CLINICAL CHARACTERIZATION OF A COHORT OF SRI LANKAN FAMILIES WITH INHERITED CANCER SYNDROMES

BY

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TABLE OF CONTENTS

DECLARATION

I certify that the contents of this dissertation are my own work and that I have acknowledged the sources where relevant.

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Signature of the candidate

This is to certify that the contents of this dissertation were supervised by the following supervisors:

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ABSTRACT

BACKGROUND: Cancer is defined as the uncontrolled growth and proliferation of cells in any part of the body. It has become a global as well as national burden. All cancers are said to be genetic but only 5-10% are inherited. They are caused by germ line mutations and most are autosomal dominantly inherited. Each type of hereditary cancer syndrome has common clinical characteristics with or without a positive family history which are more useful in clinical diagnosis in primary care. According to the common characteristics, guidelines have been developed for clinical prediction, risk assessment, genetic testing and for counseling. These measures have helped significantly to reduce cancer mortality and morbidity world wide as well as country wide. The present study was carried out with the aim of clinical characterization of a cohort of Sri Lankan families with hereditary cancer syndromes.

METHODOLOGY: The clinical characterization of hereditary cancer syndromes were carried out in 55 Sri Lankan individuals who were recruited from the Human Genetics Unit, Cancer Institute Maharagama and the National Hospital Sri Lanka. Complete medical and surgical history was obtained from each participant including personal history as well as family history of cancer up to three generations. The clinical characteristics were analyzed according to international guidelines.

RESULTS: There were 43 affected patients and 12 asymptomatic individuals with positive family history of cancer. Majority were in the 41-50 years age group and there was no significant difference in the mean age of onset in males and females ($p=0.923$). Female to male ratio was 4.5:1. Hereditary breast and ovarian cancer (HBOC) syndrome was more prevalent (34.9%) and all were females. The mean age of onset was 43.6 years and 66.7% (10/15) had a positive family history. The commonest histology type in HBOC syndrome was well differentiated invasive duct

carcinoma and only 20% (3/15) had triple negative tumor. There was only one patient who had both breast and ovarian cancer. Hereditary non-polyposis colorectal cancer (HNPCC) syndrome was seen in 14 (32.6%) patients with a majority of females 64.3% (9/14). Mean age of onset was 43.3 years and 78.6% were diagnosed before the age of 50 years. Distal colon was involved in 78.7% of individuals and extracolonic features were seen in 14.2% of individuals. There were 8 patients with familial adenomatous polyposis (FAP) with female predominance 62.5% (5/8). Their mean age of onset, presence of family history and extraintestinal manifestations were: 36 years, 50% and 37.5%, respectively. There were 2 (4.6%) individuals with Peutz Jeghers syndrome (PJS). Age of onset was less than 50 years and both had harmatomatous polyps in the colon. Two patients were diagnosed with Von Hippel Lindau (VHL) syndrome. One had recurrent heamangioblastoma in the brain and the other had multiple renal cysts with clear cell renal carcinoma. Out of 12 asymptomatic individuals, 83.3%, 75.0%, 41.5% had 1st, 2nd and 3rd degree relatives with cancer, respectively.

CONCLUSION: This study shows that in the Sri Lankan context, clinical characteristics of HBOC and HNPCC patients are generally similar to data reported in other populations. Individuals with FAP, PJS and VHL also had clinical characteristics similar to that reported in previous data. Early age of onset, significant family history with affected successive generations were seen in all types of hereditary cancers in this cohort. Genetic analysis for identification of the underlying genetic mutations in this cohort will need to be undertaken in future studies.

LIST OF FIGURES

LIST OF TABLES

CHAPTER ONE

1.0 INTRODUCTION

This dissertation describes the clinical characterization in a cohort of Sri Lankan families with hereditary cancer syndromes. This introductory chapter begins with the definition of cancer, aetiology and a brief description of oncogenesis and genes involved in the process. It also describes different types of hereditary cancer, their basic features which are useful in differentiating each type of cancer and the Knudson two hit hypothesis which describes the pathogenesis of cancer at the molecular level. The second and third sections outline the global and national cancer burdens, respectively. In these two sections, a survey is made of the available cancer statistics worldwide and countrywide. The fourth section contains a general description of the common hereditary cancer syndromes followed by a description of the individual hereditary cancer syndromes in relation to their clinical characteristics, clinical diagnostic criteria and the corresponding genes for each cancer syndrome. The introductory chapter concludes with a statement on the justification and objectives of this study.

The second chapter describes the methods used for the investigations carried out in this dissertation. It gives a description of the recruitment of the patients as well as the phenotyping and the clinical guidelines which have been used.

Results are reported in the third chapter and discussed at length in the fourth chapter, whilst the final chapter summarizes the conclusions of the dissertation.

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1.1. BACKGROUND

1.1.1. Definition, aetiology and molecular basis of oncogenesis

Cancer is defined as the uncontrolled growth and proliferation of cells which can affect any part of the body. The growth often invades surrounding tissues and can metastasize to distant sites [1].It is a complex disease with multifactorial aetiology. Genetic, medical, environmental and life style factors alone or in a combination of two or more can cause cancer in an individual. These factors can cause mutations in critical genes within a single cell, allowing it to escape normal control mechanisms of cell growth and proliferation resulting in the development of a clinically evident tumor [2].

Numerous genetic alterations that affect cell cycle regulating genes such as proto-oncogenes, tumor suppressor genes, and DNA mismatch repair genes have been identified in neoplastic cells. Proto-oncogenes are involved in regulating cell proliferation and if they get mutated they are transformed into oncogenes which promote uncontrolled cell proliferation. Such mutations are referred to as gain of function mutations which increase the expression of the gene. Mutations that occur in oncogenes are usually acquired rather than inherited. Point mutation, translocation and amplification are the three major types of genetic alterations that lead to activation of oncogenes [3]. Multiple Endocrine Neoplasia Type 2 and Hereditary Papillary Renal Carcinoma are the two best known hereditary syndromes which are caused by germline mutations in oncogenes. They are caused by an inherited mutation in the *RET* gene and *MET* gene, respectively [4]. Abnormal cell growth can be caused by mutations in tumor suppressor genes. Tumor suppressor genes usually slow down cell division, repair DNA errors and control apoptosis [4]. Loss-of-function mutation of both alleles of tumor suppressor genes contribute to abnormal cell growth and most hereditary cancer syndromes are caused by germline mutations in

these genes [3]. Retinoblastoma, Familial Adenomatous Polyposis (FAP) and Hereditary Breast/Ovarian Cancer Syndrome (HBOC) are the common inherited cancer syndromes which are caused by germline mutations in *RB1,APC* and *BRCA* genes respectively [4]. DNA mismatch repair (MMR) genes are the other common type important in carcinogenesis. They promote genomic stability by correcting single base mismatches and insertion deletion loops that may arise during DNA replication. Insertions and deletions can cause microsatellite instability and if they are not corrected due to mutations in MMR genes, it can lead to carcinogenesis [5]. Hereditary Nonpolyposis Colorectal cancer (HNPCC) syndrome is an inherited cancer syndrome which is caused by microsatellite instability or replication errors in five MMR genes (*MLH1, MSH2, MSH6, PMS1* and *PMS2*) [6].

Since genetic mutations play a role in the development of all cancers, all cancers are said to be genetic but only some are inherited. The Fisher Center for Familial Cancer Research described three main types of cancer namely, hereditary, familial and sporadic cancer [7]. Approximately 75-80% of cancers are sporadic, which are cause by acquired genetic mutations. It is possible for a family to have more than one family member with sporadic type of cancer and the risk increases with advanced age, environmental, medical and life style factors. Individuals with sporadic cancer in one family do not have the same cancer causing genetic mutation and they do not transmit the mutations. Some cancers can occur in several members in the same family (i.e. clustering of cancers in families) but without a clear pattern of inheritance. These are called familial cancers and they usually occur late in life. Approximately 5-10% of cancers are inherited and they are caused by germ line genetic mutations. They are transmitted through multiple generations and they have a clear pattern of inheritance [8].

Hereditary cancer syndromes generally follow the Knudson Two Hit hypothesis (Figure 1). In1971, Alfred Knudson explained the occurrence of tumors in individuals with and without a positive family history by studying a large number of patients with retinoblastoma. Affected individuals with a positive family history inherit an inactivated allele which is called a germline mutation and inactivation of the other allele at the same locus is acquired somatically. Therefore, the cellular phenotype is recessive but the inheritance pattern of the cancer phenotype is dominant. Germline mutations are present in every cell in the body and they only need the second hit to develop the cancer. As this has a high chance of occurrence, inherited cancers occur early in life than expected [3].

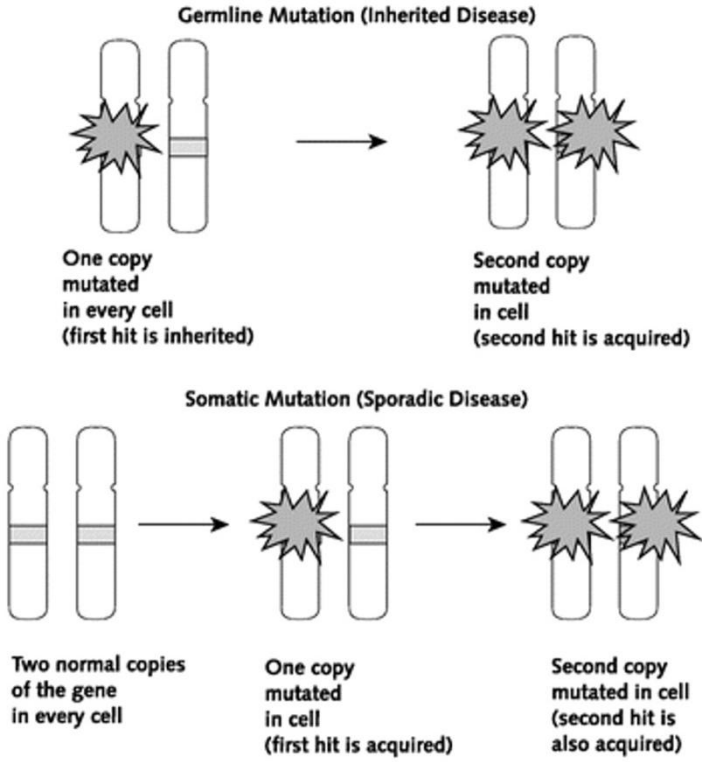

Figure 1: Knudson Two Hit Hypothesis

Adapted from Paula M. Calvert, MD; and Harold Frucht, MD. The Genetics of Colorectal Cancer. *Ann Intern Med.* 2002;137(7):603-612.

1.1.2. Global burden of cancer

Cancer is a leading cause of death both globally and nationally. It accounts for 8.2 million deaths, with 14.1 million new cancer cases and 32.6 million people living with cancer within 5 years of diagnosis in 2012. Carcinoma in lung, liver, stomach, colorectal, breast and oesophagus are the leading causes of cancer deaths worldwide [9]. The International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization (WHO) has provided an overview of 28 types of cancer in 184 countries worldwide [10].

GLOBOCAN 2012 has a prediction of 19.3 million increases in new cancer cases per year by 2025, due to growth and ageing of the global population. More than half of all cancers (56.8%) and cancer deaths (64.9%) in 2012 occurred in developing regions of the world. Age standardized cancer incidence rate between males and females varies with a 25% higher rate in males than in females. Male cancer incidence rates vary across the different regions of the world whereas females incidence rates show less variation (Figure 2 and Figure 3). In contrast to incidence, the mortality shows a less regional variability. The rates being 15% higher in developed than in developing regions in men and 8% higher in women [11].

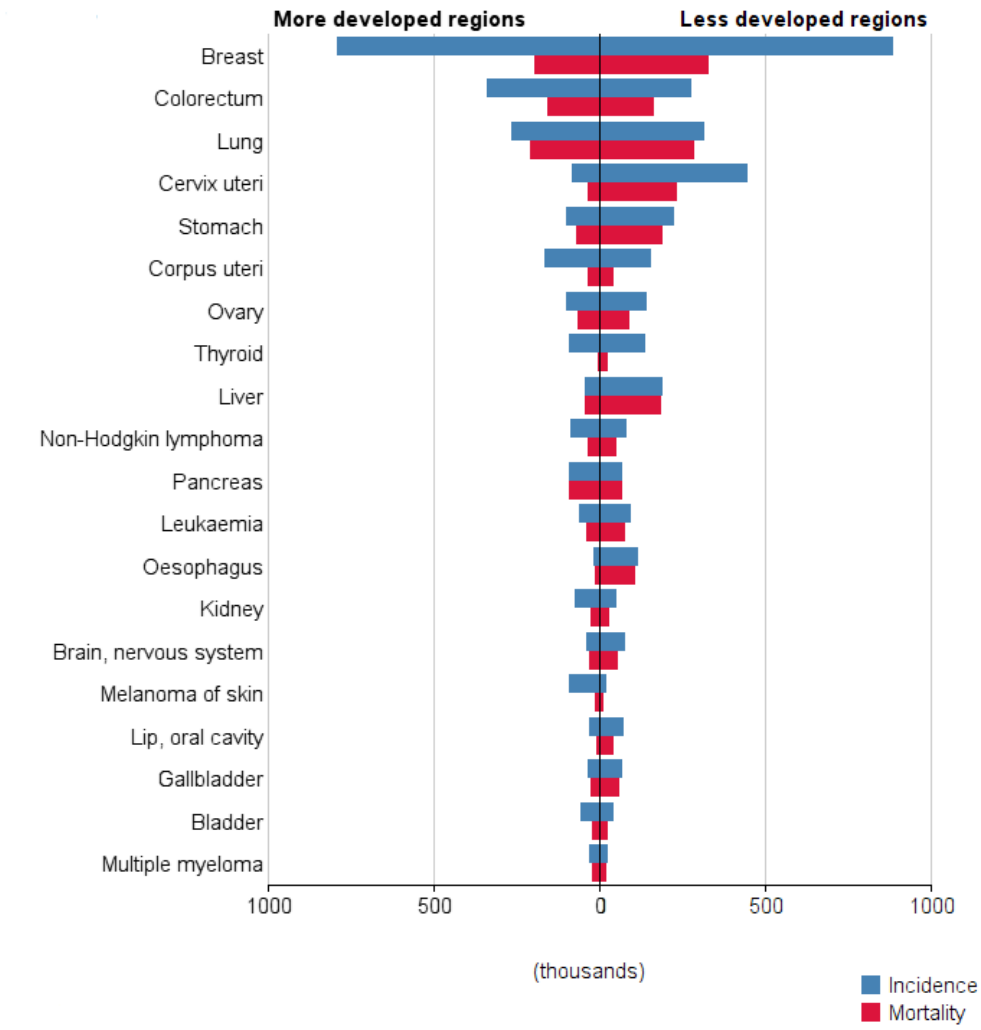

Figure 2: Cancer Incidence and Mortality in the Population by Sex (Female)

Adapted from World Health Organization, GLOBOCAN 2012 (IARC) (21.7.2014): Estimated Cancer Incidence, Mortality and Prevalence Worldwide 2012, http://globocan.iarc.fr/Pages/bar_dev_sel.aspx.

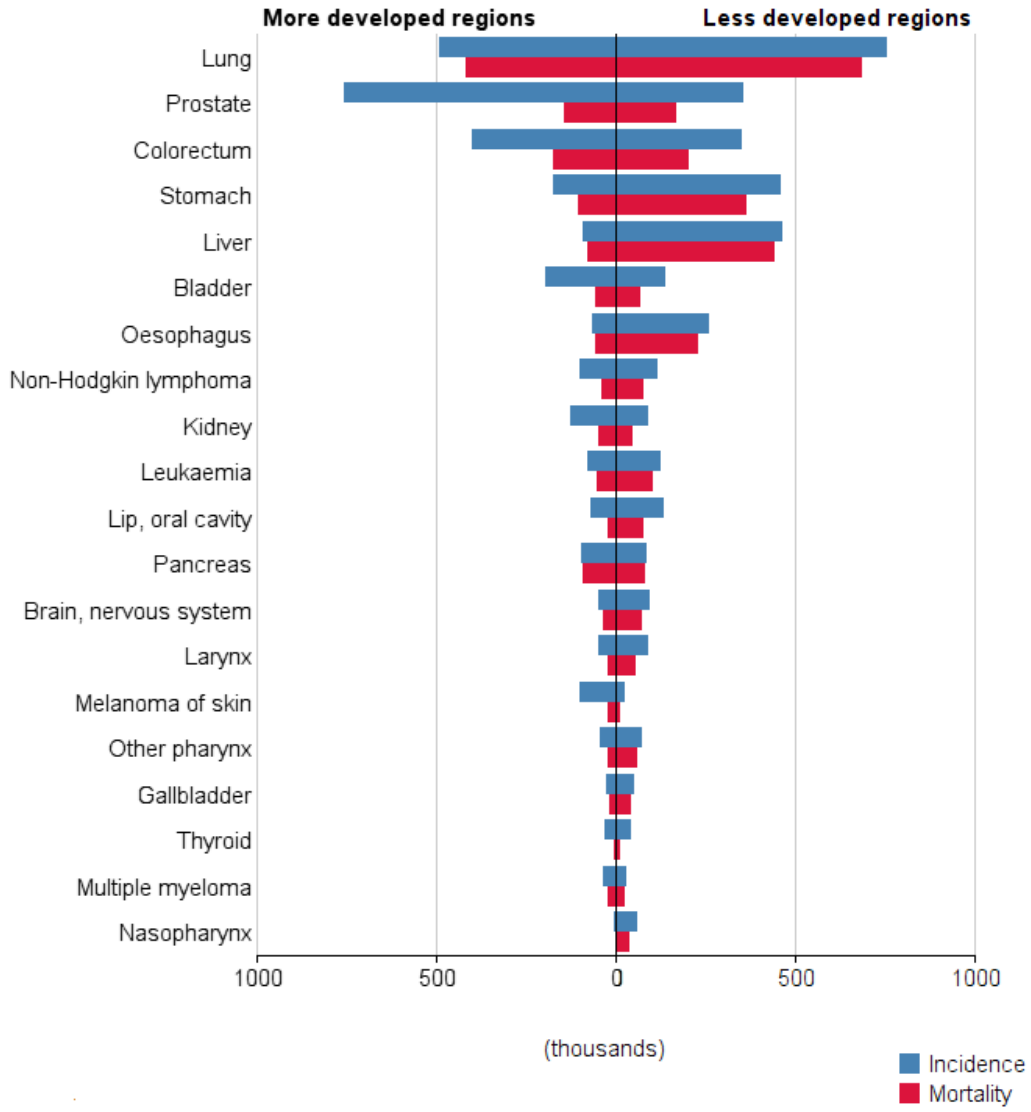

Figure 3: Cancer Incidence and Mortality in the Population by Sex (Male)

Adapted from World Health Organization, GLOBOCAN 2012 (IARC)(21.7.2014): Estimated Cancer Incidence, Mortality and Prevalence Worldwide 2012,http://globocan.iarc.fr/Pages/bar_dev_sel.aspx

Breast cancer is the second most frequent cancer among women and it accounts for 25% of total cancers in the world. GLOBOCAN 2012 has revealed a marked increase in breast cancer. In 2012 breast cancer incidence and mortality have increased by 20% and 14%, respectively when

compared to year 2008. Increased incidence shows an inequality between developed and developing countries. Incidence rates remain highest in more developed regions, but mortality is relatively much higher in developing countries. They have highlightened an urgent need in cancer control by developing effective and affordable approaches to the early detection, diagnosis and treatment of breast cancer among women living in developing countries [10].

Africa, Asia and Central and South America account for more than 60% of world's total new annual cancer cases and for 70% of the world's cancer deaths. It is expected that annual cancer cases will rise from 14 million in 2012 to 22 million within the next two decades [9]. Colorectal cancer is the third most common cancer in men with an incidence of 10% of the total cancers and second in women with 9.2% of total cancers worldwide. Colorectal cancer incidence has a wide geographical variation across the world and almost 55% of the cases occur in more developed countries and mortality is lower with 52% of cancer deaths in the developing countries [11]. Figures 4 and 5 show the incidence and five-year prevalence of breast cancer and colorectal cancer in South Central Asia in 2012 respectively [12].

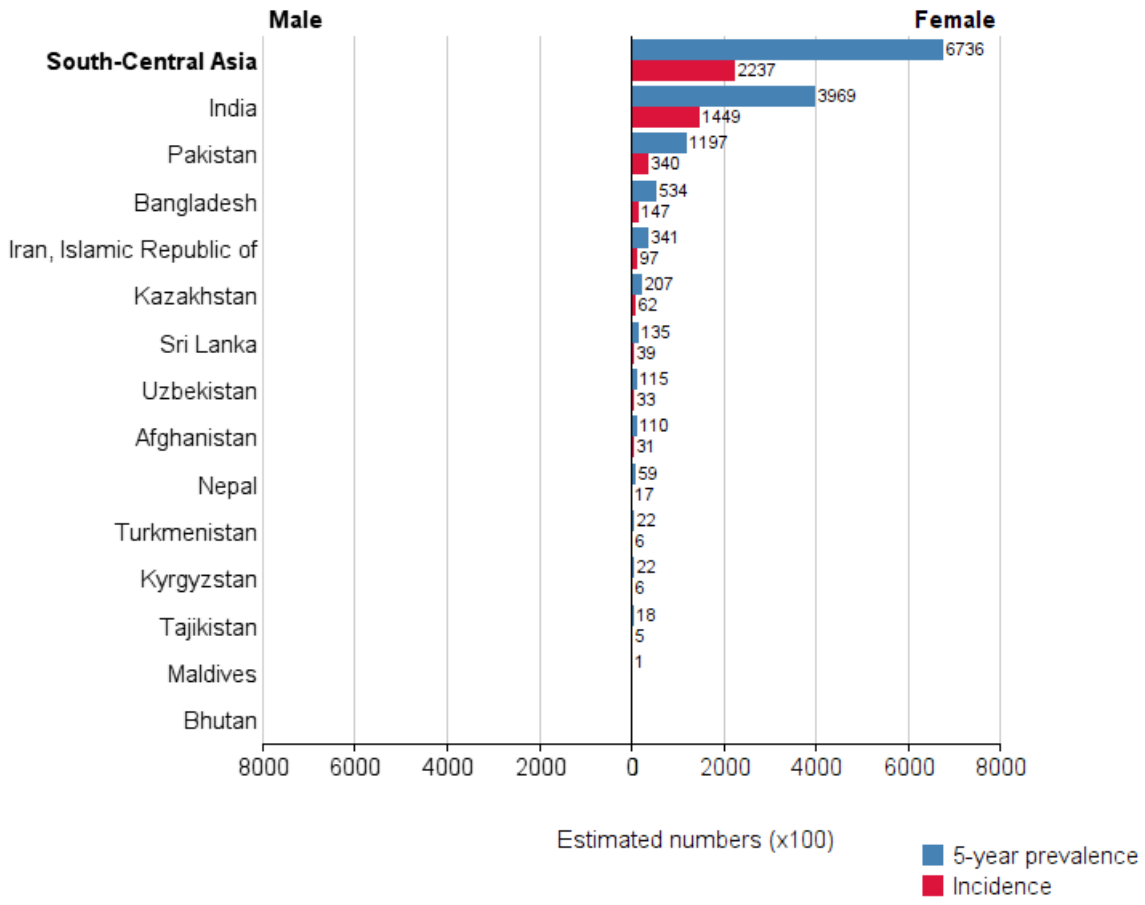

Figure 4: Incidence and 5-year Prevalence of Breast cancer in South-Central Asia 2012

Adapted from World Health Organization, GLOBOCAN 2012 (IARC)(21.7.2014): Estimated Cancer Incidence, Mortality and Prevalence Worldwide 2012,http://globocan.iarc.fr/Pages/bar_sex_pop_sel.aspx

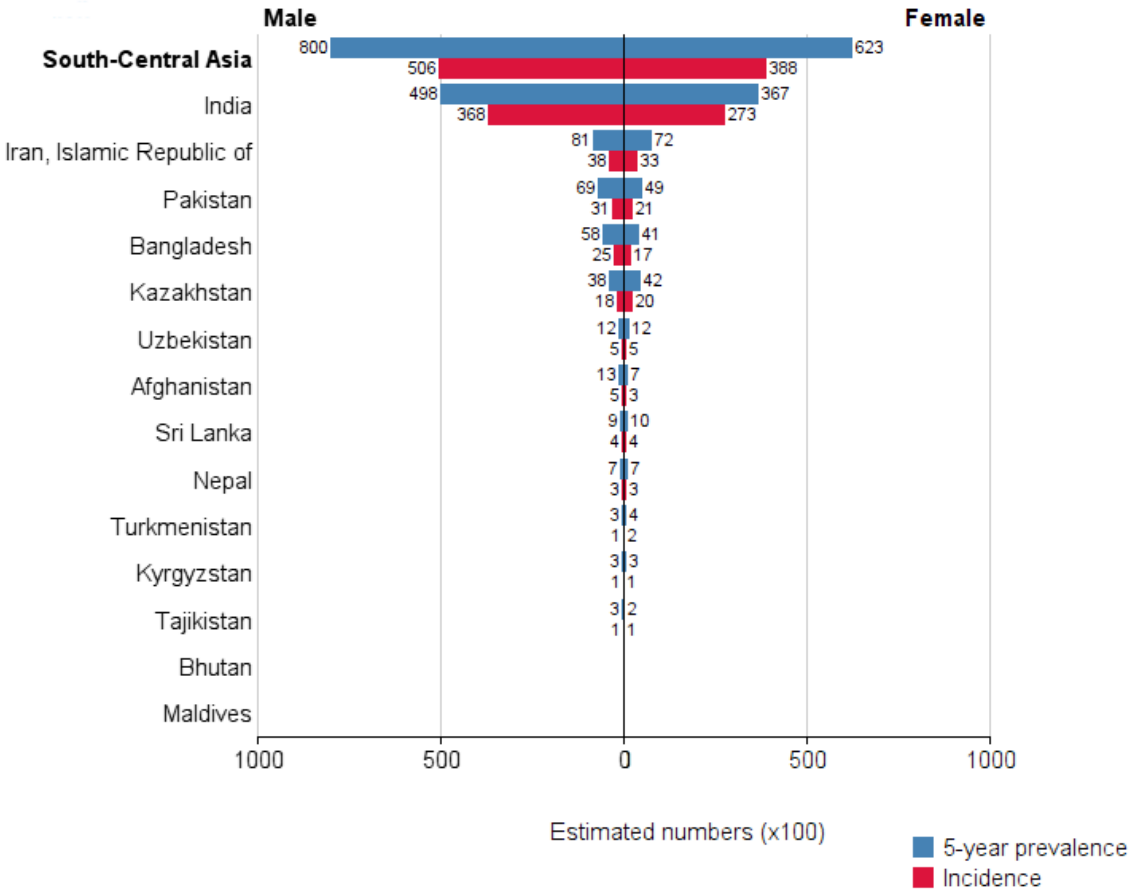

Figure 5: Incidence and 5-year Prevalence of Colorectal cancer in South-Central Asia 2012

Adapted from World Health Organization, GLOBOCAN 2012 (IARC)(21.7.2014): Estimated Cancer Incidence, Mortality and Prevalence Worldwide 2012,http://globocan.iarc.fr/Pages/bar_sex_pop_sel.aspx

1.1.3. National Burden of Cancer

The World Health Organization has stated that number of new cancer cases was 23 700 in Sri Lanka in year 2012 and the Age-Standardized Rate (ASR) was 94.8 per 100,000 persons. Total number of cancer deaths and the ASR was 14, 000 and 54.6 respectively for the same year. Risk of getting cancer before age of 75 years was 9.5% and 10.8% for males and females respectively and the risk of dying from cancer before age 75 years was 6.3% for males and 5.9% for females

[13]. Figures 6, 7, 8 and 9 illustrate the cancer incidence and mortality in males and females, respectively in Sri Lanka in 2012. Figure 10 illustrates the incidence and mortality of different types of cancer among the Sri Lankan population [14].

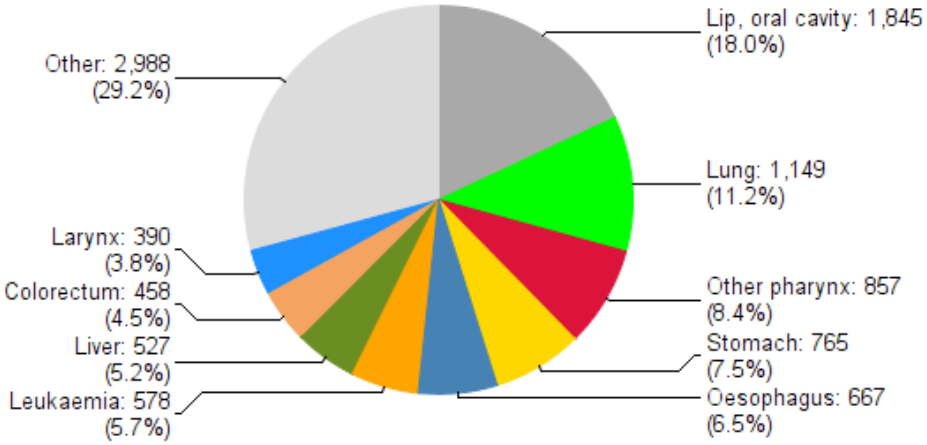

Figure 6: Estimated number of cancer cases in males, all ages (total: 13, 441) in Sri Lanka in 2012

Adapted from World Health Organization, GLOBOCAN 2012 (IARC) (21.7.2014): Estimated Cancer Incidence, Mortality and Prevalence Worldwide 2012, http://globocan.iarc.fr/Pages/pie_pop_sel.aspx

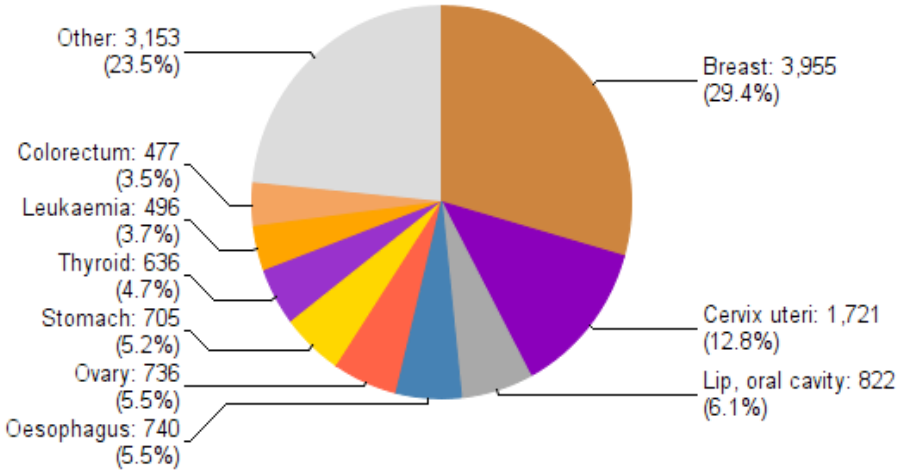

Figure 7: Estimated number of cancer cases in females, all ages (total: 13, 441) in Sri Lanka in 2012

Adapted from World Health Organization, GLOBOCAN 2012 (IARC)(21.7.2014): Estimated Cancer Incidence, Mortality and Prevalence Worldwide 2012,http://globocan.iarc.fr/Pages/pie_pop_sel.aspx

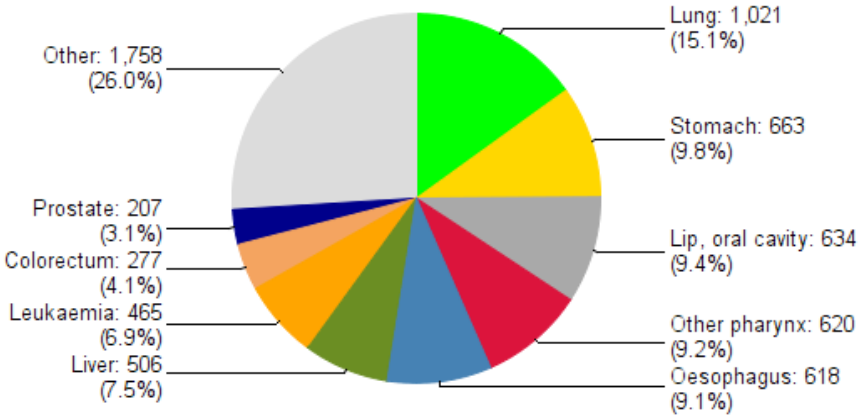

Figure 8: Estimated number of cancer deaths in males, all ages (total: 6, 769) in Sri Lanka in 2012

Adapted from World Health Organization, GLOBOCAN 2012 (IARC)(21.7.2014): Estimated Cancer Incidence, Mortality and Prevalence Worldwide 2012, http://globocan.iarc.fr/Pages/pie_pop_sel.aspx

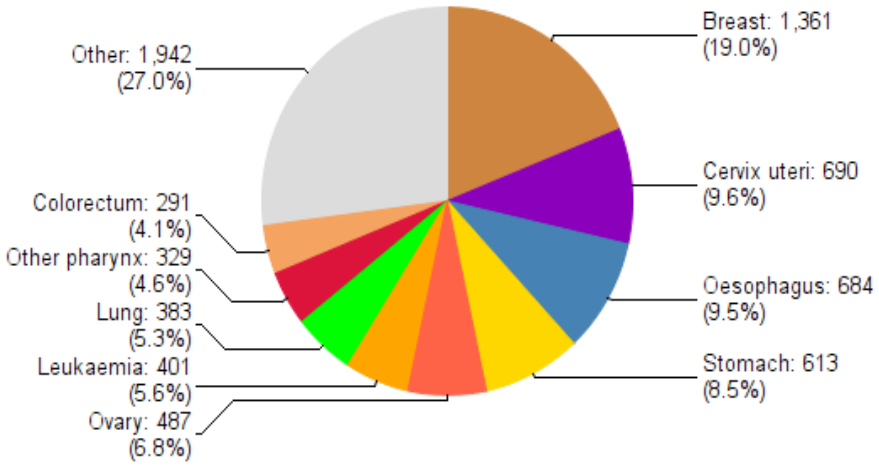

Figure 9: Estimated number of cancer deaths in females, all ages (total: 6, 769) in Sri Lanka in 2012

Adapted from World Health Organization, GLOBOCAN 2012 (IARC)(21.7.2014): Estimated Cancer Incidence, Mortality and Prevalence Worldwide 2012, http://globocan.iarc.fr/Pages/pie_pop_sel.aspx

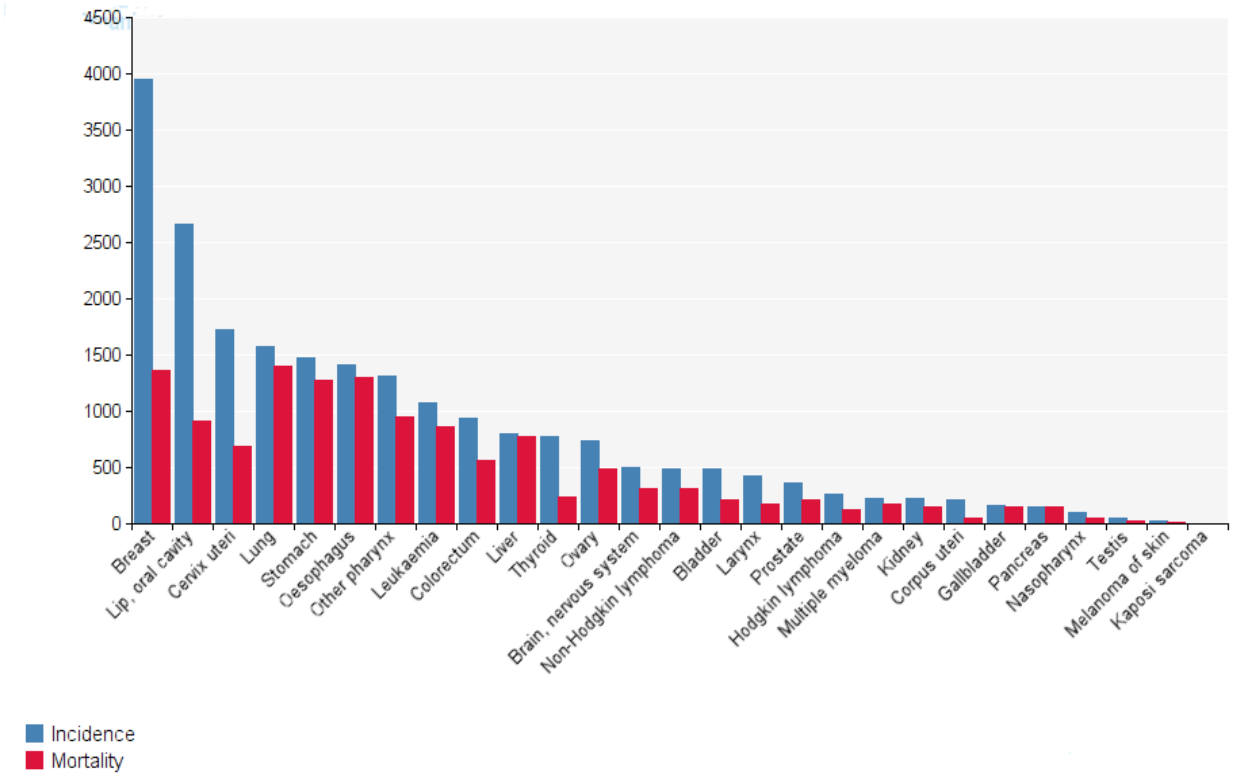

Figure 10: Incidence and Mortality rates of Different Types of Cancers in Sri Lankan Population 2012

Adapted from World Health Organization, GLOBOCAN 2012 (IARC)(21.7.2014): Estimated Cancer Incidence, Mortality and Prevalence Worldwide 2012,http://globocan.iarc.fr/Pages/bar_pop_sel.aspx

Cancer Incidence data in the Sri Lankan population was published in the 9th publication of Cancer Incidence Data: Sri Lanka Year 2007 by the National Cancer Control Program (NCCP), which is the only country wide database available on cancer statistics. The registry contains cancer data according to the age group, sex, ethnicity, cancer sites and mortality rates. According to the above published data, a total of 13,635 new cancer cases have been diagnosed in 2007 and they were collected from six cancer treatment centers in the country. The inclusion criteria of new cancer cases into the registry were changed in 2007 to be parallel with international standards. Therefore the observed reduction could be explained by the change in the inclusion

criteria. A slight increase in new male cancer cases was observed in 2007 compared to 2006 from 6205 to 6356 cases respectively. Out of 13, 635 new cases, 7279 were females while it was 7875 in 2006. The overall Crude Cancer Incidence Rate (CR) was 68.0per 100, 000 population and the age standardized rate (ASR) was 71.6 100,000 persons. The CR in males was 63.8 and in females it was 72.2, showing a female preponderance. Breast cancer remained the leading cancer in the population in 2007 and the CR and the ASR were slightly lower when compared to 2006. The five leading cancer sites in females were breast, uterine cervix, thyroid gland, oesophagus and ovary. Among males it was reported as 'lip, oral cavity & pharynx', 'trachea, bronchus & lungs', oesophagus, 'colon & rectum' and lymphoma. The life time risk of developing any type of cancer was one in every 12 for males and on in every 13 for females [15].

1.1.4. Hereditary Cancer Syndromes

The commonest hereditary cancer syndromes are hereditary non polyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), hereditary breast and ovarian cancer (HBOC) and multiple endocrine neoplasia type 2 (MEN 2). HBOC syndrome, Cowden syndrome (CS) and Li-Fraumeni syndrome (LFS) are the three most clearly described hereditary breast cancer syndromes. Approximately 7% of breast cancers and 10% of ovarian cancers are known to arise from inherited mutations in specific tumor suppressor genes, namely *BRCA1* and *BRCA2*. Women who carry mutations in *BRCA1* and *BRCA2* genes are estimated to have a 60 to 80% life time risk for breast cancer [16]. Mutations in five DNA mismatch-repair genes which cause HNPCC (*MLH1, PMS2, MSH2, MSH6, EPCAM, MUTYH*) account for approximately 5% of colorectal cancers and less than 1% are due to mutations in the *FAP* gene which causes familial adenomatous polyposis. Each type of hereditary cancer syndrome has a pattern of clinical characteristics with or without a positive family history of cancer, which is more useful in

clinical diagnosis at primary care. The discovery of genes responsible for hereditary cancer has been accompanied by technological advances in the characterization of the genetic mutations that predispose individuals to increased risk of cancer, as well as by advances in therapeutic interventions and screening strategies that effectively address hereditary cancer risk [17]. Guidelines for risk assessment, genetic counseling, and planning of appropriate therapeutic and screening options based on the phenotypic and molecular characterization of hereditary cancer syndromes have been worked out in the western world. These measures have helped to significantly reduce cancer mortality and morbidity in most of the developed countries, mainly due to improvements in early detection and treatment[18]. There is, however, a dearth in the knowledge and understanding of the clinical presentation of hereditary cancer syndromes in the Sri Lankan population. This deficit in knowledge has also resulted in sub optimal management, follow-up and surveillance of individuals with an inherited predisposition to cancer. The availability of such knowledge would lead to implementation of evidence-based strategies for cancer prevention, early detection and better management of patients with hereditary cancer syndromes in Sri Lanka.

1.1.4.1. Hereditary Breast and Ovarian Cancer Syndrome

Hereditary Breast and Ovarian Cancer Syndrome (HBOC) is an inherited cancer syndrome which is caused by germline mutations in the *BRCA1* and *BRCA2* genes. Individuals who are carrying mutations in either gene have a life time risk of 40%-80% for breast cancer, 11%-40% for ovarian cancer, 1-10% for male breast cancer, up to 39% for prostate cancer and 1%-7% for pancreatic cancer[19].Various professional societies including the National Comprehensive Cancer Network (NCCN) have published guidelines which have described characteristic features

that should consider in an individual or in the family history to suspect a mutation in the *BRCA1* or *BRCA2*genes [20],[21],[22],[23],[24].Mutations in the *BRCA1* and *BRCA2*genes is suspected in individuals with a personal or family history of breast cancer diagnosed at age 50 years or younger, ovarian cancer, multiple primary breast cancers either in the same breast or opposite breast, both breast and ovarian cancer, male breast cancer, triple negative breast cancer, pancreatic cancer with breast or ovarian cancer in the same individual or on the same side of the family, two or more relatives with breast cancer, one under age 50, three or more relatives with breast cancer at any age, a previously identified *BRCA1* or *BRCA2* mutation in the family and Ashkenazi Jewish ancestry [19].These features have been assessed in different populations and have explained their relatedness and the importance of knowing the clinical characteristics in HBOC syndrome and the advantages in detecting hereditary breast cancer early in an individual [25],[26],[27]. In a study conducted by Thomas *et al, BRCA1, BRCA2* genes and three specific Ashkenazi Jewish founder mutations were sequenced in 7,461 individuals and in 2,539 individuals with breast cancer respectively. Results were correlated with personal and family history of cancer, ancestry, invasive versus noninvasive breast neoplasia and sex of the patients. The authors concluded that specific features of personal and family history can be used to assess the likelihood of identifying a mutation in the *BRCA1* or *BRCA2* genes in individuals examined in a clinical setting [28].Many studies have described the association of early age of onset and hereditary breast cancer in different populations [29],[30],[25]. Some studies have described predictors for contralateral breast cancer including young age at diagnosis and family history of early-onset breast cancer [31],[32],[33].

Elevated breast cancer risk can be associated with some other cancer predisposition syndromes which are caused by mutations in few other genes other than *BRCA*: *TP53* gene-Li-Fraumeni

syndrome (LFS), *PTEN* gene-Cowden syndrome (CS), *CDH1* gene-Hereditary diffuse gastric cancer (HDGC), *CHEK2* variant, *ATM* gene-Ataxia telangiectasia (AT), *MMR* genes-Hereditary non-polyposis colorectal cancer syndrome (HNPCC), *STK11* gene-Peutz-Jeghers syndrome (PJS), *BLM* gene-Bloom syndrome (BS), *WRN* gene-Werner syndrome, *XPA*, *ERCC3, XPC, ERCC2, DDB2, ERCC4, ERCC5, ERCC1 and POLH* genes-Xeroderma pigmentosum (XP), *PALB2* and *RAD51C* related genes. HBOC can be distinguished from the above cancer syndromes by knowledge of the tumors present in the particular family in many instances [19]. Clinical characteristics of LFS and CS have been described in Appendix 2.

A study has been done to document the breast cancer profile of a group of Sri Lankan women and compare it with regional data. Patient-tumor characteristics and predicted prognosis were compared with immune profiles. The study conclusion was that the overall profile of breast cancer and immune characteristics of Sri Lankan women in this study was highly comparable to profiles documented elsewhere in the region despite the lower prevalence of estrogen receptors [34].

1.1.4.2. Hereditary non-polyposis colorectal cancer

Hereditary non-polyposis colorectal cancer (HNPCC) also known as Lynch syndrome accounts for 3-5% of colorectal cancers (Figure 11) and has an increased risk for cancers of the endometrium, ovary, stomach, small intestine, hepatobiliary tract, urinary tract, brain and skin [35],[36].

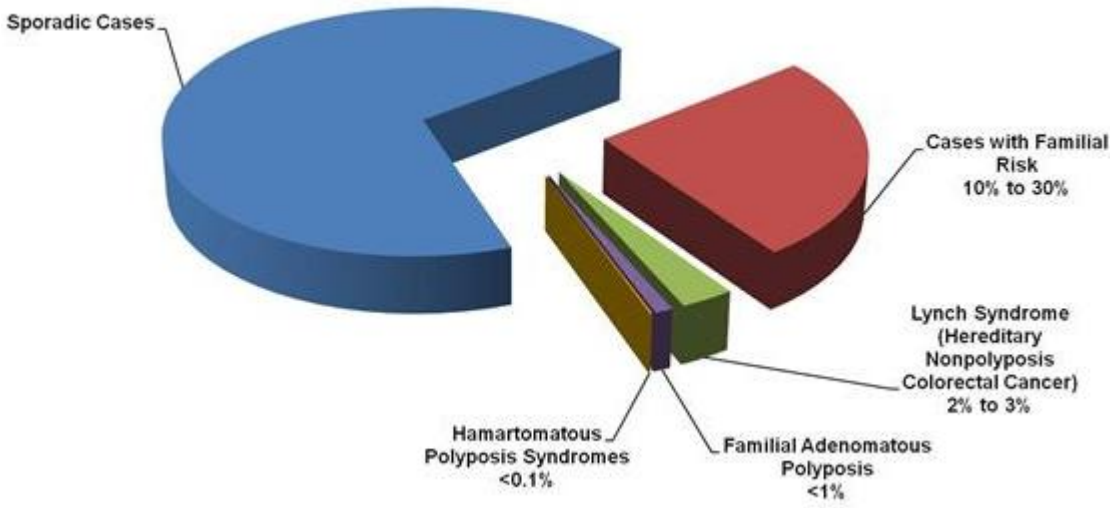

Figure 11: The fractions of colon cancer cases that arise in various family risk settings

Adapted from Randall W. Burt, Colon Cancer Screening,Gastroenterology, Vol.119, No.3, Pages 837-853.

Clinical diagnosis of HNPCC can be made by the Amsterdam criteria on the basis of the family history of patients. Amsterdam criteria was later modified to Amsterdam II criteria (Table 1) including Lynch syndrome related cancers [37].

Table 1: Amsterdam and Amsterdam II Criteria for the Clinical Diagnosis of HNPCC

Adapted from Vasen, H., Watson, P., Mecklin, J.-P., & Lynch, H. (1999). New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. Gastroenterology, 116(6), 1453–1456.

Amsterdam Criteria	**Amsterdam II Criteria**
Three or more family members, one of whom is a first-degree relative of the other two, with a confirmed diagnosis of colorectal cancer	Three or more family members (one of whom is a first-degree relative of the other two) with HNPCC-related cancers
Two successive affected generations	Two successive affected generations
One or more colon cancers diagnosed before age 50 years Exclusion of familial adenomatous polyposis (FAP)	One or more of the HNPCC-related cancers diagnosed before age 50 years Exclusion of familial adenomatous polyposis (FAP)

Bethesda guidelines (Table 2) is also used in the clinical diagnosis of individuals with HNPCC syndrome and according to this guideline one can decide on which patients should undergo the genetic testing [38], [39]. Although the Amsterdam criteria can be a significant predictor of a germline mutation in a mismatch repair (MMR) gene in families, these criteria can miss a significant proportion of families with a germline MMR gene mutation. Germline mutations in *MLH1*, *MSH2*, *PMS2*, or *MSH6* can be detected by Amsterdam II criteria with a sensitivity of 87%, 62%, 38% and 48% respectively [40].

Table 2: The revised Bethesda Guidelines for testing colorectal tumors for microsatellite instability (MSI)

Adapted from Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, et al, Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch Syndrome) and microsatellite instability, J Natl Cancer Inst. 2004 Feb 18;96(4):pages 261-268.

The Revised Bethesda Guidelines
1. Colorectal cancer diagnosed under the age of 50 years of age
2. Presence of synchronous, metachronous colorectal or other HNPCC associated tumors,* regardless of age
3. Colorectal cancer with the MSI-H** histology*** diagnosed in a patient who is less than 60 years of age.
4. Colorectal cancer diagnosed with one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years.
5. Colorectal cancer diagnosed in two or more first or second degree relatives with HNPCC-related tumor, regardless of age.
*colorectal, endometrial, stomach, ovarian, pancreas, bladder, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot Syndrome), sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel. ** high microsatellite instability in tumors refers to changes in two or more of the five NCI-recommended panels of microsatellite markers. MSI-L = low microsatellite instability in tumors refers to changes in only one of the five NCI-recommended panels of microsatellite markers. ***Presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern.

A twelve year prospective database of colorectal cancer was analysed to compare clinoco-pathological features in young (<40 years) and older patients (>50 years). Duration of symptoms and presentation was similar in both groups. The authors reported that if patients who are less than 40 years old with colorectal cancer, survive twenty months after surgery, the prognosis improves and their survival becomes predictable [41].A comparative study on the clinic-pathological features of colorectal malignancies in Sri Lankan patients aged 40 years or younger and older patients reported that there is no difference in clinical presentation between the 2 groups. From September 1996 to September 2008, all patients aged below 40 years diagnosed with colorectal cancer and treated at the department of Surgery, University of Kelaniya, were analyzed from a prospective database. It was reported that patients less than 40 years old with colorectal cancer, had better survival rates with improved prognosis due to early detection and optimized clinical management [42].

1.1.4.3. Familial Adenomatous Polyposis

Familial Adenomatous Polyposis (FAP) is one out of three known major types of inherited colorectal cancers. FAP accounts for 1% of all colorectal cancers. It is caused by germline mutations in the Adenomatous Polyposis Coli (*APC)* gene which is a tumor suppressor gene. Attenuated FAP (AFAP), Gardner syndrome and Turcot syndrome are other *APC*-associated polyposis conditions described [43]. FAP is characterized by the presence of a large number (>100) of precancerous colonic polyps usually developed at a mean age of 16 years. FAP can be associated with extracolonic manifestations such as polyps of the gastric fundus and duodenum, osteomas, dental anomalies, congenital hypertrophy of the retinal pigment epithelium (CHRPE), soft tissue tumors and desmoids tumors [44]. The National Comprehensive Cancer Network

(NCCN) has published guidelines for the clinical diagnosis of FAP and AFAP (Table 3) in the NCCN Guidelines Version 2.2014[45]. Clinical features of *APC*-associated polyposis conditions are stated in Appendix 2. In addition to *APC* gene mutations, *MUTYH* gene mutations can cause FAP and these mutations inherited in an autosomal recessive pattern. Therefore, usually they do not have affected parents and may not have affected siblings as well [43].

Table 3: NCCN Guidelines for Familial Adenomatous Polyposis/ Attenuated Familial Adenomatous Polyposis

Adapted from NCCN Guidelines Version 2.2014, Familial Adenomatous Polyposis/AFAP, National Comprehensive Cancer Network, Inc.

Classic FAP	**Attenuated FAP**
Germline *APC* mutation	Germline *APC* mutation
Presence of ≥100 polyps (sufficient for clinical diagnosis) or fewer polyps at younger ages, especially in a family known to have FAP	Presence of 10to <100 adenomas (average of 30 polyps)
Autosomal dominant inheritance (except with *de novo* mutation	Frequent right sided distribution of polyps
Possible associated additional findings - congenital hypertrophy of retinal pigment epithelium (CHRPE) - osteomas, supernumerary teeth,odontomas - desmoids, epidermoid cysts - duodenal and other small bowel adenomas - gastric fundic gland polyps	Adenomas and cancers at age older than classical FAP (mean age of cancer diagnosis >50y)
Increased risk of medulloblastoma, papillary carcinoma of thyroid (<2%), hepatoblastoma (1%-2%, usually age ≤ 5y)	Upper GI findings, thyroid and duodenal cancer risks are similar to classical FAP
Pancreatic cancers (<1%)	Other extra-intestinal manifestations, including CHRPE and desmoids are unusual
Gastric cancers (<1%)	
Duodenal cancers (4%-12%)	

1.2. Justification

Hereditary cancer is a major source of disease burden in the country. The psycho-socio-economic impact of cancer has far reaching consequences not only for the patients and their family members but also for the national economy. The economic burden of cancer is most obvious in direct health care costs, such as those for hospitals, other health services, and drugs as well as indirect costs arising from loss of productivity as a result of the illness and premature death of affected patients. There were no previously reported studies done on hereditary cancer syndromes in the Sri Lankan population.

This is the first large scale study to be conducted in Sri Lanka to document the phenotypic spectrum of hereditary cancer syndromes in the local population. Genetics plays a vital role in reducing the cancer morbidity and mortality through primary prevention, early detection, improved surveillance and effective treatment strategies. The overall aim of this study is to characterize the inherited cancer syndromes in a cohort of Sri Lankan families based on the clinical features and find out the presence of other pathognomonic features of hereditary cancer syndromes among Sri Lankan patients which have already been described in western countries. Other than the above outcomes, mapping of the phenotypic spectrum of HBOC, HNPCC and FAP in Sri Lankan patients are also expected. The findings from this study will contribute to the advancement of the generalizable knowledge in the field of cancer genetics in Sri Lanka. This study will provide novel insights into the clinical characterization of inherited cancer syndromes which would be useful in the development and validation of better methods for risk assessment, early detection and prevention of cancer syndromes in Sri Lanka. The availability of a database of the common characteristic features found in Sri Lanka will benefit hereditary cancer patients

in the early diagnosis and appropriate management of this genetic disorder resulting in improved quality of life for those affected patients and reduce overall health burden to the country.

The information gained from this study will be beneficial especially for primary care physicians for the early detection and referral of patients with inherited cancer syndromes as well as improved surveillance and screening of at risk family members. Besides that, identification of the common clinical characteristic features of inherited cancer syndromes will be beneficial in the establishment of clinical risk assessment criteria for patients with inherited cancer syndromes and their relatives. Such studies are of scientific interest and will assist in accurate genetic counseling and guide appropriate management and improved care of patients with inherited cancer syndromes. Genetic counseling will allow individuals an opportunity to learn how hereditary cancer is transmitted, understand their options for managing their cancer risk, and choose a course of action that is appropriate for them with additional resources. Unaffected individuals who are at risk can be advised on genetic testing, prophylactic surgical management as well as chemoprevention by using drugs like Tamoxifen and Raloxifene. Routine screening by mammography and magnetic resonance imaging (MRI) will also be beneficial to individuals at risk for early detection.

1.3. Objective

- Phenotypic characterization of inherited cancer syndromes in a cohort of Sri Lankan families

CHAPTER TWO

2.0. Methodology

2.1. Ethical Considerations

The study would be conducted according to the Declaration of Helsinki (2008). The study builds on collaborative links the HGU has established with patients with hereditary cancer syndromes, local clinicians and oncologists in the field. Genetics plays a vital role in reducing the cancer morbidity and mortality through primary prevention, early detection, improved surveillance and effective treatment strategies. This is the first large scale study to be conducted in Sri Lanka to document the phenotypic spectrum of hereditary cancer syndromes in the local population. The findings of this research would help to reduce the burden of hereditary cancer in the country and contribute towards national development in several ways. Awareness of the clinical diagnosis will allow patients to make informed decisions regarding genetic testing, reproduction, lifestyle and clinical risk-reduction strategies thus helping to improve prognosis, survival and quality of life of cancer patients and at risk family members. The study has social value because it would contribute to the advancement of the generalizable knowledge in the field of hereditary cancer syndromes in Sri Lanka. This study will be of immense value in heralding a clinical approach to the identification of inherited cancer syndromes in Sri Lanka. The identification of the common clinical characteristic features of inherited cancer syndromes will be beneficial in establishment of clinical risk assessment criteria for patients with inherited cancer syndromes and their relatives. This study will assist in accurate genetic counseling and guide appropriate management and improved care of patients with inherited cancer syndromes. Genetic counseling will allow individuals an opportunity to understand pattern of inheritance, options for managing their cancer risk, and choose a course of action that is appropriate for them with additional resources.

Unaffected individuals who are at risk can be advised on genetic testing and management of their clinical outcome. This study will also provide novel insights into the clinical characterization of inherited cancer syndromes which would be useful in the development and validation of better methods for risk assessment, detection and prevention of cancer syndromes in Sri Lanka. The study findings will be disseminated to stakeholders and potential beneficiaries and presented at local conferences and published in peer reviewed journals.

The study is designed appropriately to ensure scientific validity. The study is open to all patients with cancer syndromes and at risk individuals; this therefore has fair participant selection. Appropriate measures would be taken to ensure that consent is obtained in an ethical manner from all study participants. Written informed consent will be obtained from all study participants and in the case of children, from their parents or guardians. The patients would be interviewed privately in the genetic counseling room to ensure privacy and will be able to discuss the study privately with the investigators without the presence of others. Informed written consent would be obtained after providing the necessary information and giving them time to make a decision in private. The data collection booklet is designed to ensure confidentiality of information gathered. Soon after collecting the personal information, the identification page would be removed and filed separately. The only identification number in the rest of the booklet is a coded subject study number which cannot be linked to an individual without the page containing the personal information which would be kept by the principle investigator under lock and key. The electronic database containing the data will only have the subject study number thus ensuring confidentiality. The database and the computer containing the database would be password protected. These measures would ensure that loss of confidentiality is minimized. No personal information by which subjects can be identified would be released or published. The data will

not be used in a way that the subjects can be identified in any public presentation or publication.

2.2. Recruitment of subjects and study protocol

This is a descriptive analytical study. Individuals with a clinical diagnosis or a positive family history of hereditary cancer syndrome will be recruited into the study. Individuals identified from the cancer database maintained at the Human Genetics Unit will be contacted via phone or mail and those who give written informed consent will be recruited retrospectively into the study. In addition to these, patients and non affected individuals with positive family history of cancer who are referred to the Human Genetic Units, Professorial Surgical clinic at the National Hospital, Colombo (NHSL) and the Cancer Genetics clinic at National Cancer Hospital, Maharagama from 1st January 2014 to 30th June 2014 will also be recruited prospectively. Therefore this is a mixed study. Prior to recruitment, Ethical clearance was obtained from the Ethics Review Committee, Faculty of Medicine, University of Colombo.

2.2.1. Study Population and Place of Study

The study population would comprise a total of 55 participants. Most published studies of this nature in scientific literature have been done with smaller samples [46],[47],[48],[49]. The sample size has been calculated using Open Source Epidemiologic Statistics for Public Health (OpenEpi), version 3.01 (available at http://www.openepi.com/v37/Menu/OE_Menu.htm).

Equation for sample size calculation,

$$\text{Sample size } n = [\text{DEFF}*Np(1-p)]/\ [(d^2/Z^2_{1-\alpha/2}*(N-1)+p*(1-p)]$$

(sample size was calculated with 95% confidence interval)

This sample size would be sufficient to effectively describe the phenotypic characteristics in this study group. Cases have been recruited from patients clinically diagnosed with hereditary cancer

syndromes and non affected individuals with a positive family history of cancer syndromes at the Genetics Clinic of the Human Genetics Unit (HGU), Faculty of Medicine, University of Colombo as well as the Professorial Surgical clinic at NHSL, Colombo and the Cancer Genetics clinic at National Cancer Hospital, Maharagama.

2.2.2. Inclusion Criteria

Participants who meet all of the following criteria would be recruited into the study:

1. Subjects with a clinical diagnosis of an inherited cancer syndrome (e.g. HBOC, HNPCC or FAP and its variants) based on the following criteria:
    - Positive family history of cancer with multiple affected generations (autosomal dominant inheritance pattern with affected 1^{st}, 2^{nd} or 3^{rd} degree relatives)
    - Early age of onset (below 50 years of age)
    - Multiple primary cancers in an individual (e.g. colorectal and endometrial cancer)
    - Clustering of rare cancers (e.g. retinoblastoma, adrenocortical carcinoma, granulosa cell tumor of the ovary, ocular melanoma, or duodenal cancer)
    - Bilateral involvement (e.g., bilateral breast cancer or multifocal renal cancer)
    - Unusual presentation of cancer (e.g. male breast cancer)

2. Unaffected subjects with
    - Positive family history of cancer with multiple affected generations (autosomal dominant inheritance pattern with affected 1^{st}, 2^{nd} or 3^{rd} degree relatives)
    - An affected relative or relatives with onset of the disease at age <50 years
    - Clustering of rare cancers among relatives
    - A positive family history of unusual or atypical presentation of cancer

3. Country of origin – Sri Lanka

4. Being able to provide written informed consent

2.2.3. Exclusion Criteria

Participants who meet any of the following criteria would be excluded from the study:

1. Subjects without a clinical diagnosis or a family history of an inherited cancer syndrome (e.g. HBOC, HNPCC or FAP)
2. Country of origin – Non Sri Lankan
3. Being unable to provide written informed consent

2.2.4. Clinical Evaluation

Complete medical and surgical history was obtained from each participant including age of presentation, clinical symptomatology of cancer syndromes, family history – parental consanguinity, first and second degree relatives with clinically diagnosed cancer syndromes and their age of onset, current age or age at death, other associated primary cancers in the index case and/or relatives. The family pedigree included familial background up to 3 generations whenever possible. Other available laboratory reports such as biopsy and histopathological reports with tumour types and grades, mammography, MRI, ultrasonography and colonoscopy findings have been recorded. Additional clinical data has been gathered by examining the patients' medical records. Family histories reported by the probands are widely used in research and genetic counseling. In inherited cancer syndromes, the presence of a cancer in a 1^{st}, 2^{nd} or 3^{rd} degree relative is significant and useful in characterization and risk assessment. In cases where the patients' medical records lacked details of the family history and information regarding relatives

such as site, age of onset, age of death, histopathology reports etc., verification of family history of cancer as well as the site of cancer of the relatives was done by personally interviewing the relatives after obtaining their written informed consent and by examining their medical records whenever possible, or in the case of deceased relatives, their death certificates. Unaffected individuals with a positive family history were interviewed and a detailed family history was noted including three generational pedigrees with the type of cancer, age of onset, current age and if deceased, the age at death. Drug history and any other treatments received were recorded. Complete physical examination was done on all participants with their consent and in the presence of a chaperone. Patients' clinical data was entered into the data collection booklets (Annexure 3).

2.3. Guidelines used in clinical diagnosis of hereditary cancer syndromes

2.3.1. Statement of the American Society of Human Genetics on Genetic Testing for Breast and Ovarian Cancer Predisposition. Am J Hum Genet. Nov 1994; 55(5): i–iv

2.3.2. U.S. Preventive Services Task Force (USPSTF). Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility: recommendation statement. Ann Intern Med. 2005 Sep 6;143(5):355-61. http://www.preventiveservices.ahrq.gov

2.3.3. The American Society of Breast Surgeons. Position statement on *BRCA* Genetic Testing for Patients with and without Breast Cancer. https://www.**breasts**urgeons.org/**statements**

2.3.4. National Comprehensive Cancer Network (NCCN) Clinical Practical Guidelines in Oncology (NCCN Guidelines), Breast Cancer Version 3. 2014. www.NCCN.org/patients

2.3.5. American Congress of Obstetricians and Gynecologists **(**ACOG) Committee on Practice Bulletins**.** Hereditary breast and ovarian cancer syndrome. Gynecol Oncol. 2009 Apr; 113(1):6-11

2.3.6. Nancie Petrucelli, MS, Mary B Daly, MD, PhD, and Gerald L Feldman, MD, PhD, FACMG. *BRCA1* and *BRCA2* Hereditary Breast and Ovarian Cancer. GeneReviews, http://www.ncbi.nlm.nih.gov/books

2.3.7. National Comprehensive Cancer Network Clinical Practical Guidelines in Oncology (NCCN Guidelines), Colon Cancer Version 3. 2014. www.NCCN.org/patients

CHAPTER THREE

3.0. RESULTS

3.1. Overview

This chapter describes the demographic characteristics, different types of hereditary cancers with their basic characteristics and clinical characteristic features of each cancer syndrome in detail. Study population consisted of a total number of 55 participants and 43 (78.18%) of them were clinically diagnosed with an inherited cancer syndrome and 12 (21.82%) were unaffected individuals with a significant family history of inherited cancer syndromes.

3.2. Demographic characteristics

The age distribution of the study population ranged from 22 to 73 years with a mean age of 44.55±12.45 years. The median age was 45.0 years and the age group distribution of the study population is shown in Figure 12. The highest number of study subjects was in the 41 to 50 years age group accounting for 20 (36.4%) of the study population. Out of 43 affected individuals, 36 (83.7%), 4 (9.3%), 2 (4.7%) and 1 (2.3%) were Sinhalese, Sri Lankan Tamils, Burghers and Moors respectively. In the unaffected group eleven out of twelve were Sinhalese and the remaining individual was a Moor.

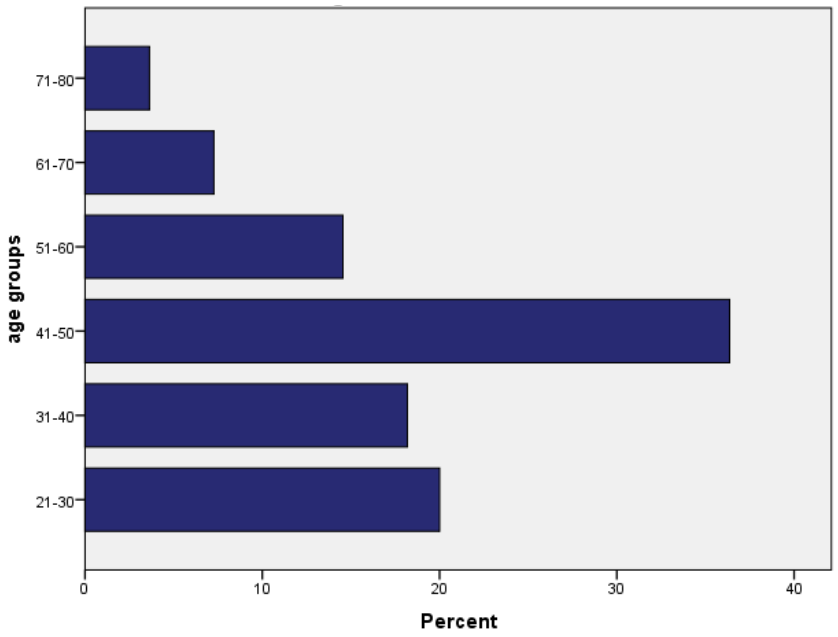

Figure 12: Age group distribution of the study population

The age in males ranged from 26 to 69 years with a mean age of 42.50±14.07 years while in females, it ranged from 22 to 73 years with a mean age of 45.00±12.19 years. There was no significant difference between mean the age of males and females in the study population (t = -0.571; p = 0.585).

The study population represented many districts of the country and the highest number was from Colombo district (43.6%) followed by Gampaha district (12.7%) (Figure 13). Out of the 12 asymptomatic individuals with a positive family history, 8 were from Colombo district and the other four from four different districts. They presented to the cancer clinics for risk assessment.

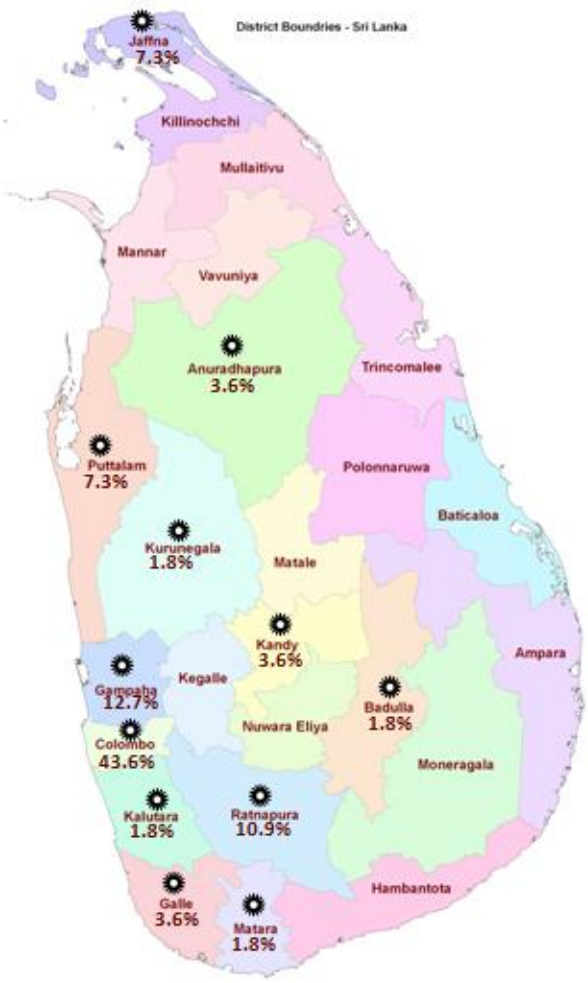

Figure 13: Districts where the study participants were present

3.3. Characteristics of affected and unaffected study groups

3.3.1. Affected study group

The age in males in the affected group ranged from 26 to 69 years with a mean age of 44.33±13.60 years while the age of onset ranged from 25 to 65 years with a mean age of 42.89±12.92 years. The age in females in the affected group ranged from 22 to 73 years with a mean age of 45.09±12.86 years and their age of onset ranged from 13 to 63 years with a mean age of 39.09±13.19 years. The mean age at recruitment and the mean age of onset between males

and female did not show a significant difference (mean age at recruitment (t = -0.155; p = 0.977, mean age of onset – t = 0.771; p = 0.923).

The age distribution of affected male and female participants is shown in figure 14 and 15 respectively.

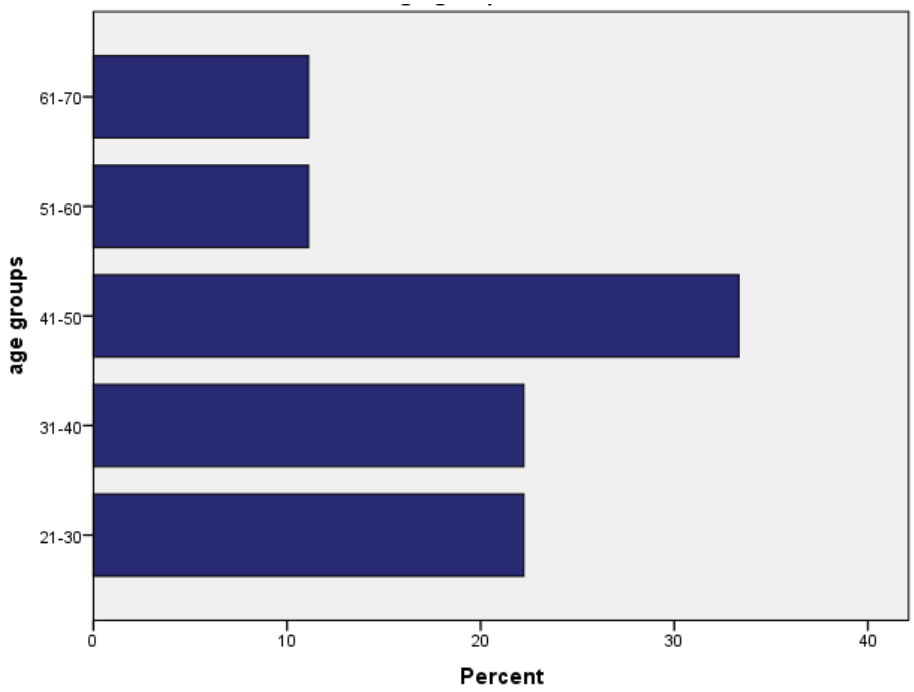

Figure 14: Age distribution of affected males in the study group

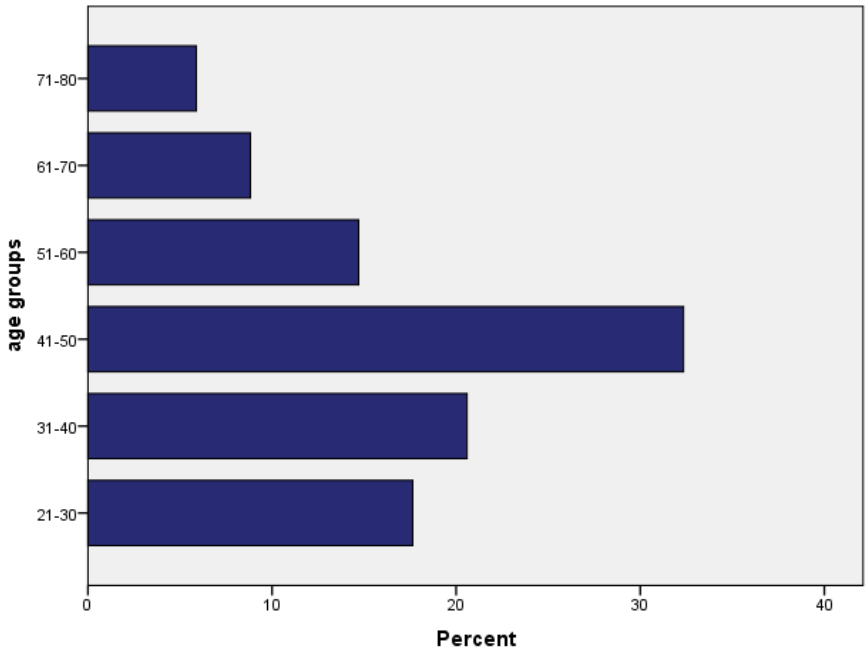

Figure 15: Age distribution of affected females in the study group

There were eight clinical diagnoses in the affected 43 individuals and they are illustrated in detail in figure 16 with their frequencies. Hereditary Breast and Ovarian cancer syndrome had the highest frequency in the affected study group with 34.9% (15/43) followed by hereditary non-polyposis colorectal cancer with a frequency of 32.6% (14/43).

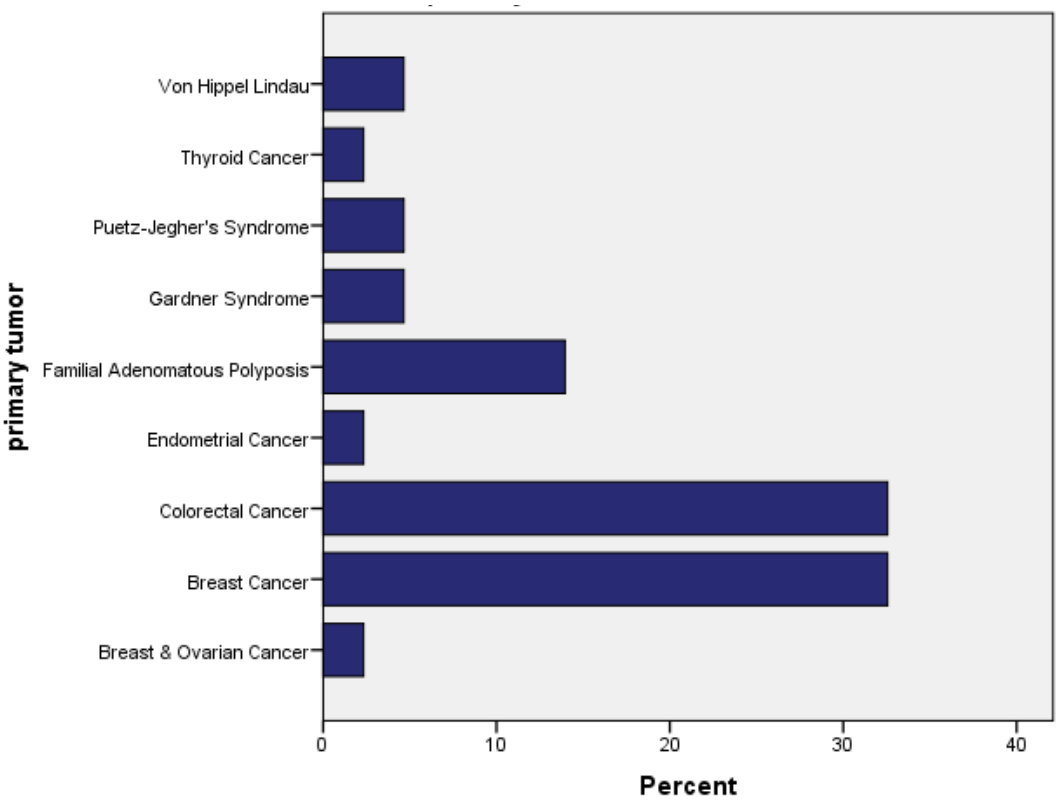

Figure 16: Types hereditary cancer in the affected group

Table 4 illustrates the mean age at recruitment, mean age of onset, male and female distribution and ethnicity in different types of cancer in the affected study group. All the individuals who had clinically diagnosed hereditary breast and ovarian cancer syndrome were females with a mean age at recruitment and onset of 48.8 and 43.6 years, respectively. Hereditary non-polyposis colorectal cancer was the most commonly diagnosed cancer in males (35.7%) followed by Familial Adenomatous Polyposis, Gardner syndrome and Von Hippel Lindau syndrome. Majority of individuals in each type were Sinhalese except for Gardner syndrome where both were Sri Lankan Tamils.

Table 4: Demographic characteristics of different types of hereditary cancer identified in the affected study group

Type of cancer	Total N (%)	Mean age at presentation (years)	Mean age of disease onset (years)	Number (%) of males	Number (%) of females	Ethnicity			
						Sinhalese N (%)	SL Tamils (%)	Moors (%)	Burghers (%)
Hereditary Breast and Ovarian cancer syndrome	15 (34.9)	48.8	43.6	00	15 (100)	13 (86.7)	-	-	2 (13.3)
Colorectal cancer									
HNPCC	14 (32.6)	46.4	43.5	05 (35.7)	09 (64.3)	13 (92.9)	1 (7.1)	-	-
FAP	06 (14.0)	38	35	02 (33.3)	04 (66.7)	4 (66.7)	1 (16.7)	1 (16.7)	-
PJS	02 (4.7)	34	16	00	02 (100)	2 (100)	-	-	-
Gardner Syndrome	02 (4.7)	35	29	01 (50.0)	01 (50.0)	-	02 (100)	-	-
Von Hippel Lindau	02 (4.7)	-	-	01 (50.0)	01 (50.0)	02 (100)	-	-	-
Miscellaneous	02 (6.9)	-	-	00	02 (100)	02 (100)	0	-	-
Total	43								

A positive family history of cancer in subsequent three generations was found in 62.8% (27/43) while 34.9% (15/43) did not have a positive family history of cancer. Out of 43 affected patients only one (2.3%) did not know about her family history at all (Figure 17).

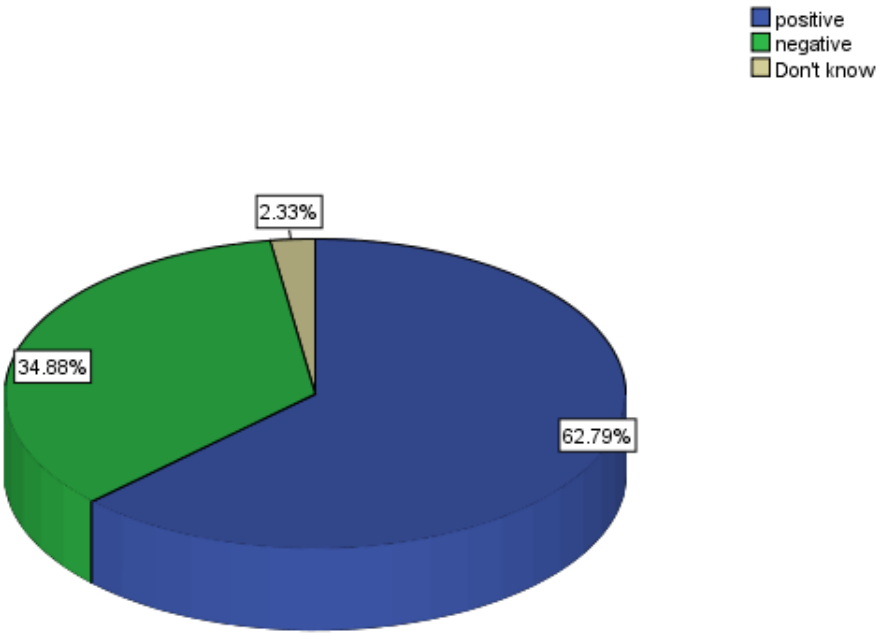

Figure 17: Family history details in patients with a cancer syndrome

3.3.2. Unaffected study group

In this study, a three-generational pedigree was constructed and history of type of cancer, age of onset and deceased age in relatives on either side of the family were recorded. In the unaffected group, there was only one unaffected male with a positive family history who was 26 years old. The age range of unaffected females was 25 to 59 years with a mean age of 44.73±10.37 years. Their demographic data is summarized in Table 5.

Table 5: Demographic data of unaffected individuals with a positive family history of hereditary cancers

	Total	Mean age of presentation (years)	Number (%) of males	Number (%) of females	Ethnicity					District of presentation		
					Sinhalese	Moor	Burgher	Colombo	Galle	Gampaha	Kurunegala	Puttalam
Unaffected participants with a positive family history	12	43.17	01 (8.3%)	11 (91.7%)	11 (91.7%)	01 (8%)	-	08 66.7%	01 8.3%	01 8.3%	01 8.3%	01 8.3%

Age group distribution of the unaffected group with positive family history is shown in figure 18. The highest percentage of unaffected individuals was present in the 41-50 years age group followed by 21-30 years age group.

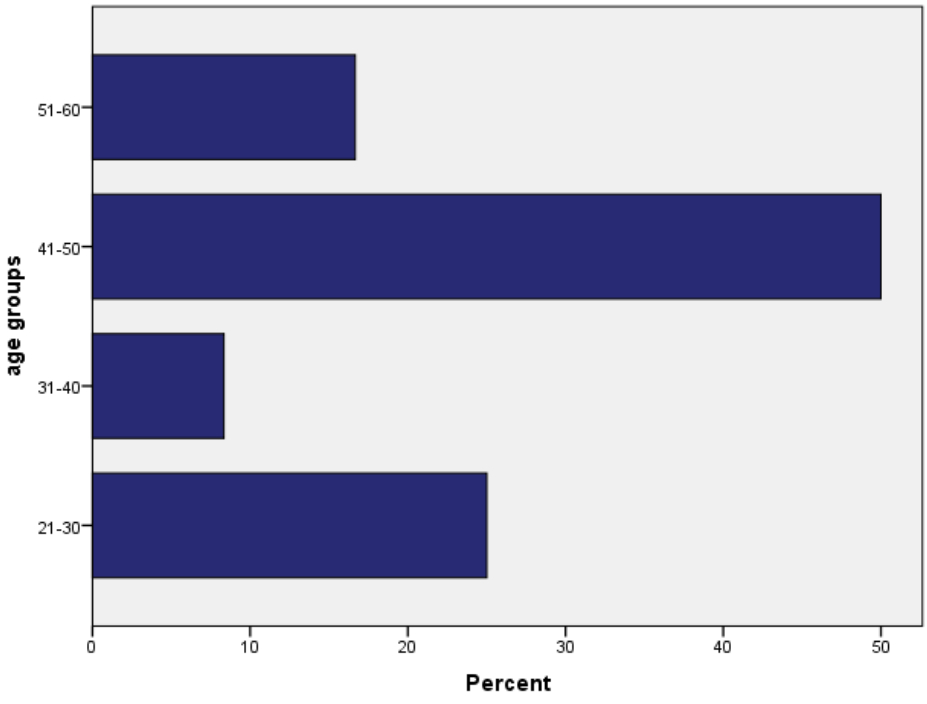

Figure 18: Age group distribution in unaffected participants with a positive family history

Analysis of the three generational pedigrees showed that out of the 12 families, 10 had a 1st degree relative or relatives who were diagnosed with a carcinoma. All the participants were able to provide history of 1st and 2nd degree relatives but 16.7% were unable to provide history of 3rd degree relatives (Table 6).

Table 6: Availability of history of cancer in 1st, 2nd and 3rd degree relatives of unaffected individuals

Degree of relatedness	**Presence of family history of cancer**		
	Yes **N (%)**	**No** **N (%)**	**Not known** **N (%)**
1st degree relatives	10 (83.3%)	02 (16.7%)	-
2nd degree relatives	09 (75.0%)	03 (25.0%)	-
3rd degree relatives	05 (41.7%)	05 (41.7%)	02 (16.7%)

A positive family history of cancer in all three degrees of relatives was seen in 50% of families. However there were no families with only 2nd or 3rd degree relatives with a history of cancer. Table 7 presents a summary of presence of family history of cancer in each degree of relatives and in combination.

Table 7: Number of unaffected individuals with positive family history of cancer among 1st, 2nd and 3rd degree relatives

	Number (%) of families with positive family history of cancer						
	1st degree relatives only	**2nd degree relatives only**	**3rd degree relatives only**	**1st& 2nd degree relatives only**	**1st& 3rd degree relatives only**	**2nd & 3rd degree relatives only**	**All 1st,2nd& 3rd degree relatives**
Yes	03 (25%)	00	00	02 (16.7%)	00	01 (8.3%)	06 (50%)
No	09 (75%)	12 (100%)	12 (100%)	10 (83.3%)	12 (100%)	11 (91.7%)	06 (50%)

Detailed analysis of family history of each unaffected individual is given in table 8 and 9. Table 8 gives the frequency and percentages of presence of a relative or relatives with a positive cancer history in relation to their degree of relatedness. Out of 12 individuals, 3 have undergone molecular genetic testing for *BRCA1* mutations and found to carry the same mutation that their affected relatives had. The three screened individuals had a positive family of affected 1st degree relatives with early age of onset of breast cancer.

The type of cancer in each affected individual and their age of onset are mentioned in the table 9 for each family. Most of the families were affected with breast cancer (45.6%) with or without ovarian cancer. Out of 14 first degree relatives 9 (64.3%) had developed the cancer before age of 50 years.

Table 8: Details of family history in each unaffected individual

Individual Identification	Age at Recruitment (years)	Sex	Genetic testing	Positive family history	Presence of affected 1st degree relatives	No. of affected 1st degree relatives	Presence of affected 2nd degree relatives	No. of affected 2nd degree relatives	Presence of affected 3rd degree relatives	No. of affected 3rd degree relatives
01	49	F	-	+	+	01	+	01	+	01
02	50	F	-	+	+	01	+	04	+	01
03	46	F	-	+	+	02	+	02	-	-
04	54	F	-	+	+	01	+	02	+	01
05	41	F	-	+	+	01	+	02	+	02
06	29	F	c.5408delG *BRCA1*	+	+	01	+	02	-	-
07	39	F	c.2838G>T *BRCA1*	+	+	01	-	-	-	-
08	50	F	c.68_69delG *BRCA1*	+	+	02	+	02	+	03
09	50	F	-	+	-	-	+	01	+	03
10	59	F	-	+	+	02	-	-	-	-
11	26	M	-	+	+	01	-	-	-	-
12	25	F	-	+	+	01	+	01	+	04

Table 9: Type of cancer and age of onset in each relative in 3 consecutive generations

Individual Identification	Type of cancer in 1st degree relative	Age of onset < 50 years / > 50 years	Type of cancer in 2nd degree relative	Age of onset < 50 years / > 50 years	Type of cancer in 3rd degree relative	Age of onset < 50 years / > 50 years
01 (i)	Endometrial	< 50 yrs	Breast Ca	> 50 years	Endometrial	-
02 (i) **(ii)** **(iii)** **(iv)**	Ovarian	> 50 years	Gastric Ca Endometrial Oral Skin	> 50 years > 50 years > 50 years < 50 years	Thyroid	< 50 years
03 (i) **(ii)**	Lung Breast	< 50 yrs < 50 yrs	Endometrial Lymphoma	> 50 years > 50 years		
04 (i) **(ii)**	Breast	> 50 years	Breast Colon	> 50 years < 50 years	Breast	> 50 years
05 (i) **(ii)**	Breast	< 50 yrs	Breast Breast	< 50 yrs < 50 yrs	Breast Breast	- -
06 (i) **(ii)**	Breast	> 50 years	Breast Breast	< 50 yrs > 50 years		
07 (i)	Breast	< 50 yrs				
08 (i) **(ii)** **(iii)**	Ovarian Breast	< 50 yrs > 50 years	Breast Breast	> 50 years > 50 years	Breast Breast Breast	< 50 yrs < 50 yrs -
09 (i) **(ii)** **(iii)**			Breast	> 50 years	Ovarian+Brain Ovarian Ovarian	> 50 years < 50 yrs > 50 years
10 (i) **(ii)**	Endometrial Endometrial	< 50 yrs > 50 years				
11 (i)	FAP	< 50 yrs				
12 (i) **(ii)** **(iii)** **(iv)**	Endometrial	< 50 yrs	Colon	> 50 years	Colon Colon Colon Colon	> 50 years < 50 yrs > 50 years < 50 yrs

3.4. Phenotypic characterization of cancer syndromes present in the affected group

There were six different types of cancers reported in the affected group while two families did not have a precise clinical diagnosis. Phenotypic characteristics of each type of cancer are described below in table 10 to 15.

3.4.1. Hereditary Breast and Ovarian Cancer syndrome (HBOC)

Hereditary Breast and Ovarian Cancer syndrome (HBOC) accounted for the highest number (34.9%) of participants in the study cohort. All the HBOC diagnosed participants were females with mean age of onset 43.6 years and 73.3% were diagnosed before or at the age of 50 years. Lump in the left breast was the commonest presentation (46.7%) while only one participant was diagnosed with a bilateral breast cancer. Only 20% of individuals had triple negative breast cancer while it was not assessed in 20% of patients. Only one patient had a combination of breast and ovarian cancer. Table 10 gives a description of HBOC syndrome characteristics that were found in the affected group.

Table 10: Characteristics of patients with HBOC syndrome in the study cohort

HBOC	**Number of individuals**	**Percent (%)**
Total Number of individuals with HBOC	15	
Clinical presentation		
- R/S Breast lump	04	26.7
- L/S Breast lump	07	46.7
- B/L Breast lumps	01	6.7
- Nipple discharge	00	-
- Nipple retraction	00	-
- Skin changes	01	6.7
- Painful breast	01	6.7
- Abdominal lump	00	-
- Abdominal pain	01	6.7
- Altered menstrual cycles	00	-
- Other	00	-

Number of female patients	15	100
Number of male patients	00	-
Mean age at recruitment	48.8 years	
Mean age of disease onset	43.6 years	
Number of individuals with onset < 50 years	11	73.3
Number of affected 1st degree relatives with the age of onset < 50 years	08	20.5
Number of affected 2nd degree relatives with the age of onset < 50 years	03	7.6
Number of affected 3rd degree relatives with the age of onset < 50 years	05	12.8
Triple Negative breast cancer	03	21.4
Multiple primary cancers in an individual	01	6.7
Number of individuals with positive family history	10	66.7
Histological type - Invasive duct carcinoma - Ductal carcinoma in situ - Serous Papillary adenocarcinoma - Epithelial ovarian cancer - Fallopian tube cancer - Multifocal cancer - Other	 09 01 01 00 00 01 01	 60.0 6.7 6.7 - - 6.7 6.7
Tumor Differentiation - Well - Moderate - Poor - Not available	 06 02 00 07	 40.0 13.3 - 46.7
Surgical intervention - Unilateral mastectomy - Bilateral mastectomy - Axillary clearance - Oophorectomy	 05 01 05 01	 33.5 6.7 33.5 6.7
Prophylactic therapy - Prophylactic mastectomy - Prophylactic oophorectomy - Chemoprevention	 00 01 01	 - 6.7 6.7

Chemotherapy	12	80.0
Radiotherapy	06	40.0

3.4.2. Hereditary Non-polyposis Colorectal Cancer (HNPCC)

Hereditary Non-polyposis Colorectal Cancer (HNPCC) was the second most common cancer in the cohort (32.6%). Most of the HNPCC diagnosed individuals were females (64.3%) and their commonest clinical presentation was per rectal bleeding (49.7%) followed by altered bowel habits (42.6%). Mean age of onset of disease was 43.5 years and 78.6% were diagnosed before the age of 50 years. Characteristic features that were assessed have been mentioned in Table 11.

Table 11: Characteristics of patients with HNPCC in the study cohort

HNPCC	**Number of individuals**	**Percent (%)**
Total number of individuals with HNPCC	14	
Clinical presentation - Altered bowel habits - Rectal bleeding - Chronic constipation - Loss of weight - Loss of appetite - Abdominal pain - Blood and mucous diarrhoea - Other	 06 07 02 05 04 04 01	 42.6 49.7 14.2 35.5 28.4 28.4 7.1
Number of female patients	09	64.3
Number of male patients	05	35.7
Mean age at recruitment	46.4 years	
Mean age of disease onset	43.5 years	
Number of individuals with onset < 50 years	11	78.6

Affected 1st degree relatives with the age of onset < 50 years	03	21.4
Affected 2nd degree relatives with the age of onset < 50 years	03	21.4
Affected 3rd degree relatives with the age of onset < 50 years	04	28.6
Number of individuals with positive family history	08	57.1
Multiple primary cancers in an individual	2	14.3
Histological type - Adenocarcinoma - Other	14	100
Tumor Differentiation - Well - Moderate - Poor	 00 12 01	 - 85.7 7.1
Tumor site - Proximal to splenic flexure - Distal to splenic flexure	 03 11	 21.3 78.7
Surgical intervention - Right Hemicolectomy - Left Hemicolectomy - Total colectomy - Transverse loop colectomy - Anterior resection	01 03 05 01 03	7.1 21.3 35.5 7.1 21.3
Prophylactic colectomy	00	-
Extracolonic cancers (personal/relatives) - Breast - Stomach - Kidney	 03 01 01	 21.4 7.1 7.1
Chemotherapy	08	57.1
Radiotherapy	04	28.6

3.4.3. Familial Adenomatous Polyposis (FAP) and its variants

There were 6 patients diagnosed with Familial adenomatous polyposis and 2 were under the FAP variant category. The FAP variant was Gardner Syndrome in both and they were diagnosed through their clinical manifestations and histology findings. Male to female ratio was 1:2 and all six were diagnosed less than 50 years of age including the two individuals with Gardner Syndrome. A positive family history was observed in 50% of families with FAP as well as Gardner syndrome. Other features which were analyzed are stated in Table 12 and 13.

Table 12: Characteristics of patients with FAP in the study cohort

FAP	**Number of individuals**	**Percent (%)**
Total number of individuals with FAP	06	
Clinical presentation - Altered bowel habits - Rectal bleeding - Chronic constipation - Loss of weight - Loss of appetite - Abdominal pain - Blood and mucous diarrhoea - Other	 03 03 00 02 03 00 01 01	 50 50 - 33.3 50 - 16.7 16.7
Number of female patients	04	66.7
Number of male patients	02	33.3
Number of individuals with positive family history	03	50
Mean age at recruitment	38 years	
Mean age of disease onset	36 years	
Number of individuals with onset < 50 years	06	100
Multiple primary cancers in an individual	02	33.3

Histological type - Tubulour - Villous - Tubulovillous - Adenocarcinoma	02 01 00 03	33.3 16.7 - 50
Tumor Differentiation - Well - Moderate - Poor	 00 05 00	 - 83.3 -
Surgical intervention - Right Hemicolectomy - Left Hemicolectomy - Total colectomy - Transverse loop colectomy - Anterior resection	 00 00 05 00 01	 - - 83.5 - 16.7

Table 13: Characteristics of patients with FAP variant (Gardner Syndrome) in the study cohort

FAP Variants (Gardner Syndrome)	**Number of individuals**	**Percent (%)**
Total number of individuals with FAP variants	02	
Clinical presentation - Altered bowel habits - Rectal bleeding - Chronic constipation - **Osteoma**/**Sebaceous cysts**/Fibromas/Desmoid tumors - Loss of weight - Loss of appetite - Abdominal pain - Blood and mucous diarrhoea - Other	 01 01 00 02 00 00 00 00 01	 50 50 - 100 - - 50 - -
Number of female patients	01	50
Number of male patients	01	50
Number of individuals with onset < 50years	02	
Number of individuals with positive family history	01	50

Multiple primary cancers in an individual	00	
Histological type - Tubulour - Villous - Tubulovillous - Adenocarcinoma	 01 00 01 00	 50 - 50 -
Tumor Differentiation - Well - Moderate - Poor	 00 01 01	 - 50 50
Surgical intervention - Right Hemicolectomy - Left Hemicolectomy - Total colectomy - Transverse loop colectomy - Anterior resection	 00 00 01 00 00	 - - 50 00 00

3.4.4. Peutz-Jeghers Syndrome (PJS)

Peutz-Jeghers syndrome was diagnosed in two individuals with hamartomatous polyps and characteristic mucocutaneous pigmentations. Both were diagnosed before the age of 50 years and only one had a positive family history (Table 14).

Table 14: Characteristics of patients with PJS in the study cohort

PJS	Number of Individuals	Percent (%)
Total number of individuals with PJS	02	
Clinical presentation - Altered bowel habits - Rectal bleeding - Mucosal hyperpigmentation - Chronic constipation - Vomiting - Loss of weight - Loss of appetite - Abdominal pain - Blood and mucous diarrhoea - Other	 00 00 02 01 02 00 00 01 00	 - - 100 50 100 - - 50 -

Number of female patients	02	100
Number of male patients	00	
Number of individuals with onset < 50 years	02	100
Number of individuals with positive family history	02	100
Multiple primary cancers in an individual	01	50
Histological type - Hamartomatous polyps	 02	 100
Surgical intervention - Duodenectomy - Polypectomy - Colectomy - Other	 01 02 00 01	 50 100 - 50

3.4.5. Von Hippel-Lindau (VHL)

Von Hippel-Lindau was diagnosed in two individuals in the cohort and one individual had undergone molecular genetic testing for confirmation of diagnosis. Both of them were diagnosed before the age of 50 years and had positive family history. At the time of recruitment their ages were 29 and 69 years, respectively and they presented with multiple heamangioblastomas in the brain and renal cell carcinoma, respectively. Other features are summarized in the table 15.

Table 15: Characteristics of patients with VHL in the study cohort

VHL	Number of individuals	Percent (%)
Total number of individuals with VHL	02	
Number of female patients	01	50.0%
Number of male patients	01	50.0%
Ethnicity - Sinhalese	 02	 100%

Number of individuals with the onset < 50 years	02	100
Multiple primary cancers in an individual	00	-
Histological type - Haemangioblastoma of brain/spine/retina - Renal cell carcinoma - Adrenal or extra-adrenal pheochromocytoma	 01 01 00 00	 100 100 -
Metastasis - Positive - Negative - Not assessed	 00 02 00	 - 100 -
Number of individuals with positive family history	01	50

3.5. Miscellaneous

Two out of 43 affected individuals in the cohort could not be clearly categorized under any major type of hereditary cancer syndrome. Their clinical descriptions and pedigrees are stated below.

Family No 1

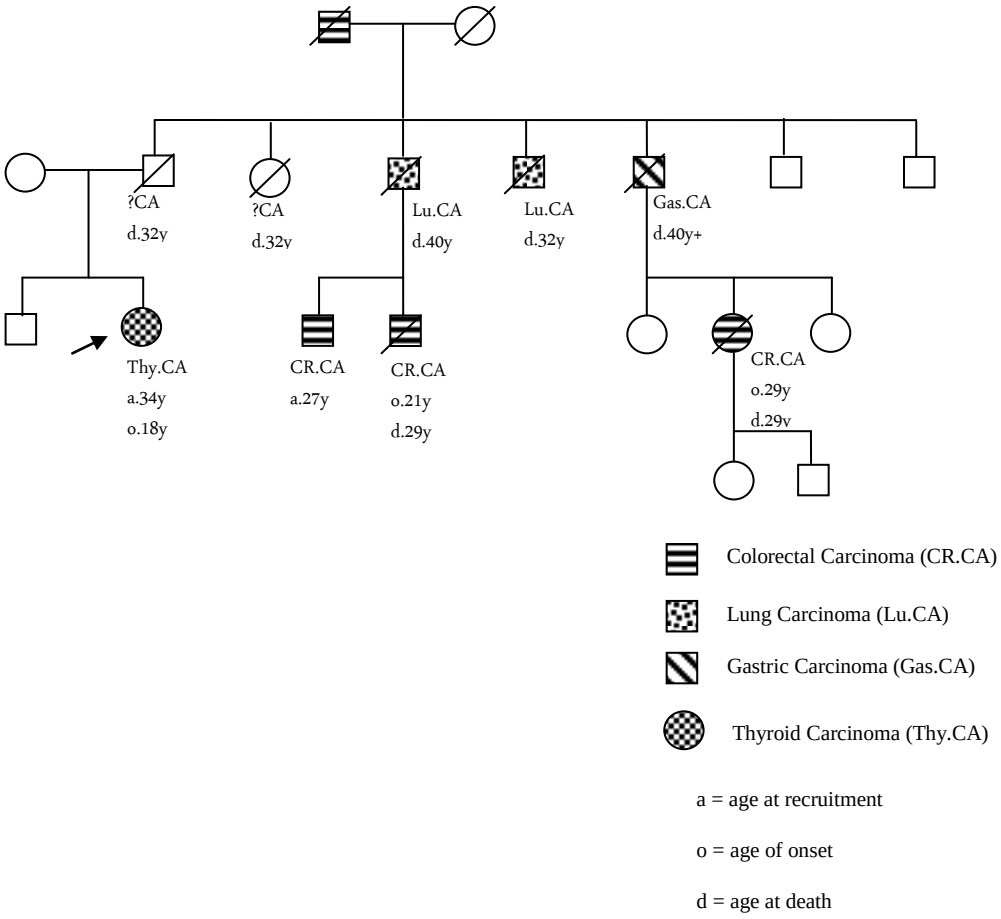

Figure 19: Pedigree of Family 1 under miscellaneous category

Proband was a 34 years old female diagnosed with a papillary carcinoma of the thyroid. She had a family history of four 2nd degree and three 3rd degree paternal relatives who were affected with different types of cancers. Two 2nd degree relatives had lung carcinoma which was diagnosed at less than 50 years of age. One 2nd degree and a 3rd degree relative had gastric carcinoma and they had been diagnosed and were deceased before the age of 50 years. The other two 3rd degree relatives had colorectal carcinoma and one had died at the age of 21 years and the other at the age of 27 years. Her paternal grandfather also had a colorectal carcinoma but the age of onset and death were not recorded (Figure 19).

Family No 2

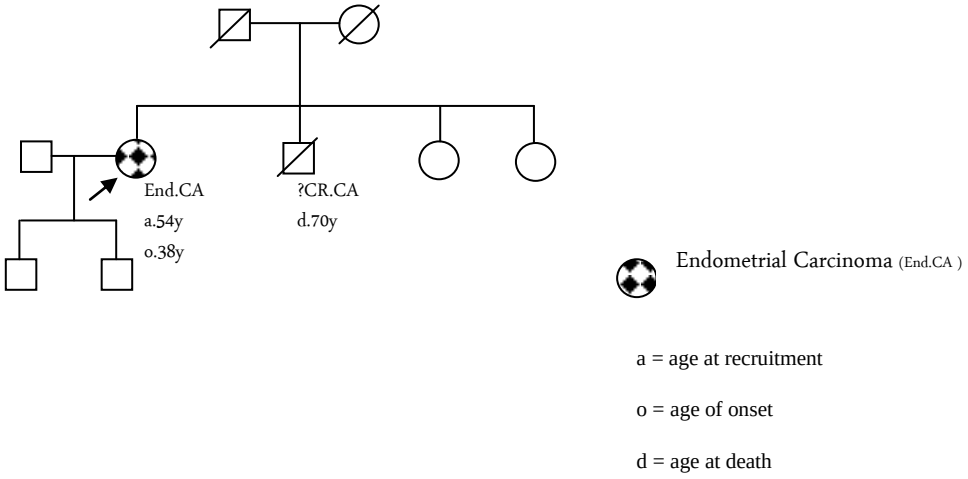

Figure 20: Pedigree of Family 2 under miscellaneous category

A 54 years old female presented with two primary cancers. She was diagnosed with a well differentiated adenocarcinoma of the endometrium at the age of 38years and treated with radiotherapy. Her brother had died from a carcinoma at the age of 70 years and it was soon after diagnosis. The primary site was not known in definite. No other significant family history was reported (Figure 20).

3.6. Clinical criteria to diagnose Hereditary Breast and Ovarian Cancer syndrome and Hereditary Non-polyposis Colorectal Cancer which are based on various professional guidelines.

3.6.1. Hereditary Breast and Ovarian Cancer syndrome

A mutation in *BRCA1* or *BRCA2* genes should be suspected in individuals with a personal or family history (1^{st}, 2^{nd}, or 3^{rd} degree relatives in either lineage) of any of the following characteristics, which are based on various professional society guidelines which were mentioned in section 2.3.

- Breast cancer diagnosed at age 50 years or younger
- Ovarian cancer
- Multiple primary breast cancers either in the same breast or opposite breast
- Both breast and ovarian cancer
- Male breast cancer
- Triple-negative (estrogen receptor negative, progesterone receptor negative, and HER2/neu [human epidermal growth factor receptor 2] negative) breast cancer
- Pancreatic cancer with breast or ovarian cancer in the same individual or on the same side of the family
- Ashkenazi Jewish ancestry
- Two or more relatives with breast cancer, one under age 50 years
- Three or more relatives with breast cancer at any age
- A previously identified *BRCA1* or *BRCA2* mutation in the family

Note: "Breast cancer" includes both invasive cancer and ductal carcinoma in situ (DCIS). "Ovarian cancer" includes epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer.

The fifteen patients with hereditary breast and ovarian cancer syndrome and nine asymptomatic individuals with positive family history of breast or ovarian cancer were analyzed according to the above criteria and they are summarized in the table 16.

Table 16: Clinical evaluation of study participants with HBOC

(*BRCA1* and *BRCA2* Hereditary Breast and Ovarian Cancer. GeneReviews. http://www.ncbi.nlm.nih.gov/books)

Characteristic features suggestive of HBOC	**Number of families**	**Percentage**
Breast cancer diagnosed at age 50 years or younger	16	73.3%
Ovarian cancer	5	20.8%
Multiple primary breast cancers either in the same breast or opposite breast	4	16.7%
Both breast and ovarian cancer	3	12.5%
Male breast cancer	0	0
Triple negative breast cancer	3	12.5%
Pancreatic cancer with breast or ovarian cancer in the same individual or on the same side of the family	0	0
Ashkenazi Jewish ancestry	0	0
Two or more relatives with breast cancer, one under age 50	8	33.3%
Three or more relatives with breast cancer at any age	9	37.5%
A previously identified *BRCA1* or *BRCA2* mutation in the family	4	16.7%

3.6.2. Hereditary Non-polyposis Colorectal Cancer (HNPCC)

Amsterdam Criteria I, Amsterdam Criteria II and revised Bethesda Guidelines were used in the clinical diagnosis of HNPCC. Table 17 gives the evaluation of our study participants under Amsterdam criteria I and Amsterdam II criteria.

Table 17: Clinical evaluation of study participants with HNPCC by Amsterdam criteria

Amsterdam Criteria I	**Number of families**	**Percentage**
Three or more family members, one of whom is a first-degree relative of the other two, with a confirmed diagnosis of colorectal cancer	3	21.4%
Two successive affected generations	6	42.8%
One or more colon cancers diagnosed before age 50 years Exclusion of familial adenomatous polyposis (FAP)	13	92.8%
All three categories fulfilled	***3***	***21.4%***
Amsterdam Criteria II		
Three or more family members (one of whom is a first-degree relative of the other two) with HNPCC-related cancers	3	21.4%
Two successive affected generations	6	42.8%
One or more of the HNPCC-related cancers diagnosed before age 50 years Exclusion of familial adenomatous polyposis(FAP)	13	92.8%

(HNPCC related cancer – colorectal, endometrium, stomach, ovaries, pancreas, ureter & pelvis, billiary tract, brain, sebaceous gland adenomas, keratoacanthomas, small intestine carcinoma)

The National Cancer Institute published the Bethesda guidelines for the identification of individuals who should receive genetic testing for HNPCC related tumors. Table 18 shows the Bethesda guidelines and the evaluation of patients with HNPCC in our study cohort.

Table 18: Bethesda guidelines and clinical evaluation of study participants with HNPCC

Bethesda Guideline	**Number of families**	**Percentage**
Colorectal cancer (CRC) diagnosed <50 years	12	85.7%
2 HNPCC cancers ** in one person (can be 2 primary CRC)	01	7.1%
CRC with MSI-H histology (**tumor infiltrating lymphocytes***, Crohn's like lymphocytic reaction, mucinous/**signet ring differentiation***, or medullary growth pattern) diagnosed <50 years	03	21.4%
CRC or HNPCC-associated tumors** diagnosed under age 50 years in at least 1 first-degree relative	03	21.4%
CRC or HNPCC-associated tumor** diagnosed at any age in 2 first- or second-degree relatives	04	28.6%
Presence of a single feature mentioned above	*13*	*92.8%*

(**colorectal, endometrial, stomach, small intestine, renal pelvis/ureter, ovarian cancer, pancreatic cancer, hepatobiliary malignancies, brain tumors (glioblastoma), sebaceous tumor and keratocanthoma)

(* histology types present in our study participants

CHAPTER FOUR

4.0. DISCUSSION

Cancer genetics plays a major role in modern clinical practice where mutational analysis benefits in many ways including exact diagnosis of cancer syndromes. Even though genetic testing has an immense value in diagnosis, counseling and risk assessment of patients with hereditary cancer syndromes, at present, patients in a developing country like Sri Lanka cannot afford the high cost of testing. Therefore, knowledge of the clinical characteristics plays a major role in appropriately identifying patients with hereditary cancer syndromes for referral for genetic assessment, counseling, screening and surveillance. Hereditary cancer syndromes have their own characteristic features and diagnostic criteria which are useful in the clinical diagnosis of different types of hereditary cancers. In this study, the characteristic clinical features of hereditary cancer syndromes in a cohort of Sri Lankan families with hereditary cancers are described. Scientific literature shows that several studies have been done in other countries to assess the characteristic clinical features of hereditary cancer syndromes [27],[50],[17],[51]. To our knowledge this is the first study done in Sri Lanka on the clinical characterization of hereditary cancer syndromes.

4.1. Demographic characteristics

Our study group consisted of 55 participants and 43 (78.8%) of them were diagnosed with a hereditary cancer while 12 (21.82%) were asymptomatic individuals with a positive family history of hereditary cancer. The highest numbers of study participants were in the 41 to 50 years age group. Considering the general population, National Cancer Registry has stated that the highest number of patients diagnosed with cancer presented in the 70 to 74 years age group in 2007. This includes hereditary as well as non hereditary (sporadic) cancer patients [15].

Hereditary cancers account for 5-10% of all cancers worldwide and most of these cancers occur before the age of 50 years[52]. Due to our study sample being selectively focused on the hereditary cancer patient population, our mean age of diagnosis is comparatively lower than that of the National Cancer Registry (45 years versus 72 years). In the affected study group, there were 35 (81.4%) patients with the age of onset less than 50 years of age. Positive family history was present in 27 families (62.8%) while consanguinity was observed in 3 (7.0%) families. Brandt *et al.* reported that hereditary cancer syndromes are likely to occur at an early age, particularly among individuals with a positive family of affected 1st degree relatives compare to sporadic cancers [29].

There were 8 cancer types which were diagnosed clinically among the 43 affected patients. They presented from different districts of the country but most were from the Western province. According to the Department of Census and Statistics in Sri Lanka, the top five districts with the highest number of population density in 2012 were Colombo, Gampaha, Kurunegala, Kandy and Kalutara [53]. The relatively higher presentation of patients from the Western province was most probably due to the high population density in that area. Also despite being hereditary cancers, according to the two hit theory, one mutation is an inherited germline mutation while the other occurs due to mutagenesis during the lifespan of the individual from exposure to various carcinogens. Colombo being the industrial and economical hub of the country, individuals residing in these regions are constantly exposed to environmental pollutants and other toxins. Therefore the population residing in the Western province may have been exposed to a higher degree of risk compared to populations living in other provinces of the country.

4.2. Characteristic clinical features of hereditary cancer syndromes

4.2.1. Hereditary Breast Cancer Syndromes

Hereditary breast cancer syndromes include mainly Hereditary Breast and Ovarian Cancer Syndrome (HBOC), Cowden syndrome, Li-Fraumeni syndrome (LFS), Peutz-Jeghers syndrome (PJS), Ataxia-telangiectasia (AT) and Hereditary Diffuse Gastric Cancer (HDGC). To identify women at risk for hereditary breast cancer syndromes, it is important to obtain an adequate, three generational family history, including ethnic background [54].

In this study cohort, there were 15 patients who were clinically diagnosed as HBOC. All were females. Their mean age at recruitment and mean age of disease onset were 48.8 and 43.6 years respectively. Various professional societies have developed guidelines for clinical identification of individuals who carry genetic mutations in *BRCA1* and *BRCA2* genes which are the commonest genes involved in HBOC [21],[22],[55],[23],[24]. According to the guidelines, individuals with hereditary breast and ovarian cancer syndrome are expected to have an early age of onset (<50yrs). The age of onset of the disease was less than 50 years in 73.3% (11/15) of the patients with HBOC in this study cohort. The mean age of onset of HBOC in the study cohort was 43.6 years and agrees with the criteria stated in the guidelines. Mutational analysis of *BRCA1* and *BRCA2* genes in Sri Lankan patients and at risk individuals was done by De Silva *et al.* and the study showed that the mean age of disease onset was 46.97± 9.05 years in patients with hereditary breast cancer [56], which is similar to the findings in this study. Several studies have been conducted on hereditary breast cancer and they have reported early age of onset of HBOC in different populations [57],[52],[29]. Hereditary breast and ovarian cancer syndrome was studied in eleven Asian countries and most of them have focused on early onset cases and found that majority of cases occur before the age of 50 years in most East Asian countries..

Mutation studies on *BRCA1* and *BRCA2* genes in the Asian populations have reported a higher proportion of *BRCA2* rather than *BRCA1* gene mutations in Asian populations. These studies noted that the mutations described for Asian patients with HBOC were more unique and specific for different populations in Asia when compared to founder mutations in European populations [58].

Out of 15 patients, most of the individuals had well differentiated (40%), invasive duct carcinoma (60%), on the left breast (46.7%). Garber and Offit have stated that the *BRCA1* associated cancers are usually high grade, poorly differentiated, infiltrating duct carcinomas and stain negative for estrogen receptor (ER), progesterone receptor (PR) and HER2/neu receptor [27]. Honrado *et al.* has reviewed several studies on the histopathology of *BRCA* associated cancer in several groups [59]. He reported that *BRCA1* associated tumors are frequently grade 3 (poorly differentiated) whereas *BRCA2* tumors are grade 2 (moderately differentiated) or grade 3. Invasive duct carcinoma is the most common histological type in all forms of hereditary breast cancer and also in hereditary non-*BRCA1/2* breast cancers [59]. A study was done on Spanish families with at least three cases of female breast cancer and one of them with onset <50 years. This study showed that 75% of cases were non-*BRCA1/2* mutations. Most of the familial non-*BRCA1/2* patients were found to have grade 1 tumors (27%-50%) when compared to *BRCA1/2* associated tumors [60],[61]. The histopathological features and clinical data can be used to predict presence of *BRCA1* mutations, while prediction of *BRCA2* and non-*BRCA1/2* status can be done to a lesser extent [59]. The main histopathology type found in the study group was well differentiated carcinoma and none of them had a poorly differentiated carcinoma. Genetic studies will need to be carried out in future in this study cohort to determine whether they are associated with *BRCA1/2* mutations or not. In this study, there were only 3 (21.4%) individuals with triple

negative breast cancer. Eight individuals had either all three receptors positive or positive-negative combinations of three receptors and in 3 individuals the tests were not done. ER-negative tumors are highly associated with *BRCA1* mutations and also poorly differentiated and diagnosed at an early age. Compared to *BRCA2*, *BRCA1* has a distinctive morphological and immunohistochemical phenotype with negative ER, PR and HER2 and positive p53 [61]. In familial non-*BRCA1/2* tumors there is a 75% and 67% positive expression of ER and PR receptors respectively. These values give a clear differentiation for *BRCA1* tumors but not for *BRCA2*. HER2 expression is low in non-*BRCA1/2* carcinomas [62]. A study was done to compare the profile of breast cancer in a group of women in Sri Lanka with regional data by Lokuhetti *et al* [34]. They have assessed 814 Sri Lankan women with breast cancer. Their assessment included patient-tumor characteristics with the immune profile. In all, 52% had moderately differentiated carcinomas and 86.3% had ductal invasive carcinoma. ER and HER2 were expressed in 31.7% and 14.5%, respectively. HER2 expression was lower in ER positive tumors and well differentiated tumors were frequently ER positive and HER2 negative. The authors concluded that when compared to regional breast cancer profiles, the breast cancer profile of their study cohort is largely comparable except for the low expression of ER [34]. ER expression in well differentiated tumors in our study cohort is compatible with the findings in studies reported in literature. Nine patients has undergone receptor assessment in our study and four (44.4%) had positive ER with negative HER2. ER was positive in 5(33.3%) individuals who had well differentiated duct carcinoma and this finding may suggest underlying non-*BRCA1/2* mutations according to literature. Therefore histopathological features of breast cancer tumors can be used in the prediction of the molecular status and aid in the planning genetic testing of patients. Our study cohort included four individuals who had undergone genetic testing. Out of

the four only one had a histopathological report. Genetic testing of this patient revealed c.3113A>G mutation in *BRCA1* gene. She was diagnosed with a moderately differentiated, invasive duct carcinoma of breast which was identified after an initial ovarian cancer which was diagnosed at the age of 47 years. Serous papillary adenocarcinoma was the histopathological finding of the ovarian cancer, which is one of the commonest ovarian tumors seen in hereditary ovarian cancer syndromes [63].

There were three individuals (12.5%) with a personal or family history of both breast and ovarian carcinoma. The histological type of the ovarian carcinoma was only known in one individual and it was serous papillary adenocarcinoma which is one of the commonest histology types found in hereditary ovarian cancer syndromes. Ovarian surface epithelial cancers are the most common types of malignant ovarian tumor and the predominant type in hereditary ovarian cancer syndrome. Ovarian surface epithelial cancers are serous, mucinous, endometrial, clear cell and Brenner type [63],[27]. There were five individuals with ovarian carcinoma that were present among 1^{st}, 2^{nd} and 3^{rd} degree relatives and their histology was not known. When considering the asymptomatic individuals with positive family history of cancer, there was a significant lack of details of family history and tumor characteristics of the relatives' tumors. Absence of ovarian cancer is also suggestive of non-*BRCA1/2* mutations [61].

Bilateral involvement in paired organs is a positive sign for hereditary cancer syndromes. Multiple breast cancers either in the same breast or opposite breast indicate hereditary breast and ovarian cancer syndrome. [19]. There was only one individual with bilateral breast cancer and one had multifocal unilateral breast cancer. Brekelmans *et al.* have assessed tumor characteristics, survival and prognostic factors of hereditary breast cancer in *BRCA1*, *BRCA2* and non-*BRCA1/2* families and compared them with sporadic breast cancer cases [64]. The study

revealed 25% and 20%, 10 year contralateral breast cancer risk in *BRCA1* and *BRCA2* mutations associated cases, respectively. It was 6% in non-*BRCA1/2* cases and 5% in sporadic cases [64]. Another study was done prospectively to assess the predictors of contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers. Women with breast cancer who were young or less than 50 years of age at diagnosis and women aged <50years with two or more 1st degree relatives with early onset of breast cancer had a increased risk of contralateral breast cancer [32]. Bilateral breast cancer is a predictor for presence of *BRCA* mutations and especially for *BRCA1* mutations. We had only one (6.6%) case with bilateral breast cancer and she was diagnosed after 60 years of age and had no significant family history as well. Genetic testing will need to be done in this patient to determine the underlying genetic mutations. Assessment of the family history is essential in clinical identification of hereditary cancer syndromes as well as hereditary breast and ovarian cancer syndrome. Importance of family history in clinical diagnosis of hereditary breast cancer syndrome has been stated in literature [16],[27], [54], [65]. Presence of personal or family history of premenopausal breast cancer, multiple family members diagnosed with breast and/or ovarian cancer, presence of male breast cancer and multiple affected generations are more suggestive of association of *BRCA* mutations [16]. Out of fifteen affected cases, ten had a positive family history and there were nine asymptomatic individuals with significant positive family history. In the affected group with breast cancer, there were 11 (73.3%) individuals with <50 years of age of onset. There were 8 (20.5%), 3 (7.6%) and 5 (12.8%) cases with onset of breast cancer at age <50 years in 1st, 2nd and 3rd degree relatives, respectively. The National Comprehensive Cancer Network has stated the assessment of family history in their guidelines (NCCN Guidelines Version 1.2014) in Breast and/or Ovarian Cancer Genetic assessment [24]. A study was done to find out the utility of NCCN guidelines in determination of *BRCA* mutations

in triple negative breast cancer patients by Sharma *et al*. [26]. Presence of more than 1 relative at age of ≤ 50 years or ≥1 relative with ovarian cancer have been taken as significant indicators of family history in their study. They have found 31.6% and 6.1% mutation prevalence with and without significant family history groups, respectively [26]. Presence of relatives with breast and/or ovarian cancer has been included in clinical criteria for consideration of *BRCA* mutation analysis [24],[19]. Prevalence of *BRCA1* and *2* among 22 Korean families was conducted by Ahn *et al.* [66]. They have recruited families with at least two first or second degree relatives with breast or ovarian cancer and found a genetic predisposition of *BRCA1* and *2* genes among those families which indicates the strong association of family history with HBOC [67]. A study was done by De Silve *et al*. [56] to identify *BRCA* mutations in Sri Lankan patients with HBOC including 66 breast cancer patients with a family history, 64 sporadic cancer patients and 70 at risk individuals. In patients with a positive family, they have found 44 patients with a single 1st or 2nd degree affected relative, 19 patients with 2 affected relatives and 3 patients with 3 affected relatives. The authors reported the presence of 19 *BRCA1* sequence variants in index cases as well as in the relatives [56]. If there are between three to six female breast cancer cases in a family, there is a possibility of having a non-*BRCA1/2* mutation in the particular family [59]. Affected and unaffected study groups in our cohort had 7 (29.2%) families with three or more but less than six family members. Therefore obtaining a detailed family history will be valuable in predicting underlying genetic mutations (*BRCA1* / *BRCA2* or non-*BRCA*) to plan genetic studies for patients and/or for their family members.

Apart from *BRCA1* and *2*, there are several other genes that involve in hereditary breast cases such as *CHEK2*, *ATM*, *NBS1*, *RAD50*, *BRIP1* and *PALB2* [50]. *PALB2* mutations have a significant contribution to hereditary breast cancer. When compared to the general population, a

study has shown a higher risk of breast cancer in individuals with *PALB2* mutations. They have found a high risk among those younger than 40 years of age and with a family history of breast cancer in two or more 1st degree relatives [68]. The youngest age of onset was 22 years in our study and the patient had two affected 1st degree relatives, one of whom had bilateral breast cancer and the other leukemia. Age of onset in both individuals was less than 50 years. She had a second degree relative with colorectal cancer. With her personal and family history *TP53* mutation can be suspected in this individual according to Chompret criteria which includes testing criteria for Li-Fraumeni syndrome [24]. A study done on a multi-ethnic Asian cohort has suggested *TP53* mutation screening in breast cancer patients who develop cancer ≤ 35 years of age [69]. There was another participant with a breast and a 1st and 2nd degree relative affected with leukemia and osteosarcoma, respectively. However her age of onset was more than 50 years. The small cohort size may have restricted the significant clinical prediction of *TP53* mutations.

There were two individuals who had received prophylactic therapy. One had received chemoprevention and other had undergone oophorectomy. Surveillance, chemoprevention and prophylactic surgery are the options that have been described in literature and guidelines for high risk individuals [54],[24].

4.2.2. Hereditary Non-polyposis Colorectal Cancer

Hereditary Non-polyposis Colorectal Cancer (HNPCC), also known as Lynch Syndrome is an autosomal dominant inherited cancer syndrome where mutation carriers have a higher risk (60-80% life time risk) of developing colorectal cancer. Family history of colorectal cancer at a young age, predominance of proximal tumors and association of types of extracolonic cancers are the main cardinal features of HNPCC and are caused by mutations in the mismatch repair

(MMR) genes. Microsatellite instability (MSI) results in MMR gene mutations and they account for 15% of colorectal cancer [69]. Percentage of MMR gene mutations were higher in families with 1st and 2nd degree relatives with colorectal cancer when compared to families without a history of colorectal cancers [38]. *MLH1, MSH2, MSH6, PMS2* and *MLH3* are the five main DNA mismatch repair genes and *MLH1, MSH2* and *MSH6* usually cause Microsatellite instability-High (MSI-H) tumors which is the commonest germline mutations in HNPCC [38]. Umar *et al.* has stated that proximal (48%) and distal (52%) colon are evenly affected in very young (<30years) patients with MSI-H tumors [38] but the majority of the HNPCC related colorectal cancers occur in the right colon [70],[71],[72]. Tumors that exhibit MSI tend to occur in the right colon and they have diploid DNA, carry characteristic mutations and behave less aggressively whereas tumors on left side usually have chromosomal instability, carry specific mutations in *K-ras, APC* and *p53* genes and behave more aggressively [71]. Among the five common MMR genes that cause HNPCC, *MSH6* gene mutations tend to cause tumors on the distal colon with typical or atypical features of HNPCC. *MLH3* is a newly identified MMR gene which also causes distally located tumors and they usually have an atypical presentation [73]. Involvement of the distal colon in our study participants may suggest association of *MLH6* or *MLH3* gene mutations or chromosomal instability. Due to heterogeneity of hereditary colorectal cancer, it is difficult to narrow down the possibilities of genetic involvement [71]. Diagnosis of HNPCC was solely dependent on clinical findings including detailed pedigree before the discovery of germline mutations in MMR genes [71].There are several types of risk assessment models like Amsterdam criteria I or II, Bethesda criteria, Japanese criteria etc. None of them provide the probability of predicting a MMR mutation carrier but instead identifies those who need to undergo MMR mutation assessment [74]. Amsterdam II criteria and Revised Bethesda

guidelines have given the minimal criteria for the clinical diagnosis of Lynch Syndrome [37],[38]. Out of 43 affected individuals, there were 14 patients with HNPCC and -9 were females while -5 were males. According to MD Anderson Cancer Center, males have a higher risk (60-80% life time risk) of developing colon cancer than females (40-60%) [75]. Colorectal tumors with MSI-H are more prevalent in females [73]. Higher prevalence of distal colon involvement is suggestive of *MSH6* and *MLH3* gene mutations but they usually cause low and variable degree of MSI, respectively. In this study, the presence of a higher number of females with colorectal cancer may be suggestive of MSI-H tumors but we need to evaluate this data further with more cases and MSI studies to make precise conclusions. Small sample size may have lead to a selection bias which results in more females in the study population. Amersi *et al.* stated that development of colorectal cancer was equal in males and females worldwide [76] but colorectal cancer due to HNPCC was more common in males [70].

Mean age of recruitment and mean age of onset of the study cohort were 46.4 years and 43.5 years, respectively. There were eleven (78.6%) affected patients who were diagnosed before the age of 50 years and 6 (42.8%) had a family history of HNPCC related cancers. Only three individuals had tumors with MSI-H histology. De Silva *et al.* have compared clinical and histological features of colorectal cancers in 60 individuals younger than 40 years of age and 245 individuals older than 40 years of age. They have found 19.7% of colorectal cancer in the 40 years or younger group with male to female ratio of 1.6:1. Mucoid and signet ring cell types were the commonest histology types seen in the younger age group. Younger patient group had a 5.5% significant family history compare to older age group. [77]. The results of the 40 year or younger patient group were in favor of hereditary colorectal cancer compare to older patient

group according to clinical criteria to diagnose HNPCC. There were five patients in our study who were diagnosed before 40 years of age and three of them had a positive family history.

Clinical diagnosis was done in the study participants using Amsterdam I, Amsterdam II and Bethesda guidelines which are commonly used in MMR gene mutation risk assessment. We were able to detect 92.8% by Bethesda guidelines and 21.4% by Amsterdam criteria. Studies have been done to assess the sensitivity and specificity of clinical criteria and they have shown that the most sensitive clinical criteria for the diagnosis and consideration of genetic testing is the Bethesda guidelines [38],[39],[74]. Amsterdam II and Bethesda guidelines include HNPCC associated carcinoma; endometrial, stomach, small intestine, renal pelvis/ureter, ovarian cancer, pancreatic cancer, hepatobiliary malignancies, brain tumors (glioblastoma) [78]. There was only 1 study participant with extracolonic tumour and it was in the renal parenchyma. Win *et al.* has revealed the risk of renal cancer in association with Lynch syndrome. According to his findings there was a higher risk for bladder cancer when compared to carcinoma of the kidney [79]. One participant had a relative with a gastric carcinoma, which is a common association of Lynch syndrome [36]but clinical details of that relative were not available. Three participants had relatives with breast cancer but the association of breast cancer with Lynch syndrome is not well defined [36]. A systematic review has demonstrated that out of 21 studies, 13 did not show an association of breast cancer and Lynch syndrome [79]. Except for gender, site of tumor and histology other classic features that have been observed in studies on HNPCC have been identified in our study cohort. According to Bethesda criteria, 92.8% of families in our study will need genetic assessment.

4.2.3. Familial Adenomatous Polyposis

Familial Adenomatous Polyposis (FAP) is one of the APC associated polyposis conditions and others are Attenuated FAP (AFAP), Gardner Syndrome and Turcot Syndrome. FAP is caused by germline mutations in the *APC* gene and has an autosomal dominant inheritance. Clinical heterogeneity can be observed even within the same family which is suggestive of modifier gene and/or environmental effects on clinical manifestations [80]. FAP is associated with an increased risk of colorectal cancer. The clinical diagnosis of FAP is made when there is at least 100 colorectal adenomatous polyps or fewer than 100 adenomatous polyps with a relative with FAP [81]. There were eight patients diagnosed with FAP out of the all 43 affected study participants in the cohort. They consisted of 3 (37.5%) individuals who had developed colorectal cancer and 2 (25%) with low and moderate dysplasia with extracolonic manifestations. The other three had FAP and they were the youngest out of the eight. Kennedy *et al.* has assessed 163 patients with FAP to understand their natural history which will aid in screening and clinical management of patients with FAP. The most common clinical symptom was rectal bleeding and the mean age of appearance of colonic polyps was 13.4 years. Family history was observed in 85% of the study group. Congenital hypertrophy of the retinal pigment epithelium (11.3%), desmoids (10.6%), osteomas (6.7%) and few more extraintestinal manifestations have been observed by the author [82]. In our study, the mean age of diagnosis of disease was 36 years and all of them were less than 50 years of age at recruitment. Female to male ratio was 2:1 and their commonest clinical presentation was rectal bleeding. Only four had positive family history (50%) and incidence of colorectal cancer was high among relatives. There were 3 individuals with extraintestinal manifestations and from this three, one had multiple osteomas and one other had sebaceous cysts which are in favor of a diagnosis of Gardner syndrome. The remaining one was a 28 years old

female patient with FAP and thyroid carcinoma which is an extraintestinal manifestation seen in FAP. There is a high risk of developing thyroid cancer in patients with FAP and especially in females. Therefore patients with FAP should undergo an ultra sound scan of the thyroid gland [83].

4.2.4. Peutz Jeghers Syndrome and Von Hippel Lindau disease

There were two individuals with Peutz Jeghers Syndrome (PJS) and two with Von Hippel Lindau (VHL) disease. Both patients with PJS had more than two histologically confirmed harmatomatous polyps with characteristic mucocutaneous pigmentation [84]. Only one individual had a family history and she was diagnosed with PJS at 13 years of age. At 39 years of age she was diagnosed with a lung carcinoma and metastatic deposits in the ovaries. PJS complicated with lung cancer has been discussed in literature but it is a rare association with poor prognosis [85].

Von Hippel Lindau (VHL) disease has characteristic lesions which aid in the clinical diagnosis of the disease. It is characterized by heamangioblastoma of the brain, spinal cord and retina; renal cysts and clear cell carcinoma; pheochromocytoma, pancreatic cysts and neuroendocrine tumors; endolymphatic sac tumors; and epididymal and broad ligament cysts [86]. Out of two participants one had bilateral renal cysts with clear cell carcinoma and the other had recurrent heamangioblastoma in brain. The latter patient had undergone genetic testing and was found to carry the c.525C>G mutation in the *VHL* gene. Mutations in the *VHL* gene are known to cause heamangioblastoma of the central nervous system (CNS) which are usually recurrent [87]. Shahzad *et al.* has done a study to evaluate the expression of *VHL* gene in patients with clear cell renal carcinoma. They have found majority of clear cell renal carcinoma expressed *VHL* gene mutations [88].

4.2.5. Miscellaneous

In e family one, the index case was diagnosed with a carcinoma in the thyroid gland at age of 18 years. She had 1st, 2nd and 3rd degree relatives affected with different types of carcinomas. All of them had an early age of onset. These features are suggestive of an inherited cancer syndrome but it is difficult categorize under a specific type. Therefore genetic testing like whole exome sequencing of index cases might be helpful in diagnosis. Detailed clinical evaluation of her 3rd degree relative (1st cousin) and performing molecular genetic testing for HNPCC may also be beneficial in the diagnosis of the inherited condition in the family.

The index case in the family 02 had two primary tumors with an early age of onset. But she did not have a significant family history. Features are suggestive of an inherited cancer syndrome which has a high chance to be an MMR gene mutation as she had 2 HNPCC associated cancers.

CHAPTER FIVE

5.0. CONCLUSION

This study shows that in the Sri Lankan context, clinical characterization of hereditary cancer patients is generally similar to reported data in other populations. Early age of onset, significant family history with affected successive generations were seen in all types of hereditary cancers that have been discussed in the study. Clinical characteristics of HNPCC as reported in other populations, such as early age of onset, significant family history and rectal bleeding as the commonest presentation were also observed in our patients as well. Presence of tumor more towards the distal colon and higher number of affected females which were seen in this cohort slightly differ from previously reported HNPCC characteristics. The clinical features of FAP, PJS and VHL patients were consistent with features reported in other populations.

5.1. Limitations of the study

The study population consisted of cases referred to the Human Genetics Unit, Cancer genetics clinic at Cancer Institute Maharagama and cases being followed up at professorial surgical clinic at the National Hospital Sri Lanka. Cancer Institute Maharagama is one of the six major cancer centers situated country wide. Therefore patients followed up at other cancer centers and tertiary care hospitals may have been missed in the study. Therefore the study population is not representative of the island wide distribution of hereditary cancer syndromes.

Another limitation was the lack of clinical details in cancers of family members. Most index cases were not aware about type of cancer, age of onset and the tumor characteristics and most of them do not have any records of their relatives as well. Lack of retrospective clinical details of the index cases was also a limitation. When clinicians do not identify cardinal features of

hereditary cancer syndromes and document them, this may cause difficulties in clinical diagnosis of cancer syndromes.

5.2. Future research in inherited cancer syndromes in Sri Lanka

Considering the clinical phenotypes observed in hereditary breast and ovarian cancer syndrome and hereditary non polyposis colorectal cancer, mutations in *BRCA1/2* genes, rare MMR genes and *APC* gene are potential etiologic factors in this study cohort. Genetic evaluation by using gene panels or whole exome sequencing will need to be undertaken in the future to determine the underlying genetic mutations. Identification of common mutations associated with the HBOC and HNPCC phenotypes in Sri Lankan patients would be useful in designing a diagnostic panel for each cancer syndrome. This would be cost effective and helpful in patient management and surveillance. Identification of the mutations and correlation with the phenotype could be used in implementation of guidelines for identification of Sri Lankan patients with hereditary cancer syndromes. This could help in the detection, screening and counseling of patients with inherited cancer syndromes which will improve their quality of life.

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APPENDIX 1: List of Abbreviations

ACOG – American Congress of Obstetrician and Gynocologists

AFAP – Attenuated Familial Adenomatous Polyposis

ASR – Age Standardized Rate

AT – Ataxia Telangiectasia

BS – Bloom Syndrome

CHRPE – Congenital Hypertrophy of The Retinal Pigment Epithelium

CR – Crude Cancer Incidence Rate

CR.CA – Colorectal Carcinoma

CS – Cowden Syndrome

DCIS – Ductal Carcinoma In Situ

End.CA – Endocrine Carcinoma

ER – Estrogen Receptor

FAP – Familial Adenomatous Polyposis

Gas.CA – Gastric Carcinoma

HBOC – Hereditary Breast And Ovarian Cancer Syndrome

HDGC – Hereditary Diffuse Gastric Cancer

HER2 – Human Epidermal Growth Factor Receptor 2

HGU – Human Genetics Unit

HNPCC – Hereditary Non Polyposis Colorectal Cancer

IARC – International Agency For Research On Cancer

Lu.CA – Lung Carcinoma

LFS – Li Fraumeni Syndrome

MEN2 – Multiple Endocrine Neoplasia Type 2

MMR – Miss Match Repair

MRI – Magnetic Resonance Imaging

MSI – Microsatellite Instability

MSI-H – Microsatellite Instability – High

NCCP – National Cancer Control Program

NCCN – National Cancer Comprehensive Cancer Network

NCI – National Cancer Institute

NHSL – National Hospital Sri Lanka

PR – Progesterone Receptor

PJS – Peutz Jeghers Syndrome

Thy.CA – Thyroid Carcinoma

USPSTF – US Preventive Services Task Force

VHL – Von Hippel Lindau Syndrome

WHO – World Health Organization

XP – Xeroderma Pigmentosa

a – age at recruitment

o – age at onset

d – age at death

APPENDIX 2: Clinical Diagnostic Criteria

Hereditary Breast and Ovarian Cancer syndrome (HBOC)

- Breast cancer diagnosed at age 50 or younger
- Ovarian cancer
- Multiple primary breast cancers either in the same breast or opposite breast
- Both breast and ovarian cancer
- Male breast cancer
- Triple-negative (estrogen receptor negative, progesterone receptor negative, and HER2/neu [human epidermal growth factor receptor 2] negative) breast cancer
- Pancreatic cancer with breast or ovarian cancer in the same individual or on the same side of the family
- Ashkenazi Jewish ancestry
- Two or more relatives with breast cancer, one under age 50
- Three or more relatives with breast cancer at any age
- A previously identified *BRCA1* or *BRCA2* mutation in the family

Note: "Breast cancer" includes both invasive cancer and ductal carcinoma in situ (DCIS). "Ovarian cancer" includes epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer.

Adapted from, *BRCA1* and *BRCA2* Hereditary Breast and Ovarian Cancer. GeneReviews, Nancie Petrucelli, MS, Mary B Daly, MD, PhD, and Gerald L Feldman, MD, PhD, FACMG., http://www.ncbi.nlm.nih.gov/books/NBK1247/

Hereditary Non-polyposis Colorectal Cancer (HNPCC)

Individuals with all three features

Amsterdam Criteria I

- Three or more family members, one of whom is a first-degree relative of the other two, with a confirmed diagnosis of colorectal cancer
- Two successive affected generations
- One or more colon cancers diagnosed before age 50 years Exclusion of familial adenomatous polyposis (FAP)

Amsterdam Criteria II

- Three or more family members (one of whom is a first-degree relative of the other two) with HNPCC-related cancers
- Two successive affected generations
- One or more of the HNPCC-related cancers diagnosed before age 50 years Exclusion of familial adenomatous polyposis(FAP)

(HNPCC related cancer – colorectal, endometrium, stomach, ovaries, pancreas, ureter & pelvis, billiary tract, brain, sebaceous gland adenomas, keratoacanthomas, small intestine carcinoma)

Bethesda Guideline

Individual with one of the following

- Colorectal cancer (CRC) diagnosed <50yrs
- HNPCC cancers ** in one person (can be 2 primary CRC)
- CRC with MSI-H histology

(tumor infiltrating lymphocytes, Crohn's like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern) diagnosed <50yrs

- CRC or HNPCC-associated tumors** diagnosed under age 50 yrs in at least 1 first-degree relative
- CRC or HNPCC-associated tumor** diagnosed at any age in 2 first- or second-degree relatives

  (**colorectal, endometrial, stomach, small intestine, renal pelvis/ureter, ovarian cancer, pancreatic cancer, hepatobiliary malignancies, brain tumors (glioblastoma), sebaceous tumor and keratocanthoma)

Adapted from, Lynch Syndrome, GeneReviews, Wendy Kohlmann and Stephen B Gruber. http://www.ncbi.nlm.nih.gov/books/NBK1211

Familial Adenomatous Polyposis (FAP)

An individual with one of the following

- At least 100 colorectal adenomatous polyps

Note: (1) The diagnosis of FAP is generally considered in individuals with polyposis occuringbefore age 40 years. (2) The presence of 100 or more colorectal polyps is not specific to FAP;genetic testing of *APC* may help distinguish FAP from *MUTYH-associated polyposis* (MAP) or colonic polyposis conditions of unknown etiology

- Fewere than 100 adenomatous polyps and relative with FAP

Gardner syndrome is the association of colonic adenomatous polyposis, osteomas, and soft tissue tumors (epidermoid cysts, fibromas, desmoid tumors)

Peutz Jeghers Syndrome (PJS)

- Two or more histologically confirmed PJS-type hamartomatous polyps
- Any number of PJS-type polyps detected in one individual who has a family history of PJS in a close relative(s)
- Characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in a close relative(s)
- Any number of PJS-type polyposis in an individual who also has characteristic mucocutaneous pigmentation

Adapted from, APC-Associated Polyposis Conditions, GeneReviews, Kory W Jasperson and Randall W Burt. http://www.ncbi.nlm.nih.gov/books/NBK1345

Von Hippel Lindau Disease

- A simplex case (individual with no known family history of VHL disease) presenting with two or more characteristic lesions
    - Two or more hemangioblastomas of the retina, spine, or brain or a single heamangioblastoma in association with a visceral manifestation (e.g. multiple kidney or pancreatic cysts)
    - Renal cell carcinoma
    - Adrenal or extra-adrenal pheochromocytomas
    - Less commonly, endolymphatic sac tumors, papillary cystadenomas of the epididymis or broad ligament, or neuroendocrine tumors of the pancreas
- An individual with a positive family history of VHL disease in whom one or more of the following disease manifestations is present:
    - Retinal angioma
    - Spinal or cerebellar heamangioblastoma
    - Adrenal or extr-adrenal pheochromocytoma
    - Renal cell carcinoma
    - Multiple renal and pancreatic cysts

Note: Other lesions characteristic of VHL are endolymphatic sac tumors (ELST) and pancreatic neuroendocrine tumors; however these are not typically used to make a clinical diagnosis of VHL

Adapted from, Von Hippel-Lindau Disease, GeneReviews, Carlijn Frantzen, MD, Thera P Links, MD, PhD, and Rachel H Giles, PhD. http://www.ncbi.nlm.nih.gov/books/NBK1463

APPENDIX 3: Documents Used For Subject Recruitment

This appendix contains the English, Sinhala and Tamil language documents which were used for subject recruitment in Sri Lanka

- Information sheet for study participants used for the recruitment of patients with inherited cancer syndromes
- Consent form used for recruitment of patients with inherited cancer syndromes
- Data collection booklet

INFORMATION SHEET

CLINICAL AND MOLECULAR GENETIC STUDIES IN A COHORT OF SRI LANKAN PATIENTS WITH INHERITED CANCER SYNDROMES

This study is conducted by me, Dr. Nirmala D. Sirisena, a Lecturer/Clinical Geneticist at the Department of Anatomy, Faculty of Medicine, University of Colombo. I would like to invite you to take part in the research study titled "CLINICAL AND MOLECULAR GENETIC STUDIES IN A COHORT OF SRI LANKAN PATIENTS WITH INHERITED CANCER SYNDROMES" conducted by myself along with my co-investigators, Prof. Vajira H.W. Dissanayake and Dr. Niluka D.W.Dissanayake at the Human Genetics Unit, Faculty of Medicine, University of Colombo.

1. Purpose of the study

The purpose of the study is to describe the clinical characteristics and the genetic defects causing inherited cancer syndromesand to correlate the clinical features with the genetic defectsin a cohort of Sri Lankan patients.

2. Voluntary participation

Your participation in this study is voluntary. You are free to not participate at all or to withdraw from the study at any time despite consenting to take part earlier. There will be no loss of medical care or any other available treatment for your illness or condition to which you are otherwise entitled. If you decide not to participate or withdraw from the study, you may do so at any time by informing us.

3. Duration, procedures of the study and participant's responsibilities

The study will be conducted over a period of 2 years. We require your permission to ask you questions examine you and have access to your medical records. We need to take 5mls of venous blood from you to do the genetic test. You only have to visit us once during the research period to provide the clinical data and blood sample for the study. We also need your permission to publish the data collected in a scientific journal. We will not mention your name or any other identifiable information about you when we publish the results.

4. Potential Benefits

Participation in this study will help you to know the genetic defect that has made you develop the type of cancer which you have. This will be a valuable opportunity as genetic testing for hereditary cancer syndromes are not freely available in Sri Lanka. Knowledge about the different genetic defects would enable the doctors caring for you to understand your clinical condition better and provide improved care. This study will also help to identify your relatives who are at risk of developing hereditary cancer. In addition, participants and/or parents/guardians will be provided genetic counseling about each participant's test results. Genetic counseling will educate you on how heredity contributes to cancer risk; help you understand your personal risk and your relatives' risk of developing cancer, options for managing the cancer risk and how to adopt appropriate risk-reducing behaviours. This study will contribute to the increasing of existing knowledge about hereditary cancer syndromes in Sri Lankan patients. When we know about the common genetic defects causing hereditary cancer syndromes in Sri Lankan patients, it will be possible for us in future to develop cheap genetic tests suitable for use in Sri Lanka to easily diagnose these conditions.

5. Risks, Hazards and Discomforts

Blood will be drawn to detect the genetic defects causing hereditary cancer syndromes. When taking blood, you will feel some discomfort due to the needle prick and after blood is drawn, rarely there can be bruising at the needle prick site. In order to ensure that these risks are minimized, blood drawing will be done by a trained phlebotomist under aseptic conditions

6. Reimbursements

There will be no payment for participating in the study, but you will be given a copy of the molecular genetic test results.

7. Confidentiality

Confidentiality of all records is guaranteed and no information by which you can be identified will be released or published. The data collection booklet is designed to ensure confidentiality of information gathered. The electronic database containing the data will have only the subject study number and the database and the computer containing the database would be password protected.If it becomes necessary to publish some of the results in scientific journals, we will make sure to publish the results protecting the identity of the subject. These data will never be used in such a way that you could be identified in any way in any public presentation or publication without your express permission.

8. Termination of Study Participation

You may withdraw your consent to participate in this study at any time, without any penalty or effect on medical care or loss of benefits. Please notify us as soon as you decide to withdraw your consent. However, it will not be possible for you to withdraw once the results are sent for publication or once the results are published.

9. Clarification

If you have any questions about any of the tests/procedures or information or need to clarify any doubts, please feel free to ask any of the persons listed below at the Human Genetics Unit by calling 11 2689 545.

Dr. Nirmala D. Sirisena– Lecturer/Clinical Geneticist, Department of Anatomy, Faculty of Medicine, University of Colombo.

Dr. NilukaD.W.Dissanayake – M.Sc. student, Human Genetics Unit, Faculty of Medicine, University of Colombo.

තොරතුරු පත්‍රිකාව

ප්‍රවේණිගත පිළිකා සහිත ශ්‍රී ලාංකීය රෝගීන්ගේ රෝග ලක්ෂණ සහ ජානමය විවිධත්වය අධ්‍යනය කිරීම.

කොළඹ වෛද්ය පීඨයේ කථිකාචාර්ය වෛද්ය නිර්මලා ඩී සිරිසේන වන මම ඇතුළු අනෙකුත් පර්යේෂණ සාමාජිකයන් විසින් කරනු ලබන ඉහත පර්යේෂණයට සහභාගී වීම සඳහා ඔබ හට ආරාධනා කිරීමට අප කැමැත්තෙමු.මෙම පර්යේෂණයේ අනෙකුත් සාමාජිකයන් වනුයේමහාචාර්ය වජිර එච් ඩබ්ලිව් දිසානායක සහ වෛද්‍ය නිලුකා ඩි. ඩබ්ලිව්. දිසානායක වන අය වේ.

1. මෙම අධ්‍යනයේ අරමුණ

මෙම අධ්‍යානයේ ප්‍රධාන අරමුණ වනුයේ, ප්‍රවේණිගත පිළිකා සහිත රෝගීන්ගේ රෝග ලක්ෂණ විස්තර කිරීමත්, එම රෝගීන්ගේ ජානමය වෙනස්කම් හඳුනා ගැනීමත් එම රෝග ලක්ෂණ හා ජානමය වෙනස්කම් අතර ඇති සහසම්බන්ධතාව හඳුනා ගැනීමත්ය.

2. ස්වෙච්චා සහභාගිත්වය

මෙම අධ්‍යනය සඳහා ඔබගේ සහභාගිත්වය ඔබගේ කැමැත්ත මත සිදු කරන්නකි. මෙම අධ්‍යනය සඳහා සහභාගි නොවීමට ඔබට පූර්ණ අයිතිය ඇති අතර, සහභාගී වීමට කලින් කැමැත්ත ප්‍රකාශ කර තිබුනද ඕනෑම අවස්ථාවක අපහට දැනුම්දී ඔබට අධ්‍යනය නිමා කිරීමට පූර්ණ අයිතිය ඇත. එමගින් ඔබට ලබා දෙන වෛද්‍ය ප්‍රතිකාර සඳහා කිසිදු බලපෑමක් ඇති නොවේ.

3. කාල සිමාව, පර්යේෂණයේ ක්‍රියා පිළිවෙල සහ සහභාගිවන්නන්ගේ වගකීම

මෙම පර්යේෂණයේ කල සිමාව අවුරුදු දෙකකි. ඔබගෙරෝගයපිළිබඳව ප්‍රශ්න ඇසීමට, ඔබව පරීක්ෂා කිරීමට සහ ඔබගේ වෛද්‍ය වාර්තා පිරික්සීමට අපහට ඔබගේ අවසරය අවශ්‍ය වේ. තවද ජාන පරීක්ෂණය සඳහා මි.ලි. 5ක රුධිර සාම්පලයක් ලබා ගැනීමට අවශ්‍ය වේ.

ඔබගේ විස්තර හා රුධිර සාම්පලය ලබා ගැනීම සඳහා පර්යේෂණ කාල සිමාව ඇතුලතදි ඔබ එක වරක් පමණක් අප ආයතනය වෙත පැමිණීම සෑහේ. තවද අප විසින් කරනු ලබන පර්යේෂණයේ දත්ත විද්‍යාත්මක සඟරාවක පල කිරීම සඳහා ද ඔබගේ අවසරය අවශ්‍ය වේ. මෙම ප්‍රතිඵල පල කිරීමේදී ඔබගේ නම හෝ ඔබව හඳුනාගත හැකි අන්දමේ වෙනයම් තොරතුරක් හෝ අප විසින් සපයන්නේ නැත .

4. මින් ලද හැකි ප්‍රතිලාභ

ප්‍රවේණිගත පිළිකා තත්ත්ව වල ජානමය වෙනස්කම් හඳුනා ගැනීම සඳහා අදාල පර්යේෂණ පහසුකම් නොමිලේ ලබා ගැනීමට නොහැකි බැවින් මෙම පර්යේෂණයට සහභාගී වීම මගින් ඔබගේ පිළිකාතත්ත්වය ඇතිවීමට බලපා ඇති ජානමය වෙනස්කම් හඳුනා ගැනීමට ඔබට අවස්ථාව ලැබෙනු ඇත. ප්‍රවේණිගත පිළිකා රෝග තත්ත්වයන් ඇති කිරීමට හේතු වන විවිධ ජානමය වෙනස්කම් ගැන දැනුම ලබා ගැනීම මගින් වෛද්‍යවරුන්ට රෝගීන්ගේ රෝග තත්ත්වයන් හොඳින් හඳුනා ගැනීමටත් ඊට අදාල ප්‍රතිකාර තත්ත්වයන් ඇති කිරීමටත් උපකාරී වේ.

මෙම පර්යේෂණයේදී පිළිකා සඳහා ඔබගේ ඥාතීන්ට ඇති අවදානම හඳුනා ගැනීමට හැකි වේ . මීට අමතරව පර්යේෂණයට සහභාගී වන ඔබටත් ඔබගේ දෙමුපියන්ට හෝ භාරකරුවන්ට ඔබගේ ප්‍රතිඵල සම්බන්ධයෙන් උපදේශනය නොමිලේ ලබා ගත හැකිය. උපදේශනය මගින් පිළිකා තත්ත්වයන් ඇති වීම සඳහා ජාන වල සහභාගිත්වයත්, ඒ සඳහා ඔබට හා ඔබගේ ඥාතීන්ටත් ඇති අවදානමත් , පිළිකා තත්ත්වයන්ට සිදු කල හැකි ප්‍රතිකාර තත්ත්වයන් දැන ගැනීමට හා පිළිකා සඳහා ඇති අවදානම් අවම කිරීමට අවශ්‍ය දැනුම ලබා ගත හැකි වේ.

මෙම පර්යේෂණය, ශ්‍රී ලංකාවේ රෝගීන් අතර දැනට පවතින දැනුම වැඩි කරගැනීමට උපකාරී වේ. ශ්‍රී ලංකාවේ පිළිකා සහිත රෝගීන්ගේ පිළිකා තත්ත්වයන් ඇති කරන බහුල ජානමය වෙනස්කම් හඳුනා ගැනීමට හැකි මිල අවම පරීක්ෂණ ක්‍රියාවලියක් අනාගතයේ නිපද වීමට හැකියාව ලැබෙනු ඇත.

5. අවදානම් තොරතුරු සහ අපහසුතා

ප්‍රවේණිගත පිළිකා සහිත රෝගීන්ගේ ජානමය වෙනස්වීම් සොයා ගැනීම සඳහා ඔබගේ කැමැත්ත මත රුධිර සාම්පලයක් ලබා ගැනීමට සිදුවේ. මෙම රුධිර සාම්පල ලබා ගැනීමේදී ඔබට යම් අපහසුතාවයක් ඇති විය හැක. කලාතුරකින් රුධිර සාම්පලය ලබා ගැනීමේදී එන්නත් කටුව නිසා යම් තැල්මක් එම ස්ථානයේ හට ගත හැක. මෙම තත්ත්වයන් අවම කර ගැනීම සඳහා රුධිර සාම්පලය ලබා ගැනීම ආරක්ෂිත තත්ත්වයන් යටතේ පළපුරුදු හෙද නිලධරිනියක් මගින් සිදු කරනු ලැබේ.

6. දීමනා

ඔබ මෙම අධ්‍යනයට සහභාගී වීම වෙනුවෙන් ඔබට දීමනාවක් නොලැබේ. එහෙත් ඔබගේ ජානමය විස්තර සඳහන් ප්‍රතිඵල සටහනක් ලැබෙනු ඇත.

7. රහසිගත බව

සියලුම තොරතුරු සහිත වාර්තාවක් සහ අධ්‍යනය මගින් ලබා ගන්න දත්තයන්ගේ රහස්‍යභාවය තහවුරු කරන අතර, ඔබගේ අනන්‍යතාව හඳුනාගත හැකි ආකාරයේ කිසිවක් හෝ ඔබගේ තොරතුරු කිසිවක් හෙළි කිරීම හෝ ප්‍රකාශයට පත් කිරීම සිදු කරනු නොලැබේ. දත්ත එකතු කිරීමේ පත්‍රිකාව සැකසා ඇත්තේ ඔබගේ රහස්‍යභාවය තහවුරු කෙරෙන අයුරිනි. පරිගණකයට ඔබගේ දත්ත ගබඩා කිරීමේදී ඔබව හඳුනා ගත හැකි අංකයක් පමණක් භාවිත කරන අතර එම දත්ත රහස් වචනයක් භාවිත කිරීම මගින් සුරක්ෂිතව ගබඩා කෙරේ. විද්‍යාත්මක සඟරාවක මෙම පර්යේෂණ වාර්තා පල කිරීමට අවශ්‍ය වූ විට එය ඔබගේ කැමැත්ත මත සිදුකරන අතර කිසිදු අයුරකින් ඔබගේ අනන්‍යතාව හෙළි නොවන අයුරින් එය පල කිරීම සිදුවේ.

8. අධ්‍යනයට සහභාගී වීම නැවත්වීම

අධ්‍යනයටසහභාගී වීමට දුන් කැමැත්ත ඉවත් කර ගැනීම,අධ්‍යනයේ කුමනඅදියරකදී හෝ සිදු කිරීමට ඔබට හැක. එසේ සිදු කරන්නේ නම් එම තීරණය ගත් විගසම ඒ බව අපහට කරුණාකර දැනුම් දෙන්න. නමුත් එකතු කරගන්නා ලද දත්ත ප්‍රකාශයට පත් කිරීමෙන් පසුව ඔබට අධ්‍යනයෙන් ඉවත් වීමට නොහැක.

9. වැඩිදුර තොරතුරු

ඔබට මෙම ක්‍රියා පටිපාටින් පිළිබඳ කිසියම් ප්‍රශ්නයක් ඇත්නම් හෝ වැඩිදුර තොරතුරු අවශ්‍යවේ නම් කරුණාකර පහත සඳහන් වෛද්‍යවරුන් අමතන්න.

වෛද්‍ය නිර්මලා ඩී. සිරිසේන, කථිකාචාර්ය, කාය ව්‍යවච්චේද අංශය, වෛද්‍ය පීඨය, කොළඹ .

වෛද්‍ය නිලුකා ඩී. ඩබ්ලිව්. දිසානායක, පශ්චාත් උපාධි අපේක්ෂිකා,මානව ප්‍රවේණි ඒකකය, වෛද්‍ය පීඨය, කොළඹ

දූ.අ. 011268954

பரம்பரைரீதியாக ஏற்படும் புற்றுநோயின் மருத்துவ மற்றும் மூலக்கூற்று இயல்புகள் பற்றி இலங்கையைச் சேர்ந்த நோயாளிகளில் மேற்கொள்ளப்படவுள்ள பேராய்வு

இந்த ஆய்வானது வைத்தியர் நிர்மலா சிரிசேன (விரிவுரையாளர்/மருத்துவ மரபியலாளர், உடல்கூற்று பிரிவு, மருத்துவ பீடம், கொழும்பு பல்கலைக்கழகம்) ஆகிய என்னால் நடத்தப்படுகிறது. 'பரம்பரைரீதியாக ஏற்படும் புற்றுநோயின் மருத்துவ மற்றும் மூலக்கூற்று இயல்புகள் பற்றி இலங்கையைச் சேர்ந்த நோயாளிகளில் மேற்கொள்ளப்படவுள்ள பேராய்வு' எனும் தலைப்பில் நடத்தப்படும் இந்த ஆய்வில் பங்குபெற்ற உங்களையும் அழைக்கின்றேன். இந்த ஆய்வானது மனித மரபியல் பிரிவுஇ கொழும்பு மருத்துவ பீடத்தைச் சேர்ந்த பேராசிரியர் வஜிரா ர்.று. திஸானாயக்க மற்றும் வைத்தியர் நிலுகா னு.று திஸானாயக்க ஆகியோருடன் இணைந்து என்னால் மேற்கொள்ளப்படுகின்றது.

1. இவ்வாய்வின் நோக்கம்

இலங்கையிலுள்ள நோயாளிகளில் பரம்பரையாக வரும் புற்றுநோய்களின் மருத்துவ அம்சங்கள் மற்றும் மரபியல் குறைபாடுகளை விவரிப்பதும்இ அந்த மருத்துவ அம்சங்களை மரபியல் குறைபாடுகளுடன் தொடர்புபடுத்துவதுமே இந்த ஆய்வின் நோக்கமாகும்.

2. தன்னார்வப்பங்கேற்பு

இந்த ஆய்வில் உங்கள் பங்கேற்பு தன்னார்வமானதாகும். முன்னைய ஒப்புதலையும் பொருட்படுத்தாது எப்பொழுது விரும்பினாலும் இதிலிருந்து விடுபடவோ சேராமல் விடவோ உங்களுக்கு சுதந்திரமுண்டு. நீங்கள் இவ்வாய்விலிருந்து நீங்கிக் கொண்டதற்காக உங்களுக்களிக்கப்படும் நோய் சிகிச்சைகளிலோ, ஏனைய மருத்துவக் கவனிப்புக்களிலோ எந்தவித குறைப்பும் அல்லது அலட்சியமும் இடம்பெறாது. நீங்கள் இவ்வாய்விலிருந்து விடுபட தீர்மானிப்பதாயின் எங்களுக்கு அறிவித்துவிட்டு எப்பொழுது வேண்டுமாயினும் உங்களால் நீங்கிக் கொள்ள முடியும்.

3. பங்குபற்றுவோரின் பொறுப்புக்களும் ஆய்வின் ஒழுங்குமுறையும், ஆய்வுக்கான காலமும்

இந்த ஆய்வானது 2 வருட காலம் வரையில் இடம்பெறும். உங்களிடம் கேள்விகளைக் கேட்பதற்கும் உங்களைப் பரிசோதிப்பதற்கும், உங்கள் மருத்துவ ஏடுகளை பார்ப்பதற்கும் உங்களிடம் அனுமதி கோருகிறோம். மரபணுப் பரிசோதனைக்காக உங்களிடமிருந்து 5அட அளவு இரத்தம் எங்களுக்குத் தேவைப்படுகின்றது. மேலும் நீங்கள் உங்களுடைய மருத்துவ தகவல்களை வழங்கும் பொருட்டு மாத்திரமே இவ்வாய்வின்போது அழைக்கப்படுவீர்கள். இந்த ஆய்வுக் காலத்தில் நீங்கள் ஒரு தரம் மாத்திரமே எங்களிடம் வந்து உங்களது மருத்துவ தகவல்கள் மற்றும் இரத்த மாதிரியை ஆய்வுக்காக தந்து செல்ல வேண்டும். மற்றும் எங்களால் சேகரிக்கப்பட்ட உங்களது மருத்துவ தகவல்களை மருத்துவ விஞ்ஞான ஏடுகளில் வெளியிடுவதற்கும் உங்களுடைய அனுமதியைக் கோருகிறோம். ஆய்வுப் பெறுபேறுகளை வெளியிடும்போது உங்களின் பெயரோ மற்றும் அடையாளங்காணக்கூடிய தகவல்களையோ நாம் குறிப்பிடமாட்டோம்.

4. கிடைக்கக்கூடிய நன்மைகள்

இந்த ஆய்வில் பங்குபெற்றுவதன் மூலம் உங்களுக்கு ஏற்பட்டிருக்கும் புற்றுநோயானது எந்த விதமான மரபியல் குறைபாட்டினால் உருவாகியுள்ளது என்பதை அறிந்து கொள்ளக்கூடியதாக இருக்கும். இலங்கையில் பரம்பரையாக வரும் புற்றுநூய்களுக்கான மரபியல் பரிசோதனைகள் இலகுவாக கிடைக்காதென்பதால்இ இது ஒரு பெறுமதிமிக்க சந்தர்ப்பமாக அமையும். மேலும்இஇந்த ஆய்வின் மூலம் வெவ்வேறு மரபியல் குறைபாடுகளைப் பற்றி அறிந்து கொள்ளும்போது உங்களுக்கு சிகிச்சை அளிக்கும் வைத்தியர்களால் அவர்களது சேவையை மேலும் நன்றாக செய்யமுடியும். உங்களது உறவினர்களில் யாருக்கு இந்த நோய் வரக்கூடும் என்பதையும் கண்டறியக்கூடியதாக இருக்கும். மேலும் இந்த ஆய்வில் பங்குபெற்றும் நோயாளிகள்ஃ பெற்றோர்ஃ பாதுகாவலர்களுக்கு மரபியல் சோதனைக்கான கருத்துரை வழங்கப்படும். இதன் மூலம் உங்களால் எவ்வாறு பரம்பரையாக புற்றுநோய் ஏற்படுகின்றது மற்றும் உங்களுக்கும் உங்களது உறவினர்களுக்கும் இருக்கும் இடையூறுகள்இ பராமரிப்பு முறைகள் விளங்கிக் கொள்ளக் கூடியதாக இருக்கும்.இவ்வாய்வின் மூலம் தற்போது கிடைக்கும் தகவல்கள் - அறிவு என்பவற்றுக்கு மேலதிகமாக பல புதிய தகவல்களின் ஊடாக பரம்பரைரீதியான புற்றுநோய் பற்றிய அறிவை மேலும் அதிகரித்துக்கொள்ள முடியும். இதன் மூலம்

இலங்கையில் எவ்வகையான மரபியல் குறைபாடுகள் பரம்பரையாக வரும் புற்றுநூய்களை உண்டாக்கின்றன என்பதை அறியக்கூடியதாக இருக்கும். மேலும் எதிர்காலத்தில் இந்த நோய்களைக் கண்டறிய செலவு குறைவான பரிசோதனைகளை உருவாக்கக்கூடியதாக இருக்கும்.

5. ஆபத்து / இடர் / அசௌகரியங்கள்

பரம்பரையாக வரும் புற்றுநோய்களை உண்டாக்கும் மரபியல் குறைபாடுகளை கண்டறியும் சோதனைகளுக்காக உங்களிடம் இருந்து இரத்தம் பெறப்படும்.. இரத்தம் ஊசியினால் குத்தி எடுக்கப்படுவதனால் சில சில சிரமங்களிற்கு உள்ளாகலாமென நீர் உணரலாம். அவ்வாறு ஊசி குத்தி இரத்தம் எடுக்கப்பட்ட இடத்தில் அரிதாக ஊமைக் காயம் ஏற்படலாம். இதனைத் தவிர்ப்பதை உறுதிசெய்யும் பொருட்டு உங்கள் இரத்தம் நன்கு பயிற்றுவிக்கப்பட்ட மருத்துவ தாதிஒருவரினால்முற்றிலும் தொற்றுநீக்கிய நிலையில் மேற்கொள்ளப்படும்.

6. கொடுப்பனவு

இவ்வாய்வில் பங்கேற்பவர்களுக்கு எவ்வித கொடுப்பனவுகளும் வழங்கப்படமாட்டாது. எனினும் மூலக்கூற்று பரிசோதனை முடிவுகள் வழங்கப்படும்.

7. இரகசியத்தன்மை

எல்லாவிதமான தகவல்களினதும் இரகசியத்தன்மை பேணுவதில் உத்தரவாதமளிக்கிறோம். உங்களால் அடையாளம் காணக்கூடிய எவ்வித தகவல்களும் வெளிப்படுத்தப்பட மாட்டாதென்றும் உத்தரவாதமளிக்கிறோம். எமது தகவல் பதிவேடும் இரகசியத்தன்மையைப் பேணும் விதத்திலே வடிவமைக்கப்பட்டுள்ளது. கணினி மயப்படுத்தப்பட்ட இவ்வேடு கடவுச்சொல் மூலம் பாதுகாப்பாக பேணப்படும். சில நேரங்களில் விஞ்ஞான குறிப்புக்களில் சில தகவல்களை வெளியிட தேவை ஏற்பட்டால் அந்த தகவல்கள் அடையாளங்காண முடியாதவாறு வெளியிடுவதை நாம் உறுதிசெய்வோம். மேலும் இத்தரவுகள் நாம் ஒருபோதும் உங்களால் அடையாளங்காணும் விதத்தில் உங்கள் அனுமதியின்றி

பொதுப்படையாக வெளியிடவோ குறிப்பிடவோ முயலமாட்டோம் என்பதை உறுதி செய்கிறோம்.

8. ஆய்வில் பங்கேற்பதும் அதிலிருந்து நீங்கிக் கொள்வதும்

இவ்வாய்விலிருந்து எப்போதுவேண்டுமாயினும் நீங்கிக்கொள்ள உங்களுக்கு முடியும். இதற்காக எந்தத் தண்டனையோ உங்கள் மருத்துவ சிகிச்சையில் குறைப்போ, ஏனைய புறக்கணிப்புக்களோ மேற்கொள்ளப்படமாட்டாது. நீங்கள் விலக அல்லது நீங்கிக்கொள்ளத் தீர்மானித்தால் அதுபற்றி உடனே எங்களுக்க அறியத்தரவும். எவ்வாறாயினும் பெறுபேறுகள் அச்சுக்கு சென்றவேளையிலும், பெறுபேறுகள் வெளியிடப்பட்ட நிலையிலும் உங்களால் இதிலிருந்து நீங்கிக்கொள்வது அசாத்தியமானதொன்றாகும்.

9. தெளிவு அல்லது விளக்கம் பெறல்

உங்களுக்கு இந்த நடைமுறையில் / பரிசோதனையில் ஏதாவது கேள்விகள் எழுமாயின், அவற்றுக்கு விளக்கம் பெறவேண்டுமென கருதும்பட்சத்தில் பின்வருபவர்களுடன் தயக்கமின்றி தொடர்புகொள்ளுங்கள்

மனித மரபணுப் பிரிவு 0112689545

வைத்தியர் நிர்மலா னு. சிரிசேன (விரிவுரையாளர்ஃமருத்துவ மரபியலாளர்இ உடல்கூற்று பிரிவுஇ மருத்துவ பீடம்இ கொழும்பு பல்கலைக்கழகம்)

வைத்தியர் நிலுகா னு.று. திஸாநாயக்க (ஆ.ளுஉ மாணவி) மனித மரபணுப் பிரிவு, மருத்துவபீடம், கொழும்பு பல்கலைக்கழகம்

CONSENT FORM

CLINICAL AND MOLECULAR GENETIC STUDIES IN A COHORT OF SRI LANKAN PATIENTS WITH INHERITED CANCER SYNDROMES

A. To be completed by the participant/guardian

The participant/guardian should complete the whole of this sheet by himself/herself.

1. Have you read the information sheet? (Please keep a copy for yourself) YES/NO

2. Have you had an opportunity to discuss this study and ask any questions? YES/NO

3. Have you had satisfactory answers to all your questions? YES/NO

4. Have you received enough information about the study? YES/NO

5. Who explained the study to you? ……

6. Do you understand that you are free to withdraw from the study at any time, without having to give a reason and without affecting your medical care?

YES/NO

7. Sections of your medical notes, including those held by the investigators relating to your participation in this study may be examined by other research assistants. All personal details will be treated as STRICTLY CONFIDENTIAL. Do you give your permission for these individuals to have access to your records? YES/NO

8. Do you agree to have left over blood samples and DNA to be stored under the supervision of the investigators and used for future research into inherited cancer syndromes with the approval of the Ethics Review Committee?

YES/NO

9. Do you agree for your blood samples to be sent abroad? YES/NO

10. Have you had sufficient time to come to your decision? YES/NO

11. Do you agree to take part in this study? YES/NO

Participant's/Guardian's signature…….....… Date…….……...

Name (BLOCK CAPITALS)……..…

B. To be completed by the investigator

I have explained the study to the above volunteer and he/she has indicated his/her willingness to take part.

Signature of investigator……...…….. Date……..……..…

Name (BLOCK CAPITALS)…….……

කැමැත්ත ප්‍රකාශකිරීමේ පත්‍රය

ප්‍රවේණිගත පිළිකා **සහිත ශ්‍රී ලාංකීය රෝගීන්ගේ රෝග ලක්ෂණ සහ ඥානමය විවිධත්වය අධ්‍යනය කිරීම.**

(a) සහභාගීවන්නන්/භාරකරුවන් විසින් පිරවීම සඳහාය.

මෙම පත්‍රය සහභාගීවන්නන්/භාරකරුවන් විසින් සම්පූර්ණයෙන් පිරවිය යුතුය.

1) අධ්‍යයනය සම්බන්ධයෙන් තොරතුරු පත්‍රිකාවෙ පැහැදිලි කරන ලද කරුණු ඔබට තේරුනාද?
(කරුණාකාර තොරතුරු පත්‍රිකාවේ පිටපතක 'ඔබ ලබාගන්න)

ඔව්/නැහැ

2) මෙම අධ්‍යයනය සම්බන්ධව සාකච්ඡා කිරීමට හා ඒ පිළිබඳව ප්‍රශ්න ඇසීමට ඔබට අවස්ථාවක් ලැබුණා ද?

ඔව්/නැහැ

3) ඔබ ඇසූ ප්‍රශ්න සියල්ලටම සෑහීමකට පත්විය හැකි පිළිතුරු ලැබුණාද?

ඔව්/නැහැ

4) මෙම අධ්‍යයනය සම්බන්ධයෙන 'ප්‍රමාණවත් තොරතුරු ලැබුණාද?

ඔව්/නැහැ

5) මෙම අධ්‍යයනය සම්බන්ධයෙන් ඔබට පැහැදිලි කරන ලද්දේ කවුරුන් විසින්ද?

.....

6) කිසිඳු කරුණු දැක්වීමකින් තොරව, මෙම අධ්‍යයනයෙන 'ඉවත්වීමට ඔබහට ඕනෑම අවස්ථාවක හැකියාව ඇති බව සහ එයින් ඔබගේ ඉදිරි වෛද්‍ය ප්‍රතිකාර සඳහා බලනොපානබවත් පැහැදිලිවුවාද?

ඔව්/නැහැ

7) ඔබගේ වෛද්‍ය වාර්තා සහ පර්යේෂණ දත්ත මෙම අධ්‍යයනය සම්බන්ධ සාමාජිකයින් විසින් අධ්‍යයනය කෙරේ. සියළු වාර්තා සහ දත්තවල රහස්‍යභාවය තහවුරු කෙරෙන මෙම අධ්‍යයනය සම්බන්ධ සාමාජිකයින්ට තොරතුරු ලබා දීමට එකඟ වෙනවාද?

ඔව්/නැහැ

8) මෙමඅධ්‍යයනයෙන්පසුවඉතිරිවනරුධිරසාම්පලයක්ඇතොත්සදාචාරසමාලොචනකමිටුවේඅනුමැතිය ඇතිවඉදිරියෙකෙරෙනප්‍රවේණිගත
පිළිකාපර්යේෂණයසඳහාභාවිතාකිරීමටහාගබඩාකිරීමටඔබඑකඟවෙනවාද?

ඔව්/නැහැ

9) රුධිරසාම්පලවෙනත්රටවලදීපරීක්ෂාකිරීමටඑකගද ?

ඔව්/නැහැ

10) මෙම අධ්‍යයනයට සහභාගීවීම සම්බන්ධයෙන් තීරණයකට එලඹීමට ඔබට ඇති තරම් කාලය ලැබුණාද?

ඔව්/නැහැ

11) ඔබ මෙම අධ්‍යයනයට සහභාගීවීමට එකඟ වෙනවාද?

ඔව්/නැහැ

සහභාගීවන්නන්ගේ/භාරකරුවන්ගෙඅත්සන ..... දිනය .....

නම:.....

(b) පර්යේෂක විසින් පිරවීම සඳහාය.

මෙම අධ්‍යයනය සම්බන්ධ කරුණුමා විසින්අධ්‍යයනයටස්වේච්ඡාවෙන්සහභාගීවන්නන්හටපැහැදිලිකරන ලදී. ඔහු/ඇවිසින්මෙමඅධ්‍යයනයටසහභාගීවීමටකැමැත්ත ප්‍රකාශකරන ලදි.

පර්යේෂකගේ අත්සන:..... දිනය:.....

නම:.....

விருப்பம் தெரிவிப்புப் படிவம்

பரம்பரைரீதியாக ஏற்படும் புற்றுநோயின் மருத்துவ மற்றும் மூலக்கூற்றுஇயல்புகள் பற்றி இலங்கையைச் சேர்ந்த நோயாளிகளில்மேற்கொள்ளப்படவுள்ள பேராய்வு

A. பங்குபற்றுவரால்அல்லது பாதுகாவலரால் முழுமையாக பூரணப்படுத்தப்பட வேண்டும்.

1. தகவல் ஏட்டை நீங்கள் வாசித்திருக்கிறீர்களா?
(தயவுசெய்து ஒரு பிரதியை உங்களுக்காக வைத்துக்கொள்ளலாம்)

ஆம் / இல்லை

2. இவ்வாய்வு பற்றி கலந்துரையாட அல்லது கேள்வி கேட்பதற்கு சந்தர்ப்பம் அமைந்ததுண்டா?

ஆம் / இல்லை

3. உங்கள் கேள்விகளுக்கு திருப்திகரமான பதில் கிட்டியதா?

ஆம் / இல்லை

4. ஆய்வு பற்றி போதுமான தகவல்கள் உமக்குக் கிட்டியதா?

ஆம் / இல்லை

5. இவ்வாய்வு பற்றி உமக்கு விளக்கமளித்தது யார்?
.....

6. இவ்வாய்விலிருந்து எந்தக்காரணமும் கூறாது, உங்கள் சிகிச்சையையும் பாதிக்காது நீங்கிக்கொள்வதற்கு எப்பொழுதும் உங்களுக்கு சுதந்திரம் உண்டு என்பதை நீங்கள் அறிவீர்களா?

ஆம் / இல்லை

7. உங்கள் மருத்துவ குறிப்புக்களின் ஒரு பகுதி இவ்வாய்வோடு சம்பந்தப்பட்ட ஏனைய உதவி ஆய்வாளர்களால் பரிசோதிக்கப்படலாம்.

எல்லாவிதமான தனிப்பட்ட குறிப்புக்களும் கடுமையான இரகசியம் பேணலின் கீழ் மேற்குறிப்பிட்ட தனிப்பட்ட உதவியாளர்களால் பரிசீலினை செய்யப்பட உங்கள் அனுமதியை வழங்குகுகிறீர்களா?

ஆம் / இல்லை

8. மீதம் இருக்கும் இரத்த மாதிரி மற்றும் மரபணுவை சேமித்துவைக்கவும் மற்றும் எதிர்காலத்தில் பரம்பரை ரீதியாக வரும் புற்றுநோய்கள் சம்பந்தமான ஆய்வில் நு.சு.ஊயின் அனுமதியுடன் இவற்றை உபயோகிக்கவும் சம்மதிக்கின்றீர்களா?

ஆம் / இல்லை

9. உங்கள் இரத்த மாதிரியை மேல் பரிசோதனைகளுக்காக வெளிநாடுகளுக்கு அனுப்ப சம்மதிக்கின்றீர்களா?

ஆம் / இல்லை

10. நீங்கள் இத்தீர்மானத்தி;ற்கு வருவதற்குப் போதுமான காலஅவகாசம் எடுத்தீர்களா?

ஆம் / இல்லை

11. இவ்வாய்வில் பங்கேற்பதற்கு நீங்கள் உடன்படுகிறீர்களா?

ஆம் / இல்லை

பங்கேற்பவர்ஃபாதுகாவலரின் கையொப்பம் ..... திகதி .....

பெயர் (ஆங்கில கெப்பிடல் எழுத்துக்களில்)

.....

B. ஆய்வாளரால் பூரணப்படுத்தப்பட வேண்டும்.

மேற்கூறப்பட்ட சுயேட்சையான ஆய்வுக்குட்படுத்தப்பட்டவருக்கு இவ்வாய்வு பற்றி பூரண விளக்கமொன்றை வழங்கினேன். அவர் இதில் பங்குபற்ற தனது சுயவிருப்பத்தைத் தெரிவித்தார்;.

ஆய்வாளரின் கையொப்பம் ..... திகதி .....

பெயர் (ஆங்கில கெப்பிடல் எழுத்துக்களில்)

.....

DATA COLLECTION FORM

CLINICAL AND MOLECULAR GENETIC STUDIES IN A COHORT OF SRI LANKAN PATIENTS WITH INHERITED CANCER SYNDROMES

FAMILY NUMBER ☐☐☐☐

FAMILY MEMBER ID ☐☐☐☐

Name of Subject……

Date of Birth ……/……../……

Age ……..

Address ……..

……..

……..

……..

Telephone ……..

Email address ……..

Date of entry into study ……../……/……

Referring Physician ……

Hospital ……**Ward:** ……...

Clinic No/ BHT No ……..

Data Protection and Confidentiality

After completion of this page, ensure that the subject study number is entered on **all pages** of this booklet. Then detach this page and store separately from the remainder of the booklet.

FAMILY NO: | | | | |

FAMILY MEMBER ID | | | | |

FAMILY PEDIGREE

Draw the family pedigree indicating all illnesses present, document abortions/still births/neonatal deaths as well.

Consanguinity Yes/No

V
IV
III.
II.
I.

Cancer Diagnosis

FAMILY NO: | | | | | **FAMILY MEMBER ID** | | | |

Family Member ID	Name	Details

FAMILY NO: ☐☐☐☐

FAMILY MEMBER ID ☐☐☐☐

A. Age ☐☐

B. Age of onset ☐☐

C. Sex Male ☐ Female ☐

D. Race

Sinhalese	☐	
Sri Lanka Tamil	☐	
Indian Tamil	☐	
Moor	☐	
Malay	☐	
Burgher	☐	
Mixed	☐	Specify: ……..
Other	☐	Specify: ……..

E. Religion Specify: ……

F. Occupation

G. Past Medical History

FAMILY NO: | | | | |

FAMILY MEMBER ID | | | | |

H. Clinical Presentation

I. Past Surgical history

J. Laboratory Findings

FAMILY NO: | | | | |

FAMILY MEMBER ID | | | | |

K. Social History (smoking/dietary habits/chemical exposure/etc.)

L. Clinical Examination

M. Bilateral Involvement (when relevant) Yes ☐ No ☐

FAMILY NO ☐☐☐☐

FAMILY MEMBER ID ☐☐☐☐

N. Cancer's Primary Origin

NA) HEAD AND NECK

NA1) Lip and oral cavity ☐
NA2) Pharynx (Base of tongue, soft palate, uvula) ☐
NA3) Larynx ☐
NA4) Nasal Cavity and Paranasal Sinuses ☐
NA5) Salivary Glands ☐
NA6) Thyroid ☐

NB) DIGESTIVE SYSTEM

NB1) Esophagus ☐
NB2) Stomach ☐
NB3) Small Intestine ☐
NB4) Colon and Rectum ☐
NB5) Anal canal ☐
NB6) Liver (including Intrahepatic Bile Ducts) ☐
NB7) Gallbladder ☐
NB8) Extrahepatic Bile ducts ☐
NB9) Ampulla of Vater ☐
NB10) Exocrine Pancreas ☐

NC) THORAX

NC1) Lung ☐
NC2) Pleural Mesothelioma ☐

ND) MUSCULOSKELETAL

ND1) Bone ☐
ND2) Soft Tissue Sarcoma ☐

NE) SKIN

NE1) Carcinoma of the Skin (Excluding Eyelid, Vulva and Penis) ☐
NE2) Melanoma of the Skin ☐

NF) BREAST

NF1) Breast ☐

FAMILY NO ☐☐☐☐

FAMILY MEMBER ID ☐☐☐☐

NG) GYNECOLOGICAL ☐

- NG1) Vulva
- NG2) Vagina
- NG3) Cervix Uteri
- NG4) Corpus Uteri
- NG5) Ovary
- NG6) Fallopian Tube
- NG7) Gestational Trophoblastic Tumors

NH) GENITOURINARY ☐

- NH1) Penis
- NH2) Prostate
- NH3) Testis
- NH4) Kidney
- NH5) Renal Pelvis and Ureter
- NH6) Urinary Bladder
- NH7) Urethra

NI) OPTHALMIC ☐

- NI1) Eyelid
- NI2) Conjunctiva
- NI3) Retinoblastoma
- NI4) Lacrimal Gland
- NI5) Orbit

NJ) CENTRAL NERVOUS SYSTEM ☐

- NJ1) Brain
- NJ2) Spinal Cord

NK) HODGKINS LYMPHOMA ☐

NL) NON_HODGKINS LYMPHOMA ☐

NM) SKIN ☐

- NM1) Basal Cell Carcinoma
- NM2) Melanoma

FAMILY NO ☐☐☐☐

FAMILY MEMBER ID ☐☐☐☐

NN) UNKNOWN PRIMARY ORIGIN ☐

O. Cancer stage at Tissue Removal ☐

P. Tumor Marker Indicators

Breast	ER	☐		
	PR	☐		
	HER2	☐		
GI	p53 gene expression	☐		
Lung	TTF1 antibody	☐		
Thyroid	TTF1 antibody	☐		
Prostate	PSA level	☐	Date	☐☐ ☐☐ ☐☐☐☐
GYN/GU/GI	hCG level	☐	Date	☐☐ ☐☐ ☐☐☐☐
GYN/GI	CA 125 level	☐	Date	☐☐ ☐☐ ☐☐☐☐
Lymphoma	B2M level	☐	Date	☐☐ ☐☐ ☐☐☐☐
Thyroid	Calcitonin level	☐	Date	☐☐ ☐☐ ☐☐☐☐
	Thyroglobulin level	☐	Date	☐☐ ☐☐ ☐☐☐☐
	CEA level	☐	Date	☐☐ ☐☐ ☐☐☐☐
	LDH level	☐	Date	☐☐ ☐☐ ☐☐☐☐

FAMILY NO ☐☐☐☐

FAMILY MEMBER ID ☐☐☐☐

Q. Tumor differentiation Well ☐

Moderately ☐

Poorly ☐

R. Was subject on Radiotherapy(RT)before SurgeryYes ☐

No ☐

Don't know ☐

If Yes, Date RT was completed ☐☐ ☐☐ ☐☐☐☐

S. Was subject on Chemotherapy before Surgery Yes ☐

No ☐

Don't Know ☐

If yes, Date of Chemo T completed ☐☐ ☐☐ ☐☐☐☐

Chemo T Type

T. Has the subject ever been diagnosed with another cancer (not this primary)?

Yes ☐

No ☐

Don't know ☐

If Yes,
Other Cancer Diagnosis

FAMILY NO ☐☐☐☐

FAMILY MEMBER ID ☐☐☐☐

Age, other cancer diagnosed ☐☐

Has subject received prior chemotherapy for the other cancer?

Yes ☐

No ☐

Don't know ☐

If Yes, Type of Chemotherapy ☐

Has subject received prior Radiation Therapy for the other cancer?

Yes ☐

No ☐

Don't know ☐

If yes, Year other RT was completed ☐

U. Venous Blood Sampling Done

Yes ☐

No ☐

Date ☐☐ ☐☐ ☐☐☐☐

K/EDTA vial

Label	Volume	Storage	Comments
1 2	1 2	1 2	

FAMILY NO | | | | |

FAMILY MEMBER ID | | | | |

COMMENTS

Record reasons for missing data and any additional relevant comments

ENSURE THAT ANONYMITY IS PRESERVED.

The booklet should be signed when ALL available data have been entered and cross checked with relevant data recorded elsewhere in this booklet.

I certify that data collected above has been entered to the electronic data base and that the blood sample has been stored at -80^{0}C.

Signed……. **Date……**

Investigator/Research Assistant