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Organization and Running of the First Comprehensive Hereditary Cancer Clinic in India

T. Rajkumar[1], N. Soumittra[1], E. Vidubala[2], V. Sridevi[3], V. Mahajan[3], S.G. Ramanan[4], S. Vijaya[5]

[1]Dept. of Molecular Oncology, [2]Dept. of Preventive Oncology, [3]Dept. of Surgical Oncology, [4]Dept. of Medical Oncology, [5]Dept. of Radiation Oncology, Cancer Institute (WIA), Adyar, Chennai – 600020, India

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Corresponding author: T. Rajkumar, Cancer Institute (WIA), Adyar, Chennai – 600020, India, tel. +91-44-22350340, fax +91-44-24912085, e-mail: cancer_institute_wia@vsnl.com

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Abstract

Hereditary cancers are thought to account for around 5% of cancers, particularly breast/ovarian and colorectal cancers. In India there is a paucity of data on hereditary cancers and the mutations in some of the common genes linked to hereditary cancers, such as BRCA1, BRCA2, hMSH2 and hMLH1. The country's first comprehensive hereditary cancer clinic was established in February 2002. The article describes the organization and running of the Clinic. It also discusses some of the social issues relevant to the given population in running the Hereditary Cancer Clinic.

Introduction

Although the cancer burden is very high in India, the incidence of cancer is lower than in the West. In Chennai (formerly Madras), the population-based cancer registry has recorded a crude incidence rate (CIR) of 90.5/100,000 and 102.7/100,000 in males and females, respectively [1], which is nearly 3 – 4 fold lower than that seen in the West (464.6/100,000 and 377.9/100,000 in males and females, respectively) [2]. In women, the most common cancers seen in Chennai are breast cancer (CIR 26.09/100,000), cervix cancer (CIR 23.37/100,000), stomach cancer (CIR 5.14/100,000) and ovarian cancer (CIR 5.14/100,000). The incidence of colo-rectal cancers is much lower than in the West (2.25/100,000 in men and 1.6/100,000 in women) [1]. Around 5% of cancers are considered to be due to a hereditary background. Until a few years ago there were very few data available on the hereditary cancers in the Indian population and the mutation rates in the common hereditary cancers, such as BRCA1, BRCA2, MSH2 and MLH1 [3-6]. Again due to the ethnic diversity, studies done in one part of India may not be representative of the whole country.

The Indian population is also unique in that marriages usually occur within a given caste and sometimes within the family (consanguineous marriage) (uncle-niece marriages are common in South India). This leads to the potential for relative inbreeding and possible segregation of genes. In view of the lack of information on hereditary cancer incidence and the types of mutation, the first comprehensive Hereditary Cancer Detection and Prevention Programme (HCDPP) in India was started in February 2002 at the Cancer

Institute (WIA), Chennai. The Programme has the following components:
1. The Population-Based Hereditary Cancer Registry.
2. The Hereditary Cancer Clinic (HCC).
3. The Mutation Analysis Laboratory.

This article will discuss the organization and running of the Hereditary Cancer Clinic at the Cancer Institute (WIA).

Organization of the Hereditary Cancer Clinic

Day and time: The Hereditary Cancer Clinic is run as a free clinic once a week on Saturdays between 8.30 am and 1.00 pm. On the days when there are more patients the Clinic runs until all the patients are seen.

Personnel: The Clinic is manned by an oncologist (T.R.), a doctoral student (N.S.) and a part-time Psychologist (E.V.). The oncologist is involved in the clinical examination, analysis of the information obtained from the patients regarding their family and their personal history, assessing the eligibility of the proband for gene testing, counselling the proband/patients and their families with regard to their cancer risk, the intervention procedures and preventive measures available, and after gene testing the announcement of the results and the investigations/preventive measures that need to be followed by the proband/patient. The doctoral student collects the questionnaire-based information from the proband, draws the pedigree chart, and is responsible for data entry, sample collection and analysis. The part-time psychologist evaluates the patients at least once before the gene testing results are announced.

Charges for the service: The entire service, including mutation analysis where indicated, is provided free of charge.

Procedural details:

I. Questionnaire-based data collection:

The questionnaire is a modified version of the format presented in *Cancer and Genetics. A manual for clinicians and their patients, 1998* [7]. All probands are required to provide as much information as possible about their families, personal history and diet history. If the proband is educated and is unable to provide all the information at the time of interview, he or she is encouraged to take a copy of the questionnaire and complete it in consultation with their elders in the family and mail it to us. The questionnaire used in the Clinic is appended as a Word document. On average the administration of the questionnaire takes 20 minutes. All the probands with cancer or a history of cancer in the family (first- or second-degree relatives) are administered the questionnaire. The exception to this is individuals who attend the Clinic either to obtain more information on the hereditary cancers or those with only a distant relative (third degree or beyond) with cancer or those who are unwilling to provide information about their family.

II. Initial counselling:

The oncologist analyses the information provided and requests additional information if indicated, particularly with regard to types of cancers in the family. The ability to provide additional information is always better in the upper socio-economic group compared to the lower socio-economic group. A complete physical examination is performed, following which, based on the information provided, the proband is counselled with regard to the possibility of the cancer seen in him or in his family being hereditary in origin. If there are specific genes linked with the cancer/s seen in the family, the proband is offered gene testing if the eligibility criteria for gene testing are satisfied. Probands are counselled with regard to preventive strategies, early detection approaches and therapeutic interventions available. They are also informed about the option of predictive testing in their siblings and children.

The eligibility criteria for gene testing are given below.

1. **Hereditary breast/ovarian cancer**

a. Early onset of breast cancer (at or less than 35 years of age)
b. Two cases of breast cancer diagnosed under the age of 50 years
c. Three cases of breast cancer diagnosed under 60 years of age
d. Four or more cases of breast cancer diagnosed at any age
e. Presence of breast and ovarian cancer in the family or in the same individual
f. Male breast cancer with a relative (of either sex) with breast cancer.

2. **HNPCC**

Bethesda guidelines are used [8]

a. Families meeting the Amsterdam criteria
b. Individuals with two HNPCC-related cancers
c. Individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extra-colonic cancers or a colorectal adenoma, in which one of the cancers was diagnosed before 45 years of age and adenoma was diagnosed before 40 years of age
d. Individuals with colorectal or endometrial cancer diagnosed before 45 years of age

e. Individuals with right-sided colon cancer with undifferentiated pattern diagnosed <45 years of age.
f. Individuals with signet ring type C-R cancer Dx <45 years of age
g. Individuals with adenoma diagnosed under 40 years of age.

3. Multiple Endocrine Neoplasia (MEN) 2 [9]
a. MEN 2A
b. MEN 2B
c. Familial Medullary Thyroid Carcinoma (FMTC)

4. Li-Fraumeni (LFS) and Li-Fraumeni Like (LFL) Syndrome

Li and Fraumeni defined criteria for LFS as follows [10,11]:

a. A proband diagnosed with sarcoma when younger than 45 years AND
b. A first-degree relative with any cancer diagnosed when younger than 45 years
AND
c. Another first- or second-degree relative of the same genetic lineage with any cancer diagnosed when younger than 45 years or sarcoma diagnosed at any age.

Eeles' definition of LFL (Eeles, 1995)

Two first- or second- degree relatives with LFS-related malignancies at any age.

III. Informed consent and providing of blood sample for gene testing:

All patients considered eligible for gene testing were required to provide an informed consent for willingness to have a sample of blood and tumour tissue provided and willingness to have the gene testing done. Only after the signing of the informed consent were blood samples drawn for gene testing.

In patients who had had their surgery performed elsewhere, paraffin blocks were requested.

IV. Gene testing

At present, gene testing is being performed for BRCA1, BRCA2, MSH2, MLH1, RET and p53. The methodology for mutation analysis for BRCA1 and BRCA2 [5] and for hMSH2 and hMLH1 [6] has been as described, using the PCR-dHPLC. RET and p53 are studied using PCR followed by direct sequencing of the PCR products [12,13,14].

V. Follow-up

Once the gene test results are ready, a note is inserted in the case records of the patients asking the treating physician to refer the patient to the Hereditary Cancer Clinic. Patients who had been referred from outside the Cancer Institute (WIA) were informed by a letter to their contact address that the gene test results were ready and that they could visit the Clinic to know the results. Prior to announcing the results, the proband was asked to provide an informed consent that they would like to know their gene test results. On obtaining the consent, a psychological assessment was made using a long form of general health questionnaire and the Hamilton rating scale for depression. The test results were then announced and an interpretation of the results was made. The proband and the family were counselled about their risk for a second primary, their siblings and children's risk of developing cancer, the strategies for cancer prevention, regular monitoring and early detection. If a deleterious mutation was detected then predictive testing for the unaffected members in the family (first and second degree) was offered.

Patients with deleterious mutations were advised closer follow-up and the treating physicians were informed about the results and suggested line of management. The patients were advised once in six monthly reviews in the Hereditary Cancer Clinic.

Results

The number of cases/families registered in the Hereditary Cancer Clinic is given in Table 1. The details of the families/individuals registered are given in Tables 2 and 3. Among the hereditary cancer families, hereditary breast and/or ovarian cancers predominate in the Clinic (15%). There are also a large number of

Table 1. Number of cases registered in the HCC

Total number of cases registered in HCC	442
Number of families with proband affected with cancer	342
Number of families without proband affected with cancer	100
With Proband Affected	
Number of families with more than 2 members affected with proband affected	73
Number of families with 2 members affected with proband affected	107
Proband with multiple cancers	6
Early onset cancers	156
Without Proband Affected	
Number of families with more than 2 members affected without proband being affected	42

Table 2. Details of the type of hereditary cancers seen in families which also had the proband affected

Hereditary Breast and Ovarian Cancer	50
Hereditary Ovarian Cancer	3
Hereditary Non-Polyposis Colorectal Cancer	12
Early onset breast cancer	59
Early onset colorectal cancer	87
Early onset ovarian cancer	6
Early onset endometrium cancer	2
Early onset stomach cancer	1
Early onset bladder cancer	1
Li-Fraumeni Syndrome	2
Li-Fraumeni-like syndrome	6

Table 3. Details of the type of hereditary cancers seen in families in which the proband was not affected

Hereditary Breast and Ovarian Cancer	14
Hereditary Non-Polyposis Colorectal Cancer	4
others	82

Table 4. Gene testing and results

BRCA1 & BRCA2	80
deleterious or mutation of probable significance detected in BRCA1 or BRCA2	12
hMSH2 & hMLH1	76
deleterious or mutation of probable significance detected in hMSH2 & hMLH1	9
RET	2
deleterious or mutation of probable significance detected in RET	1
p53 & CHEK2 (1100delC)	6
deleterious or mutation of probable significance detected in p53	3

early onset cancers (156/342) (45.6%), particularly breast (≤35 years of age; 17.3%) and colorectal (≤45 years of age; 25.4%), registered in the Clinic. The 'Others' group includes cervical cancer, tobacco-related cancers, gastric cancer, leukaemia, etc., in the family involving more than one family member.

Table 5. Acceptability for gene testing HBC/HBOC and HNPCC

No. of patients who were offered gene testing	203
No. of patients who declined gene testing	9
No. of patients with a deleterious mutation/mutation of probable significance, who declined treatment at the Institute after the initial diagnosis and registration in the hereditary cancer clinic	1/21
No. of patients with deleterious mutation/mutation of probable significance, who did not want to know the results, in spite of regular follow-up at the Institute	12/21
No. of patients with deleterious mutation/mutation of probable significance, who took the results	8/21
Number of patients who wanted predictive testing for their children/sibs	2/8

Gene testing has been performed for 80 hereditary breast and/or ovarian cancers and/or early onset breast or ovarian cancers, and 12 deleterious mutations or mutations of probable significance were detected (15%). Among the 76 HNPCC syndrome patients included as per the Bethesda criteria, 9 deleterious mutations or mutations of probable significance were detected. The MEN 2B patient was found to have the classic mutation in the RET oncogene in Ex16- c. 2943T >C; p. M918T. Of the two LFS and four LFL syndrome families studied for p53 mutation, both the LFS and one of the LFL were found to carry a germline mutation in the p53 gene (Table 4).

The acceptability for gene testing was 95.6% with 194 of the 203 individuals offered gene testing providing an informed consent for the gene testing and a blood sample. However, of the 21 patients with a deleterious mutation or mutation of probable significance in the hereditary breast and/or ovarian cancers, early onset breast or ovarian cancers and the HNPCC syndrome, only 8 (38%) opted to know the result (Table 5). Among the 8, only 2 families wanted to have predictive testing for their siblings or children.

Discussion

This is the first report on the functioning of a comprehensive hereditary cancer clinic in India. The Clinic currently draws patients not only from the southern states of Tamil Nadu, Andhra Pradesh and Karnataka, but patients are also being referred from New Delhi and other parts of the country. When the idea of a hereditary cancer clinic was mooted in the Institute, there were concerns regarding the utilization of such a service from the conservative population.

The foremost concern was that a family would try to avoid reference to cancer in the family, particularly with regard to the marriage of their children and the potential 'stigma' of being from a cursed family. The second concern was with regard to the reliability of the family history of cancer particularly with regard to the type of cancer and the age at onset in the relative. This was further worsened by the breaking up of the joint family system in urban India.

Once the Clinic started functioning, we tried to circumvent some of the problems, by providing the proband with the questionnaire and asking him/her to complete it in consultation with the elders in the family who may not be staying with them. In addition, wherever doubts existed with regard to the site and type of cancer, the individuals were counselled on the need to obtain old records. The success rate with this was directly proportional to the anxiety in the family/proband about the cancer in the family being hereditary in origin. In spite of this, in at least 15% of cases, particularly from the lower socio-economic group, information regarding their first-degree relatives may not be available and this percentage increases to above 30% for second-degree relatives.

The off-take of the gene testing services was much above our expectations, at nearly 95%. However, this is tempered by the relatively low interest to know the result of the gene tests. This indicates also the undercurrent of anxiety in individuals and their families about having a deleterious mutation detected. While the Clinic discusses the issues related to gene testing and the follow-up measures required in the event of a deleterious mutation being detected, and the risk to the siblings and their children, it apparently is not sufficient to allay all the fears they have. In addition, the understanding of the implications in the uneducated needs to be further improved. However, the social issues are unlikely to be overcome in the near future and this will require community education on the general aspects of cancer and the curability of cancer when detected early.

One of the families seen and tested exemplifies the current realities in the lower middle income group. This family had the mother and her daughter affected with colorectal cancer and a novel splice junction mutation was detected in both. A letter was sent to the family asking them to report to the Institute. A week later the family reported and the results were announced after taking an informed consent for knowing the results. The family was counselled with regard to the follow-up measures to be followed by the affected mother and the daughter. There were two other siblings younger than the affected daughter and both were offered predictive testing. Although the family wanted the predictive testing done, they wanted it deferred for some time. The family also requested that no communication be sent to their residence as it was a joint family and none of the other residents knew about the illness the daughter had. The family wanted to proceed with the marriage arrangements for the affected daughter and sought our opinion. Since the daughter had hardly completed a year after her initial treatment, she was advised against this. Subsequent to this, in deference to the wishes of the family, we have not communicated with the family for further follow-up and it is quite likely that the affected daughter has had her marriage completed.

This contrasts with an educated upper middle class family, wherein the brother of an affected patient with HNPCC not only convinced his sister to undergo the gene testing, but once a deleterious abnormality was detected in her, had himself tested (he had a keratocanthoma). He was also found to be a carrier of the same mutation and was counselled with regard to the follow-up measures, which he undertook shortly thereafter. He then convinced his two other sisters to undergo predictive testing, who when tested did not carry the same mutation.

The establishment and running of the country's first comprehensive hereditary cancer clinic has thrown up surprises and challenges. The challenges will need to be addressed keeping the sensitivities of the population in mind.

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