Original Article

Hereditary nonpolyposis colorectal cancer in Pakistan: Results of a pilot study

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ABSTRACT

Objective: Hereditary nonpolyposis colorectal cancer (HNPCC) is the most common form of hereditary bowel cancer. Multiple generations are affected with colorectal cancer at relatively young age, between 25 and 45 years. We conducted this study to investigate the frequency of HNPCC in Pakistani population, due to the high incidence of colorectal cancer in younger Pakistani adults and prevalence of consanguinity in this region.

Methodology: Ninety histopathologically confirmed colorectal cancer patients between 12-50 years and their families were interviewed using a detailed questionnaire. The questions about family history of colorectal cancer, history of other cancers, age at diagnosis and consanguinity were asked. The pedigrees were drawn for all families based on given information. To confirm cancers reported in relatives, hospital records were also reviewed. Amsterdam criteria were used to label a family as HNPCC.

Results: Seventeen patients (18.9%) had one or more first or second degree relatives under age 50 years with colorectal cancers suggestive of HNPCC. Another 15 patients (16.7%) had first or second degree relatives with a family history of other extra-colonic cancers including ovarian, breast, endometrium, lung, parotid, brain and bladder cancer. Of these 30 patients (33.3%) reported that their parents were first degree cousins.

Conclusion: High frequency of HNPCC was seen in Pakistani population; higher proportion of colorectal cancer in young Pakistanis, strong prevalence of consanguineous marriages could be important factors for HNPCC occurrence in Pakistan. However future studies with large sample size along with genetic testing and screening programmes are warranted.

KEY WORDS: Hereditary non polyposis colorectal cancer, Consanguinity.

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INTRODUCTION

Colorectal cancer (CRC) is amongst the common cancers worldwide. The incidence of colo-rectal carcinoma in Pakistan is similar to other Asian countries, but much lower than in the developed countries. The risk is equal in both sexes at present. However a 41% rise in incidence was noted in the males between 1995 to 1999, which may indicate a higher risk in the males in future.[1] Various factors and mechanisms have been discovered which play key role in the development of CRC.[2,3] It has been thought that one-third of CRC patients have a genetic background. Hereditary nonpolyposis colorectal cancer (HNPCC) is a common autosomal dominant colorectal disorder

with special clinicopathological features.[4] In clinic, it is diagnosed by Amsterdam criteria I:[5] (1) three or more relatives with histologically confirmed colorectal cancer, one of whom is the first-degree to the other two; (2) colorectal cancer affecting at least two generations; and (3) one or more colorectal cancer cases diagnosed before the age of 50. Amsterdam criteria I is too rigid, it excludes extra-colonic cancers and it may not be applicable for small families.[6] Alternatively, Amsterdam criteria II was defined:[7] (1) atleast three relatives must have a cancer associated with HNPCC (colorectal, endometrial, stomach, ovary, ureter or renal pelvis, brain, small bowel, hepatobiliary tract or skin tumors), (2) one must be first degree relative of other two, (3) atleast two successive generations must be affected, (3) atleast one of relative should have diagnosed before the age of 50, (5) familial adenomatous polyposis (FAP) should have been excluded in any relative with colorectal cancer and (6) tumor should be verified whenever possible.

The porportion of HNPCC varies by country, with rates ranging from 1 to 10% among all colorectal cancer patients (median 2-5%).[8] Our previous studies mentioned that colorectal cancer patients under age 30 represent more than 30% of total colorectal cancer in our country.[9,10]

Therefore, we conducted this pilot study to evaluate the frequency of HNPCC and associated colorectal and extra-colonic cancers according to Amsterdam criteria I and II in Pakistani patients and their families.

METHODOLOGY

Between November 2008 and January 2010, ninety histologically confirmed colorectal cancer patients aged between 16-50 years and their families were interviewed regarding risk factors for colorectal cancers after taking written consent. These patients represented about 60% of total colorectal cancer patients treated in same institute. The patients and families were interviewed by two of authors using a detailed questionnaire. The questions regarding family history of colorectal cancer, extra colonic cancer, age at time of diagnosis, symptoms, type of treatment and consanguinity (intercousin marriages) were asked. The pedigrees were drawn for the all families based on given information. All hospital histopathology reports were collected to confirm the diagnosis. Similarly to confirm the diagnosis in relative, the families were asked to provide the hospital record whenever possible. The Pakistani families have strong family ties and are aware of their relatives' cancer history.

The pedigrees were drawn using Smart Draw software. All data were analyzed by software SPSS version 16.0.

RESULTS

Ninety patients with confirmed colorectal cancer with median age 34.7 years (16-50) and their families were interviewed. Study population was predominantly males; 63 patients (70%). Rectosigmoid was found most frequent site (55.5%) of colorectal cancer in study population. 58 patients (64.4%) had no cancer family history and were considered sporadic. 32 patients (35.6%) had one or more first or second degree relative under age 45 years with colorectal cancers and extra-colonic cancers suggestive of HNPCC family (Table-I).

The extra-colonic cancers seen were ovarian, breast, endometrium, lung, parotid, brain, bladder and esophageal cancer and most of these cancers occurred in paternal relatives (Table-II).

Seventeen patients and their families fulfilled the Amsterdam criteria I for HNPCC for relatives in three generations were affected with colorectal cancers. Figure-1 shows the pedigree of a patient with a family history of colorectal cancers. The frequency of extra-colonic cancers were as; stomach cancer in 5 families (15.6%), non small cell lung cancers in 4 families (12.5%), breast cancer in 4 families (12.5%), endometrial cancers in 3 families (9.4%), brain astrocytomas in 3 families (9.4%), renal cell carcinoma in one family (3.1%), bladder cancer in one family (3.1%), ovarian cancer in one family (5.9%) and esophageal cancer in one family (5.9%). Figure-2 shows the pedigree of a patient with history of extra-colonic cancers.

Table-I: Characteristics of patients aged between 16- 50 years with colorectal cancer.

Variable	*Patients (%)*
Median age (range)	34.7 years (16-50)
Gender	
Male	63 (70%)
Female	27 (30%)
Site of primary tumor	
Proximal to splenic flexure	21 (23.4%)
Descending colon	19 (21.1%)
Rectosigmoid	50 (55.5%)
Median number of first degree relatives (range)	10 (3-17)
Relatives with cancer	
None	58 (64.4%)
Relatives with colorectal cancers	17 (18.9%) 35.6%
Relatives with extra-colonic cancers	15 (16.7%)
Consanguinity among first degree relaties (%)	30 (33.3%)

Table-II: Colorectal cancer patients with family history of one or more relative with extra-colonic cancer.

Colorectal cancer patient (age and gender)	*Relation with patient and age of diagnosis of cancer*	*Type of extra-colonic cancer*
25 years, Female	Paternal grandfather (50years)	Non- small call Lung cancer
30 years, Female	Sister (34 years)	Endometrial cancer
	Brother (45 years)	Non- small cell lung cancer
	Mother (50 years)	Breast cancer
30 years, Male	Sister (35 years)	Breast cancer
	Mother (50 years)	Ovarian cancer
30 years, Male	Brother (32 years)	Stomach
	Paternal uncle (50 years)	Non-small cell lung cancer
35 years, Male	Brother (45 years)	Stomach
	Paternal uncle (41 years)	Stomach
25 years, Male	Paternal grandmother (50 years)	Parotid gland cancer
	Maternal grandfather (52 years)	Brain astrocytoma
45 years, Male	Maternal uncle (40 years)	Brain astrocytoma
	Maternal aunt (35 years)	Breast cancer
30 years, Male	Paternal uncle (47 years)	Lung cancer
	Maternal aunt (45 years)	Renal cell cancer
	Maternal uncle (40 years)	Non-small cell lung cancer
	Maternal grandfather (50 yrs)	Brain astrocytoma
32 years, Male	Father (50 years)	Non-small cell lung cancer
	Mother (47 years)	Breast cancer
	Maternal uncle (41 years)	Non-small cell Lung cancer
40 years, Female	Sister (43 years)	Endometrial cancer
33 years, Male	Paternal uncle (60 years)	Bladder cancer
49 years, Female	Paternal grandmother (55 years)	Endometrial cancer
20 years, Male	Paternal uncle (49 years)	Stomach cancer
33 years, female	Paternal grandfather (52 years)	Esophageal cancer
41 years, Male	Brother (44 years)	Stomach cancer

Interestingly, 30 patients (33.3%) in study reported that their parents were first degree cousins. All patients with family history of consanguinity were relatively younger patients and had locally advanced cancers.

Further, ten families of colorectal cancers (11.1%) did not meet all of Amsterdam criteria, but they had colorectal cancers in two generations.

DISCUSSION

In 1913, Warthin described first time some families with an excess of colorectal, endometrial and gastric cancers. After 50 years, Lynch collected data that led to accurate description of these cancer-prone families.[11] According to the absence or presence of extracolonic malignancies, these families were divided into Lynch syndrome I and Lynch syndrome II. Later, the Lynch syndrome was re-named as herediatry non-polyposis colorectal cancer (HNPCC).[12] HNPCC is an autosomal dominant disease with special clinicopathological features; early onset (average <45ys), high frequency of cancers in right sided colon (60-70%), excess of synchronous (tumors which appear on different sites of colon within six months of surgery for first diagnosed colon cancer) (18.1%) and metachronous (tumors which appear on different sites of colon after six months of surgery for first diagnosed colon cancer) (24.2%) tumors and extra-colonic malignancies.[13] It is often diagnosed by Amsterdam criteria, but the criteria is too strict for families with small number of members but with strong genetic basis for colorectal cancer (CRC), in these cases Amsterdam criteria II is very useful.[14]

Presentation of Pakistani population at relatively younger age in our institute is alarming sign and was the basis of this study. Though this study was with small sample size, 35.6% of patients with typical HNPCC in these patients according to Amsterdam criteria explain higher proportion of HNPCC is our population. Another 11.1% of families who did not meet all Amsterdam criteria may still have HNPCC and may need more investigations and screening.

CRC is multifactorial disorder and there can be several factors for its cause. One criticism may be about false positive rates in this study as affected relatives in families might have been exposed to environmental factors rather than genetic clustering of cancer. Explanation for this could be that family history of

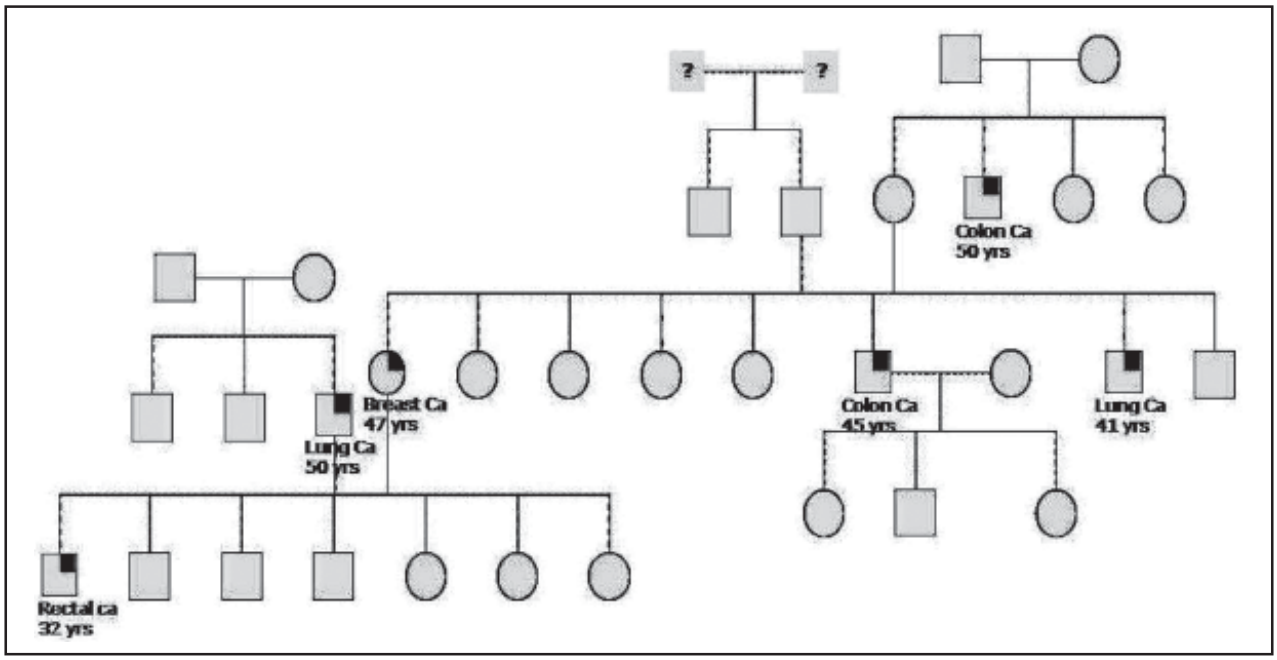

Fig-1: the pedigree of a 32 years old male patient with a family history of colorectal cancers (maternal uncle, maternal grandfather). Other extra-colonic cancers were seen in his father, mother and maternal uncle. (Note: box represents male and circle represents female).

colorectal cancer is an important risk factor for CRC, and there is no evidence that familial clustering of CRC is affected by environmental factors.[15] There can be two other reasons for higher frequency of HNPCC is our population; (1) more prevalence of intercousin marriages (consanguinity) in Pakistan, as in our study 33.3% patients reported that their parents were first degree cousins ans (2) Pakistani families are usually large, as our study showed median number of first degree relatives in a family were 10 (3-17). This factor may increase the relative risk of a positive HNPCC diagnosis, as suggested by Percesepe et al.[16]

Because early age is the feature of HNPCC, however cancer can also be detected in many families after age of 50 years, as we found in our study four relatives were aged above 50 years. This can also be

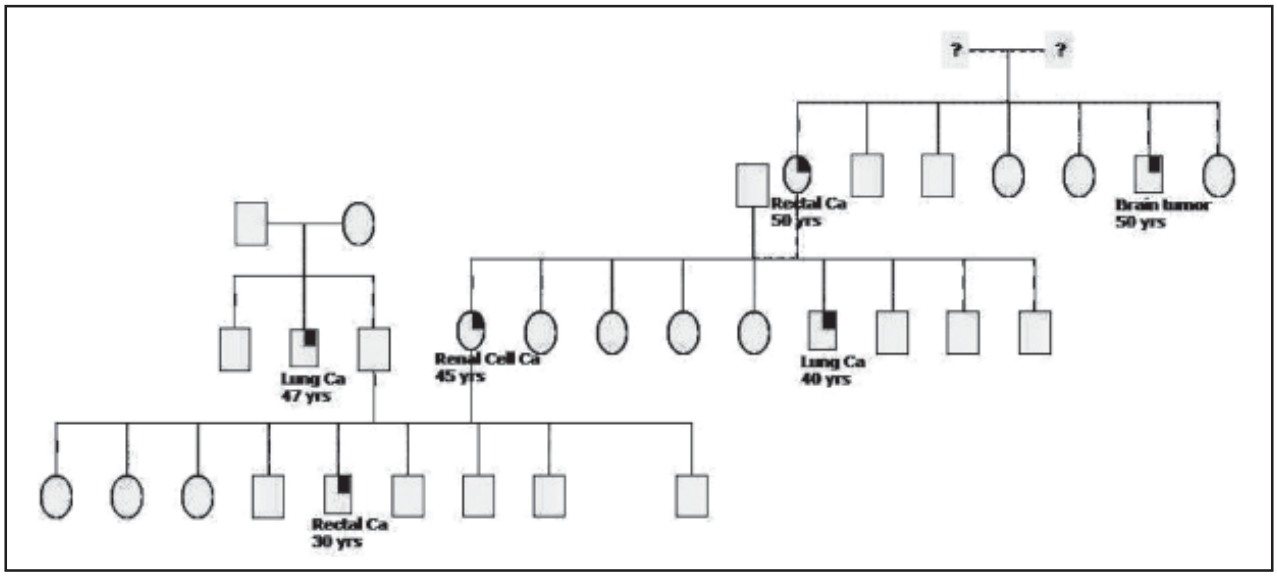

Fig-2: the pedigree of 30 years old male patient with family history of predominant extra-colonic cancer (mother, paternal uncle, maternal uncle, maternal grandmother, and maternal grand father). (Note: box represents male and circle represents female).

explained by that, HNPCC is autosomal dominant disease and 50% of children with parents with HNPCC should be affected. However it takes years before the HNPCC is clinically manifested.[17] One limitation of our study was that we did not include the patients with colorectal cancers who were aged above 50 years.

Identification of HNPCC is not always simple because this disease can not be verified untill many relatives have been affected with cancer and their exact age at time of diagnosis not exactly known to families (recall bias) are the key issues. Apart from Amsterdam criteria, genetic testing including microsatellite instability and mismatch repair gene mutations are required to confirm our results.[18,19] Already we are working on this and results will be provided in near future.

In conclusion, HNPCC is relatively more prevalent in Pakistan especially in colorectal cancer patients who present at early ages. This study highlights the importance for conducting future multi-institutional trial with large sample size incorporating genetic testing and screening of family members of young patients with colorectal cancer.

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