*
3.6.2 Risk of carrying a BRCA mutation *43*
3.6.3 Screening and/or prophylactic surgery for breast and/or ovarian cancer *44*
3.7 REFERRALS TO GENETIC COUNSELLING 45
3.7.1 Additional comments from respondents *46*

CHAPTER 4 DISCUSSION 49

4.1 COUNSELLEE NUMBERS 49
4.1.1 Referrals *50*
4.2 WHO ATTENDS GENETIC COUNSELLING AND WHY? 51
4.2.1 Attendees *51*
4.2.2 Reasons for attending genetic counselling *52*
4.2.3 Expectations of genetic counselling *54*
4.3 *BRCA* MUTATION TESTING 54
4.3.1 BRCA mutations identified *56*
4.4 *BRCA1/2* AND ASSOCIATED CANCERS 56

4.5 ARE THE AIMS OF CANCER RISK ASSESSMENT AND COUNSELLING BEING ATTAINED? 57
4.5.1 Risk perception *57*
4.5.2 Understanding of information received *59*
4.6 HOW IS THE GENETIC COUNSELLING SERVICE RECEIVED? 60
4.7 LIMITATIONS 62
4.8 SUMMARY OF FINDINGS 64
4.9 RECOMMENDATIONS 65
CHAPTER 5 CONCLUSIONS AND FUTURE RESEARCH 67
CHAPTER 6 REFERENCE LIST 69
6.1 ELECTRONIC REFERENCES 75
APPENDIX A: DATA COLLECTION SHEET 76
APPENDIX B: TELEPHONIC QUESTIONNAIRE 79
APPENDIX C: ETHICS CLEARANCE CERTIFICATE 82

LIST OF FIGURES

Figure 1.1: The metastasis of a malignant breast tumour. The tumour grows from a single cell, invading neighbouring tissue and, in some cases, spreading to other parts of the body via the circulatory system (metastasis) (taken from Campbell et al. (2004)).....2
Figure 1.2: Outline of a genetic counselling session for inherited breast and/or ovarian cancer offered by the Division of Human Genetics, WITS and NHLS.....18
Figure 2.1: Calculation of the number of counsellees on which the analysis of other cancers in the family was performed.....29
Figure 3.1: Number of counsellees attending genetic counselling from January 2001 to December 2010 (n=218).....32
Figure 3.2: The number of individuals present at a genetic counselling session 33
Figure 3.3: Descent/ancestry of counsellees attending genetic counselling (n=218).....34
Figure 3.4: Breakdown of the number of counsellees who were offered *BRCA* mutation testing and the risk category they were classified into.....35
Figure 3.5: Number of counsellees offered *BRCA* mutation testing and for whom *BRCA* mutation testing was performed 36
Figure 3.6: The types of *BRCA* tests performed in 138 counsellees (n=147) 37
Figure 3.7: The number and degree of relationship of affected relatives of counsellees, both affected and unaffected with breast and/or ovarian cancer 39
Figure 3.8: The number and type of "other" cancers reported in families of counsellees 40
Figure 3.9: Descent/ancestry of the respondents interviewed telephonically (n=50) 41
Figure 3.10: Respondents' reasons for attending genetic counselling (n=57*) 41
Figure 3.11: Respondents' recollection of the risk category they were classified into during their genetic counselling session for breast and/or ovarian cancer (n=50) 44
Figure 3.12: Respondents' reasons for referring friends/family to the genetic counselling (n=51) 46
Figure 3.13: Positive comments made by respondents regarding: the service, the counsellor and the atmosphere for genetic counselling for breast and/or ovarian cancer (n=72).....47

LIST OF TABLES

Table 1.1: Histological grading categories of breast cancer (Elston & Ellis, 1991) 2
Table 1.2: Comparison of *BRCA1* and *BRCA2* genes (Miki, Swensen, Shattuck-Eidens et al., 1994; Wooster et al., 1995) 9
Table 1.3: Cancer risks associated with *BRCA1/2* mutations (Kerr et al., 2010).....9
Table 1.4: Founder mutations identified in *BRCA1* and *BRCA2*.....12
Table 1.5: *BRCA* mutation testing available at the National Health Laboratory Service in Johannesburg and Bloemfontein (van der Merwe, N., 2009, personal communication, 28 May) 14
Table 2.1: Reconciliation of the number of breast and/or ovarian cancer files expected and those available for review.....26
Table 2.2: Degree of relationship between individuals and the proportion of genes they share (Adapted from Harper (2004)) 28
Table 3.1: *BRCA1/2* mutations present in 49 mutation positive families.....38
Table 3.2: Respondent's initial expectation of a genetic counselling session.....42
Table 3.3: Summary of responses to questions pertaining to the information giving aspect of a genetic counselling session for breast and/or ovarian cancer.....43

LIST OF ABBREVIATIONS

%	Percentage
£	Great British Pound
AJCC	American Joint Committee on Cancer
ASR	Age standardised incidence rates
BCLC	Breast Cancer Linkage Consortium
BRCA1	Breast Cancer Gene 1
BRCA2	Breast Cancer Gene 2
BSO	Bilateral salpingo-oophorectomy
COC	Combined oral contraceptive
CHBH	Chris Hani Baragwanath Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
DGMC	Donald Gordon Medical Centre
DNA	Deoxyribonucleic acid
EOC	Epithelial ovarian cancer
ER	Oestrogen receptor
GP	General Practitioner
HBOC	Hereditary breast and ovarian cancer
Her2	Human epidermal growth factor receptor 2
IARC	International Agency for Research on Cancer
MIM	Mendelian Inheritance in Man
MLPA	Multiplex ligation-dependent probe amplification
MRI	Magnetic resonance imaging
NHS	National Health Service
NHLS	National Health Laboratory Service
NSGC	National Society of Genetic Counselors
OCCR	Ovarian cancer cluster region
PR	Progesterone receptor
PTT	Protein truncation test
TNM	Tumor-node-metastasis system
UFS	University of the Free State

UK	United Kingdom
USA	United States of America
WITS	University of the Witwatersrand

CHAPTER 1 INTRODUCTION

Breast cancer is the most common cancer worldwide and the leading contributor to mortality caused by cancer. Ovarian cancer is the leading cause of death amongst gynaecological cancers (Althuis, Dozier, Anderson et al., 2005; Bast, Hennessy & Mills, 2009). Five to ten percent of both breast and ovarian cancer cases are attributable to dominantly inherited genetic mutations that predispose to cancer (Kerr, Lalloo, Clancy et al., 2010). Screening for individuals at a high risk of having an inherited cancer syndrome, through genetic counselling, has the potential to improve outcomes for these individuals and lower mortality rates.

This chapter gives an overview of various aspects of breast and ovarian cancer, with a specific focus on inherited breast and/or ovarian cancer, and therefore the principles and practices of genetic counselling. The motivation for the study, as well as the aims and objectives, are discussed at the end of this chapter.

1.1 BREAST CANCER

Breast cancer is a malignancy of the epithelial tissue of the breast (mammary carcinoma) affecting both females and males (Weiss, Moysich & Swede, 2005). It begins either in the cells of the lobules or the ducts. Non-invasive breast cancer remains in either the cells of the lobules or the ducts. If the cancer tumour spreads to the normal tissue surrounding the breast it is then called invasive. Should the cancer spread to other parts of the body via the blood or lymph system, the cancer is termed metastatic breast cancer (Figure 1.1) (Campbell, Reece & Simon, 2004).

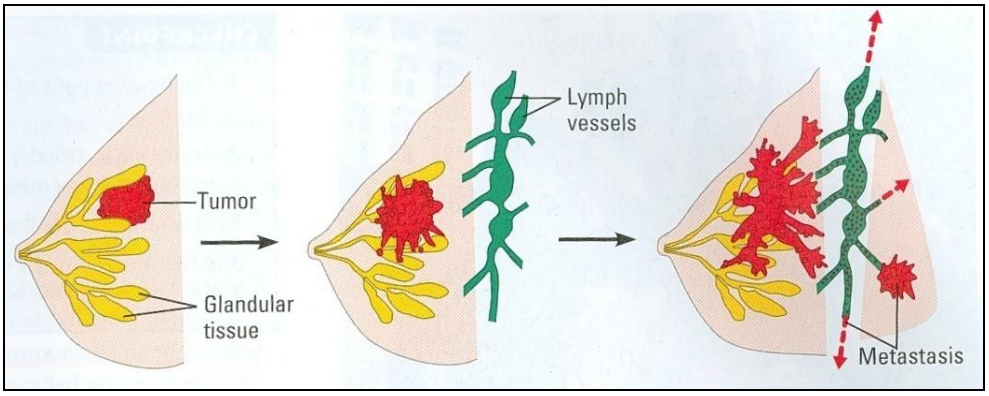


Figure 1.1: The metastasis of a malignant breast tumour. The tumour grows from a single cell, invading neighbouring tissue and, in some cases, spreading to other parts of the body via the circulatory system (metastasis) (taken from Campbell et al. (2004))

1.1.1 Breast cancer classification

Breast cancers can be classified based on staging, histology and receptor status. Staging involves classifying tumours according to a description of the primary tumour (T), whether the cancer has spread to the lymph nodes (N) and the extent of any spread to the lymph nodes and whether there is metastasis (M). This is the basis of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) system. Once the TNM classification has been determined, the results are combined and the tumours are further classified into stages I to IV (American Joint Committee on Cancer, 2010).

Histological grading of breast cancer cells classifies them into grades based on their level of differentiation compared to normal cells (Table 1.1). There is a strong correlation between histological grade and prognosis in breast cancer. Poorly differentiated tumours that look very different from normal cells tend to be more aggressive with a poorer prognosis (Elston & Ellis, 1991).

Table 1.1: Histological grading categories of breast cancer (Elston & Ellis, 1991)

Grade	Differentiated	Growth rate
1 (low)	Well	Slow
2 (intermediate)	Moderately	Moderate
3 (high)	Poorly	Fast

Further classification is based on the fact that breast cells may express receptors on their surfaces that recognise hormones such as oestrogen and progesterone. Hormone therapy in the form of Tamoxifen® can be targeted to breast cancer patients with tumours expressing oestrogen (ER) or progesterone receptors (PR). Hormone therapy either blocks the ER or PR or reduces the amount of these hormones in the body and therefore assists in preventing the tumour from growing (Hamilton & Piccart, 2000).

Another breast cell receptor is human epidermal growth factor receptor 2 (Her2) which functions in the control of cell growth and repair. Breast cancers with over expressed Her2 tend to grow faster and have a poorer prognosis. However, for Her2 positive breast cancer there is targeted treatment in the form of Herceptin® (Hamilton & Piccart, 2000).

1.1.2 Risk factors for breast cancer

There are a number of factors that have been associated with an increased risk for breast cancer. Reproductive factors determining oestrogen exposure are the most significant indicators for breast cancer risk. An early menarche, older age at first pregnancy, late menopause, postmenopausal obesity and use of oral contraceptives and hormone replacement therapy all contribute to increased breast cancer risk. Women with a mammographic density of between 50% and 75% have an increased relative risk of breast cancer. Demographic and lifestyle factors also contribute to an increased breast cancer risk (Neuhausen, 1999; Althuis et al., 2005; Evans & Howell, 2007; Amir, Freedman, Seruga et al., 2010). Depending on an individual's risk profile, appropriate screening and risk reducing surgery is recommended to manage the risk and for early detection of breast cancer.

1.1.3 Screening and risk reducing surgery for breast cancer

Screening allows for the early detection of breast cancer and therefore, potentially, a better outcome (Smith, Saslow, Sawyer et al., 2003; Amir et al., 2010). Surgical interventions are a means of reducing the risk of breast cancer, especially in high risk individuals (Kerr et al., 2010)

According to the American Cancer Society guidelines for breast cancer screening, updated in 2003, all females should have annual mammography from 40 years of age (Smith et al., 2003). However, studies and population-based data has shown that individuals who test positive for a mutation associated with breast cancer development as well as women with a high risk family history but no identifiable mutation are at high risk of developing breast cancer (Claus, Risch & Thompson, 1994; Easton, Ford & Bishop, 1995; Collaborative Group on Hormonal Factors in Breast Cancer., 2001). It has therefore been suggested that these women begin screening five to 10 years earlier than the earliest age of onset of breast cancer in their family (Smith et al., 2003). Ultrasound and magnetic resonance imaging (MRI) are also recommended as adjuncts to mammography (Smith et al., 2003).

Surgical interventions are a means of reducing the risk of breast cancer, especially in high risk individuals. Surgery can reduce breast cancer risk by up to 95% (Rebbeck, Friebel, Lynch et al., 2004). The surgical methods that are available include bilateral mastectomy and subcutaneous mastectomy, whereby the glandular tissue is scooped out and both the skin and the nipple-areola complex are conserved, both with or without reconstruction (Gerber, Krause, Reimer et al., 2003; Kerr et al., 2010).

1.2 OVARIAN CANCER

Ovarian cancer is a malignancy of the ovaries that may develop from the germ cells or sex cord-stromal cells of the ovaries (Chen, Ruiz, Killeen et al., 2003). However, the most common form, occurring in more than 90% of cases, is epithelial ovarian cancer (EOC) that develops from the surface epithelium of the ovary; cells that are subject to prolonged hormone exposure (Landen, Birrer & Sood, 2008). Unlike most cancers, epithelial ovarian tumours become more differentiated over time, developing from epithelial cells into one of four distinct histotypes: serous, endometriod, mucinous or clear cell. Each of these histotypes resemble normal cells lining either the fallopian tube (serous), endometrium (endometroid) or endocervix (mucinous) and cells forming nests within the vagina (clear cell) (Bast et al., 2009). Each histological subtype of EOC has a different clinical presentation and molecular basis. This heterogeneity, along with the lack of data on early stage ovarian cancers, makes the aetiology of ovarian cancer poorly understood (Landen et al., 2008).

1.2.1 Ovarian cancer classification

Ovarian tumours can be classified based on their histology – whether the tumour is a surface epithelial-stromal tumour, a sex cord-stromal tumour, a germ cell tumour or another type of tumour (Chen et al., 2003). Histological classification is performed according to the guidelines published by the World Health Organisation in 1973 (Chen et al., 2003). Staging of ovarian tumours is performed using either the TNM system, discussed in section 1.1.1 above, or the staging system created by the International Federation of Gynecology and Obstetrics (FIGO) (Heintz, Odicino, Maisonneuve et al., 2001).

1.2.2 Risk factors for ovarian cancer

There are a number of factors that have been associated with an increased risk for ovarian cancer (Hunn & Rodriguez, 2012). Reproductive and hormonal factors contributing to an increased ovarian cancer risk include nulligravity, early age at menarche, use of hormone replacement therapy and late age at natural menopause (Hunn & Rodriguez, 2012). However, use of the combined oral contraceptive (COC) is protective on ovarian cancer risk. For a member of the general population, use of the COC for more than 10 years halves ovarian cancer risk and three years of use reduces risk by 20%. Tubal ligation and hysterectomy is also known to decrease ovarian cancer risk in the general population (Kerr et al., 2010).

1.2.3 Screening and risk reducing surgery for ovarian cancer

Screening for ovarian cancer includes annual trans-vaginal ultrasound and CA125 biomarker analysis (Kerr et al., 2010). For women more than 35 years of age and with an ovarian cancer risk of more than 1 in 10, annual trans-vaginal ultrasound with colour Doppler may be useful (Kerr et al., 2010). CA125 biomarker screening is recommended for women at a high or intermediate risk for ovarian cancer (Kerr et al., 2010). However, these screening methods are not always effective and therefore screening for EOC has not had a significant impact on mortality and only 20% of ovarian cancer cases are diagnosed when the cancer is still limited to the ovaries (Bast et al., 2009). The result is that most EOCs are only diagnosed at a later stage and therefore prognosis for women diagnosed with EOC is poor, with survival statistics of 45% at 5 years (Landen et al., 2008).

Due to the limitations of screening techniques, the current strategy is to identify high risk patients and offer them risk reducing surgery (Landen et al., 2008). Prophylactic bilateral salpingo-oophorectomy (BSO), the removal of both ovaries and both Fallopian tubes, has been proven to significantly reduce ovarian and breast cancer risks in *BRCA1/2* mutation carriers (Kauff, Satagopan, Robson et al., 2002; Rebbeck, Lynch, Neuhausen et al., 2002; Eisen, Lubinski, Klijn et al., 2005; Finch, Beiner, Lubinski et al., 2006; Kauff, Domchek, Friebel et al., 2008). However, it does not reduce ovarian cancer risk completely as a small percentage of women may still develop primary peritoneal carcinomatosis following BSO (Chand, Moore, Clarke et al., 2007).

1.3 INCIDENCE OF BREAST AND OVARIAN CANCER

The latest global cancer statistics, produced by the International Agency for Research on Cancer (IARC) for 2008, state that breast cancer is the most frequently diagnosed cancer and the leading cause of death as a result of cancer in females in both the economically developing and the developed world (Jemal, Bray, Center et al., 2011)**.**

In 2008, worldwide, breast cancer accounted for 23% of the total new cancer cases (1.38 million) and 14% (458 400) of all cancer related deaths in females. In the same year, ovarian cancer was responsible for an estimated 225 500 of new cancer cases and 140 200 cancer related deaths in females worldwide. The incidence rates of breast cancer are higher in developed countries (66.4 per 100 000), particularly in Northern America and Northern Europe, possibly due to many factors including the availability of early detection services, the use of the oral contraceptive pill and post-menopausal hormone therapy, a late age at first birth (> 30 years) or not bearing children (Hulka & Moorman, 2001; Jemal et al., 2011).

1.3.1 South African incidence of breast and ovarian cancer

In South Africa during 1998 and 1999, female breast cancer accounted for 5 606 (18.6%) and 5 901 (19.4%), respectively, of all cancer cases reported. Breast cancer was the second most prevalent cancer in females in 1998, after cervical cancer, and the leading cancer in 1999. The age standardised incidence rates (ASR) were 32.7 and 33.4 per 100 000 in 1998 and 1999, respectively (Mqoqi, Kellett, Sitas et al., 2004).

For a Caucasian woman in South Africa, her risk for breast cancer is one in 12 (with an ASR of 76 per 100 000, comparable to those of developed countries such as the United States of America (USA) and United Kingdom (UK)). Black South African women have a one in 50 lifetime risk for breast cancer. In both Asian and women of mixed ancestry the lifetime risk of breast cancer is one in 18 (Mqoqi et al., 2004).

In 1999, ovarian cancer accounted for 2.6% of all reported cancer cases in South Africa and the lifetime risk of a woman developing ovarian cancer was calculated to be one in 180 with an ASR of 4.6 per 100 000 (Mqoqi et al., 2004).

1.4 GENETICS OF HEREDITARY BREAST AND OVARIAN CANCER

Breast cancer is caused by an accumulation of mutations in critical oncogenes (genes when mutated or expressed at abnormally high levels, contribute to turning a normal cell into a cancerous cell) involved in deoxyribonucleic acid **(**DNA) repair and cell growth. The majority (90 to 95%) of breast cancer cases is sporadic and caused by an accumulation of genetic mutations over a period of time as well as environmental factors. Five to ten percent of breast cancer cases are caused by the inheritance of germline mutations in genes associated with cancer, with 20 to 40% caused by mutations in the breast and ovarian cancer predisposing genes *BRCA1* and *BRCA2* (Haites & Gregory, 2002; Ripperger, Gadzicki, Meindl et al., 2009). Features of inherited versus sporadic breast cancer include an earlier age of onset (<50 years) of both invasive and non-invasive breast cancers, multiple affected family members, increased frequency of bilateral tumours, a higher incidence of male breast cancer and negative hormone receptor status (Lynch, Holden, Buys et al., 1998; Petrucelli, Daly & Feldman, 2011).

The majority of epithelial ovarian cancers develop from a group of single cells with five or more genetic alterations in any one of more than 30 oncogenes and tumour suppressor genes that have been implicated in ovarian oncogenesis (Bast et al., 2009). Approximately 10% of ovarian cancers are inherited, with 90% caused by mutations in the breast and ovarian cancer predisposing genes *BRCA1* and *BRCA2* (Landen et al., 2008). In contrast to sporadic ovarian

cancer, inherited ovarian cancer cases progress faster and are often multifocal (Bast et al., 2009).

As discussed above, a large number of inherited breast and ovarian cancers are attributable to mutations in two genes, *BRCA1* (MIM #113705) and *BRCA2* (MIM #600185) (Ripperger et al., 2009). The genetic condition associated with mutations in *BRCA1* and *BRCA2* is hereditary breast and ovarian cancer syndrome (HBOC) (Simon & Petrucelli, 2009).

1.4.1 *BRCA1* and *BRCA2*

BRCA1 was mapped to chromosome 17q21 in 1990 (Hall, Lee, Newman et al., 1990) and *BRCA2* was mapped in 1995 to chromosome 13q12 (Wooster, Bignell, Lancaster et al., 1995). *BRCA1* consists of 22 exons coding for a protein product of 1863 amino acids and *BRCA2* consists of 27 exons coding for a protein product of 3418 amino acids (Table 1.2). *BRCA1* and *BRCA2* are tumour suppressor genes that normally function in the repair of DNA damage and the regulation of cell growth and therefore the maintenance of genomic stability (Bast et al., 2009). Mutations in these genes are transmitted in a family in an autosomal dominant manner. Therefore a mutation carrier has a 50% chance of passing on the faulty gene to his/her offspring (Petrucelli et al., 2011).

More than 1 000 different *BRCA1* and *BRCA2* mutations have been identified, the majority of which are individually rare (Walsh, Casadei, Coats et al., 2006). Most *BRCA* mutations are frameshift or nonsense leading to a truncated protein product. Only a small percentage of *BRCA* mutations are missense mutations causing a change in an amino acid resulting in an altered protein product that may not be functional. There is a correlation between the genotype and phenotype in that different mutations in *BRCA1/2* are associated with different breast and ovarian cancer risks. *BRCA1* mutations that occur at the 3'end of nucleotides 4200-4400 confer a lower risk for ovarian cancer than mutations at the 5'end. In addition *BRCA1* mutations in and around exon 11 are associated with a lower risk of breast cancer than mutations occurring at the 5' and 3' ends of the gene. For *BRCA2*, mutations occurring in or around exon 11 confer an increased ovarian cancer and lower breast cancer risk than mutations

falling outside this region. The region in and around exon 11 of *BRCA2* is called the ovarian cancer cluster region (OCCR) (Nagy, Sweet & Eng, 2004).

Table 1.2: Comparison of *BRCA1* and *BRCA2* genes (Miki, Swensen, Shattuck-Eidens et al., 1994; Wooster et al., 1995)

	BRCA1	***BRCA2***
Chromosomal locus	17q21	13q12-13
No. coding exons	22	27
No. amino acids in protein	1863	3418

The proportion of inherited breast and ovarian cancer that is attributable to *BRCA* mutations varies from 30 to 81% depending on the population group, the number of breast and ovarian cancer cases in the family as well as the method used to detect the *BRCA* mutations (Nagy et al., 2004). *BRCA1/2* mutations are linked to an increased breast cancer risk of up to 80% and ovarian cancer risk of up to 60% (Table 1.3). Individuals carrying a *BRCA2* mutation are also at risk for associated cancers including prostate, pancreatic, stomach and melanoma (Kerr et al., 2010).

Table 1.3: Cancer risks associated with *BRCA1/2* mutations (Kerr et al., 2010)

	BRCA1	***BRCA2***
Breast cancer	60-80% lifetime risk 60% risk of a second primary breast cancer	50-80% lifetime risk 60% risk of a second primary breast cancer
Male breast cancer	1%	5-10%
Ovarian cancer	40-60% lifetime risk	20-30% (mutation in OCCR) 10% (mutation outside OCCR)
Associated cancers	None	Prostate – 14% lifetime risk Pancreas, biliary tree, stomach and melanoma (ocular and skin)

It is important to mention that, in addition to HBOC, there are a number of other genetic syndromes that confer an increased risk for breast and ovarian cancer. Cowden syndrome and Li-Fraumeni syndrome are associated with an increased for breast cancer and Lynch syndrome

and Gorlin syndrome are associated with an increased risk for ovarian cancer. However, more than 50% of suspected inherited breast and ovarian cancer cases have unknown causes (Landen et al., 2008; Ripperger et al., 2009).

1.4.2 Penetrance of breast and ovarian cancer in *BRCA* mutation carriers

Although carrying a *BRCA1/2* mutation puts one at high risk of developing cancer, the risk is not 100%. Some individuals carrying a *BRCA* mutation may never develop cancer and may live to an old age. The term "incomplete penetrance" is used to describe such cases. In addition, for those individuals that do develop breast and/or ovarian cancer the age at diagnosis as well as the type of cancer varies. For example, in the case of two individuals carrying the same *BRCA* mutation one may get multiple primary tumours before the age of 50 years and the other individual may only develop cancer in their 70's (Petrucelli et al., 2011). There is no clear explanation for this incomplete penetrance. The variation may be in part due to allelic risk heterogeneity as well as the effects of both genetic and environmental modifying factors (Nagy et al., 2004).

1.5 *BRCA1/2* MUTATION TESTING

Only individuals identified as being at a high risk for HBOC are usually offered *BRCA* testing (Nelson, Huffman, Fu et al., 2005). Testing is offered to individuals 18 years of age or older (Trepanier, Ahrens, McKinnon et al., 2004). Testing for *BRCA* mutations is a time consuming and expensive process with medical, social and psychological consequences (Evans, Moller & Kerr, 2005).

Individuals who have already had breast and/or ovarian cancer are referred for **diagnostic** *BRCA* testing. Unaffected individuals with a family history of breast and/or ovarian cancer are referred for **predictive** testing. The type of mutation analysis that is performed depends on a number of factors, including ethnicity. It is also limited to the testing that is available. Individuals with a known *BRCA* mutation, or specific ethnic groups with known mutations are offered targeted mutation analysis. The remaining high risk individuals may be offered other testing including DNA sequencing to detect small deletions or duplications or substitutions with multiplex ligation-dependent probe amplification (MLPA) to detect larger

rearrangements of the DNA sequence. DNA sequencing and MLPA look for different mutations in *BRCA* and therefore both should be performed to increase the sensitivity of testing (Evans et al., 2005). *BRCA* mutation testing offered varies by country and individual laboratory (Walsh et al., 2006). The South African situation is discussed in Sections 1.5.1 and 1.5.2 below.

1.5.1 Targeted mutation analysis

Unaffected individuals, from families in which a *BRCA* mutation has already been identified, are offered predictive testing for the family specific mutation. In several population groups certain *BRCA* mutations are found at relatively higher frequencies than in the general population due to what is termed the "founder effect" (Nelson et al., 2005). Founder effects occur when populations arise from a small gene pool. When the small initial population begins to expand certain mutations that are present become more prevalent. Founder mutations in the *BRCA1/2* genes are well documented amongst the Ashkenazi Jews worldwide and the Afrikaner people of South Africa (Neuhausen, 1999). Recently, a recurrent founder mutation was identified in the black Xhosa population (van der Merwe, Hamel, Schneider et al., 2012). Individuals from these population groups are tested for the mutations that are common to their population group.

- ***Founder mutations in Ashkenazi Jews***

There are three founder Ashkenazi Jewish *BRCA* mutations; two in *BRCA1* and one in *BRCA2* (Table 1.4) (Shattuck-Eidens, McClure, Simard et al., 1995; Struewing, Brody, Erdos et al., 1995; FitzGerald, MacDonald, Krainer et al., 1996; Neuhausen, Gilewski, Norton et al., 1996). The combined frequency of these three mutations in the Ashkenazi Jewish population is more than 2% (1 in 40) (Struewing, Abeliovich, Peretz et al., 1995; Oddoux, Struewing, Clayton et al., 1996; Roa, Boyd, Volcik et al., 1996). The *BRCA1* mutation 185delAG, accounts for 16% of breast and 39% of ovarian cancer in Jewish women below the age of 50 years. The *BRCA2* mutation, 6174delT, accounts for 8% of breast cancer in Jewish women under the age of 50 years. In families with a history of breast and ovarian cancer the three founder Ashkenazi Jewish mutations account for 90% of the inherited breast and ovarian cancer in this population group (Kerr et al., 2010).

For Ashkenazi Jewish individuals with a *BRCA1* or *BRCA2* mutation, the risk of breast cancer is 56%, ovarian cancer 16% and prostate cancer 16% (Struewing, Hartge, Wacholder et al., 1997).

- ***Founder mutations in Afrikaners***

The Afrikaner population in South Africa has three founder mutations, two in *BRCA1* and one in *BRCA2* (Table 1.4) (Reeves, Yawitch, van der Merwe et al., 2004; van der Merwe & Jansen van Rensburg, 2009). It has been reported that these three mutations account for 94% of *BRCA* mutation positive Afrikaner families (van der Merwe & Jansen van Rensburg, 2009). However, there is some question around this high percentage and it is more likely that these mutations account for approximately 60% of Afrikaner women with HBOC (Krause, A., 2012, personal communication, 3 April). Therefore, for Afrikaner women undergoing *BRCA* mutation testing, approximately 60% will test positive for a *BRCA* mutation and for those who test positive, 94% will have one of the three founder mutations.

Table 1.4: Founder mutations identified in *BRCA1* and *BRCA2*

Population	**Mutation**	**Reference**
Ashkenazi Jewish	*BRCA1* – 185delAG & 5382insC *BRCA2* – 6174delT	(Struewing et al., 1997)
Afrikaner	*BRCA1* – E881X & 1493delC *BRCA2* – 8162delG	(Reeves et al., 2004) (van der Merwe & Jansen van Rensburg, 2009)

Ashkenazi Jews and Afrikaners are only tested for the three *BRCA* mutations that are common to their population group. Therefore, a negative result does not exclude the possibility that the counsellee may carry a different clinically significant *BRCA* mutation (Petrucelli et al., 2011). For Afrikaners who test negative for the three founder Afrikaner *BRCA* mutations, gene sequencing and MLPA is offered in some cases. However, a negative result from *BRCA* sequencing does not reduce a high risk individual's risk to that of the general population. They may carry a mutation that is not detectable via current technology or the cancer in the family may be caused by a different breast/ovarian cancer susceptibility gene (Ripperger et al., 2009).

- ***Targeted mutation analysis in South Africa***

Testing for the Ashkenazi Jewish and Afrikaner founder mutations was established at the National Health Laboratory Service (NHLS) in Johannesburg in 2009. Testing is also available in Pretoria at the University of Pretoria, on a research basis, and in Bloemfontein at the University of the Free State (UFS) (Table 1.5). Some private laboratories also offer *BRCA* testing, however bloods from private laboratories often get referred to the NHLS in Johannesburg for testing.

1.5.2 Other testing methods

- ***DNA sequencing***

Sequencing is a method of determining the precise order of nucleotide bases in a sample of DNA (Sanger, Nicklen & Coulson, 1977). DNA sequencing of the entire coding regions of the *BRCA1* and *BRCA2* genes is performed in the absence of a known family mutation or for high risk Afrikaners and Ashkenazi Jews who test negative for the founder mutations. *BRCA* sequencing is also performed for those patients who are not of Afrikaner or Ashkenazi Jewish ancestry and therefore do not have founder mutations that can be tested for.

- ***Multiplex ligation-dependent probe amplification***

Multiplex ligation-dependent probe amplification is a high resolution method of detecting genomic rearrangements. Large genomic rearrangements in *BRCA1/2* are estimated to be responsible for up to 10% of cases of HBOC. There have been more than 170 genomic rearrangements identified in *BRCA1* and 30 in *BRCA2*. Highly similar duplicated DNA sequences, such as Alu repeats, are prone to rearrangement due to the breakpoints that cluster in them. *BRCA1* consists of approximately 42% Alu sequences and therefore has a higher incidence of genomic rearrangement than *BRCA2*. However, *BRCA2* rearrangements have been found to be more frequent in families with cases of male breast cancer (del Valle, Feliubadaló, Nadal et al., 2010).

Due to the size of the *BRCA1/2* genes, the diversity of their mutations and the complexity of testing, it is recommended that testing begin with a relative who is affected with breast and/or ovarian cancer and it is preferable to use a specialised laboratory that performs *BRCA* gene

sequencing and MLPA on a regular basis (Nelson et al., 2005). *BRCA* sequencing is not available through the Molecular Laboratory of the NHLS and University of the Witwatersrand (WITS); therefore at the request of the counsellees seen through the NHLS and WITS, DNA is extracted locally and sent overseas usually to the United Kingdom for *BRCA1/2* sequencing and MLPA.

- ***Protein truncation test***

The protein truncation test (PTT) was initially designed to detect mutations in the *dystrophin* gene that causes Duchenne Muscular Dystrophy. The protein truncation test looks for mutations in the coding region of genes that lead to the premature termination of translation of ribonucleic acid (RNA) into protein, resulting in a truncated protein product (Den Dunnen & Van Ommen, 1999). The protein truncation test is ideal for *BRCA1/2* testing as the majority of *BRCA1/2* mutations are frameshift or nonsense leading to a truncated protein product (Hogervorst, Cornelis, Bout et al., 1995; Lancaster, Cochran, Brownlee et al., 1996; Petrucelli et al., 2011). In South Africa, PTT is performed in Bloemfontein at the University of the Free State (Table 1.4).

Table 1.5: *BRCA* mutation testing available at the National Health Laboratory Service in Johannesburg and Bloemfontein (van der Merwe, N., 2009, personal communication, 28 May)

Laboratory	**NHLS/WITS, Johannesburg**	**NHLS/UFS, Bloemfontein**
Diagnostic/Research	Diagnostic	Diagnostic

Targeted mutation analysis	• Founder mutations
	  ○ Afrikaner
	  ○ Ashkenazi Jewish
	• Family specific mutation
		• Founder mutations
		  ○ Afrikaner
		  ○ Ashkenazi Jewish
		• Family specific mutation

DNA Sequencing		*BRCA1* exons 2-12 *BRCA1* exons 13-24 *BRCA2* exons 2-14 *BRCA2* exons 15-27
Protein truncation test		*BRCA1* Exon 11 *BRCA2* Exons 10,11

1.5.3 Cost of *BRCA* mutation testing

For those individuals with a medical aid, the cost of local Ashkenazi Jewish and Afrikaner *BRCA* founder mutation testing is usually paid for out of one's medical savings allowance, but only to certain extents, depending on the medical aid scheme. International *BRCA* testing, involving sequencing and MLPA, is not covered by medical aid. The current cost is £530 and must be paid for by the individual. Cost is the main limitation of *BRCA* testing. Most patients, especially those in the state hospital system, cannot afford *BRCA* sequencing or MLPA, thus making testing largely inaccessible to them. In cases where there is a strong concern about a *BRCA* mutation being present, state patients' DNA is sent to the NHLS in Bloemfontein for limited sequencing and PTT, but no MLPA is performed. Testing performed through the NHLS on state patients is covered by the state.

1.6 GENETIC COUNSELLING

There are a number of issues that individuals at risk for HBOC may be faced with including: what their risk of developing breast and ovarian cancer is, whether or not to have genetic testing, the effect of their test result on other family members, what preventative measures to implement and whether those measures will be effective. These factors are all likely to generate many powerful emotional responses for the individual including guilt at possibly having passed on a condition to one's children, 'survivor guilt' for those who test negative for the family mutation, grief and loss at having watched family members die of breast and/or ovarian cancer (Duric, Butow, Sharpe et al., 2003). The genetic counsellor is skilled in addressing such emotions and assisting patients in making decisions appropriate for themselves.

Genetic counselling provides a space in which emotions can be expressed and addressed thereby enabling understanding of the information provided and informed decision making (Trepanier et al., 2004). Genetic counselling is the process of "helping people understand and adapt to the medical, psychological, and familial implications of the genetic contributions to disease" (Resta, Biesecker, Bennett et al., 2006). As defined by the National Society of Genetic Counselors (NSGC), of America, the process includes:

1. Risk assessment – reviewing the family and medical histories of an individual in order to evaluate the risk of a condition occurring or recurring.
2. Education - informing individuals of the inheritance patterns of a condition, the testing options available, means of prevention, their management options, resources available to them and any current research into the condition.
3. Counselling – encouraging informed decision making and assisting individuals in adapting to a condition or their risk for a condition.

According to Nelson et al. (2005), in genetic counselling, the process of identifying individuals who may be more susceptible to inherited breast and/or ovarian cancer involves:

i. Pedigree analysis
ii. Risk assessment
iii. Genetic testing
iv. Surveillance

Genetic counselling for breast and/or ovarian cancer is therefore a multistep interactive process of incorporating both information gathering and information giving. It is guided by the counsellee's expectations for the session as well as their motivation for attending (Trepanier et al., 2004).

1.6.1 Reasons for attending genetic counselling for breast and/or ovarian cancer

Individuals reportedly attend genetic counselling for cancer in order to receive medical information and to reduce anxieties (Pieterse, Ausems, Van Dulmen et al., 2005; Roshanai, Lampic, Ingvoldstad et al., 2011). A study by van Asperen, van Dijk, Zoeteweij et al. (2002) determined that individual motives differ according to demographic, medical and psychological factors. The researchers found that older women tended to attend genetic counselling to establish the risks for their children as well as other family members. Women already affected with breast cancer also attended genetic counselling to determine the risks for their children and were less concerned about their own risks; however, they were concerned about their own cancer recurrence risk. Younger women were more concerned with their own risk of breast cancer, recurrence risks and the option of prophylactic mastectomy.

1.6.2 Genetic counselling for hereditary breast and/or ovarian cancer in Johannesburg

The Genetic Counselling Clinics of the Division of Human Genetics, WITS and NHLS, Johannesburg, were established more than 40 years ago (Jenkins, Wilton, Bernstein et al., 1973). A genetic counselling session for inherited breast and/or ovarian cancer at the NHLS and WITS has become more structured over the past two to three years. Figure 1.2 illustrates the process of how a counsellee is guided through a consultation, beginning with an assessment of the counsellee's family history of cancer to, potentially, *BRCA* mutation testing and recommended screening or surgical measures (Sections 1.6.3 to 1.6.4 discuss this figure in detail). The genetic counselling team consists of genetic counsellors, medical geneticists, medical officers working in the field of genetics and genetic nurses. All of these individuals are qualified to offer genetic counselling regarding cancer. For the purpose of this study, any reference to "genetic counsellor" refers to any member of the genetic counselling team.

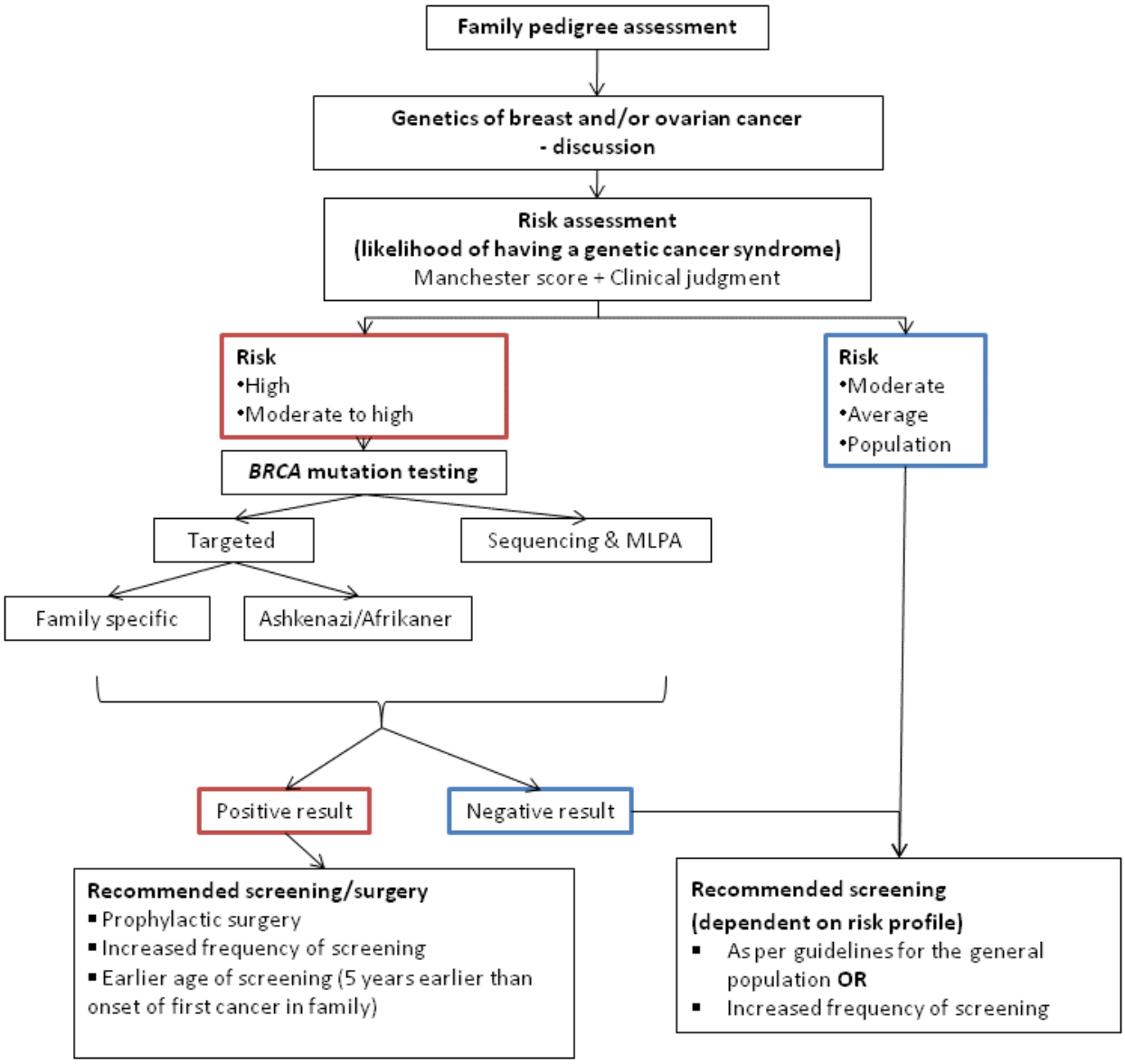


Figure 1.2: Outline of a genetic counselling session for inherited breast and/or ovarian cancer offered by the Division of Human Genetics, WITS and NHLS

1.6.3 Pedigree analysis

Counsellees attending the NHLS/WITS Genetic Counselling Clinics regarding cancer are requested to complete a questionnaire. The questionnaire asks about their personal and family history of cancer. The use of a self-administered family history questionnaire was first proposed and implemented in the Division by van der Westhuizen (2008) as part of his MSc (Med) in Genetic Counselling degree. Genetic counselling is largely dependent on the

accuracy and relevance of the information that is gathered from the counsellee. The questionnaire is sent back to the counsellor prior to the consultation. A family pedigree is then drawn up from the questionnaire and assessed (Figure 1.2).

The family pedigree, constructed using standardised pedigree symbols, is a graphical representation of a family history. A comprehensive pedigree includes at least three generations of the family, the relevant health information of each relative including their age at onset of any conditions and their ethnicity (Wolpert & Speer, 2005).

The pedigree shows both the paternal and maternal lineage and thus through which side of the family a condition is segregating. It also reflects the number and sex of affected individuals in a family, their age at diagnosis and their relationship to the counsellee. A family pedigree is an inexpensive and noninvasive means of screening families and assessing an individual's risk of developing inherited breast and/or ovarian cancer (Wolpert & Speer, 2005).

1.6.4 Risk assessment

There are a number of statistical models and methods used to determine an individual's risk of carrying a *BRCA* mutation. The two methods most often employed by the Division of Human Genetics, WITS and NHLS, are the Manual Method and the Manchester model (Evans, Eccles, Rahman et al., 2004).

- ***Manual Method***

One of the strongest risk factors for hereditary breast and/or ovarian cancer is a family history. A manual assessment of the family history without the use of a computer is one of the most effective ways to assess risk in an individual (Evans & Howell, 2007). Risk estimation is based on the number of family members affected with breast and/or ovarian cancer and their ages at diagnosis. This estimation of risk by the counsellor gives a point of reference against which the risk calculated by a risk assessment model can be compared for reasonability (Evans, Kerr & Lalloo, 2006).

- ***Manchester Model***

The Manchester Model (Evans et al., 2004; Evans, Lalloo, Cramer et al., 2009) is an empirical model used to estimate the likelihood that a *BRCA1* or *BRCA2* mutation will be detected through genetic testing, without taking into account underlying genetic risks such as penetrance and mode of inheritance (Amir et al., 2010). The Manchester Model uses a scoring system whereby a different score is allocated to each affected relative of the counsellee according to their age, sex and type of cancer they are affected with; breast, ovarian or pancreatic cancer. Adjustments are made to the score for histology and receptor status of the cancer. The threshold for offering mutation testing, in the United Kingdom, is a score of 20 points that equates to a 20% possibility of detecting a *BRCA1* or *BRCA2* mutation (Kerr et al., 2010).

Using the Manchester scoring system and the Manual Method, the counsellee's risk for carrying a *BRCA* mutation is calculated and the counsellee is then classified into the following risk categories: high, moderate to high, moderate, average and population risk for having a genetic cancer syndrome. Counsellees with a high or moderate to high probability of HBOC, and at risk relatives of individuals with identified *BRCA1/2* mutations, are offered *BRCA* testing (Figure 1.2).

Based on the counsellee's risk profile and the results of their *BRCA* mutation testing, a management plan aimed at preventing breast and/or ovarian cancer through screening and surgery is conveyed to the counsellee (Figure 1.2). Educating the counsellee on aspects of breast and/or ovarian cancer, including screening and surgery, is one of the goals of a genetic counselling session, however, attending to psychosocial issues is important for the counselling to be effective (Trepanier et al., 2004).

1.6.4.1 Communication of risk

Like all genetic tests, expertise in the field of genetics is necessary for the correct interpretation and presentation of *BRCA* test results to a patient. The specificity and sensitivity of the *BRCA* testing needs to be discussed with the patient and reiterated at the result giving

session, as well as how the results may affect their risks of developing cancer (Trepanier et al., 2004).

Individuals vary in how they understand and interpret risk. Risk perception depends on many factors including but not limited to: degree of understanding of mathematical concepts and general population risks, gender, cultural identity, religious beliefs, personality and personal experience with the condition (Smith, 1998; McCarthy Veach, Leroy & Bartels, 2003). Studies have found that many people's perception of their risk of inheriting a genetic condition differs substantially from the reality. It has been documented that women tend to overestimate their risk for breast cancer (Nelson et al., 2005).

The emotional impact of test results should be assessed and addressed by the counsellor in the session and the appropriate support provided. It is recommended that individuals attending genetic counselling in Johannesburg for HBOC attend the result giving session with a support person. The genetic counsellor needs to identify and address any verbal and non-verbal cues about the counsellee's reaction to their risk for HBOC. This includes feelings of anxiety, fear, anger and guilt. The manner in which a counsellee reacts to their risk may indicate how they may be able to cope with the information received in the genetic counselling session (Trepanier et al., 2004).

Communication between the counsellor and the patient is therefore central to the effectiveness of the genetic counselling session (Pieterse, van Dulmen, Beemer et al., 2007). A number of studies have focused on communication in cancer genetic counselling. The majority of communication in pretest genetic counselling is reported to be educational in nature focusing on the provision of medical information rather than psychosocial issues, with counsellors asking more questions and providing more information than patients (Ellington, Roter, Dudley et al., 2005; Ellington, Baty, McDonald et al., 2006). Awareness of communication processes in the genetic counselling session may assist in achieving improved counselling outcomes (Pieterse et al., 2007)

1.6.5 Psychosocial aspects of being at risk for hereditary breast and ovarian cancer

There is conflicting research on how addressing psychosocial issues impacts counsellee's levels of anxiety and depression and overall satisfaction. Pieterse et al. (2007) observed that an increase in the level of psychosocial issues discussed in the cancer genetic counselling session and a longer counsellor gaze both contributed to increased counsellee anxiety. This is in accordance with Lobb, Butow, Barratt et al. (2004) who found that the use of supportive communication led to increased anxiety levels for counsellees attending familial breast cancer clinics. However, Duric et al. (2003) reported that when the counsellee's distress was attended to with empathy by the counsellor in a breast cancer counselling session, there was no change in anxiety levels and counsellee level of satisfaction appeared to be independent of counsellor attentiveness to emotional signals. Equally, in another study that analysed the psychological outcomes of genetic counselling for familial cancer, it was concluded that genetic counselling did not increase levels of anxiety, distress or depression (Braithwaite, Emery, Walter et al., 2004).

It has been suggested that by genetic counsellors responding empathically, counsellees are more likely to offer more emotional signals, leading to a significant reduction in depression. It is best to keep in mind, however, that counsellees usually only attend one to two sessions which may not be enough time within which to adequately address emotional issues that are raised in the session (Duric et al., 2003).

1.7 MOTIVATION FOR RESEARCH

Genetic counselling is a relatively 'new' profession and is therefore not well known in the medical community or amongst the general public. However, genetic counselling is important in identifying those individuals who may be at risk for inherited breast and/or ovarian cancer so that an appropriate management plan, incorporating potentially life-saving screening and surgery measures and informing at-risk relatives, can be implemented. To date, the genetic counselling service offered by the NHLS in Johannesburg has not been assessed. It is important to establish who attends genetic counselling for breast and/or ovarian cancer and why, as well as how individuals experience the service. Such information can highlight areas of the service that require improvement and strategies for reaching a larger target audience in the future can be designed and implemented.

In addition, *BRCA* testing in South Africa appears to be limited to certain population groups, with the cost of testing being a possible limiting factor. Understanding who opts for testing and the type of testing they choose should identify deficiencies within the current system.

1.8 AIM

The aim of the research was to describe, review and assess the available genetic counselling and *BRCA* mutation testing services at WITS and the NHLS in Johannesburg, for individuals with a personal and/or family history of breast and/or ovarian cancer.

1.9 OBJECTIVES

1. To determine the number of individuals counselled at the Genetic Counselling Clinics, of the Division of Human Genetics, WITS and NHLS, for breast and/or ovarian cancer from 2001 to 2010.
2. To describe characteristics of the individuals attending genetic counselling, including independent variables such as age, sex, ethnicity and descent.
3. To assess the files and family pedigrees of individuals counselled to determine:
    a. Their reason for attending genetic counselling
    b. Whether or not the individual attending genetic counselling was affected with breast and/or ovarian cancer
    c. The number and ages of family members affected with breast and/or ovarian cancer as well as their relation to the individual counselled
    d. What cancers, other than breast and/or ovarian cancer, were present in *BRCA1* and *BRCA2* mutation positive families
    e. What genetic testing was offered, if testing was pursued, what testing was performed, where it was carried out, what mutation was found, what costs were incurred and by whom
4. To assess the genetic counselling service experienced by a sample of counsellees previously seen through the Clinics for breast and/or ovarian cancer counselling.

CHAPTER 2 SUBJECTS AND METHODS

This chapter describes the subjects and methods employed and has been divided into two sections; Section A describes the retrospective file based study and Section B describes the participants of the telephonic questionnaire component. Ethics approval for the research was granted by the Human Research Ethics Committee (Medical), Faculty of Health Sciences, the University of the Witwatersrand, reference number: M10M101141 (Appendix C).

SECTION A: FILE REVIEW

This was a descriptive, retrospective, file-based section of the study aimed at understanding who utilises the breast and/or ovarian cancer genetic counselling service and assessing what the service offers to patients in terms of counselling and testing.

2.1 SUBJECTS

The subjects of this study were individuals counselled regarding inherited breast and/or ovarian cancer at the Genetic Counselling Clinics of the Division of Human Genetics, WITS and the NHLS, Johannesburg, during the ten year period, 2001 to 2010. The genetic counselling took place at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), The Donald Gordon Medical Centre (DGMC), Rahima Moosa Mother and Child Hospital and the Outpatients Department of the NHLS, Johannesburg.

Individuals were from both the state and private hospital sector and included individuals with either a personal or family history of breast and/or ovarian cancer, or individuals with a *BRCA1* or *BRCA2* mutation previously described in another family member.

A specific Genetic Counselling Clinic for breast cancer was established through the Breast and Plastic Clinic at the Chris Hani Baragwanath Hospital (CHBH) in Soweto, Johannesburg on 9th June 2010. Patients seen at this clinic formed the basis of the research project of Tasha Wainstein, as part of her MSc (Med) Genetic Counselling degree. In order to prevent any overlap between the results obtained from the two projects, these patients were not included in this study. No patients were seen at CHBH for breast cancer counselling prior to 2010.

2.1.1 File collection

A counselling file is created and stored for each individual counselled at the Division of Human Genetics. The counselling files contain standard information on the counsellee(s) (the "counsellee" is the individual attending the genetic counselling session and in whose name the counselling file is opened), a three generation pedigree representing all family members at the time of the consultation, any medical documentation, case notes and a counselling letter. The counselling letter includes a detailed account of what was discussed between the counsellee and the counsellor in the session.

All breast/ovarian cancer counselling files are kept in a separate filing cabinet. In order to keep a record of each individual counselled, their details are logged onto a card entitled "Breast/ovarian cancer". The records reflected that 216 breast/ovarian cancer files should have been present in the filing cabinet. However, some files were excluded and more files were available due to incorrect categorisation, making a total of 218 files available for review (Table 2.1). Files that had been incorrectly categorized were identified by examining the patient files filed under "Other cancer" and "Cancer in the family".

Table 2.1: Reconciliation of the number of breast and/or ovarian cancer files expected and those available for review

	Number of files
Expected	216
Less:	
• Individuals counselled at the Breast and Plastic Clinic at CHBH	36
• Files not found	12
• Files incorrectly recorded under "Breast/ovarian cancer"	2
Add:	
• Breast/ovarian cancer files incorrectly categorised as "Other Cancer" and "Cancer in the family"	42
• Breast/ovarian cancer files not correctly recorded (incorrectly recorded under other diagnoses)	10
Actual	218

2.2 METHODS

2.2.1 Data collection

Data were collected from the 218 files using a data collection sheet (Appendix A). Information gathered on each counsellee included:

i. Demographics

Demographics of the counsellee included the counsellee's age at first consultation, their ethnicity (e.g. black, white, coloured or Indian) and descent (e.g. African, American or European). Ethnicity of counsellees was determined from the information reported by the counsellee and recorded by the counsellor in the file. The counsellees' area of descent focused particularly on whether the individuals were of Ashkenazi Jewish and/or Afrikaner ancestry.

The counsellee's genetic risk classification was determined from the files. The genetic counselling sessions for breast and/or ovarian cancer have become more standardised over the past two to three years and now include a risk assessment. Prior to this, individuals were not classified into specific risk categories during a genetic counselling session. The risk categories infer the likelihood of an individual having an inherited cancer syndrome. The risk categories for an inherited cancer syndrome were as follows: high, moderate to high, moderate, average and population. Average risk is slightly higher than population risk.

ii. Session indicators

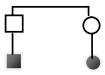
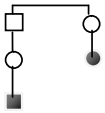
Session indicators included the date of the counsellee's first genetic counselling session, the number of individuals present at the session and the counsellee's reason for attending the session.

iii. Pedigree analysis

The pedigree analysis determined whether or not the counsellee was the person affected with breast and/or ovarian cancer, the presence and types of other cancers in each family as well as the degree of relationship between the counsellee and family

members affected with breast and/or ovarian cancer. The degree of relationship between the counsellee and relatives affected with breast and/or ovarian cancer was calculated as shown Table 2.2 (a "relative" refers to an individual related to the counsellee by blood and as such excludes those members related by marriage or adoption).

Table 2.2: Degree of relationship between individuals and the proportion of genes they share (Adapted from Harper (2004))

Degree of relationship		**Relationship (between shaded individuals)**	**Proportion of genes shared**
First	Siblings		1/2
First	Parent-child		1/2
Second	Uncle (Aunt) – Nephew (Niece)		1/4
Third	First cousins		1/8
Fourth	First cousins once removed		1/16

iv. *BRCA* mutation testing

The counselling letter, documented notes and molecular reports in the counselling file were analysed to determine if *BRCA1/2* genetic testing was offered to counsellees, if testing was performed, where and what type of testing was performed, who covered the cost of testing and whether a *BRCA1* or *BRCA2* mutation was identified.

2.2.2 Classification of "counsellee"

A unique subject code was assigned to each file to ensure anonymity. Each of the 218 files represented 218 individuals counselled. If more than one individual attended the genetic counselling session (e.g. two siblings) and both were counselled, a separate counselling file was opened for each counsellee. However, to avoid duplication of information when analysing

the other cancers in families, pedigrees of linked counsellees (55 related individuals) were excluded and information was only gathered from one counsellee per family (Figure 2.1). In addition, when the counsellee attended the genetic counselling session with a support person, the support person was not counted as a counsellee. All the data were entered into an Excel spreadsheet.

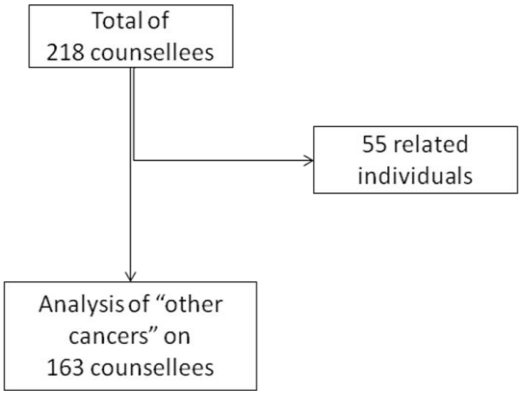


Figure 2.1: Calculation of the number of counsellees on which the analysis of other cancers in the family was performed

2.2.3 Data analysis

Most of the data were expressed as numbers or percentages. The data were analysed using Microsoft Excel. Means and standard deviations were calculated using Microsoft Excel's Statistical Analysis application. Means were rounded off to the nearest whole percent and standard deviations to one decimal place. Percentages were rounded to the nearest whole percent.

Data were grouped into categories and counted. Percentages were then calculated from the counts. Means were calculated for the age of counsellees seen as well as the number of counsellees counselled over the entire ten year period (2001 to 2010).

SECTION B: TELEPHONIC QUESTIONNAIRE

In order to assess a counsellee's experience of the genetic counselling service for breast and/or ovarian cancer, a telephonic questionnaire was compiled (Appendix B). The aim of the

questionnaire was to gain a better understanding of how genetic counselling is received by patients, as well as whether patients feel more informed regarding their risks, screening methods and testing for inherited breast and/or ovarian cancer after attending genetic counselling. This knowledge may assist in improving the genetic counselling service offered by the NHLS and WITS.

Respondents were telephoned and asked if they would like to participate in research aimed at assessing our breast and/or ovarian cancer genetic counselling service. It was explained to the respondents that the research would form part of my Masters degree.

2.3 PILOT STUDY

A pilot study of the telephonic questionnaire was conducted to determine whether the time allocation of ten minutes per interview was accurate and adequate, whether the questions were easily understandable and whether additional questions were necessary. Individuals counselled in 2010 were randomly selected. A total of four counsellees were telephoned for the purposes of the pilot study.

The time allocation of ten minutes was found to be adequate. The telephonic questionnaire was adjusted slightly based on the responses of the four individuals interviewed. One question asking respondents to explain how genetic counselling clarified their understanding of the genetics of breast and/or ovarian cancer was excluded as it was not necessary in order to fulfill the objectives of the study. Included in the revised questionnaire was a question asking which risk category for having a genetic cancer syndrome respondents were classified into by the counsellor during the genetic counselling session, and a question asking if they felt more informed about their risk for developing breast and/or ovarian cancer after genetic counselling.

The four respondents of the pilot study were not included in the final total of 50 completed telephonic questionnaires.

2.4 SUBJECTS

Files were randomly selected from the 218 files analysed as part of the file review. Counsellees were telephoned and invited to partake in the telephonic questionnaire. Counsellees were contacted until 50 completed questionnaires were obtained. Fifty counsellees represented almost a quarter of the files analysed and therefore, due to time constraints, was deemed to be sufficient for the telephonic questionnaire section of the study.

2.5 METHODS

2.5.1 Data collection

The first 50 individuals that were contacted all agreed to participate in the telephonic questionnaire. They were each asked a series of questions (Appendix B). The questions were close-ended; however, respondents were encouraged to make additional comments. A unique subject code was assigned to each questionnaire to ensure anonymity. Information gathered from the questionnaires included the respondent's reason for attending genetic counselling, their expectation of a genetic counselling session, whether genetic counselling clarified their understanding of the genetics of breast and/or ovarian cancer as well as what risk category for having a genetic cancer syndrome they were classified into. Respondents were also asked whether they had made any lifestyle changes after attending genetic counselling and whether they would refer anyone else to the service.

2.5.2 Data analysis

The data were entered into Microsoft Excel and expressed as numbers or percentages. Percentages were rounded to the nearest whole percent. Responses were grouped into categories and sub categories (Appendix B) and counted. Respondents' additional comments were also grouped into categories and counted. As an example, respondents were initially asked their reason for attending genetic counselling for breast and/or ovarian cancer. A large proportion of respondents commented that they had a family history of breast and/or ovarian cancer. Therefore, comments of this nature were grouped together under "family history of breast and/or ovarian cancer", counted and included as part of the results for respondents' reasons for attending genetic counselling.

CHAPTER 3 RESULTS

The results of this study have been split into two sections based on the data collection methods: the file review and the telephonic questionnaire. When reference is made to 'the Genetic Counselling Clinics' and 'genetic counselling', it specifically refers to the Genetic Counselling Clinics of the Division of Human Genetics, WITS and the NHLS, Johannesburg and for breast and/or ovarian cancer counselling, respectively.

SECTION A: FILE REVIEW

The results were generated from the data collection sheets collected from 218 files of individuals counselled at the Genetic Counselling Clinics.

3.1 SESSION INDICATORS

3.1.1 Yearly counsellee attendance numbers

The 218 counsellees included in this study were grouped according to the year in which they first attended genetic counselling for breast and/or ovarian cancer. The mean number of counsellees seen per year over the ten year period (2001 to 2010) was 22 ± 18.2. The number of counsellees seen per year ranged from 3 to 55. There has been a steady increase in counselling numbers since 2004, peaking in 2009 at 55 counsellees and then decreasing to 34 in 2010 (Figure 3.1).

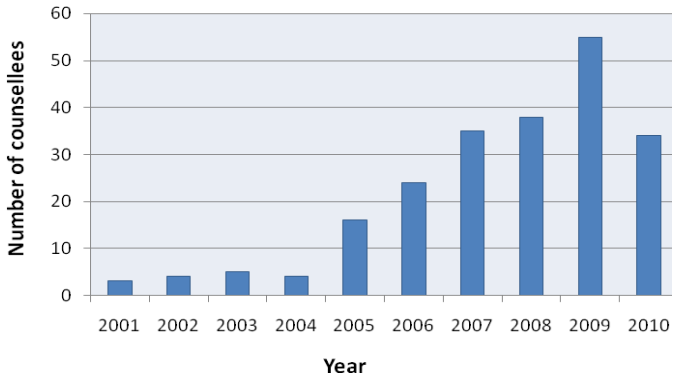


Figure 3.1: Number of counsellees attending genetic counselling from January 2001 to December 2010 (n=218)

3.1.2 Number of individuals in attendance per genetic counselling session

The majority (52%; 114/218) of individuals attending genetic counselling for breast and/or ovarian cancer did so alone. Two individuals were present at 39% (86/218) of sessions and these counsellees were often accompanied by a spouse or a family member, often a sibling. Three individuals were present at 6% (12/218) and four individuals at 3% (6/218) of sessions (Figure 3.2). These individuals were mostly accompanied by siblings or other family members.

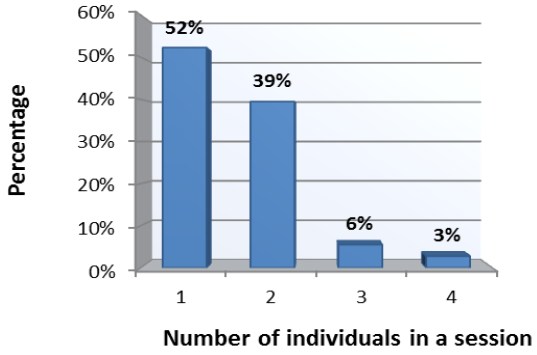


Figure 3.2: The number of individuals present at a genetic counselling session

3.1.3 Reason for attending a genetic counselling session

The majority of counsellees (44%, 97/218) attended genetic counselling for predictive *BRCA* mutation testing and a further 30% (65/218) attended for diagnostic *BRCA* testing. The remaining counsellees attended for other reasons, predominantly information gathering (26%, 56/218).

3.2 DEMOGRAPHICS

Of the 218 files collected, the majority of counsellees were female (95%) and private patients (90%) (i.e. they were seen at the private clinics and were usually members of a medical aid scheme). The majority of counsellees counselled for breast and/or ovarian cancer (61%; 132/218) were not affected and the remaining counsellees (39%; 86/218) were breast and/or ovarian cancer survivors.

Eighty two percent (179/218) of counsellees were white, 3% (7/218) Indian, 2% (5/218) black, 2% (3/218) coloured, and 11% (24/218) were of unknown ethnicity (not recorded in the file). The ages of the counsellees at the time of their first genetic counselling session ranged from 19 to 86 years of age with a mean age of 46 ± 12.3 years. The majority of counsellees (77%) were between 30 and 59 years of age.

3.2.1 Descent

Only a small percentage of counsellees were of African (5/218) or Asian (8/218) descent. Figure 3.3 illustrates that the vast majority of counsellees were either of Ashkenazi Jewish (98/218) or Afrikaner (45/218) ancestry. Two percent (5/218) of counsellees were of both Afrikaner and Ashkenazi Jewish ancestry. Of the 14% (31/218) of counsellees that were of other European origin, the majority were from the United Kingdom.

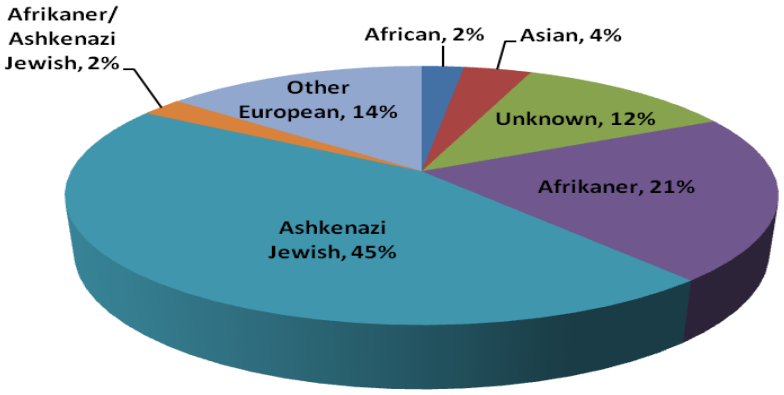


Figure 3.3: Descent/ancestry of counsellees attending genetic counselling (n=218)

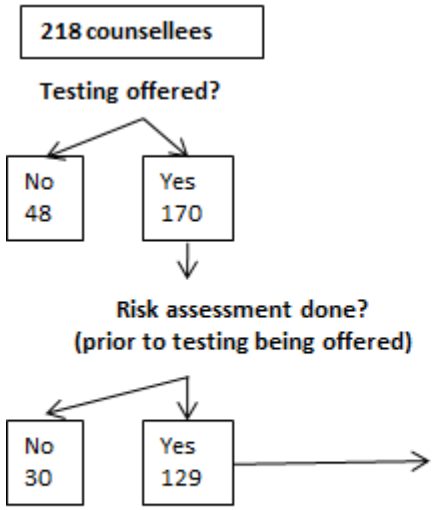
3.2.2 Genetic risk classification

Risk assessment has only occurred more recently and therefore only 159 of the 218 counsellees (73%) were classified into risk categories prior to or during the genetic counselling session. Almost half (49%) of all counsellees (79/159) that were classified into a risk category were classified as being at high risk. Nineteen percent (31/159) of counsellees were classified at moderate to high risk, 26% (41/159) at moderate risk, 3% (4/159) at average risk and 3% (4/159) at population risk for breast and/or ovarian cancer.

3.3 *BRCA* MUTATION TESTING

3.3.1 *BRCA* mutation testing offered

Of the total 218 counsellees, 170 (78%) were offered *BRCA* testing (Figure 3.4). From a clinical genetics perspective, *BRCA* mutation testing should only be offered to those individuals who are assessed to be either at a high or moderate to high risk of having inherited breast and/or ovarian cancer. Of these 170 counsellees, 129 (76%) were categorised into a risk category. Figure 3.4 indicates the risk categories the counsellees were categorised into. The majority of counsellees who were offered testing and classified into a risk category (72/129, 56%) were at a high risk of having inherited breast and/or ovarian cancer. Twenty seven counsellees (21%) were classified as being a moderate risk but were still offered testing. In some instances, even though a counsellee's risk assessment may not place them at a high risk for inherited breast and/or ovarian cancer, their family history or genetic risk factors may indicate that they be offered testing.



Risk Category	No. counsellees (n=129)	% counsellees
High	72	56
Moderate to high	27	21
Moderate	27	21
Average	1	1
Population	2	1

Figure 3.4: Breakdown of the number of counsellees who were offered *BRCA* mutation testing and the risk category they were classified into

The majority of *BRCA* mutation testing that was offered was nationally based testing (81%, 138/170), with a smaller percentage offered overseas (19%, 32/170). Of the nationally based testing that was offered, only 12% (16/138) was Johannesburg based with the majority (88%;

122/138) based in Pretoria and Bloemfontein. The majority of internationally based testing that was offered was in the United Kingdom (Figure 3.5).

3.3.2 *BRCA* mutation testing performed

BRCA mutation testing was performed for 138 of the 170 counsellees that were offered testing, equating to an uptake of 81%. The majority of counsellees who declined testing did so for personal reasons (81%, 26/32) with only a small percentage declining due to financial reasons (19%, 6/32).

Figure 3.5 shows that of the *BRCA* mutation testing performed, only 10% was performed internationally with 90% of all testing performed nationally. Only 11% of national testing was performed in Johannesburg by the NHLS, which is due to the fact that they only offered testing from 2009. The balance was performed in Pretoria and Bloemfontein.

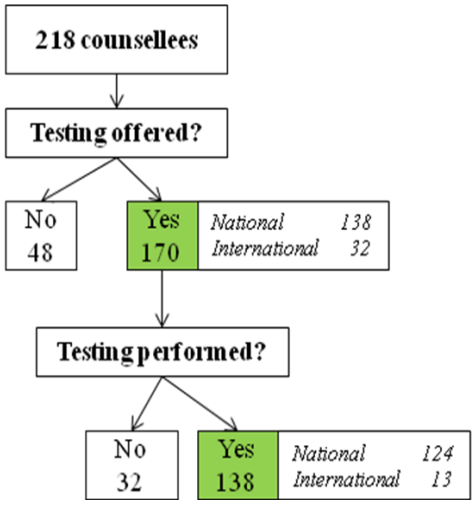


Figure 3.5: Number of counsellees offered *BRCA* mutation testing and for whom *BRCA* mutation testing was performed

3.3.3 Number of *BRCA* mutation tests performed

In total, 147 *BRCA* mutation tests were performed for the 138 counsellees, with some counsellees having more than one test. This would occur if a high risk Ashkenazi Jew or Afrikaner tested negative for the founder mutations and then chose to have further testing in the form of sequencing or MLPA. By far, the majority (56%, 82/147) of testing performed was

targeted Ashkenazi Jewish founder mutation testing, followed by targeted Afrikaner mutation testing (18%, 27/147) (Figure 3.6). Full *BRCA1* and *BRCA2* sequencing was only performed for eight counsellees. Twenty four counsellees had family-specific mutation analysis (Figure 3.6). Of these 24 counsellees, 75% (18/24) was performed locally, mostly in Pretoria, and 25% (6/24) internationally.

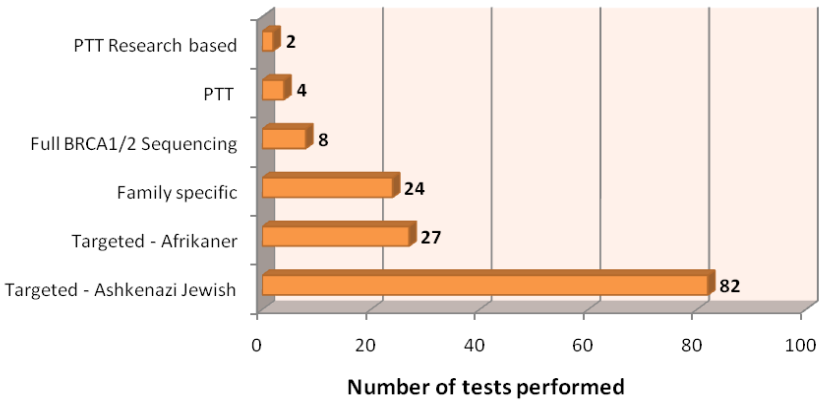


Figure 3.6: The types of *BRCA* tests performed in 138 counsellees (n=147)

3.3.4 Cost of *BRCA* mutation testing

Ninety one percent of mutation testing performed was paid for by the counsellee. Some medical aids may have contributed to the payment; however a financial breakdown was not available for analysis. Overseas testing is paid for solely by the counsellee and/or their medical aid scheme if they belong to one. Eight percent of testing was paid for by the state. The remaining 1% was included as part of research and therefore no cost was involved.

3.3.5 *BRCA* disease-causing mutations identified

A total of 49 *BRCA* positive families, constituting 61 counsellees, were identified as part of the study. Thirty one (63%) of these families had a known *BRCA* mutation at the time of genetic counselling and 18 families (37%) were identified as having a *BRCA* mutation following genetic counselling and testing (mutation previously unknown in each family). Table 3.1 lists the *BRCA1/2* mutations that were present in the 49 families. The most common mutation was the *BRCA1* Ashkenazi Jewish mutation 185delAG, followed by the *BRCA2* Ashkenazi Jewish mutation 6174delT.

Table 3.1: *BRCA1/2* mutations present in 49 mutation positive families

Gene	Mutation	No. families that tested positive	Founder population
BRCA1	185delAG	14	Ashkenazi Jewish
	5382insC	4	Ashkenazi Jewish
	c.4957insC	1	Afrikaner
	1493delC	1	Afrikaner
	4184delTCAA	1	None
	c.164insT	1	None
	delexon22	1	None
	Exon13 dupl	1	None
	E881X	1	Afrikaner
	c.5302delT	1	None
BRCA2	6174delT	13	Ashkenazi Jewish
	8162delG	4	Afrikaner
	c.7757G>A	2	None
	8167G>C	1	None
	Exon7 c.517-2A>G	1	None
	R3128X	1	None
	6621delA	1	None

3.4 PEDIGREE ANALYSIS

The pedigree for each counsellee was analysed to determine the relationship between the counsellee and relatives affected with breast and/or ovarian cancer. The presence of other cancers in each family was also assessed. Of the 218 counsellees included in this study, 61% (132/218) were unaffected and 39% (86/218) had already had breast and/or ovarian cancer (Section 3.2).

Figure 3.7 illustrates the number of counsellees, either affected or unaffected with breast and/or ovarian cancer, who had relatives affected with breast and/or ovarian cancer. Of the

unaffected counsellees, the majority had a first degree (89%, 117/132) and/or a second degree relative (67%, 89/132) with breast and/or ovarian cancer. The results for the affected counsellees are similar in that they also show that the majority (57%, 49/86) had a first degree relative and 51% (44/86) had a second degree relative affected with breast and/or ovarian cancer.

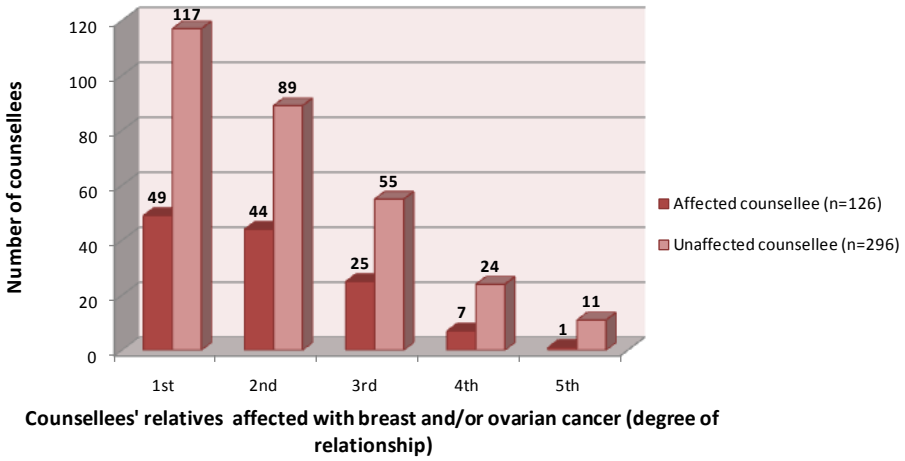


Figure 3.7: The number and degree of relationship of affected relatives of counsellees, both affected and unaffected with breast and/or ovarian cancer

3.4.1 Other cancers in the family of the counsellee

For the analysis of other cancers in the family, where more than one family member attended genetic counselling, the pedigree analysis of only one family member was included to prevent any duplication of information. Therefore, 163 families were included in this analysis and 55 related individuals were excluded (Figure 2.1).

Based on the family pedigrees drawn, a history of other cancers, in addition to breast and/or ovarian cancer, was reported in all 163 families analysed. Figure 3.8 illustrates that overall prostate, stomach and colon cancer were the most common "other" cancers among all 163 families. Prostate cancer was observed in 26% (43/163), stomach cancer in 25% (40/163) and colon cancer in 24% (39/163) of families.

In the 49 *BRCA* positive families, prostate cancer was also the most common "other cancer", observed in 11 families (22%), and stomach cancer was the second most common, observed in

nine families (18%). Prostate and stomach cancer were the top two ranked cancers, besides breast and/or ovarian cancer, among all families, including those who were *BRCA* positive.

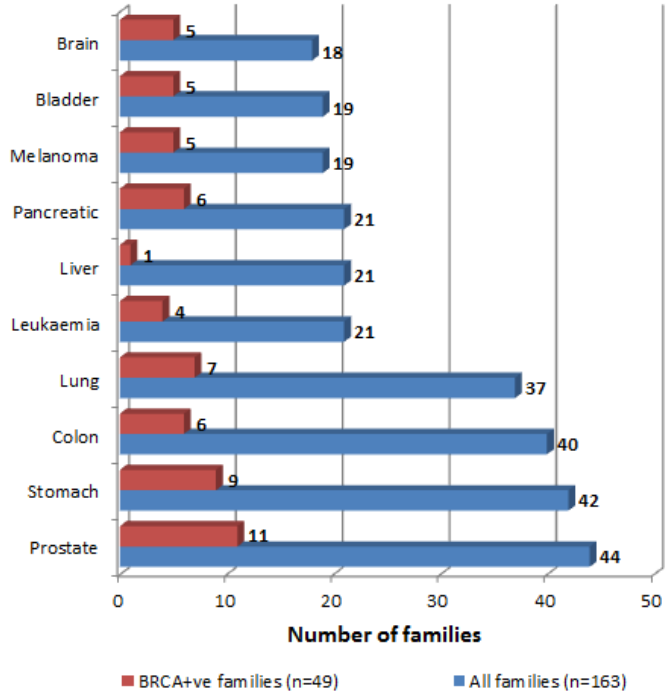


Figure 3.8: The number and type of "other" cancers reported in families of counsellees

SECTION B: TELEPHONIC QUESTIONNAIRE

The results for this section were generated from the telephonic questionnaires of 50 individuals previously seen at the Genetic Counselling Clinics.

3.5 THE RESPONDENTS

A total of 50 individuals were telephoned and all 50 agreed to participate. The majority (96%) of respondents attended genetic counselling between 2007 and 2010. All of the respondents were female and private patients, as expected. The ages of the respondents at the time of their first genetic counselling session for breast and/or ovarian cancer ranged from 29 to 70 years of age (mean age 49 ± 10.9 years). The majority of respondents (54%) were between 40 and 59 years of age. The majority of respondents were of Ashkenazi Jewish ancestry (54%, 27/50) and 18% (9/50) of respondents were of Afrikaner ancestry (Figure 3.9).

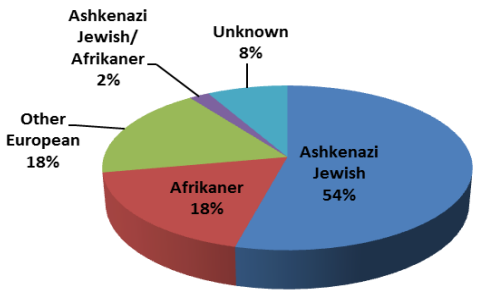


Figure 3.9: Descent/ancestry of the respondents interviewed telephonically (n=50)

3.5.1 Reason for attending genetic counselling

The opening question to respondents asked why they attended genetic counselling. Respondents' reasons were then grouped into four categories (Figure 3.10). Some respondents' reasons for attending genetic counselling fell into more than one category, therefore the total number of responses was 57 and not 50. Forty six percent (26/57) of respondents said they attended genetic counselling for *BRCA* mutation testing, 28% (16/57) said they came because they were referred by a medical professional, 24% (14/57) attended in order to clarify their risks or find out more information and one respondent (2%) said they attended after reading the NHLS pamphlet on inherited breast/ovarian cancer in the doctor's room. The majority (66%, 33/50) of respondents commented that they attended genetic counselling due to a personal or family history of breast and/or ovarian cancer.

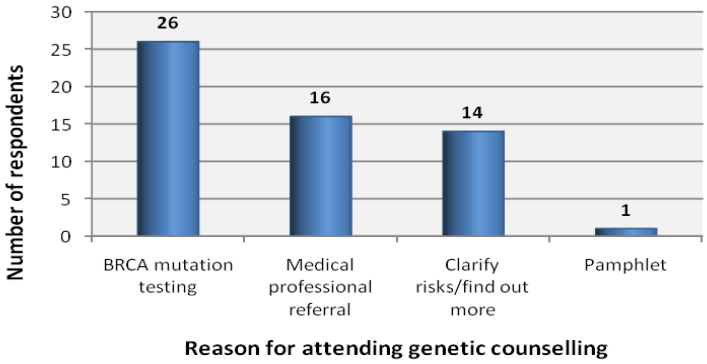


Figure 3.10: Respondents' reasons for attending genetic counselling (n=57*)

* Some respondents' reasons for attending genetic counselling fell into more than one category; therefore the total number of responses is 57 and not 50

3.5.2 Initial expectation of genetic counselling

Respondents' initial expectation of genetic counselling was grouped into five categories (Table 3.2). Some respondents' initial expectation of genetic counselling fell into more than one category, therefore the total number of responses was 54 and not 50. None of the 50 respondents anticipated genetic counselling to be a psychotherapy session. Thirty three percent (18/54) of respondents reported having no expectation or no idea what to expect of the session, 24% (13/54) thought it would entail a risk assessment and a further 20% (11/54) anticipated a medical fact-giving session. Of the remaining 23% (12/54) of respondents, the majority (75%) anticipated genetic counselling to involve molecular testing.

Table 3.2: Respondent's initial expectation of a genetic counselling session

Respondents' initial expectation	No. respondents (n=54*)
Psychotherapy	0 (0%)
Medical facts	11 (20%)
Risk assessment	13 (24%)
No idea/no expectation	18 (33%)
Other – including molecular testing	12 (23%)

* Some respondents' initial expectation of genetic counselling fell into more than one category, therefore the total number of responses is 54 and not 50

3.6 INFORMATION CONVEYED DURING GENETIC COUNSELLING

In order to establish whether the information given during a genetic counselling session was effective, the respondents were asked whether genetic counselling clarified their understanding of the genetics of breast and/or ovarian cancer and their risk for developing hereditary breast and/or ovarian cancer. They were also asked whether the concept of screening and surgery for breast and/or ovarian cancer was explained to them in the session.

3.6.1 Genetics of breast and/or ovarian cancer

Eighty six percent (43/50) of respondents stated that genetic counselling clarified their understanding of the genetics of breast and/or ovarian cancer (Table 3.3). Ten percent (5/50)

of respondents felt that genetic counselling did not clarify their understanding, 2% (1/50) could not remember the information given to them in the genetic counselling session and an additional 2% (1/50) said genetic counselling only partially clarified their understanding.

Table 3.3: Summary of responses to questions pertaining to the information giving aspect of a genetic counselling session for breast and/or ovarian cancer

Question asked	**Counsellee response (n=50)**			
	Yes	**No**	**Partially**	**Cannot recall**
Did genetic counselling clarify your understanding of:	**n (%)**			
Genetics of breast and/or ovarian cancer?	43 (86)	5 (10)	1 (2)	1 (2)
Risk of carrying a *BRCA* mutation?	37 (74)	11 (22)	0 (0)	2 (4)
Screening and surgery for breast and/or ovarian cancer?	36 (72)	2 (4)	0 (0)	12 (24)

3.6.2 Risk of carrying a *BRCA* mutation

Out of the 50 respondents, 37 (74%) confirmed that genetic counselling elucidated their risk of carrying a *BRCA* mutation, two respondents (4%) could not remember and 11 respondents (22%) stated that genetic counselling did not assist in clarifying their risks (Table 3.3). Of these 11 respondents, three stated that they were already aware of their risks prior to attending genetic counselling, a further three had already developed breast cancer and were therefore already aware of their risks and two respondents felt that their risks were not clearly communicated to them in the genetic counselling session.

3.6.2.1 Recollection of genetic risk assessment

Respondents were asked if they could recall the risk category for inherited breast and/or ovarian cancer that they were classified into during their genetic counselling session. As stated previously, the use of risk categories to classify counsellees has only become routine in the past few years, therefore it was expected that a percentage of the respondents would not have been classified into a risk category during the genetic counselling session. For 26% (13/50) of

respondents, as per their file, no risk estimate was given to them during the session (Figure 3.11).

Of the total 50 respondents, 36% (18/50) recalled the same risk category that they were classified into during the genetic counselling session, as documented in their files (Figure 3.11). Twenty eight percent (14/50) could not remember which risk category they were classified into, 10% (5/50) recalled a risk category lower than what they were classified into and no respondent recalled a higher risk category than the one they were classified into.

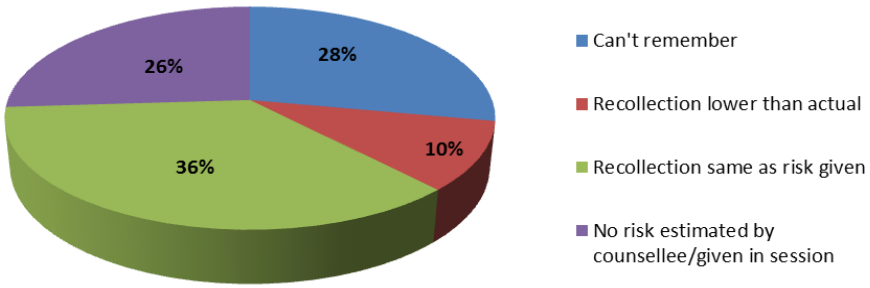


Figure 3.11: Respondents' recollection of the risk category they were classified into during their genetic counselling session for breast and/or ovarian cancer (n=50)

3.6.3 Screening and/or prophylactic surgery for breast and/or ovarian cancer

Thirty six (72%) out of the 50 respondents stated that the genetic counsellor explained the concept of screening and prophylactic surgery for breast and/or ovarian cancer to them during the genetic counselling session. Two (4%) respondents stated that screening and surgery was not explained and 12 (24%) could not remember (Table 3.3). Seventeen of the respondents commented that they were already vigilant about screening for breast and/or ovarian cancer prior to attending genetic counselling.

In accordance with these results, none of the respondents increased or changed their screening regime for breast and/or ovarian cancer following genetic counselling. The majority of respondents (62%, 31/50) also reported that they did not make any lifestyle changes after attending genetic counselling. Of the 38% (19/50) that did make lifestyle changes, nine (46%)

respondents made lifestyle changes involving diet and exercise and ten chose surgery: four respondents (21%) chose to have mastectomies, two respondents (11%) chose to have salpingo-oophorectomies and two respondents (11%) chose to have a hysterectomy.

3.7 REFERRALS TO GENETIC COUNSELLING

In order to evaluate how genetic counselling is received by individuals, respondents were asked if they would refer someone to genetic counselling. The vast majority (94%, 47/50) of respondents said they would refer. The remaining three respondents stated that they were unsure as to whether they would refer someone for genetic counselling. No respondent stated that they would not refer.

The 47 respondents who said they would refer were asked why they would refer someone for genetic counselling. Their responses were grouped into six categories (Figure 3.12). Some respondents' reasons for referring friends/family to genetic counselling fell into more than one category and some did not comment, therefore the total number of responses was 51 and not 50. The most common reason for referral was that genetic counselling led to increased knowledge and improved understanding of the genetics of breast and/or ovarian cancer thus enabling more informed and timeous decision making. In addition, respondents commented that they would especially refer individuals with a family history of breast and/or ovarian cancer or individuals in high risk population groups, such as the Ashkenazi Jewish population.

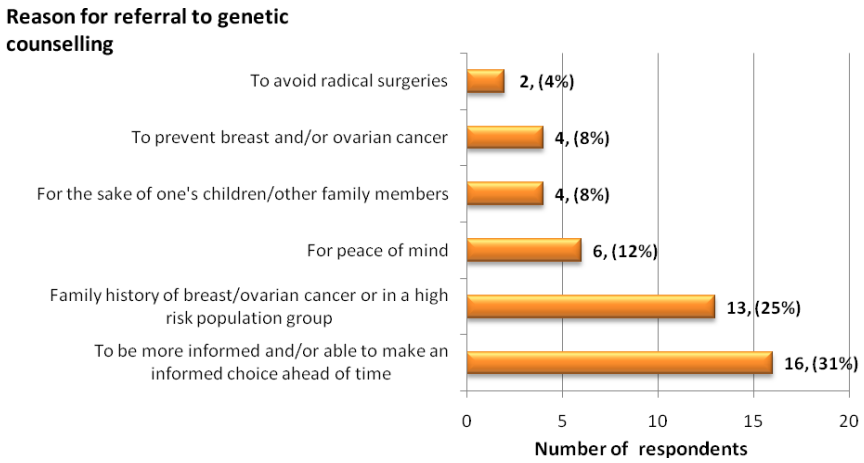


Figure 3.12: Respondents' reasons for referring friends/family to the genetic counselling (n=51)

(Some respondents' reasons for referring friends/family to genetic counselling fell into more than one category, therefore the total number of responses is 51 and not 50)

3.7.1 Additional comments from respondents

At the end of the questionnaire respondents were asked if there was anything they would like to add regarding the genetic counselling service they received. Forty four of the 50 respondents made additional comments, making 101 comments in total. The majority of respondents (79%, 33/42) made more than one comment. There were both positive and negative comments made by respondents regarding the service; however, respondents mostly either made positive or negative comments, not both. In total there were 72 positive comments, 17 negative comments and 12 suggestions that were made.

- ***Positive comments***

Positive comments made by the respondents regarding the genetic counselling service were grouped into categories. Figure 3.13 illustrates the positive comments made. Of the 72 positive comments, 44 (61%) were about the genetic counselling service, saying that it was "excellent", "fantastic", "very good", "worthwhile", "phenomenal" and "superb service". Respondents also commented that all the relevant information was explained clearly in the genetic counselling session thereby enabling informed decision making.

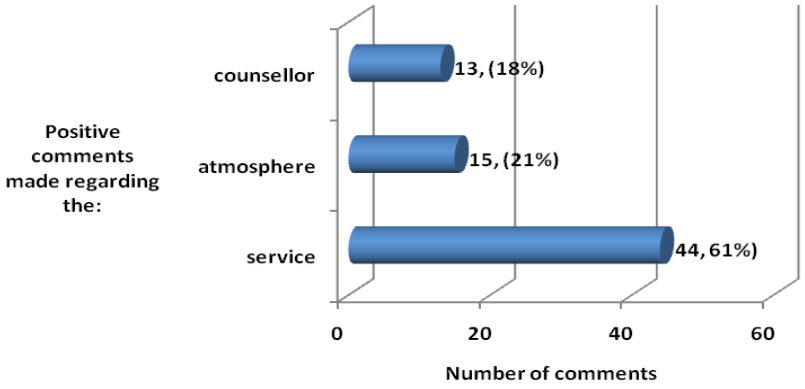


Figure 3.13: Positive comments made by respondents regarding: the service, the counsellor and the atmosphere for genetic counselling for breast and/or ovarian cancer (n=72)

Thirteen comments (18%) were received on the counsellors stating that they were "lovely, wonderful people", "very nice", "very pleasant", "took time, answered questions", "answered questions honestly and straight forward" and were "very efficient and thorough". There were also 15 comments (21%) regarding the atmosphere in the genetic counselling session, stating that it was "caring, empathic and sympathetic" with the counsellor attending to the emotional side of the discussion regarding the impact of breast and/or ovarian cancer.

- ***Negative comments***

Of the 17 negative comments received, six of the respondents (35%) commented that the genetic counselling service was not ideal in that it was "confusing", "no risk assessment was done", the service was "not great", there was "not much counselling" and the "result giving could have been more informative". Four respondents (24%) felt that their outcome from genetic counselling was "pointless" or "vague" in that even if they tested positive for a *BRCA* mutation they felt that their options to prevent breast and/or ovarian cancer were limited. Three respondents (18%) stated that genetic counselling was very expensive especially if one was not on a medical aid plan.

It is worth noting that two respondents stated that in their result giving session, they felt that it took too long to receive their results. They stated that they would have preferred to have been told their results at the very beginning of the session, especially if they tested negative for a

BRCA mutation, as the longer the session progressed without receiving their results the more anxious they became.

- ***Suggestions made by respondents***

When asked if there was anything they would like to add regarding the service offered in terms of genetic counselling for breast and/or ovarian cancer, a number of respondents made a few suggestions. It was suggested by eight respondents that there is a need to increase the general awareness of the genetic counselling clinics among doctors and other medical practitioners. They suggested that the Genetic Counselling Unit market themselves more effectively. Two respondents suggested that a follow up service be implemented to keep in touch with counsellees and to inform them if new testing becomes available.

CHAPTER 4 DISCUSSION

The results of the study have produced valuable information regarding who utilises the genetic counselling service and why, and given an indication of how the service is received by individuals attending the clinics. The study has also highlighted areas requiring attention in the future that may assist in expanding the referral base for genetic counselling.

4.1 COUNSELLEE NUMBERS

The number of individuals counselled for breast and/or ovarian cancer increased steadily from 2004 until 2009, decreasing in 2010 (Figure 3.1). This increase in attendance may be due to increased media advocacy campaigns focusing on breast cancer awareness. As an example, October is breast cancer awareness month in South Africa and in this month a lot of focus is placed on educating the public on breast cancer and the importance of self-breast examination and annual mammograms. In addition, over time, more genetic counsellors qualified within the Division of Human Genetics, WITS and the NHLS, and began seeing patients for breast and/or ovarian cancer, thus contributing to the increase in patient numbers. The genetic counsellors also initiated the introduction of information pamphlets on inherited breast and/or ovarian cancer and genetic counselling into doctors' waiting rooms in 2008/2009.

A global recession, that began in 2008 (Imbs, 2010), may be partly to blame for the reduction in attendance numbers observed in 2010. Individuals may not have had funds to attend genetic counselling or chose to spend their medical savings accounts on other medical expenditure. In addition, the recent decline in the number of staff members at the Division of Human Genetics, WITS and the NHLS may be a contributing factor to the decrease in patient numbers. Ninety percent of individuals counselled over the ten year period were private patients and private patients are mostly seen at the Donald Gordon Medical Centre (DGMC). The staff shortages have resulted in the clinic at the DGMC only operating for two mornings a week resulting in long waiting periods for an appointment to become available. The waiting period may well be the cause of the decline in patient numbers observed in 2010.

4.1.1 Referrals

The term "genetic counselling" was first coined by Dr Sheldon Reed in 1947 (Reed, 1975; Resta, 1997). The first formal definition of genetic counselling was formulated by the American Society of Human Genetics in 1975 (American Society of Human Genetics Ad Hoc Committee on Genetic Counseling, 1975) and revised in 2006 (Resta et al., 2006), with the subsequent formation of the National Society of Genetic Counsellors in 1979 in the US (McCarthy Veach et al., 2003). In South Africa, genetic services were only developed in the 1950s and informal genetic counselling began in the 1960s in Johannesburg and Cape Town (Jenkins, 1990). Genetic counselling is therefore a relatively "new" profession and, in spite of the availability of genetic services in South Africa, there appears to be a lack of knowledge of the benefits of genetic counselling among both medical professionals and the public (Kromberg, Sizer & Christianson, 2012). A study by van der Westhuizen (2008), as part of his MSc (Med) in Genetic Counselling degree, highlighted the lack of awareness of genetic counselling services in South Africa and the need for an effective referral system to identify individuals at high risk for inherited cancer. This general lack of awareness is sure to impact the number of referrals for genetic counselling. Collins, Halliday, Kahler et al. (2001) found that the main reason for individuals not attending genetic counselling was because they were unaware of the service.

Van Riel, Wárlám-Rodenhuis, Verhoef et al. (2010) report that although some women refer themselves for genetic counselling and *BRCA* testing, a large number of women rely on a medical professional or their general practitioner (GP) for referral. However, this does not seem to be the case for the individuals attending the Genetic Counselling Clinics of the Division of Human Genetic, WITS and the NHLS. From observation, the majority of patients refer themselves which is confirmed by the results of the telephonic questionnaire - of the 50 respondents participating in the telephonic questionnaire, only 28% were referred by a medical professional (Figure 3.10). Studies have shown that GPs lack sufficient knowledge to be able to select high risk women, which may be the case in South Africa. A study conducted by van Wyk (2008) as part of her MSc (Med) in Genetic Counselling degree, assessed the cancer genetics knowledge of GPs in the Johannesburg area. Of the 61 GPs that participated in the research, only 25% reported assessing a patient's risk for inherited cancer. These GPs were

also not aware of the genetic counselling facilities available; however, they did feel that patients would benefit from genetic counselling prior to genetic testing. In the current study, 8 of the 50 respondents of the telephonic questionnaire commented that doctors need to be made more aware of the genetic counselling service offered. The Division of Human Genetics has attempted to improve this by providing pamphlets on inherited cancers, and the genetic counselling service, to doctors to have on display in their rooms. However, the efficacy of these pamphlets in reaching the individuals at high risk for inherited breast and/or ovarian cancer is unknown. In addition to pamphlets, a series of talks aimed at educating GPs on the availability and services of genetic counselling facilities and genetic testing may be more effective.

4.2 WHO ATTENDS GENETIC COUNSELLING AND WHY?

Analysing who attends genetic counselling for breast and/or ovarian cancer and why they attend, gives insight into whether the genetic counselling service is reaching an appropriate group of individuals and, if not, how this can be improved.

4.2.1 Attendees

According to this study the majority of counsellees attending genetic counselling for breast and/or ovarian cancer are white/Caucasian females in their forties who are private patients (attend genetic counselling in the private hospital and are likely to belong to a medical aid scheme). In addition, they usually attend the session alone (Figure 3.2).

The 2011 midyear population statistics for South Africa report a population size of 50.6 million (m) consisting of 40.2m African, 4.5m coloured, 4.6m white and 1.3m Indian/Asian individuals (Statistics South Africa, 2011). However, the vast majority of individuals who attended genetic counselling for breast and/or ovarian cancer were white. The high incidence of breast cancer among white women (1 in 12) (Mqoqi et al., 2004) partly accounts for the high representation of this group at the genetic counselling clinics as does the availability of testing for white women of Afrikaner or Ashkenazi Jewish ancestry. As stated previously, South Africa has two founder populations: the Ashkenazi Jewish and the Afrikaners, both with

founder *BRCA* mutations. Therefore, as expected, a large number of the individuals attending genetic counselling for breast and/or ovarian cancer were from these two populations (Figure 3.3). There is a documented higher rate of *BRCA* testing among Ashkenazi Jewish women due to the founder mutations prevalent in this population and the associated increased cancer risks (Armstrong, Weiner, Weber et al., 2003). Ashkenazi Jewish women in South Africa may be more aware of their risks due to increased community awareness which may explain their over representation in the Genetic Counselling Clinics.

Black women have a 1 in 50 and Asian and coloured women have a 1 in 18 risk for breast cancer (Mqoqi et al., 2004) and therefore it appears as though there is an underrepresentation of these population groups in the Genetic Counselling Clinics. Many coloured women often have an Afrikaner heritage (de Wit, Delport, Rugamika et al., 2010) and therefore the attendance of coloured women at the Genetic Counselling Clinics is far lower than would be expected. *BRCA* mutation testing is mainly limited to the founder mutations for the Ashkenazi Jewish and Afrikaner populations and little is known on the predisposing mutations in the black population of South Africa. The lack of testing available to the black population may then also explain their underrepresentation. More black patients may be referred if there is testing available for them. Future research is necessary to identify the disease causing or predisposing mutations in these population groups so that they can be offered testing. Recently, a recurrent founder mutation was identified in the black Xhosa population (van der Merwe et al., 2012). The Genetic Counselling Clinic that was established in 2010 at the Breast and Plastic Clinic, CHBH, in Soweto, Johannesburg, partly addresses the need for a breast and/or ovarian cancer genetic counselling service aimed at the black population. However, there also appears to be a need to increase awareness of the genetic counselling service for breast and/or ovarian cancer among coloured women and women of other population groups.

4.2.2 Reasons for attending genetic counselling

The results reflect that the majority (61%) of individuals counselled for breast and/or ovarian cancer were not as yet affected with cancer. Of the unaffected counsellees, 89% had a first degree relative and 67% reported having a second degree relative with breast and/or ovarian

cancer (Figure 3.7). The majority of affected counsellees also reported having a first or second degree relative with breast and/or ovarian cancer. This would suggest that individuals tend to seek genetic counselling when someone in the family is diagnosed with breast and/or ovarian cancer, not necessarily themselves. Individuals with a family history of breast and/or ovarian cancer are more likely to be aware of their increased risks compared to the general population. In this study, 24% of respondents of the telephonic questionnaire stated that they attended genetic counselling to clarify their risks and gather more information (Figure 3.10). Peters and Petrill (2011) found that individuals seeking cancer genetic counselling usually had some kind of family history of cancer and although they were more informed about the cancer they sought genetic counselling to find out more information on the surveillance and treatment options. The results of this study, with respect to having a family history of cancer, support Peters and Petrill's findings.

One of the main motivations for respondents attending genetic counselling was for genetic testing. This would imply that a large proportion of the respondents were already aware of the availability of genetic testing for susceptibility to inherited breast and/or ovarian cancer prior to attending genetic counselling. Almost half (46%) of the 50 respondents participating in the telephonic questionnaire stated that they attended genetic counselling specifically for testing (Figure 3.10). Four of the respondents (8%) also commented that they attended genetic counselling for their children's sake. A study by Bruno, Digennaro, Tommasi et al. (2010) found that one of the prevailing reasons for individuals seeking genetic testing for inherited breast cancer was to determine the risks to their children.

- ***Cost of a genetic counselling consultation***

Genetic counselling is a speciality service and therefore specialist prices are charged in accordance with the Board of Health Care Funders rates. Only four out of the 50 respondents (8%) of the telephonic questionnaire commented that the cost of a genetic counselling consultation was high and therefore not accessible for everyone. However, it is worth stating that individuals usually attend one genetic counselling session and the cost is covered, to a certain degree, by medical aid schemes.

4.2.3 Expectations of genetic counselling

Individuals' first exposure to genetic counselling is usually at the time of their first genetic counselling session. Therefore, they may be unaware of what a session entails and expectations may vary between individuals. In addition, as stated previously, genetic counselling is a relatively new field and therefore there appears to be little awareness of the profession amongst the general population. This was true for the majority of respondents from the telephonic questionnaire who reported having little idea of what a genetic counselling session for breast and/or ovarian cancer would entail. Table 3.2 shows that the respondents' expectations of a genetic counselling session seemed to be equally split between: medical fact giving (20%), risk assessment (24%) and not having any expectation at all (33%). Medical fact finding and risk assessment can together be viewed as information gathering. In another South African study, Macaulay, Gregersen and Krause (2012) found that the main reason for counsellees attending genetic counselling was for information gathering. It is noteworthy that none of the respondents anticipated genetic counselling to involve psychotherapy. However, in this study, the fact that few respondents knew what to expect highlights a need to better market the genetic counselling service in Johannesburg. Perhaps if more individuals were made aware of genetic counselling for inherited disorders, including inherited breast and/or ovarian cancer, there may be more referrals and the service would reach a larger target audience?

4.3 *BRCA* MUTATION TESTING

Of the 218 individuals in this review, the vast majority (78%) were offered *BRCA* mutation testing (Figure 3.5). *BRCA* mutation testing is only indicated for those individuals who have a high or moderate to high risk for inherited breast and/or ovarian cancer. However, should an individual insist on testing and be willing to cover the cost of testing, testing may still be performed. This would account for the three counsellees who were classified into a risk category lower than moderate risk but were still offered testing (Figure 3.4). The majority of the 129 individuals who were offered testing and for whom a risk assessment had been done were classified into either a high or moderate to high risk category (Figure 3.4). This indicates that although there are not a large number of referrals for inherited breast and/or ovarian cancer, those cases that are referred are appropriate. However, there may be a bias towards

women at a high risk for inherited breast and/or ovarian cancer. Women with a family history of breast and/or ovarian cancer or genetic risk factors who are not classified as being at high risk for inherited breast and/or ovarian cancer should also be referred to the service to be advised of their risks and screening options In this way, genetic counselling will be able to reach a wider group of women.

The majority of testing offered (81%) was nationally based *BRCA* mutation testing (Figure 3.5). This correlates with the fact that the *BRCA* founder mutation testing is performed nationally and the majority of individuals attending genetic counselling for breast and/or ovarian cancer are of either Ashkenazi Jewish or Afrikaner heritage. National *BRCA* mutation testing is usually paid for by medical aid schemes and therefore the uptake of this *BRCA* testing (90%) was expected to be higher than the uptake of international *BRCA* mutation testing (41%). International *BRCA* testing is performed in the UK at a substantial cost that is not covered by the local medical aid schemes. Only 31 of the 218 counsellees (14%) of this study were of European descent (Section 3.2.1). The overall testing performed is therefore biased towards individuals of Ashkenazi Jewish or Afrikaner heritage.

It appears as though when the cost of *BRCA* mutation testing is covered by a medical aid scheme there is a greater uptake of testing. Therefore, although cost to the individual may be an influential factor regarding whether one pursues testing or not, there are also other factors that may influence decision making. Bruno et al. (2010) found that the reason most cited for declining genetic testing for inherited breast cancer was a fear of the psychological consequences. Of those individuals that declined testing (32/170, 19%) in the current study (Figure 3.5, Section 3.3.2), the minority reported declining testing for financial reasons, with the vast majority declining for personal reasons. These ‘personal reasons’ may well have included a fear of psychological harm or the impact of testing on their families or the potential for discrimination from medical aids or insurance companies. Further investigation may elucidate the actual reasons why counsellees declined testing.

4.3.1 *BRCA* mutations identified

As 74% of *BRCA* mutation testing performed was targeted Ashkenazi Jewish and Afrikaner testing (Figure 3.6), it is not surprising that of the 49 *BRCA* positive families included in this study, the top three mutations identified were the *BRCA1* mutations 185delAG and 5382insC and the *BRCA2* mutation, 6174delT, all Ashkenazi Jewish founder *BRCA* mutations, followed by the Afrikaner *BRCA2* mutation 8162delG in joint third place (Table 3.1). Many of the other *BRCA* mutations identified (Table 3.1) were only found once each in the cohort, supporting the fact that many *BRCA* mutations are individually rare (Walsh et al., 2006).

4.4 *BRCA1/2* AND ASSOCIATED CANCERS

The major risk conferred by *BRCA1* and *BRCA2* on women is for cancer of the breast and ovaries. However, carriers of mutations in either of these genes are also at risk of developing other cancers including cancer of the prostate, stomach and pancreas (Table 1.3). A history of "other cancers" was reported in the 114 families in the study that were not known to be *BRCA* positive. These families cannot be called *BRCA* negative as some of them may in fact be *BRCA* positive, but have not yet pursued testing. Comparing "other cancers" in the mentioned 114 families to the 49 confirmed *BRCA* positive families would therefore not be a true comparison. It would be ideal to compare *BRCA* positive and *BRCA* negative families.

In this study prostate and stomach cancer were the most frequently observed "other cancers" in the 49 *BRCA* positive families (Figure 3.8). This is in line with *BRCA*-associated cancers reported in the literature. A clinic-based study of *BRCA1* families identified cancers that were significantly associated with *BRCA1* carriers, including colon, pancreatic and gastric cancer (Brose, Rebbeck, Calzone et al., 2002). A cohort study by the Breast Cancer Linkage Consortium (BCLC), based on 11,847 individuals from 699 *BRCA1* mutation positive families, also found an increased risk for pancreatic cancer (Thompson, Easton & The Breast Cancer Linkage Consortium, 2002). A study by the BCLC in 1999 showed a correlation between *BRCA2* mutation carriers and an increased risk for pancreatic, prostate, stomach, gallbladder and bile duct cancer as well as melanoma of the skin and eye (Kerr et al., 2010).

In the current study colon cancer was in the top five other cancers of the *BRCA* positive families; however, the link between *BRCA1/2* mutation carriers and colon cancer is controversial, with limited evidence for an association between the two (Thompson et al., 2002; Kerr et al., 2010). Further research, especially on larger samples, is needed to elucidate whether there is an association between colon cancer and *BRCA* mutation carriers. There may be modifying factors, such as diet, that contribute to the increased prevalence of colon cancer in *BRCA* positive individuals amongst some populations. However, the prevalence of "other cancers" in this study may also simply be a reflection of the background incidence of these cancers in the general population.

4.5 ARE THE AIMS OF CANCER RISK ASSESSMENT AND COUNSELLING BEING ATTAINED?

The goals of a genetic counselling session include: increasing patient knowledge and understanding of a genetic condition, assessing and conferring risks, facilitating decision-making, providing support and empowering patients so that they feel in control (Meiser, Irle, Lobb et al., 2008). The aim of the telephonic questionnaire was to assess whether the genetic counselling service for breast and/or ovarian cancer offered by the Division of Human Genetics, WITS and NHLS, is achieving these goals.

4.5.1 Risk perception

Risk is a central theme in the context of genetic counselling for inherited breast and/or ovarian cancer: individuals are referred for genetic counselling if they are thought to be at risk for cancer and are subsequently only offered testing if they are calculated to be at a high or moderate to high risk based on risk assessment tools. Individuals differ in how they interpret their assessed risks, with many factors contributing to their perception of their risk. One of the respondents of the telephonic questionnaire stated that attending genetic counselling and being informed of one's risk for breast and/or ovarian cancer was "pointless" as she felt that there was nothing one could do to change the risk. Armstrong et al. (2003) comments that individuals have difficulties in realising the potential benefits of something that is preventative

in nature as the rewards are often delayed, intangible and the unwanted event may not happen anyway, which may be the case for this respondent.

The accuracy of perceived risk can impact an individual's screening practices for breast and/or ovarian cancer as well as their feelings of anxiety and their coping mechanisms (Smerecnik, Mesters, Verweij et al., 2009; Quillin, Bodurtha, McClish et al., 2011). It is well documented that most women tend to overestimate their risk for developing breast cancer (Quillin et al., 2011). However, contrary to other research findings, when the telephonic respondents were asked to recall the risk category that they were classified into, 36% recalled the correct risk category and not a single respondent reported a risk category higher than the one they were classified into (Figure 3.11). A further 10% of respondents recalled a risk category lower than the one they were classified into and 28% could not recall which category they were classified into (Figure 3.11).

A retrospective study by Vos, Oosterwijk, Gomez-Garcia et al. (2011) analysed the recollections and interpretations of breast cancer risk and the likelihood of the cancer being hereditary among women who had been tested for a *BRCA* mutation. They found that the majority of women could not recall the numerical risk (percentage risk) they had been given in the genetic counselling session. In addition, they observed discrepancies between the risks that the women recollected and their perception of that risk. The authors therefore suggested that risk information be presented in categories rather than percentages and that this risk information be tailored to the counsellee in order to improve the accuracy of the counsellee's risk perception. At the Genetic Counselling Clinics at the Division of Human Genetics, WITS and the NHLS in Johannesburg inherited breast and/or ovarian cancer risks are presented to counsellees as categories, not as numbers (Section 1.6.3). This may then explain why the majority of respondents (74%) in this study stated that genetic counselling clarified their understanding of their risks (Table 3.3).

In summary, studies have shown that counsellees tend to have a better understanding of cancer risks after attending genetic counselling (Meiser & Halliday, 2002) which appears to be the case in this study. The risks are clearly communicated in the genetic counselling session as

well as in the summary letter that is sent to each counsellee after the session. In a study by Lobb et al. (2004) that assessed the influence of genetic counselling on high risk breast cancer patients, effective communication and the provision of a summary letter was shown to lead to improved knowledge, more accurate perception of risk and lower anxiety and depression. The results are therefore encouraging and suggest effective communication within the current system.

4.5.2 Understanding of information received

Eighty six percent of respondents of the telephonic questionnaire stated that genetic counselling clarified their understanding of the genetics of breast and/or ovarian cancer (Table 3.3). A study by Kwiatkowski, Dessenne, Laquet et al. (2012) that analysed the retention of information given during oncogenic counselling showed that counsellee's knowledge of hereditary predisposition to breast/ovarian and/or colon cancer improved after genetic counselling and did not deteriorate over time. Genetic counselling is therefore essential in educating women on the genetics of breast and/or ovarian cancer.

Interestingly, although 72% of respondents stated that genetic counselling clarified their understanding of surveillance for breast and/or ovarian cancer (Table 3.3), none of the respondents changed their screening measures after their consultation and only 38% made lifestyle changes. Many of the respondents (34%) commented that they were already vigilant about screening. It is reasonable to assume that individuals with a personal or family history of breast and/or ovarian cancer, such as those in the current study, are more likely to be aware of the importance of screening in the prevention of breast and/or ovarian cancer. On the other hand, the respondents' awareness of screening for breast and/or ovarian cancer may be due to the increased media focus on breast cancer and the importance of self-breast examination and annual mammograms.

Of those respondents who did make lifestyle changes after genetic counselling (19/50, 38%), only 10 chose to have surgery. Two respondents chose to have a salpingo-oophorectomy, only one of whom was *BRCA* positive and the other was of European descent and had elected not to

have international testing but had surgery anyway based on family history. Four respondents chose to have mastectomies, only one of whom had tested *BRCA* positive. This study mirrors that of Julian-Reynier, Mancini, Mouret-Fourme et al. (2011) that analysed the cancer risk strategies of unaffected carriers and non-carriers of a *BRCA* mutation five years after predictive *BRCA*1/2 testing. In their study, of the *BRCA1/2* carriers only 38% chose to have a risk reducing salpingo oophorectomy in conjunction with breast surveillance and only 2% opted for risk reducing mastectomy alone.

One area of this study that is of concern is the recollection of screening information. When asked what the counsellor told them about screening or surgery for breast and/ or ovarian cancer there was an observed overall poor recollection of facts. Twenty four percent of respondents could not recall if the counsellor had informed them about screening and four respondents commented that they could not remember what they were told (Section 3.6.3). It would appear that individuals require more assistance in complying with screening for breast and/or ovarian cancer. Kwiatkowski et al. (2012) also noted in their study that patients' retention of screening and surgery measures did decrease over time and therefore necessitated follow up. It may also be helpful to identify what screening the counsellee's doctor has recommended so that the genetic counsellor and doctor can work together to ensure adherence to screening measures.

4.6 HOW IS THE GENETIC COUNSELLING SERVICE RECEIVED?

A major component of this study was to identify how genetic counselling was received by individuals attending the Genetic Counselling Clinics. The fact that 94% of respondents said they would refer individuals to the service, and no one said they would not refer to the service, is testament to the value of the service offered through the Genetic Counselling Clinics of the Division of Human Genetics, WITS and the NHLS. In addition, the number of positive comments regarding the service far outweighed the negative comments (Section 3.7.1).

When the respondents of the telephonic questionnaire were asked why they would refer to genetic counselling the most common reason given was for increased knowledge about the genetics of breast and/or ovarian cancer. Respondents commented that attending genetic

counselling and becoming educated on the genetics of breast and/or ovarian cancer empowered them to make timeous informed decisions. Studies have shown that the main motivating factor for individuals to seek genetic counselling is to gather information on risks, testing options and surveillance options (Roshanai et al., 2011). A number of individuals (13/50, 26%) also stated that they would refer someone with a family history of breast and/or ovarian cancer or someone from a high risk population group such as Ashkenazi Jewish.

Genetic counsellors are not only trained to educate individuals on the genetic basis of a disease in a manner that is appropriate and comprehensible to the counsellee, but also to create an atmosphere that is empathic, caring and non-judgmental (Egan, 2002). Genetic counsellors therefore need to possess certain qualities such as empathy and compassion in order to effectively perform their role. The results of the telephonic questionnaire suggest that the genetic counsellors of the Division of Human Genetics, WITS and NHLS, possess these qualities. The respondents commented positively on the characteristics of the genetic counsellors themselves as well as the environment the counsellors created in the genetic counselling session. Respondents found the genetic counsellors engaging and honest (Figure 3.13). They also felt that the counsellors created a comfortable atmosphere and attended to emotional issues that arose, not just focusing on information giving. Attending to emotional issues can assist in reducing counsellee anxiety levels. High levels of anxiety have been shown to interfere with understanding risks and an inclination towards radical preventative mastectomy (Meiser & Halliday, 2002).

Genetic counsellors are trained to give results according to a six step protocol that was devised for clinicians to assist them in breaking bad news to cancer patients. Step two of the six steps involves assessing how the patient perceives their medical situation before discussing any test results or medical findings (Baile, Buckman, Lenzi et al., 2000). This is done in order to tailor the result giving to the patient and their understanding of their medical situation. However, a couple of respondents of the telephonic questionnaire commented that at the result-giving session it felt as though there was too much “small talk” before they received their results, leading to increased anxiety. In the future, it may be more beneficial for the counsellee to receive their results up front as opposed to later in the session to relieve any anxiety the

counsellee may be feeling. Counsellors may therefore need to reassess how they give results and tailor the genetic counselling to the counsellee. The same procedure may not apply to all counsellees as some counsellees may find "small talk" reassuring prior to being given their results. Therefore, gaining a good understanding of the personality of a counsellee may help a counsellor adapt how they break news.

4.6.1.1 Follow up service

Two respondents suggested a follow up service be implemented whereby the counsellor contacts the counsellee a year after the last consultation just to keep in touch and to update the counsellee when new testing options become available. In the UK, the Breast Screening Programme was established by the NHS in 1987, following the recommendations suggested in The Forrest Report (Forrest, 1986). Women eligible for routine breast cancer screening are identified through a GP's database. Computerised invitations are then sent out to these eligible women for both the initial and subsequent visits (Forrest, 1986). However, in Johannesburg, SA, such a system does not exist and there are a number of limitations to the implementation of a follow up service including limited staff resources and the problem of counsellees' contact numbers changing over time. Staff shortages within the Division of Human Genetics may make a follow up service improbable at this time. However, should circumstances change in the future, a follow up service would be ideal to assess how counsellees are coping with their risks, whether they are following recommended screening and whether further genetic counselling is warranted.

4.7 LIMITATIONS

In terms of the data collection methods, a limitation of this study was that not all of the counselling files could be obtained and were therefore not included in the research. This study was based on the files of individuals attending genetic counselling through the Genetic Counselling Clinics of the Division of Human Genetics, WITS and the NHLS and therefore the information collected only pertains to individuals counselled in Johannesburg. It is therefore not a national representation of individuals attending genetic counselling for breast and/or ovarian cancer. In addition, the results of the telephonic questionnaire represent only 50

individuals and therefore cannot be extrapolated to all individuals counselled for inherited breast and/or ovarian cancer either in Johannesburg or nationally. Being file-based, information recorded in the files may have been inaccurate or incomplete. The study sample is biased towards counsellees at a high risk for inherited breast and/or ovarian cancer and this may have influenced their responses to the telephonic questionnaire.

4.8 SUMMARY OF FINDINGS

The study aimed to assess who uses the genetic counselling service for breast and/or ovarian cancer, why they use it and the *BRCA* mutation testing that is currently offered. In addition, the telephonic questionnaire aimed to assess how the service is received by those individuals who attended genetic consultations. Based on the results of the study, all of the aims were achieved. In summary, the following findings were made:

- Most individuals are self-referred to the Genetic Counselling Clinics.
- The majority of individuals counselled are white. Black, coloured and Asian individuals are underrepresented in the Genetic Counselling Clinics. Ashkenazi Jewish and Afrikaner individuals are overrepresented.
- The main reasons for individuals attending are to gather information, determine their risks of having a cancer syndrome and for *BRCA* mutation testing.
- Most individuals attend counselling sessions alone.
- Most of the counsellees have not been diagnosed with cancer but rather have a family history of breast and/or ovarian cancer.
- The majority of individuals counselled for breast and/or ovarian cancer are at a high to moderate to high risk for inherited breast and/or ovarian cancer.
- Prostate and stomach cancer were the most frequently observed "other cancers" in the *BRCA* positive families.
- The majority of *BRCA* mutation testing offered is nationally based testing; mostly for the Ashkenazi Jewish and Afrikaner founder mutations. The cost of testing does not appear to be a limiting factor when the testing is performed nationally and when the counsellee belongs to a medical aid scheme. However, the uptake of international testing is limited, with cost being a potential contributing factor.
- The study shows that overall the genetic counselling service offered for breast and/or ovarian cancer by the Division of Human Genetics, WITS and the NHLS, is viewed in a positive light by counsellees and therefore it can be said that the Division is providing a valuable and effective service to the appropriate patients.
- Genetic counselling is effective in conveying the necessary information in a manner that is comprehensible for patients.

4.9 RECOMMENDATIONS

Based on the findings of this study, the following recommendations can be made:

- There is a need to more adequately educate medical professionals on the genetic counselling service that is available for breast and/or ovarian cancer. This may be achieved through lectures or workshops, particularly aimed at GPs as they have primary contact with the patients and their families.
- Members of the Division of Human Genetics, WITS and the NHLS, need to market the genetic counselling service more effectively to the general public.
- There is a need to increase the number of referrals of individuals with a moderate risk of inherited breast and/or ovarian cancer or with a less striking family history or breast and/or ovarian cancer.
- There is a need to educate doctors on the influence of the Afrikaner heritage in coloured patients as the coloured population of Johannesburg is underrepresented in the Genetic Counselling Clinics for breast and/or ovarian cancer.
- Future molecular research is needed in the Asian and South African black populations, to hopefully identify founder breast and/or ovarian cancer predisposing gene mutations.
- A larger study, following on from the results of the telephonic survey from this study, will be beneficial to more accurately assess how the genetic counselling service is received by counsellees attending the Genetic Counselling Clinics of the Division of Human Genetics, WITS and the NHLS. A qualitative analysis on patients' experiences would be also be valuable.
- A follow up service for those individuals who attended genetic counselling for breast and/or ovarian cancer could be beneficial in the long term. It may be useful to implement the UK database method. This type of proactive identification of women eligible for screening has the potential to reduce breast cancer mortality rates and therefore, although not feasible at this time due to staff and resource shortages, would be suggested as a long term goal in South Africa.
- It would be ideal to offer full *BRCA* sequencing and MLPA to counsellees nationally, as national testing is covered, to certain extents, by medical aids.

- It may be beneficial to assess how counsellees attending genetic counselling for other conditions view the service.

CHAPTER 5 CONCLUSIONS AND FUTURE RESEARCH

The study aimed to assess who uses the genetic counselling service for breast and/or ovarian cancer, why they use it and the *BRCA* mutation testing that is currently offered. Furthermore, the service received by those individuals who attended counselling services was also assessed. This is the first study that has reviewed the counsellees attending the Genetic Counselling Clinics of the Division of Human Genetics, WITS and the NHLS, in Johannesburg for breast and/or ovarian cancer counselling.

The study's findings showed that testing is currently mainly offered to the Ashkenazi Jewish and Afrikaner populations. Individuals with European heritage are limited to testing overseas, which is expensive. Testing is also limited in the black, coloured and Asian populations of South Africa as little research has been performed on the disease predisposing mutations within these population groups. Individuals from these population groups would benefit from genetic counselling and risk assessment even if testing is not available at the present time. Knowledge on appropriate screening for breast and/or ovarian cancer empowers individuals to make informed decisions about their health.

The results of the telephonic questionnaire showed that the vast majority of counsellees were satisfied with the genetic counselling service they received. Counsellees left the session with an increased knowledge of their risks for and the genetics of inherited breast and/or ovarian cancer. However, the sample size in this study was relatively small and although many positive comments were made about the service, these results cannot be extrapolated to all individuals attending genetic counselling.

Overall, through patient comments and few doctor referrals, the study pointed to the general lack of understanding and public awareness of genetic counselling. However, the number of individuals counselled at the clinics has steadily increased over the years, dropping only slightly in 2010. It can be suggested that more effective marketing of the genetic counselling service to the general public and to other medical professionals is imperative in order to reach more individuals who may be at high or even moderate risk of inherited breast and/or ovarian

cancer. Moderate risk individuals will benefit from genetic counselling as their risks can be defined and appropriate screening can be recommended.

The study identified a number of opportunities for further research including assessment of how the genetic counselling service is received by a larger sample of counsellees in order to highlight where the service requires improvement. In addition, further research into the predisposition of gene mutations in black and Asian populations is recommended so that these individuals can also be offered the appropriate genetic counselling and testing in the future.

On a practical level, a follow up service was suggested by a number of respondents. A follow up service would be beneficial in ensuring counsellees adhered to screening measures, informing counsellees on changes to testing protocols and identifying family members who may be at an increased risk of inherited breast and/or ovarian cancer. Although not feasible at this time, due to staff constraints, it should be a future goal of the Genetic Counselling Unit.

Genetic Counselling is an integral part of the medical field. Without it many individuals would be uninformed and unaware of their risks of developing a genetic condition. Early detection and implementation of preventative measures has the potential to save lives. This study has shown that genetic counselling is effective and is well received by those who utilise it. By educating individuals on their risks and options, they are able to make informed, potentially life changing, decisions.

CHAPTER 6 REFERENCE LIST

Althuis, M. D., Dozier, J. M., Anderson, W. F., Devesa, S. S., & Brinton, L. A. (2005). Global trends in breast cancer incidence and mortality 1973–1997. *International Journal of Epidemiology, 34*(2), 405-412.

American Society of Human Genetics Ad Hoc Committee on Genetic Counseling. (1975). Genetic Counseling. *American Journal of Human Genetics, 27*, 240-242.

Amir, E., Freedman, O. C., Seruga, B., & Evans, D. G. (2010). Assessing Women at High Risk of Breast Cancer: A Review of Risk Assessment Models. *Journal of the National Cancer Institute, 102*(10), 680-691.

Armstrong, K., Weiner, J., Weber, B., & Asch, D. A. (2003). Early adoption of BRCA1/2 testing: who and why. *Genetics in Medicine, 5*(2), 92-98.

Baile, W. F., Buckman, R., Lenzi, R., Glober, G., Beale, E. A., & Kudelka, A. P. (2000). SPIKES-A six-step protocol for delivering bad news: application to the patient with cancer. *Oncologist, 5*(4), 302-311.

Bast, R. C., Jr., Hennessy, B., & Mills, G. B. (2009). The biology of ovarian cancer: new opportunities for translation. *Nature Reviews: Cancer, 9*(6), 415-428.

Braithwaite, D., Emery, J., Walter, F., Prevost, A. T., & Sutton, S. (2004). Psychological impact of genetic counseling for familial cancer: a systematic review and meta-analysis. *Journal of the National Cancer Institute, 96*(2), 122-133.

Brose, M. S., Rebbeck, T. R., Calzone, K. A., Stopfer, J. E., Nathanson, K. L., & Weber, B. L. (2002). Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. *Journal of the National Cancer Institute, 94*(18), 1365-1372.

Bruno, M., Digennaro, M., Tommasi, S., Stea, B., Danese, T., Schittulli, F. et al. (2010). Attitude towards genetic testing for breast cancer susceptibility: a comparison of affected and unaffected women. *European Journal of Cancer Care (Engl), 19*(3), 360-368.

Campbell, N. A., Reece, J. B., & Simon, E. J. (2004). The Cellular Basis of Reproduction and Inheritance *Essential Biology with Physiology* (pp. 127-127). San Francisco: Pearson Benjamin Cummings.

Chand, M., Moore, P. J., Clarke, A. D., Nash, G. F., & Hickisk, T. (2007). A diagnostic dilemma following risk-reducing surgery for BRCA1 mutation – a case report of primary papillary serous carcinoma presenting as sigmoid cancer. *World Journal of Surgical Oncology, 5*(1), 102-102.

Chen, V. W., Ruiz, B., Killeen, J. L., Cote, T. R., Wu, X. C., & Correa, C. N. (2003). Pathology and classification of ovarian tumors. *Cancer, 97*(10 Suppl), 2631-2642.

Claus, E. B., Risch, N., & Thompson, W. D. (1994). Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer, 73*(3), 643-651.

Collaborative Group on Hormonal Factors in Breast Cancer. (2001). Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet, 358*(9291), 1389-1399.

Collins, V., Halliday, J., Kahler, S., & Williamson, R. (2001). Parents' experiences with genetic counseling after the birth of a baby with a genetic disorder: An exploratory study. *Journal of Genetic Counseling, 10*(1), 53-72.

de Wit, E., Delport, W., Rugamika, C. E., Meintjes, A., Möller, M., van Helden, P. D. et al. (2010). Genome-wide analysis of the structure of the South African Coloured population in the Western Cape. *Human Genetics, 128*(2), 145-153.

del Valle, J., Feliubadaló, L., Nadal, M., Teulé, A., Miró, R., Cuesta, R. et al. (2010). Identification and comprehensive characterization of large genomic rearrangements in the BRCA1 and BRCA2 genes. *Breast Cancer Research and Treatment, 122*(3), 733-743.

Den Dunnen, J. T., & Van Ommen, G. J. B. (1999). The protein truncation test: A review. *Human Mutation, 14*(2), 95-102.

Duric, V., Butow, P., Sharpe, L., Lobb, E., Meiser, B., Barratt, A. et al. (2003). Reducing Psychological Distress in a Genetic Counseling Consultation for Breast Cancer. *Journal of Genetic Counseling, 12*(3).

Easton, D. F., Ford, D., & Bishop, D. T. (1995). Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *American Journal of Human Genetics, 56*(1), 265-271.

Egan, G. (2002). *The Skilled Helper: A problem-management and opportunity-development approach to helping* (7th ed.). United States of America: Brooks/Cole.

Eisen, A., Lubinski, J., Klijn, J., Moller, P., Lynch, H. T., Offit, K. et al. (2005). Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. *Journal of Clinical Oncology, 23*(30), 7491-7496.

Ellington, L., Baty, B. J., McDonald, J., Venne, V., Musters, A., Roter, D. et al. (2006). Exploring genetic counseling communication patterns: the role of teaching and counseling approaches. *Journal of Genetic Counseling, 15*(3), 179-189.

Ellington, L., Roter, D., Dudley, W. N., Baty, B. J., Upchurch, R., Larson, S. et al. (2005). Communication analysis of BRCA1 genetic counseling. *Journal of Genetic Counseling, 14*(5), 377-386.

Elston, C. W., & Ellis, I. O. (1991). pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology, 19*(5), 403-410.

Evans, D. G., Lalloo, F., Cramer, A., Jones, E. A., Knox, F., Amir, E. et al. (2009). Addition of pathology and biomarker information significantly improves the performance of the Manchester scoring system for BRCA1 and BRCA2 testing. *Journal of Medical Genetics, 46*(12), 811-817.

Evans, D. G. R., Eccles, D. M., Rahman, N., Young, K., Bulman, M., Amir, E. et al. (2004). A new scoring system for the chances of identifying a BRCA1/2 mutation outperforms existing models including BRCAPRO. *Journal of Medical Genetics, 41*(6), 474-480.

Evans, D. G. R., & Howell, A. (2007). Breast cancer risk-assessment models. *Breast Cancer Research: BCR, 9*(5), 213-213.

Evans, D. G. R., Kerr, B., & Lalloo, F. (2006). Risk estimation in breast cancer *Risk Assessment and Management in Cancer Genetics* (pp. 47-64). Great Britain: Oxford University Press.

Evans, D. G. R., Moller, P., & Kerr, B. (2005). Principles and applications of gene testing for common cancers *Risk Assessment and Management in Cancer Genetics* (pp. 31-46). Great: Oxford University Press.

Finch, A., Beiner, M., Lubinski, J., Lynch, H. T., Moller, P., Rosen, B. et al. (2006). Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women

with a BRCA1 or BRCA2 Mutation. *Journal of the American Medical Association, 296*(2), 185-192.

FitzGerald, M. G., MacDonald, D. J., Krainer, M., Hoover, I., O'Neil, E., Unsal, H. et al. (1996). Germ-line BRCA1 mutations in Jewish and non-Jewish women with early-onset breast cancer. *New England Journal of Medicine, 334*(3), 143-149.

Gerber, B., Krause, A., Reimer, T., Müller, H., Küchenmeister, I., Makovitzky, J. et al. (2003). Skin-Sparing Mastectomy with Conservation of the Nipple–Areola Complex and Autologous Reconstruction is an Oncologically Safe Procedure. *Annals of Surgery, 238*(1), 120-127.

Haites, N., & Gregory, H. (2002). Overview of the clinical genetics of breast cancer *Familial Breast and Ovarian Cancer* (pp. 6-21): Cambridge Universoty Press.

Hall, J. M., Lee, M. K., Newman, B., Morrow, J. E., Anderson, L. A., Huey, B. et al. (1990). Linkage of early-onset familial breast cancer to chromosome 17q21. *Science (New York, N.Y.), 250*(4988), 1684-1689.

Hamilton, A., & Piccart, M. (2000). The contribution of molecular markers to the prediction of response in the treatment of breast cancer: A review of the literature on HER-2, p53 and BCL-2. *Annals of Oncology, 11*(6), 647-663.

Harper, P. S. (2004). *Practical Genetic Counselling* (Sixth ed.). London: Arnold.

Heintz, A. P., Odicino, F., Maisonneuve, P., Beller, U., Benedet, J. L., Creasman, W. T. et al. (2001). Carcinoma of the ovary. *Journal of Epidemiology and Biostatistics, 6*(1), 107-138.

Hogervorst, F. B. L., Cornelis, R. S., Bout, M., Vliet, M. v., Oosterwijk, J. C., Olmer, R. et al. (1995). Rapid detection of BRCA1 mutations by the protein truncation test. *Nature Genetics, 10*, 208-212.

Hulka, B. S., & Moorman, P. G. (2001). Breast cancer: hormones and other risk factors. *Maturitas, 38*(1), 103-113; discussion 113-106.

Hunn, J., & Rodriguez, G. C. (2012). Ovarian cancer: etiology, risk factors, and epidemiology. *Clinical Obstetrics and Gynecology, 55*(1), 3-23.

Imbs, J. (2010). The First Global Recession in Decades. *IMF Economic Review, 58*(2), 327-354.

Jemal, A., Bray, F., Center, M. M., Ferlay, J., Ward, E., & Forman, D. (2011). Global cancer statistics. *CA: A Cancer Journal for Clinicians, 61*(2), 69-90.

Jenkins, T. (1990). Medical genetics in South Africa. *Journal of Medical Genetics, 27*(12), 760-779.

Jenkins, T., Wilton, E., Bernstein, R., & Nurse, G. T. (1973). The genetic counselling clinic at a children's hospital. *South African Medical Journal, 47*, 1834-1838.

Julian-Reynier, C., Mancini, J., Mouret-Fourme, E., Gauthier-Villars, M., Bonadona, V., Berthet, P. et al. (2011). Cancer risk management strategies and perceptions of unaffected women 5 years after predictive genetic testing for BRCA1/2 mutations. *European Journal of Human Genetics: EJHG, 19*(5), 500-506.

Kauff, N. D., Domchek, S. M., Friebel, T. M., Robson, M. E., Lee, J., Garber, J. E. et al. (2008). Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. *Journal of Clinical Oncology, 26*(8), 1331-1337.

Kauff, N. D., Satagopan, J. M., Robson, M. E., Scheuer, L., Hensley, M., Hudis, C. A. et al. (2002). Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *New England Journal of Medicine, 346*(21), 1609-1615.

Kerr, B., Lalloo, F., Clancy, T., & Evans, G. (2010). The Manchester Clinical Guide to Cancer Genetics: Genetic Medicine, St Mary's Hospital, Manchester, UK.

Kromberg, J. G., Sizer, E. B., & Christianson, A. L. (2012). Genetic services and testing in South Africa. *Journal of Community Genetics*

Kwiatkowski, F., Dessenne, P., Laquet, C., Petit, M. F., & Bignon, Y. J. (2012). Permanence of the information given during oncogenetic counseling to persons at familial risk of breast/ovarian and/or colon cancer. *European Journal of Human Genetics: EJHG, 20*(2), 141-147.

Lancaster, J. M., Cochran, C. J., Brownlee, H. A., Evans, A. C., Berchuck, A., Futreal, P. A. et al. (1996). Detection of BRCA1 Mutations in Women With Early-Onset Ovarian Cancer by Use of the Protein Truncation Test. *Journal of the National Cancer Institute, 88*(8), 552-554.

Landen, C. N., Birrer, M. J., & Sood, A. K. (2008). Early Events in the Pathogenesis of Epithelial Ovarian Cancer. *Journal of Clinical Oncology, 26*(6), 995-1005.

Lobb, E. A., Butow, P. N., Barratt, A., Meiser, B., Gaff, C., Young, M. A. et al. (2004). Communication and information-giving in high-risk breast cancer consultations: influence on patient outcomes. *British Journal of Cancer, 90*(2), 321-327.

Lynch, B. J., Holden, J. A., Buys, S. S., Neuhausen, S. L., & Gaffney, D. K. (1998). Pathobiologic characteristics of hereditary breast cancer. *Human Pathology, 29*(10), 1140-1144.

Macaulay, S., Gregersen, N., & Krause, A. (2012). Uptake of genetic counselling services by patients with cystic fibrosis and their families. *South African Family Practice, 54*(3), 250-255.

McCarthy Veach, P., Leroy, B. S., & Bartels, D. M. (2003). *Facilitating the Genetic Counselling Process*. United States of America: Springer.

Meiser, B., & Halliday, J. L. (2002). What is the impact of genetic counselling in women at increased risk of developing hereditary breast cancer? A meta-analytic review. *Social Science and Medicine, 54*(10), 1463-1470.

Meiser, B., Irle, J., Lobb, E., & Barlow-Stewart, K. (2008). Assessment of the content and process of genetic counseling: a critical review of empirical studies. *Journal of Genetic Counseling, 17*(5), 434-451.

Miki, Y., Swensen, J., Shattuck-Eidens, D., Futreal, P. A., Harshman, K., Tavtigian, S. et al. (1994). A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science (New York, N.Y.), 266*(5182), 66-71.

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.

Nagy, R., Sweet, K., & Eng, C. (2004). Highly penetrant hereditary cancer syndromes. *Oncogene, 23*(38), 6445-6470.

Nelson, H. D., Huffman, L. H., Fu, R., & Harris, E. L. (2005). Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility: Systematic Evidence Review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine, 143*(5), 362-379.

Neuhausen, S., Gilewski, T., Norton, L., Tran, T., McGuire, P., Swensen, J. et al. (1996). Recurrent BRCA2 6174delT mutations in Ashkenazi Jewish women affected by breast cancer. *Nature Genetics, 13*(1), 126-128.

Neuhausen, S. L. (1999). Ethnic differences in cancer risk resulting from genetic variation. *Cancer, 86*(11 Suppl), 2575-2582.

Oddoux, C., Struewing, J. P., Clayton, C. M., Neuhausen, S., Brody, L. C., Kaback, M. et al. (1996). The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%. *Nature Genetics, 14*(2), 188-190.

Peters, K. F., & Petrill, S. A. (2011). A comparison of the background, needs, and expectations of patients seeking genetic counseling services. *American Journal of Medical Genetics Part A, 155A*(4), 697-705.

Pieterse, A. H., Ausems, M. G. E. M., Van Dulmen, A. M., Beemer, F. A., & Bensing, J. M. (2005). Initial cancer genetic counseling consultation: Change in counselees' cognitions and anxiety, and association with addressing their needs and preferences. *American Journal of Medical Genetics Part A, 137A*(1), 27-35.

Pieterse, A. H., van Dulmen, A. M., Beemer, F. A., Bensing, J. M., & Ausems, M. G. (2007). Cancer genetic counseling: communication and counselees' post-visit satisfaction, cognitions, anxiety, and needs fulfillment. *Journal of Genetic Counseling, 16*(1), 85-96.

Quillin, J. M., Bodurtha, J. N., McClish, D., & Wilson, D. B. (2011). Genetic risk, perceived risk, and cancer worry in daughters of breast cancer patients. *Journal of Genetic Counseling, 20*(2), 157-164.

Rebbeck, T. R., Friebel, T., Lynch, H. T., Neuhausen, S. L., van 't Veer, L., Garber, J. E. et al. (2004). Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *Journal of Clinical Oncology, 22*(6), 1055-1062.

Rebbeck, T. R., Lynch, H. T., Neuhausen, S. L., Narod, S. A., Van't Veer, L., Garber, J. E. et al. (2002). Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *New England Journal of Medicine, 346*(21), 1616-1622.

Reed, S. C. (1975). A short history of genetic counseling. *Social Biology, 21*, 332-339.

Reeves, M. D., Yawitch, T. M., van der Merwe, N. C., van den Berg, H. J., Dreyer, G., & van Rensburg, E. J. (2004). BRCA1 mutations in South African breast and/or ovarian cancer families: evidence of a novel founder mutation in Afrikaner families. *International Journal of Cancer, 110*(5), 677-682.

Resta, R., Biesecker, B. B., Bennett, R. L., Blum, S., Hahn, S. E., Strecker, M. N. et al. (2006). A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. *Journal of Genetic Counseling, 15*(2), 77-83.

Resta, R. G. (1997). The Historical Perspective: Sheldon Reed and 50 Years of Genetic Counseling. *Journal of Genetic Counseling, 6*(4), 375-377.

Ripperger, T., Gadzicki, D., Meindl, A., & Schlegelberger, B. (2009). Breast cancer susceptibility: current knowledge and implications for genetic counselling. *European Journal of Human Genetics: EJHG, 17*(6), 722-731.

Roa, B. B., Boyd, A. A., Volcik, K., & Richards, C. S. (1996). Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nature Genetics, 14*(2), 185-187.

Roshanai, A. H., Lampic, C., Ingvoldstad, C., Askmalm, M. S., Bjorvatn, C., Rosenquist, R. et al. (2011). What information do cancer genetic counselees prioritize? *Journal of Genetic Counseling*.

Sanger, F., Nicklen, S., & Coulson, A. R. (1977). DNA sequencing with chain-terminating inhibitors. *Proceedings of the National Academy of Sciences of the United States of America, 74*(12), 5463-5467.

Shattuck-Eidens, D., McClure, M., Simard, J., Labrie, F., Narod, S., Couch, F. et al. (1995). A collaborative survey of 80 mutations in the BRCA1 breast and ovarian cancer susceptibility gene. Implications for presymptomatic testing and screening. *Journal of the American Medical Association, 273*(7), 535-541.

Simon, M. S., & Petrucelli, N. (2009). Hereditary breast and ovarian cancer syndrome : the impact of race on uptake of genetic counseling and testing. *Methods in Molecular Biology, 471*, 487-500.

Smerecnik, C. M., Mesters, I., Verweij, E., de Vries, N. K., & de Vries, H. (2009). A systematic review of the impact of genetic counseling on risk perception accuracy. *Journal of Genetic Counseling, 18*(3), 217-228.

Smith, A. C. M. (1998). Patient education *A Guide to Genetic Counselling* (pp. 99-199). Canada: Wiley-Liss Inc.

Smith, R. A., Saslow, D., Sawyer, K. A., Burke, W., Costanza, M. E., Evans, W. P., 3rd et al. (2003). American Cancer Society guidelines for breast cancer screening: update 2003. *CA: A Cancer Journal for Clinicians, 53*(3), 141-169.

Struewing, J. P., Abeliovich, D., Peretz, T., Avishai, N., Kaback, M. M., Collins, F. S. et al. (1995). The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. *Nature Genetics, 11*(2), 198-200.

Struewing, J. P., Brody, L. C., Erdos, M. R., Kase, R. G., Giambarresi, T. R., Smith, S. A. et al. (1995). Detection of eight BRCA1 mutations in 10 breast/ovarian cancer families, including 1 family with male breast cancer. *American Journal of Human Genetics, 57*(1), 1-7.

Struewing, J. P., Hartge, P., Wacholder, S., Baker, S. M., Berlin, M., McAdams, M. et al. (1997). The Risk of Cancer Associated with Specific Mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *The New England Journal of Medicine, 336*(20), 1401-1408.

Thompson, D., Easton, D. F., & The Breast Cancer Linkage Consortium. (2002). Cancer Incidence in BRCA1 Mutation Carriers. *Journal of the National Cancer Institute, 94*(18), 1358-1365.

Trepanier, A., Ahrens, M., McKinnon, W., Peters, J., Stopfer, J., Grumet, S. C. et al. (2004). Genetic Cancer Risk Assessment and Counseling: Recommendations of the National Society of Genetic Counselors. *Journal of Genetic Counseling, 13*(2), 83-114.

van Asperen, C. J., van Dijk, S., Zoeteweij, M. W., Timmermans, D. R. M., de Bock, G. H., Meijers-Heijboer, E. J. et al. (2002). What do women really want to know? Motives for attending familial breast cancer clinics. *Journal of Medical Genetics, 39*(6), 410-414.

van der Merwe, N. C., Hamel, N., Schneider, S. R., Apffelstaedt, J. P., Wijnen, J. T., & Foulkes, W. D. (2012). A founder BRCA2 mutation in non-Afrikaner breast cancer patients of the Western Cape of South Africa. *Clinical Genetics, 81*(2), 179-184.

van der Merwe, N. C., & Jansen van Rensburg, E. (2009). P017 Hereditary Breast/Ovarian Cancer and BRCA Mutations: A South African Perspective. *Current Oncology, 16*(5), 91-110.

van der Westhuizen, A. (2008). *The development of a genetic counselling program to identify, test and manage families at risk for inherited colorectal cancer*. Faculty of Health Sciences. University of the Witwatersrand.

Van Riel, E., Wárlám-Rodenhuis, C. C., Verhoef, S., Rutgers, E. J., & Ausems, M. G. (2010). BRCA testing of breast cancer patients: medical specialists' referral patterns, knowledge and attitudes to genetic testing. *European Journal of Cancer Care (Engl), 19*(3), 369-376.

van Wyk, C. (2008). *The practices, knowledge, and attitudes about common hereditary cancers: survey of general practitioners in Johannesburg*. Faculty of Health Sciences. University of the Witwatersrand.

Vos, J., Oosterwijk, J. C., Gomez-Garcia, E., Menko, F. H., Jansen, A. M., Stoel, R. D. et al. (2011). Perceiving cancer-risks and heredity-likelihood in genetic-counseling: how counselees recall and interpret BRCA 1/2-test results. *Clinical Genetics, 79*(3), 207-218.

Walsh, T., Casadei, S., Coats, K. H., Swisher, E., Stray, S. M., Higgins, J. et al. (2006). Spectrum of Mutations in BRCA1, BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer. *JAMA: The Journal of the American Medical Association, 295*(12), 1379-1388.

Weiss, J. R., Moysich, K. B., & Swede, H. (2005). Epidemiology of Male Breast Cancer. *Cancer Epidemiology Biomarkers & Prevention, 14*(1), 20-26.

Wolpert, C. M., & Speer, M. C. (2005). Harnessing the Power of the Pedigree. *Journal of Midwifery & Women's Health, 50*(3), 189-196.

Wooster, R., Bignell, G., Lancaster, J., Swift, S., Seal, S., Mangion, J. et al. (1995). Identification of the breast cancer susceptibility gene BRCA2. *Nature, 378*(6559), 789-792.

6.1 ELECTRONIC REFERENCES

American Joint Committee on Cancer. (2010). American Joint Committee on Cancer: What is Cancer Staging? Retrieved 28 February 2012, from www.cancerstaging.org/

Forrest, P. (1986). Breast Cancer Screening: Report to the Health Ministers of England, Wales, Scotland & Northern Ireland. Retrieved 22 July, 2012 from http://www.cancerscreening.nhs.uk/breastscreen/publications/forrest-report.html

Petrucelli, N., Daly, M. B., & Feldman, G. L. (2011). BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer - GeneReviews - NCBI Bookshelf. Retrieved 9 May 2012, from http://www.ncbi.nlm.nih.gov/books/NBK1247/

Statistics South Africa. (2011). Mid-year population estimates 2011. Retrieved 14 June 2012, from http://www.statssa.gov.za/publications/statsdownload.asp?PPN=P0302&SCH=4986

Appendix A: Data Collection Sheet

File Code _____

Related to other family file code _____

Date of first genetic counselling session _____

Number of counselees _____

Proband

Person with cancer ☐

1st Degree relative of person with cancer ☐

2nd Degree relative of person with cancer ☐

3rd Degree relative of person with cancer ☐

Type of cancer of the proband

Breast ☐ Ovarian ☐ Other (specify) ☐ _____

Age _____

Descent

African ☐ European ☐ American ☐ Middle eastern ☐ Australasian ☐

Unknown ☐

Is the proband Ashkenazi Jewish or Afrikaans?

Yes ☐ No ☐

Afrikaans ☐ Ashkenazi ☐

Ethnicity

White ☐ Black ☐ Coloured ☐ Indian ☐ Unknown ☐

State patient ☐ **Private patient** ☐

Reason for attending genetic counselling

Predictive ☐

Diagnostic ☐

Other ☐

Likelihood of inherited cancer in the family

High ☐

Moderate to high ☐

Moderate ☐

Average ☐

Population ☐

Testing

Was mutation analysis offered in the family?

Yes ☐ No ☐

Who offered the testing?

Johannesburg ☐ Other local ☐ International ☐

Was mutation analysis performed in the family?

Yes ☐ No ☐

Why was testing not performed?

Financial constraints ☐ Other ☐

What testing was performed?

Targeted- Ashkenazi ☐

Afrikaner ☐

Family specific ☐

Sequencing ☐

Where was testing performed?

Locally ☐ Overseas ☐

Who paid for the testing?

State ☐ Patient ☐

Was a BRCA mutation found in the family?

Yes ☐ No ☐

BRCA1 ☐ or

BRCA2 ☐

What BRCA mutation was found?

_____

Appendix B: Telephonic Questionnaire

File Code _____

Good day, my name is Marianne Jefferies. I am a Masters student at the Division of Human Genetics of WITS and the NHLS. I am doing research on the Genetic Counselling Clinics for breast and/or ovarian cancer to assess the service that we offer. Would you be willing to take part in this research by answering some questions? It should take approximately 10 minutes.

1. **Introductory question: Would you mind telling me why you attended genetic counselling?**

☐ Testing

☐ I was referred

☐ To clarify my risks/find out more

☐ Other

Additional notes

_____

_____

2. **What was your initial expectation of genetic counselling?**

☐ Therapy session

☐ Medical facts

☐ Risk assessment

☐ No idea what it entailed

Additional notes

_____

_____

3. **Did genetic counselling clarify your understanding of the genetics of breast and/or ovarian cancer?**

☐ Yes

☐ No

a. **If No, why not? Was the information too complex or too full of medical terminology?**

_____

_____

4. **Did you feel more informed about your risk for developing breast and/or ovarian cancer after genetic counselling?**

☐ Yes

☐ No

a. **Do you recall what risk category you were classified into?**

☐ Average/Low

☐ Moderate

☐ High

☐ Can't remember

5. **Did the genetic counsellor explain the concept of screening or surveillance for breast and ovarian cancer?**

☐ Yes

☐ No

☐ Can't remember

a. **What did they tell you?**

_____

_____

6. **Did you make any lifestyle changes after attending genetic counselling?**

☐ Yes

☐ No

If yes:

☐ Increased breast/ovarian cancer screening/surveillance

☐ Surgery – mastectomy

☐ Surgery – salpingo-oophorectomy

☐ Other

7. **Would you refer anyone for genetic counselling?**

☐ Yes

☐ No

   a. **Why/Why Not?**

_____

_____

8. **Is there anything else you would like to add regarding the genetic counselling service?**

_____

_____

_____

Appendix C: Ethics Clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Ms Marianne Jefferies

CLEARANCE CERTIFICATE	**M10M101141**
PROJECT	Inherited Breast and Ovarian Cancer: A Review of the Avaiblabe Genetic Counselling and testing
Services	in Johannesburg
INVESTIGATORS	Ms Marianne Jefferies.
DEPARTMENT	Division of Human Genetics
DATE CONSIDERED	26/11/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 26/11/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Ms TM Wessells

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 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...