
FAMILIAL COLORECTAL CANCER

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Summary

Most colorectal cancers regardless of etiology are believed to arise from adenomatous polyps. Both environmental and genetic factors are important in colorectal carcinogenesis. Twenty five percent of patients with colorectal cancer have relevant family history. We tried to verify the spectrum of manifestations of hereditary non polyposis colorectal cancer HNPCC and what practical preventive measures could be applied. In related families, 4 generations were studied via interviewing. Seventeen patients fulfilled the Amsterdam's criteria for the diagnosis of HNPCC (Lynch II), with a mean age of 59.11 ± 11.75 , 10 patients were females and 7 were males. All were not smokers. The pedigree we mapped for these families showed an autosomal dominant inheritance. HNPCC is heterogeneous syndrome. Although has certain gene defect. We should always think of HNPCC in presence of positive family history of colorectal cancer or other malignancy specially those affecting young age groups. Regular colonoscopy and aspirin prophylaxis are important preventive measures.

Introduction

Although relatively rare in the underdeveloped world, colorectal cancer is the second most common internal malignancy in western countries^{1,2}. Most colorectal cancers, regardless of etiology are believed to arise from adenomatous polyps^{3,4}. Carcinogenesis¹ and dietary factor are commonly implicated, and a direct correlation between mortality from colorectal cancer and per capita consumption of 1-calories, meat protein and dietary fat and 2-oil³ is thought to exist. Ingestion of

animal fat lead to an increased proportion of anaerobes in the gut micro flora resulting in the conversion of normal bile acids into carcinogens³. Genetic influences have been known for some time to be independent risk factors for the development of cancer⁵.

Twenty five percent of patients with colorectal cancer may have family history of the disease suggesting hereditary predisposition that can be classified into two groups:

- Uncommon polyposis syndrome
- More common non-polyposis syndrome.

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Warthin, 453 Lynch and colleagues have defined two clinical variants of hereditary non polyposis colorectal

cancer (HNPCC): Lynch syndrome (1) and Lynch syndrome(2)⁶. Both are characterized by autosomal dominance, early age at onset, predominance of proximal bowel involvement and multiple primary colon tumours while Lynch2 additionally shows an excess of adenocarcinoma of adenometrium and ovary^{5,7,8}.

We tried to verify the spectrum of manifestations of familial colorectal cancer and to look for practical preventive measures that could be applied.

Patients and Methods

In related families, 4 generations were studied from 1961-2001. Apparently there was a cluster of cases of colorectal cancers so stressing on detailed history, via interviews of surviving propounds or nearest relatives and studying available medical records, expanded family history, history of premature deaths, smoking and dietary history all were covered.

Investigations that had been done and that we did prospectively were; proctoscopy, colonoscopy, abdominal ultrasound, chest x-ray and MRI abdomen. And because some relatives gave a history of hyperuricaemia, we raised serum uric acid assay as a routine in our study. Criteria utilized for the diagnosis of familial colorectal cancer were that of Amsterdam.

- At least three relatives with colorectal cancer, one of whom must be a first degree relative of the other two.
- Involvement of two or more generations.
- At least one case diagnosed before the age of 50.
- Familial adenomatous polyposis has been excluded.
- Extracolonic neoplasms (Amsterdam 2)^{9,10}.

Results

Seventeen patients fulfilled the Amsterdam criteria for the diagnosis of HNPCC; 7 were males and 10 were females. The mean age was (59.11±11.757), 3 patients were below 50 years.

Four patients had only extra-colonic malignancy (2 endometrium, 1 larynx, 1 pancreas). Ten patients had colorectal cancer, 2 patients had both carcinoma and colon and carcinoma of endometrium and one patient had been diagnosed as disseminated malignancy.

The lowest mean age was that for endometrium cancers and in those of age below 50 years, 2 had endometrial cancer.

Clinical presentation was variable, 5 out of 12 had colorectal cancers (41.6%) and came because of intestinal obstruction others were having anemia hematochesia and abdominal pain. Those with endometrial cancer came with vaginal bleeding, while obstructive jaundice for pancreatic cancer and hoarseness of voice for larynx cancer. One patient came with disseminated malignancy of unknown primary.

All patients (HNPPC) studied were not smokers. For those with colorectal cancers only two showed survival rates more of than 5 years, others ranged from few days to 6 months.

We found clusters of cases of hyperuricemia and gout in 6 cases.

	Extra colonic	Colonic	Colonic extra colonic	Undefined	Total
No patients	4	10	2	1	17
Age (mean)					59.11±11.757
<50 years	1	1	1		3
Sex					
Male	1	6			7
Female	3	4	2	1	10

	Age / year	Sex	Clinical presentation	Smoking	HNPCC	Treatment	Outcome
1	65	F	Intestinal obstruction	Negative	Colorectal	Colectomy	Died after 8 m
2	60	M	Intestinal obstruction	Negative	Colorectal	Colectomy	Died after 6 m
3	55	M	Anemia, hematochesia	Negative	Colorectal	Colectomy	Died after few months
4	80	F	Hematochesia	Negative	Colorectal	Beyond surgery	Died after few months
5	55	M	Anemia, hematochesia	Negative	Colorectal	Colostomy beyond surgery	Died after few months
6	35	F	Vaginal b., hematochesia	Negative	Ca cervix colorectal	Colecotmy, hysterectomy	Still alive, 5 years
7	50	M	Change bowel motion	Negative	Colorectal	Colectomy	Still alive, 5 years
8	45	M	Intestinal obstruction	Negative	Colorectal	Colectomy	1 year, survival
9	70	M	Obstructive janudise	Negative	Ca pancrease	Ioperable	2 months survival
10	65	F	Cachexia	Negative	Ca cervix, colon	Beyond surgery	Few months survival
11	60	M	Anemia abdominal pain	Negative	Colorectal colectomy	Alive, 1 year	12
12	80	F	Hoarseness voice	Negative	Ca larynx	Radiotherapy	Died after 3 years
13	60	F	Intestinal obstruction	Negative	Colorectal	Colectomy	Died after 2 years
14	45	F	Anemia abdominal pain	Negative	Ca endometrial	Hysterectomy	Alive 5 years
15	55	F	Vaginal bleeding	Negative	Ca endometrial	Hysterectomy	Alive, 8 years
16	60	F	Per rectal bleeding	Negative	Colorectal	Beyond surgery	Died after 6 months
17	65	F	Cachexia	Negative	Disseminat ed ca	Conservative	Died early

Discussion

Familial risk factors are known to play important role in colorectal cancer risk particularly when the relatives are affected by early onset cancer¹¹.

The 17 patients picked up and studied in related families had fulfilled the Amsterdam criteria for HNPCC.

The pedigree we mapped for these families, showed an autosomal dominant inheritance, which is a well known fact

for HNPCC whether Lynch 1 or Lynch2^{3,12,13}.

Ten patients were females (60%), such high frequency possibly existed because endometrial cancer was included in this syndrome.

The mean age for the patients was 59.11 years; three were below 50 years of age. Lynch and coworkers identified an average age of 44.6 years in HNPCC with initial colorectal cancer⁵, our figure was higher. Possibly the number of

patients was small while late presentation and older age were important factors. Literature showed a mean age of sporadic colorectal cancer of 63 years for men and 62 years for women¹⁴.

The lowest mean age was for endometrial cancer, 2 out of 3 patients with endometrial cancer were below 50 years of age and this a well known fact for this type of tumor in its age distribution¹⁵.

Clinical presentation was variable and heterogeneous (table I), this is in agreement with what had been mentioned about Lynch 2 HNPCC^{7,8,16} for which Lynch 2 was called familial cancer syndrome.

In the present study there was a case with ca larynx, there is no such mention for this cancer in particular in HNPCC even though any extra colonic malignancy is to be considered in Lynch 2. This could be explained by the fact that there are defects in several DNA repair pathways in HNPCC and, consequently different cancer types could develop¹⁷.

In colorectal cancer the commonest presentation was intestinal obstruction (41.6%) and the records revealed a proximal colorectal cancer. Lynch and coworker identified that about 70% of colorectal cancer were located in right colon⁵.

HNPCC occurs mostly in the proximal colon. Rijcken et al. (2002) investigated whether this preponderance was due to a tendency for adenomas to develop more proximally and / or whether transformation rates were higher in proximal adenomas. One hundred HNPCC adenomas were compared with 156 sporadic adenomas; although both groups exhibited dysplasia, this was significantly more severe in proximal HNPCC adenomas 5mm or more in size. Small HNPCC adenomas were no different from sporadic adenomas, except for their proximal location compared with sporadic adenomas. 1- Thus, progression to high grade

dysplasia was more common in proximal than distal HNPCC adenomas, indicating a faster transformation rate from early adenoma to cancer in the proximal colon¹⁸.

A late presentation of our patients could explain why intestinal obstruction dominated the presenting features.

Two patients had both colorectal and endometrial cancers and this is a well known fact in Lynch 2 where there is multiple primary cancers⁵.

In this study one patient had two primary colorectal cancers (metachronous) in descending colon and rectum; this is also a recognized manifestation of HNPCC. That's why in young patient with metachronous colorectal cancer, one has always to consider HNPCC even with negative family history¹⁹.

In the present study, we put in consideration other risk factors for colorectal cancer that affect the incidence or behaviour of presentation. All patients had no such factors (animal fat, ulcerative colitis and smoking) and these results showed that the defective gene in HNPCC is an independent risk factor for the development of colorectal cancer⁵.

Ascertainment of a detailed family history in early age onset of colorectal cancer patients identified frequent familial clustering of colorectal cancer and HNPCC²⁰.

Interestingly we observed that hyperuricemia has a protective effect.

Regarding survival rate, only two patients with colorectal cancer had a survival rate above 5 years, in the others were it ranged from few days to 1 year. Three patients with ca endometrium showed a survival rate above 5 years. Again, this could be explained by late presentation of colorectal cancer.

Conclusion & Recommendations

In presence of positive family history of colorectal cancer or other

malig-nancy especially affecting younger age group, we should think of familial colorectal cancer.

- 2- HNPCC, is a heterogeneous syndrome although has certain gene defect.
- 3- Because of a cure rate in colorectal cancer by early diagnosis and treatment, affected families should be offered genetic evaluation
- 4- In societies where genetic study is not available, high risk group should be subjected to regular colonoscopy.
- 5- Aspirin prophylaxis is valid for those high risk families as a possible colorectal cancer inhibitor.

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