

# The impact of hereditary colorectal cancer on the Indian population

Maharaj R, Shukla PJ, Sakpal SV, Naraynsingh V<sup>1</sup>, Dan D<sup>1</sup>, Hariharan S<sup>1</sup>

Department of Surgical Oncology, Gastrointestinal Service, Tata Memorial Hospital, Mumbai, Maharashtra, India, <sup>1</sup>Department of Clinical Surgical Sciences, University of the West Indies, Trinidad

Correspondence to: Dr. Ravi Maharaj, E-mail: [drravi\\_maharaj@yahoo.com](mailto:drravi_maharaj@yahoo.com)

## Abstract

**INTRODUCTION:** The incidence of colorectal cancer in India is lower compared to the Western world. In Western countries, most cases of colorectal cancer are sporadic and the hereditary variety accounts for only 10-15% of all cases. The aim of the present review is to determine the clinical and epidemiological characteristics of hereditary colorectal cancer in India. **MATERIALS AND METHODS:** A Medline search was conducted to review the literature published from India regarding colorectal cancer. The keywords used included India, colorectal cancer, hereditary nonpolyposis, and familial adenomatous polyposis. All relevant articles were reviewed and the characteristic features of this disease in Indian population were collated and presented. **RESULTS:** Literature search revealed eighty two articles pertinent to India, of which only ten articles had relevant information on hereditary cancers. Although the overall incidence of colorectal cancer was low in both genders, there were a high proportion of patients developing colorectal cancer before the age of 45 years. Additionally, there was a higher proportion (10-15%) of hereditary nonpolyposis colorectal cancer cases, as confirmed by microsatellite instability. **CONCLUSION:** The overall incidence of colorectal cancer is low in India. There is a tendency to affect a relatively younger age group, and we infer that the incidence of hereditary colorectal cancer is high and is similar to the Western countries.

**Key Words:** Hereditary, colorectal cancer, India

## Introduction

The incidence of cancer varies widely according to the geographic location.<sup>[1]</sup> The most common cancers in the Western world are those of the lung, colon and rectum and prostate in men and breast in women. However in India, the leading cancers are those of the oropharynx, stomach and esophagus in men and uterine cervix, breast and oropharynx in women.<sup>[2]</sup> Despite a high incidence of *H. pylori* infection, the incidence of stomach cancer is relatively lower in India compared other Oriental countries, but colorectal cancer incidence is even lower.

The incidence of colorectal cancer (CRC) in the Western world is almost eight times that of India.<sup>[2]</sup> This has been attributed to predominantly the dietary pattern of the population. The low fat and high fruit and vegetable content in the Indian diet as well as the use of certain spices, such as turmeric (curcumin) may have an anti-oxidant role in cancer prevention.<sup>[3]</sup> However, several studies have revealed a proportionately high incidence of CRC in the younger age group, especially in males under the age group of 40 years.<sup>[4,5]</sup> Additionally, the ratio of colon cancer to rectal cancer appears to be equal, which is typical of geographic locations with low incidence of CRC. In comparison, in the Western World where the incidence of CRC is high, this ratio is approximately 2:1.<sup>[1]</sup>

There are also genetic influences in different ethnic groups for the development of hereditary CRC. The Lynch syndrome [Hereditary Nonpolyposis Colorectal Cancer (HNPCC)] is a dominantly inherited syndrome characterized by the development of a variety of cancers frequently including cancer of colorectum, endometrium, and other locations such as the small bowel, stomach, urinary tract, ovaries, and brain.<sup>[6]</sup> The Human Variome Project

which aims to facilitate sharing of all genetic variations effecting human disease, found that there are differences in the gene variants of the Chinese population which may be a contributing factor for development of hereditary CRC.<sup>[7]</sup> Hereditary Non-Polyposis Colorectal Cancer (HNPCC) is linked to pathogenic mutations in one of the mismatch repair (MMR) genes and Familial Adenomatous Polyposis (FAP) may be caused by high-penetrant mutations within the Adenomatous Polyposis Coli (APC) gene.<sup>[8]</sup> Such genetic variants for CRC in the South Asian population remain to be elucidated.


In general, most cases of CRC are sporadic worldwide and hereditary CRC accounts for only up to 15% of all cases.<sup>[9]</sup> Hereditary cancers usually occur in the younger age group. Although CRC in the young population may be more aggressive, if detected during early stages, young patients have better overall 5-year survival rates.<sup>[10]</sup> It may be useful to know the epidemiological characteristics of hereditary CRC in India especially when it involves younger age group patients, so that the morbidity and mortality associated with this condition could be reduced.

With this background, this review aimed to determine the characteristic features of hereditary CRC in the Indian population from data collected at a cancer hospital and also from published literature.

## Materials and Methods

After approval of the relevant authorities, data were collected from the Tata Memorial Hospital Mumbai, India retrospectively for a five year period ranging from 2004 through 2008. Data were collected from the operating log of the electronic medical records system enlisting all operated cases for colon and rectal cancer irrespective of the intent of operation (palliative or curative). The number of patients having colonic cancer (based on colectomies) and rectal cancer (based on anterior resection or abdominoperineal resection (APR)) was noted. Patients having APR for other reasons such as poor preoperative sphincteric function were excluded. Demographic and clinical data for all these patients were collected codifying them for confidentiality purposes.

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Additionally, a systematic search of the scientific literature was carried out using the MEDLINE® and the PubMed® with its Medical Subject Headings (MeSH) feature to obtain access to publications on CRC, particularly with regards to study of the disease in the Indian population. The search strategy was that described by Robinson and Dickersin with the appropriate search terms for ‘cancer’, ‘colon’, ‘colorectal’, ‘familial adenomatous polyposis’, ‘FAP’, ‘hereditary’, ‘India’, ‘malignancy’, and ‘rectum’ in variable combinations.<sup>[11]</sup> Selected articles were retrieved and reviewed.

## Results

Data regarding CRC and surgeries were collected at the Tata Memorial Hospital, Mumbai during a five year period ranging from 2004 through 2008. A total of 715 patients underwent surgical operations for CRC of which 255 patients (35.7%) were operated for colon cancer, while 460 patients (64.3%) were operated for rectal cancer. The mean age at diagnosis varied between colonic and rectal cancers. This was 52.6 years for colonic cancer [Figure 1] while it was 47.4 years for rectal cancer [Figures 2 and 3]. However, for patients who underwent abdominoperineal resection for low rectal cancer, the mean age at diagnosis was relatively low at 42.7 years. The ratio of sphincter-preserving surgery as opposed to abdominoperineal resection for rectal cancer was 1.2:1.

### Review of the published literature from India

A total of 82 articles were retrieved using the search strategy described in the methodology section. Of these, twenty six articles were relevant to epidemiology of CRC in young adults, and only 10 of these elaborated on hereditary or familial CRC.

### Overall incidence of colorectal cancer in India

Analysis of cumulative data from nine Cancer Registries named by the cities throughout India including Ahmedabad, Bangalore, Chennai, Delhi, Karunagappally, Mumbai, Nagpur, Poona and Trivandrum revealed CRC to be the sixth most common cancer among both males and females.<sup>[2]</sup> The most remarkable finding is that the incidence of CRC in India is approximately 4.7/100,000 amongst males and 3.2/100,000 amongst females.

### Epidemiological characteristics

A retrospective review by Deo *et al.* from the All India Institute of Medical Sciences (AIIMS), New Delhi found that the mean age of CRC patients at diagnosis to be 45.3 years.<sup>[4]</sup> Pal reported that the incidence of CRC in patients aged < 40 years to be proportionately higher in Kolkata when compared to Population Based Cancer Registries (PBCR) from other cities such as Bangalore, Mumbai, Delhi and Chennai.<sup>[12]</sup>

Deo *et al.* also reported that there was a strong preponderance of rectal cancer over colonic cancer (76% versus 24%) in New Delhi. In addition, the average distance of the tumour from the anal verge in rectal cancer was 4 cm, and abdominoperineal resection was the most common operation performed for CRC in that institution.<sup>[4]</sup>

### Ulcerative colitis and CRC

The risk of CRC in patients with ulcerative colitis in the Indian population was variable according to different reports. Venkataraman *et al.* published a retrospective review of 532 patients with ulcerative colitis and found that the risk of developing CRC in the first 10 years of diagnosis to be zero, in those with disease duration of between 10-20 years the risk to be 2.3% and for those with the disease for greater than 20 years had a risk of 5.8%.<sup>13</sup> A report from Kolkata quoted a high incidence of 10% CRC in ulcerative colitis patients.<sup>[14]</sup> 75% of these patients had suffered ulcerative colitis for more than 20 years. On the other hand, another report from the Postgraduate Institute of Medical Education and Research, Chandigarh reported a low incidence of CRC (1.8%) in ulcerative colitis patients.<sup>15</sup>

### Hereditary colorectal cancer in India

Hereditary and familial CRCs account for approximately 10% of all cases.<sup>[6]</sup> Generally there is agreement that there is proportionate increase in the number of younger patients affected by CRC. A report from Srinagar, Kashmir, India indicated that even in the 1980s, about 69% of patients with CRC belonged to the age-group ranging from 41-60 years.

Rajkumar *et al.* reviewed 31 patients who satisfied the Bethesda guidelines for microsatellite instability testing (MSI).<sup>[16]</sup> Twelve patients exhibited MSI-H, 9 patients were MSI-L and the remaining 10 were MSS. For the 12 patients with MSI-H, five mutations were detected, 3 of which were deleterious, one was probably significant and the other was unknown. This revealed that even in patients satisfying the Bethesda guideline, most are MSI low or stable. In addition, Pandey *et al.* reviewed paraffin embedded blocks from 46 CRC cases also satisfying the Bethesda guidelines and found 2 patients with MSI-H, 3 patients with MSI-L and the remaining 41 were MSS.<sup>[17]</sup>

Considering all these, it may be possible to postulate that the incidence of hereditary CRC in India is comparable to that of the Western countries, although the overall incidence is far lower.

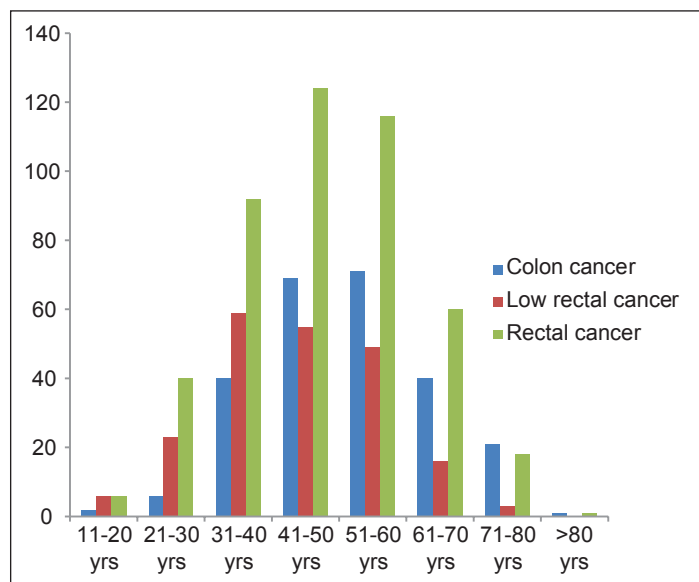


Figure 1: Age distribution in years of patients with colonic cancer. (Tata Memorial Hospital, Mumbai, 2004-2008)

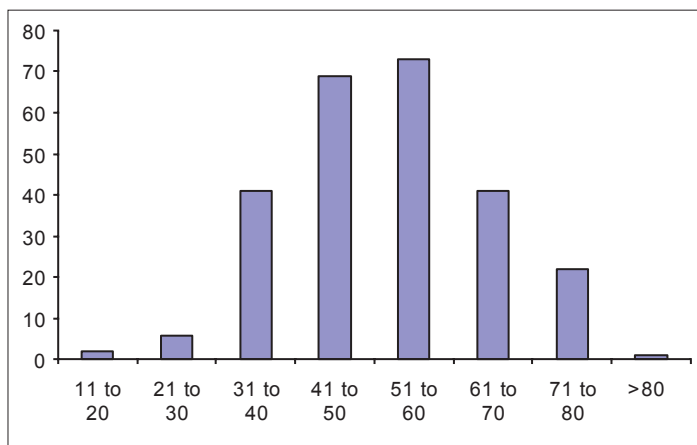


Figure 2: Age distribution in years of patients with rectal cancer. (Tata Memorial Hospital, Mumbai, 2004-2008)

## Discussion

CRC is the sixth most common of all cancers in India, which is in contrast to Western nations where CRC is the third most common cancer regardless of gender. Similarly the incidence of CRC in India is lower as compared to Western countries. It is 4.7/100,000 amongst males and 3.2/100,000 amongst females, while the corresponding figures in the West are 37.1/100,000 and 26.6/100,000 respectively.<sup>[2]</sup> Thus the overall incidence is almost eight fold lower in India when compared to Western countries.

There are many postulated reasons for this discrepancy; the major speculation revolves around dietary factors. Numerous articles have been written on the association of processed meat, high saturated fat diet and CRC as well as the possible protective effects of fruits and vegetables.<sup>[18-21]</sup> The typical Indian diet is usually vegetarian and therefore comprises mainly fruits and vegetables. In addition, there also has been published report on the association of curcumin, an Indian spice, and its preventative role in CRC.<sup>[22,23]</sup>

The mean age at diagnosis for CRC in the Western countries is 65 years.<sup>[24]</sup> Published data from Deo *et al.* and Pal have shown that CRC occurs in a younger age group in India with the average age of diagnosis being 20 years earlier than in the West.<sup>[4,12]</sup> Data from Tata Memorial Hospital has also revealed that the mean age at diagnosis of CRC to be 50 years, again much earlier than the Western patients.

The average age of patients with low rectal cancer was 42.7 years in TMH which is comparable to the data from other institutions in India.<sup>[5,12]</sup> In addition, there is a higher preponderance of rectal cancer over colon cancer in India especially in the younger age group. Data from TMH showed that rectal cancers amounted to around 64% compared to 36% colonic cancers, a ratio of almost 1.8:1. In contradistinction, countries with a higher incidence of CRC, the ratio is in the reverse with a higher preponderance of colonic cancers.<sup>[1]</sup> Although data from TMH alone may be biased due to the limitation that it is referral centre, the overall evidence is in favour of a higher preponderance of rectal cancer. The reasons for this finding need to be elucidated by a prospective large scale follow-up study.

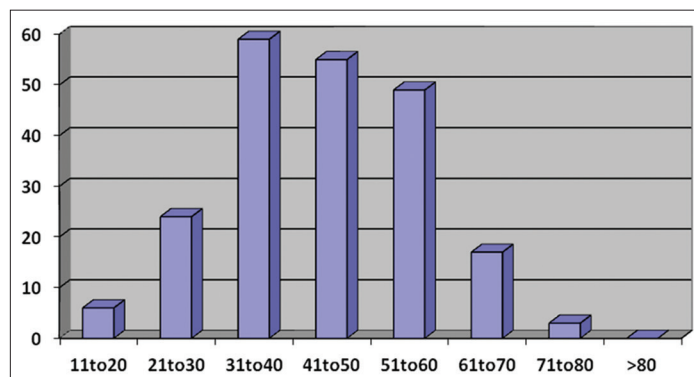


Figure 3: Age distribution in years of patients with low rectal cancer undergoing abdominoperineal resection. (Tata Memorial Hospital, Mumbai, 2004-2008)

The overall low incidence of CRC as well as the younger age at diagnosis may possibly infer that hereditary CRC may account for a larger proportion of CRC cases.

Hereditary predisposition to CRC was first described by Henry Lynch.<sup>[25]</sup> Lynch described two hereditary cancer syndromes based on the absence or presence of extra-colonic cancers<sup>[26]</sup> which were termed Hereditary Nonpolyposis Colorectal Cancer (HNPCC) 1 and 2 respectively. Apart from early age of onset, colorectal cancer in Lynch syndrome is also by a propensity for the tumours to involve the proximal colon with 70% arising proximal to the splenic flexure, the figures of which are opposite to sporadic cancers.<sup>[27]</sup> Data from Tata Memorial Hospital showed that tumours proximal to the splenic flexure account for 21.7% of all CRC and the average age was 52.4 years.

The genetic mutation in Lynch Syndrome lies in the mismatch repair (MMR) genes. Mutations in four (4) mismatch repair genes have been identified namely MLH1, MSH2, MSH6 and PMS2. The majority of patients have a mutation in MLH1 and MSH2.<sup>[28]</sup> A mutation in the MMR gene leads to the molecular hallmark of Lynch syndrome known as microsatellite instability (MSI). Numerous criteria for the diagnosis of HNPCC have been described including the Amsterdam<sup>[23]</sup> and Bethesda<sup>[29]</sup> criteria. The Bethesda guidelines identifies patients for microsatellite instability testing and if positive, will require further testing for mutations in the mismatch repair genes, namely MSH and MLH. In the studies by both Pandey and Rajkumar, the incidence of MSI ranged from 5-10%. Having stated this, it is important to consider that up to 40% of the family pedigrees that satisfy the Amsterdam criteria are found to be MSI negative. This syndrome has recently been termed "Familial Colorectal Cancer Type X".<sup>[30]</sup> However this is associated with a later age of onset than HNPCC.

Another important finding is that CRC in Indian patients with ulcerative colitis was lower than those in the Western world.<sup>[13]</sup> Although we cannot speculate any specific reason for this finding, again it may be related to environmental, dietary and genetic factors. A multi-ethnic study from Malaysia involving Malay, Chinese and Indian ethnic groups found that although the Ulcerative Colitis was much more extensive in the Indian group, there were no cases of colonic cancer following this disease.<sup>[31]</sup>



There are many limitations to the present report. Firstly, only operated cancer patients were included for data collection in TMH. There can be an institutional bias associated with this. Again due to the paucity of research as well as published literature in this area from the sub-continent, only postulations could be made with the available studies.

## Conclusion

Despite the low incidence of CRC in India compared to the Western world, presentation and diagnosis at relatively younger age groups points to the fact that the incidence of hereditary CRC is similar to that of the Western society. This phenomenon in India is inexplicable thus far and further research is necessary in this area.

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