REVIEW

Cancer genetics and the surgeon – new frontiers

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Keywords: Genetics, genetic testing, hereditary cancer, germline mutations, risk assessment

Abstract

Cancer is a leading cause of death both globally and nationally. Recent advances in research have unraveled the molecular mechanisms responsible for many cancers. This has helped to transform the continuum of cancer care - from primary prevention, to screening and diagnosis, to treatment and follow-up using genetic information gathered by testing patients, their families, and the tumour tissue itself. New guidelines for risk assessment, genetic counseling, and planning of appropriate therapeutic and screening options based on the phenotypic and molecular characterization of cancers have now been developed. Such knowledge is vital not only for the treatment and follow up of patients but more importantly for screening of at risk family members with a hereditary predisposition to cancer. Awareness of their mutation status will allow such family members to make informed decisions regarding reproduction, lifestyle and clinical risk-reduction strategies to prevent future occurrence of cancer. At the national level adopting evidence-based strategies for early detection, counseling, improved surveillance and selection of effective therapeutic options will help to significantly reduce the mortality and morbidity associated with cancer in the country.

Introduction

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]. Cancer is known to result from mutations in critical genes within a single cell, allowing it to escape the normal control mechanisms of cell growth and proliferation resulting in the development of a clinically evident tumor [2].

Since genetic mutations play a role in the development of all cancers, all cancer is said to be genetic but only some are inherited. Inherited mutations account for about 5 to 10 percent of all cancers [2]. Genetics is known to play a vital role in the entire continuum of cancer care - from primary prevention, to screening and diagnosis, to treatment and follow-up procedures. Over the past few decades, research into cancer genetics has unraveled the molecular mechanisms responsible for many cancers. It has opened up the possibility of defining cancer from a molecular pathological standpoint which is more accurate than the currently practiced histopathological gradings. This has led to the development of guidelines for risk assessment, genetic counseling, and planning of appropriate therapeutic and screening options based on the phenotypic and molecular characterization of hereditary cancers. Such knowledge is vital not only for the treatment and follow up of patients but more importantly for screening of individuals with a hereditary predisposition to cancer. Characterization of such genetic mutations allows at risk family members to make informed decisions regarding reproduction, lifestyle and adoption of preventive, clinical risk-reduction measures leading to improved survival and quality of life. 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 [3].

There is, however, a dearth in the knowledge and understanding of the clinical and molecular mechanisms associated with 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

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with an inherited predisposition to cancer. This paper aims to describe the vital role genetics plays in the entire continuum of cancer care - from primary prevention, to screening and diagnosis, to treatment and follow-up.

Global Burden of Cancer

Cancer is a leading cause of death globally [1]. According to GLOBOCAN 2008, about 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred in 2008. Among them, 56% of cases and 64% of deaths occurred in the economically developing world. Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer deaths among females while lung cancer is the leading cancer in males worldwide. Cervical cancer was the commonest cause of cancer deaths during previous decades but has now been replaced by breast cancer in the developing world. Although overall cancer incidence rates in developing countries are half that seen in developed countries, the overall cancer mortality rates are almost similar. Cancer survival is poorer in developing countries due to late stage diagnosis and limited standard management protocols [4].

National Burden of Cancer

The World Health Organization has stated that proportional mortality of cancers was 9.0% in Sri Lanka in year 2008. Age standardized death rate per 100,000 population for cancer was reported to be 90.0 and 77.8 for males and females respectively [5]. One of the main functions of the National Cancer Control Programme (NCCP) is surveillance and monitoring of the cancer disease burden in Sri Lanka. It maintains a cancer registry database of pathology, epidemiology and public health related data [1]. The registry contains cancer incidence data in the Sri Lankan population according to the age groups, sex, ethnicity, cancer sites and mortality rates.

According to the 8th publication of the Cancer Registry in 2012, the increasing trend in the incidence of cancers which was observed from 1985 had continued in 2006 as well [1]. In the year 2006, a total of 14, 080 new cancer cases were diagnosed and the crude cancer incidence rate was estimated to be 70.9 per 100,000 population. The crude incidence rates of cancer in males and females were 62.7 and 79.0 per 100, 000 population respectively. Breast cancer is the commonest cancer among Sri Lankan women, accounting for 27% of all female cancers and also the leading cancer among Sri Lankans, contributing to 12.6% of all cancers [1]. An increase in breast cancer incidence in 2006 of approximately 1 per 100, 000 population compared to the year 2005 has been recorded. 'Lip, oral cavity and pharynx', trachea, 'bronchus and lungs', oesophagus, 'colon and rectum' and lymphoma were the five commonest cancer sites in males. Among the females, the top five cancer sites were breast, uterine cervix, ovary, thyroid and oesophagus. However, the contribution of genetic factors to these figures remains unknown as no large scale research into cancer genetics has been conducted in the country. Treatment modalities were recorded for cancer cases diagnosed in the year 2006. Out of all patients, 46% had received surgical treatment, 52% chemotherapy and 50% radiotherapy while 1.4% of patients had received only symptomaic treatment [1]. According to the Department of Census and Statistics, with the increase in cancer incidence, the deaths due to cancer have also increased. The death rates were reported to be higher in males compared to females [6].

In Sri Lanka, a large number of cancer patients tend to seek treatment when the disease is at an advanced stage, at which point currently available treatments are of little benefit. This has led to the increased burden of cancer in the country with huge amounts of public health sector funds being expended on management of patients who present in late stages, with very low quality results as the outcome [7]. The economic burden of cancer is most obvious in health care costs, such as those for hospitals, other health services, and drugs. This has resulted in an alarming increase in the national cancer budget. Indirect costs arise from loss of productivity as a result of the illness and premature death of those affected.

Genetic Basis of Hereditary Cancer

Cancers can be broadly classified into: hereditary, familial and sporadic [8]. Inherited mutations play a major role in the development of about 5 to 10 percent of all cancers due to highly penetrant germ-line mutations in cancer predisposition genes, while 10–15% are familial due to a combination of multiple low penetrant genes and shared environmental or lifestyle risk factors

[2]. Numerous genetic alterations that affect cell cycle regulating genes such as proto-oncogenes, tumour suppressor genes, DNA mismatch repair genes and p53 genes have been identified in neoplastic cells. Hereditary cancer syndromes generally follow the Knudson "Two Hit" hypothesis [9]. According to this hypothesis, dominantly inherited predisposition to cancer entails a germline mutation ("first hit"), while tumorigenesis requires a somatic mutation ("second hit"). A positive family history usually indicates possibility of hereditary cancer. Beside positive family history, specific or common characteristic features can be identified among different hereditary cancer syndromes. These include: earlier age of onset, multiple primary cancers in an individual, clustering of rare cancers and bilateral or multifocal cancers [8].

Hereditary Cancer Syndromes

Hereditary cancers are caused by highly penetrant, germline pathogenic mutations in cancer susceptibility genes. They are commonly inherited as autosomal dominant traits but autosomal recessive traits also exist. The commonest hereditary cancer syndromes are hereditary breast and ovarian cancer (HBOC), hereditary non polyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), multiple endocrine neoplasia type 2 (MEN 2), Von Hippel-Lindau disease (VHL) and familial retinoblastoma (RB1). Genetically determined breast cancer syndromes include: Hereditary breast and ovarian cancer syndrome (HBOC) – BRCA1 and BRCA2 genes; Cowden syndrome (multiple hamartoma syndrome) - PTEN gene; Li-Fraumeni syndrome - TP53 and CHEK2 genes; Peutz-Jeghers syndrome - STK11 gene; Ataxia-telangiectasia - ATM gene and Hereditary Diffuse Gastric Cancer – CDH1 gene. 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 [10]. Although BRCA1 and BRCA2 mutations are inherited in an autosomal dominant manner, their expression depends on acquiring a second mutation in the normal BRCA1 or BRCA2 gene in somatic cells. Even though children of mutation carriers are at 50% risk of inheriting the mutation, the age of onset of their cancer is difficult to predict. It is important therefore to explain the difference between inheriting the mutation and development of the cancer to those seeking genetic counseling to help them understand the meaning of a positive test result and discuss with them the estimated lifetime risk of cancer.

Mutations in five DNA mismatch-repair genes which cause HNPCC (MLH1, PMS2, MSH2, MSH6, EPCAM) account for approximately 5% of colorectal cancers and less than 1% are due to mutations in the FAP gene which causes familial adenomatous polyposis. 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 [11].

Identifying Hereditary Cancer Syndromes

The key to identifying individuals who are at risk for a hereditary predisposition to cancer lies in obtaining and analyzing a complete and accurate three-generation family history (pedigree). Pedigrees should include detailed medical history of the person seeking consultation (who may or may not be a person affected with cancer at the time of consultation), as well as their first-, second- and third-degree maternal and paternal relatives (i.e. children, parents, siblings, grandparents, aunts, uncles, nephews, nieces and first cousins). The pedigree should document the type and primary site of cancer, bilaterality, age at diagnosis and the current age or, if deceased, the age at death for each affected individual as well as information about other family members. Confirmation of cancer diagnosis through review of medical records, pathology reports or death certificates of family members will be useful in families where the verbal history appears to be unreliable. The extended pedigree of a family with hereditary breast cancer is shown in Figure 1.

When to Suspect Hereditary Cancer Syndromes

Table 1 shows the criteria for suspecting hereditary cancer syndromes in patients and their families [12].

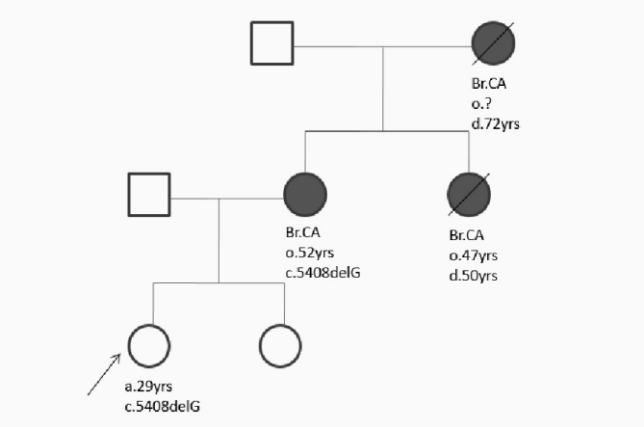

Figure 1. Pedigree of a family with hereditary breast cancer syndrome due to mutation in the BRCA1 gene.

When to Refer Patients for a Genetic Consultation

Knowledge of the guidelines for referral for genetic evaluation would guide clinicians in the decision making process by providing evidence-based strategies for early detection, counseling, improved surveillance and selection of effective therapeutic options for patients and family members with predisposition to hereditary cancer syndromes [12]. The referral guidelines for genetic consultation for breast and colorectal cancer are shown in Table 2 and Table 3 respectively.

Genetic Counselling for Hereditary Cancer Syndromes

Genetic counseling allows individuals an opportunity to learn how heredity contributes to cancer risk, understand their personal risk of developing cancer, understand their options for managing their cancer risk and encourage adoption of risk-reducing behaviors that are appropriate for them. All individuals undergoing genetic testing should be offered pre-test and post-test counseling.

Pre-test counseling is a process that includes discussion of personal risks of cancer based on the family history, the possible outcomes of genetic testing, including benefits, risks, limitations of testing and obtaining informed consent prior to testing.

Post-test counseling is a process in which the genetic test results and their significance are discussed, and medical management is reviewed, including screening and treatment options.

Other matters to be discussed during counselling include: privacy and confidentiality of genetic information; potential insurance, employment and social discrimination; adverse psychological reactions;

Table 1: Characteristic Features of Hereditary Cancer Syndromes [12]

In the Individual Patient	In the Patient's Family
Multiple primary tumours in the same organ	Two or more first-degree relatives on the same side of family with tumours of the same site
Multiple primary tumours in different organs	Two or more first-degree relatives with tumour types belonging to a known familial cancer syndrome (e.g. breast and ovary)
Bilateral primary tumours in paired organs	Two or more first-degree relatives with rare tumours
Multi-focality within a single organ	Three or more relatives in two generations with tumours of the same site or aetiologically related sites
Younger-than-usual age at tumour diagnosis	Evidence of autosomal dominant transmission – cancer occurring in multiple generations in the family
Tumours with rare histology	Diagnosis of a hereditary cancer syndrome in a family member.
Tumours occurring in the sex not usually affected (e.g. breast cancer in men)	
Tumours associated with congenital anomalies	
Tumours associated with an inherited precursor lesion	
Tumours associated with another rare disease	
Tumours associated with cutaneous lesions known to be related to cancer susceptibility disorders (e.g. the genodermatoses)	
Characteristic combination of cancers	

Table 2: Breast Cancer - Referral Guidelines for Genetic Consultation [12-15]

Multiple cases of breast and/or ovarian cancer in the family occurring in two or more close relatives:
Two 1st degree, or one 1st and one 2nd degree relative with breast cancer <60 years and/or ovarian cancer at any age on the same side of the family.
Three or more family members (1st or 2nd degree) with breast or ovarian cancer on the same side of the family, any age.
Patient or 1st degree relative with breast cancer <40 years, with or without family history.
Triple negative disease <60 years.
A family member with bilateral breast cancer.
A family member with both breast and ovarian cancers.
A family member with primary cancer in both breasts if one or both cancers diagnosed before age 50 years.
A family member with male breast cancer.
A family member with ovarian cancer.
A family history with characteristic combinations of cancers.
Diagnosis of a hereditary breast cancer syndrome in a family member.
A family member with an identified *BRCA1* or *BRCA2* mutation.

and sharing test results with relatives.

Genetic Diagnosis of Hereditary Cancer Syndromes

The identification of specific genes associated with hereditary cancer has enabled direct diagnosis of hereditary cancer syndromes through genetic analysis. Knowledge of the genetic mutations in families with hereditary cancer syndromes is vital for planning effective treatment strategies and for the early detection of hereditary cancer risk in other first and second degree relatives. Several studies have shown a reduction in breast and ovarian cancers in BRCA1 and BRCA2 mutation carriers through risk-reduction procedures such as bilateral prophylactic mastectomy and salphingo-oophorectomy respectively [3] as well as by chemoprevention using drugs like Tamoxifen and Raloxifene [18]. Germ line mutations of DNA mismatch-repair genes are a characteristic feature of HNPCC. Clinical surveillance of mutation carriers with hereditary predisposition to colorectal cancer can help prevent cancer. It is known that a significant proportion of hereditary cancers can be cured by surgery, radiotherapy, chemotherapy or hormone therapy, especially if detected early [3].

Genetic Testing

Genetic testing for Hereditary Breast and Ovarian Cancer (BRCA1 and BRCA2), Von Hippel-Lindau (VHL) and Retinoblastoma (RB1) mutations are available in Sri Lanka. Testing is done on DNA extracted from peripheral venous blood. In addition to these, the following pharmacogenomic tests are also available: k-Ras mutation testing (metastatic colorectal cancer), EFGR mutation testing (non small cell lung cancer) and BRAF mutation testing (papillary thyroid cancer, melanoma, colorectal cancer). In pharmacogenomic tests the tumour tissue is tested to predict response to chemotherapy so that chemotherapy can be modified accordingly.

The steps involved in genetic testing

• Test an affected family member FIRST after providing pre-test counseling and obtaining written informed consent.

Table 3: Colorectal Cancer - Referral Guidelines for Genetic Consultation [12, 13, 16, 17]

Colorectal cancer (CRC) diagnosed < 60 years.
Endometrial cancer diagnosed < 50 years.
CRC or Endometrial cancer at any age with a family history of 2 or more family members with Lynch Syndrome-related cancers.
Pancreatic adenocarcinoma < 50 years.
All epithelial ovarian cancers.
>10 adenomatous polyps.
>2 "Peutz Jegher" type hamartomas.
>3 Juvenile type polyps.
Diffuse gastric cancer < 50 years.
Diffuse gastric cancer > 50 years + additional relatives with gastric cancer.
1st or 2nd degree relative with CRC ≤ age 35 years.
1st or 2nd degree relative with 2 or more HNPCC/Lynch Syndrome-related cancers.
2 or more 1st or 2nd degree relatives on same side of family with CRC diagnosed < age 50 years.
3 or more relatives with any HNPCC/Lynch Syndrome-related cancers at any age, on same side of family, at least 1 of whom has CRC.
Family member with an identified HNPCC/Lynch Syndrome mutation.

• If a mutation is found, then other family members, including those who are not affected, can be tested for that mutation.

• If a mutation is not found, consider testing other genes.

• Always provide post-test counseling.

Benefits of genetic testing

• Clarify risks of cancer.

• Identify individuals who are at increased risk who could benefit from increased cancer surveillance, or measures to decrease risk.

• Identify individuals who may not be at increased risk.

Implications of a positive test result

• Modify the age at initial screening & frequency of screening e.g. mammography, colonoscopy, upper GI endoscopy & endometrial screening.

•Family members at risk can be offered testing and identified.

• Healthy life styles can be reinforced.

• Clinical intervention can improve outcomes e.g. risk reduction mastectomy reduces risk of breast cancer, hysterectomy reduces risk of endometrial cancer, prophylactic colectomy reduces risk of colorectal cancer and salpingo-oophorectomy reduces risk of ovarian and breast cancer (in premenopausal women).

Implications of a negative test result

• Reassures the individual and their family members.

Characterization of Cancer Syndromes in Sri Lanka

In a study conducted to document the breast cancer profile of a group of Sri Lankan women [19], patient-tumor characteristics and predicted prognosis were compared with immune profiles. The authors concluded that the overall profile of breast cancer and immune characteristics of Sri Lankan women were highly comparable to profiles documented elsewhere in the South Asian region despite the lower prevalence of estrogen receptors [19]. Even though BRCA1 and BRCA2 gene mutations are the common genetic variants found in hereditary breast cancer, geographical variation due to population heterogeneity is known to occur in HBOC. In a study conducted by De Silva et al. among Sri Lankan breast cancer patients and in high risk individuals, novel sequence variants and a high frequency of recurrent polymorphisms in BRCA1 gene were identified. After screening 66 patients with family history and 64 sporadic breast cancer patients, six novel sequence variants were discovered [20]. However, no genotype-phenotype correlations were done in this study. A study conducted by Perera et al. to determine the prevalence of colorectal cancer and survival in patients from the Gampaha district, North Colombo region indicated that the burden of colorectal cancer in Sri Lanka is on the rise. Up to a third of cancers were found to occur in those under 50 years, and the majority of cancers were in the rectum or recto-sigmoid region [21]. A twelve year prospective database of colorectal cancer patients was analyzed by Chan et al. to compare the clinico-pathological features in young (<40 years) and older (>50 years) patients. They observed that duration of symptoms and clinical presentation was similar in both groups [22]. Another comparative study on the clinico-pathological features of colorectal malignancies in Sri Lankan patients aged 40 years or younger and older patients conducted by De Silva et al. reported that there is no difference in clinical presentation between the 2 groups. In this study, all patients aged below 40 years diagnosed with colorectal cancer and treated at the Department of Surgery, University of Kelaniya, from September 1996 to September 2008, 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 [23].

Future Outlook for Cancer Genetics Research in Sri Lanka

There is a dire need to undertake large scale studies in Sri Lanka to document the phenotypic spectrum and the pattern of genetic mutations causing hereditary cancer syndromes in the local population. To date, there is paucity of data in this area in the Sri Lankan population. Moreover, due to marked population heterogeneity, the distribution of cancer predisposing genetic variants is known to differ among racial and ethnic groups. Therefore, it is necessary to map the clinical and genetic pattern of hereditary cancer syndromes in the local population to determine the prevalent genotypes and phenotypic characteristics. The findings from such studies will contribute to the advancement of the generalizable knowledge in the field of cancer genetics in Sri Lanka. The ultimate goal being to reduce cancer morbidity and mortality and improve the quality of life of cancer patients through primary prevention, early detection, improved surveillance and effective treatment options [24].

References

1. National Cancer Control Programme (NCCP) – 2012, 8th publication. Cancer Incidence Data Sri Lanka 2006.

2. National Cancer Institute FactSheet. Genetic Testing for Hereditary Cancer Syndromes. Available from: http://cancer.gov/cancertopics/factsheet/risk/genetic-testing, accessed on 05/03/14.

3. Thomas SF. Hereditary Cancer Syndromes. Arch Pathol Lab Med 2001; 125: 85-90.

4. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011; 61(2): 69-90.

5. WHO/Sri Lanka; 2013. Available from: http://who.int/countries/lka/en/, accessed on 06/03/14.

6. Department of Census and Statistics. Number of deaths by cause, age and sex (2001-2006); 2012.

7. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 10/06/14.

8. Fostira F, Thodi G, Konstantopoulou I, et al. Hereditary cancer syndromes. Journal of BUON 2007; 12 (Suppl 1): S13-S22.

9. Fearon ER. Human cancer syndromes: clues to the origin and nature of cancer. Science 1997; 278(5340): 1043-1050.

10. Allain DC. Genetic Counseling and Testing for Common Hereditary Breast Cancer Syndromes. Journal of Molecular Diagnostics 2008; 10(5): 383-395.

11. Frank TS. Hereditary Cancer Syndromes. Archives of Pathology & Laboratory Medicine 2001; 125(1): 85-90.

12. Lindor NM, McMaster ML, Lindor CJ, Greene MH. Concise handbook of familial cancer susceptibility syndromes. J Natl Cancer Inst Monogr 2008; 38: 1-93.

13. Predictive Cancer Genetics Steering Committee (PCGSC). Ontario physicians' guide to referral of patients with family history of cancer to a familial cancer genetics clinic. Toronto, ON: Ontario Medical Association; 2001. Available from: http://oma.org/pcomm/OMR/Nov/01genetics.htm, accessed on 10/03/14.

14. Gronwald J, Byrski T, Huzarski T, Oszurek O, et al. Hereditary breast and ovarian cancer. Hereditary Cancer in Clinical Practice 2008; 6(2): 88-98.

15. Thull DL, Vogel VG. Recognition and Management of Hereditary Breast Cancer Syndromes. The Oncologist 2004; 9: 13-24.

16. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Genetics/Familial High-Risk Assessment: Colorectal Cancer Screening. Version 2.2014. Available from: http://nccn.org, accessed on 06/06/14.

17. National Cancer Institute: The Genetics of Colorectal Cancer PDQ. Available from: http://cancer.gov/cancertopics/pdq/genetics/colorectal/healthprofessional, accessed on 08/06/14.

18. Robson M, Offit K. Management of an Inherited Predisposition to Breast Cancer. The New England Journal of Medicine 2007; 357: 2.

19. Lokuhetty MDS, Ranaweera GG, Wijeratne MDM, et al. Profile of Breast Cancer in a Group of Women in a Developing Country in South Asia: Is There a Difference? World Journal of Surgery 2009; 33(3): 455-459.

20. De Silva W, Karunanayake EH, Tennekoon KH, et al. Novel sequence variants and a high frequency of recurrent polymorphisms in BRCA1 gene in Sri Lankan breast cancer patients and at risk individuals. BioMed Central Cancer 2008; 8: 214.

21. Perera T, Wijesuriya RE, Suraweera PHR, et al. The prevalence of colorectal cancer and survival in patients from the Gampaha District, North Colombo region. The Ceylon Medical Journal 2008; 53(1): 17-21.

22. Chan KK, Dassanayake B, Deen R, et al. Young patients with colorectal cancer have poor survival in the first twenty months after operation and predictable survival in the medium and longterm: Analysis of survival and prognostic markers. World Journal of Surgical Oncology 2010; 8: 82.

23. De Silva M, Fernando M, Fernando D. Comparison of some clinical and histological features of colorectal carcinoma occurring in patients below and above 40 years. The Ceylon Medical Journal 2000; 45(4): 166-168.

24. Shannon KM and Patel D: Principles of Cancer Genetic Counseling and Genetic Testing. In: Chung DC and Haber DA (eds). Principles of Clinical Cancer Genetics: A Handbook from the Massachusetts General Hospital, 23. DOI 10.1007/978-0-387-93846-2_2, Springer Science and Business Media, LLC 2010.