dren with HLA-B27-associated enthesopathy and arthropathy permits an accurate diagnosis and also helps to distinguish these patients from those with other rheumatic disorders in childhood.

REFERENCES


Hereditary non-polyposis colorectal cancer in a Namaqualand kindred

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Summary

A family with hereditary non-polyposis colonic cancer affecting 16 males over three generations is described. Autosomal dominant inheritance with male predominance is demonstrated. The clinical features of this condition and methods for screening family members are discussed. S Afr Med J 1990; 77: 42-44.

Colorectal cancer is a common disease and the estimated cumulative risk in South Africans of mixed racial ancestry is about 0.8/100 population.1 It is usually a sporadic disorder but there are two hereditary types of colorectal cancer: the best known (but less common) form is associated with familial adenomatous polyposis while the other is hereditary non-polyposis colonic cancer (HNPPC). Although familial adenomatous polyposis is rare in most populations, the natural history of polyps followed by cancer and the need for prophylactic colectomy are well known. In contrast, HNPPC sufferers lack a consistent precursor lesion and this makes both diagnosis and family screening difficult. These two conditions affect both sexes equally.

The unusual occurrence of HNPPC segregating as an autosomal dominant condition confined to men is reported.

Patients and method

A Namaqualand kindred of mixed racial ancestry was studied at the Kleinzee diamond mine where many family members are employed. All medical facilities for mine employees and their families are provided at the hospital in the mining town, which is about 100 km from the nearest alternative source of medical care. The diagnosis of HNPPC was made in 16 men over 3 generations on the basis of clinical, surgical and pathological data and hospital or family records. The pedigree is shown in Fig. 1.

Results

None of the affected men had overt extracolonic malignant disease and no women with large bowel cancer were identified. The miners were not exposed to any obvious noxious environmental agent during the open-cast mining process. There was...
no increased incidence of colorectal carcinoma among unrelated
mine employees and some of those affected were not directly
involved in the mining process but worked as kitchen staff,
storemen or drivers.

The pattern of vertical inheritance with male-to-male trans­
mision suggests an autosomal dominant disorder. The age of
presentation ranged from 19 years to 68 years (average age 47
years). The 3 youngest subjects (IV-55, IV-54, IV-43) were
aged 19, 23 and 36 years respectively when the diagnosis was
histologically proven. Of the 16 patients identified all but 2
have died of the disease (estimated mean survival of 4.7 years
from diagnosis where information was available). In
all but 1 of the 14 patients who had died of carcinoma and for whom
surgical or pathological records were available, the carcinomas
had occurred in the left colon.

High-resolution chromosome studies of peripheral blood
lymphocytes showed a normal 46,XY karyotype in all the
affected males tested. Linkage studies were undertaken with
conventional markers, including blood groups and the HLA
system, but no significant cosegregation was obtained with any
polymorphic marker. This analysis is continuing at the mole­
cular level with probes specific to chromosome 5.

Eighteen family members at risk for HNPCC and also the 3
youngest cases with carcinoma (IV-55, IV-54, IV-43) were
examined clinically and underwent colonoscopy. Biopsies were
taken from 8 of the 18 screened cases, and the resected
specimens were reviewed in the 3 patients
with carcinoma. Haematoxylin and eosin paraffin sections were examined in
each case. In 7 of the screened cases no neoplastic lesion was
found and in 5 of them histological examination was normal,
while 1 had intestinal spirochaetosis associated with mild non­
specific inflammatory changes and another had intestinal
spirochaetosis but was otherwise normal on histological exami­
nation. One screened patient had isolated tubular adenomas in
the caecum and the descending colon as well as severe dysplasia
in a tubulovillous adenomatous polyp in the transverse colon.
Of the patients with carcinoma, case IV-43 had synchronous
Dukes B adenocarcinoma of the caecum and ascending colon
resected and died of a histologically proven local recurrence
after 3 years. Case IV-54 had undergone total colectomy with
ileocecal anastomosis for a Dukes B mucin-secreting ade­
ocarcinoma of the sigmoid colon, together with a small intra­
mucosal area of pre-cancerous dysplasia in the caecum that
was not associated with an adenomatous polyp. Colonoscopy
with random mucosal biopsies 9 years later revealed no abnor­
mality. Case IV-55 had undergone left hemicolectomy for a
Dukes C adenocarcinoma of the sigmoid colon and 11 years
later was found to have isolated small tubular adenomas in the
ascending and transverse colon, associated with intestinal spiro­
chaetosis in adjacent mucosal biopsies.

Thus histological examination did not reveal any consistent
predisposing lesion for carcinoma. Three patients showed mild
nonspecific inactive inflammation: 1 in follow-up biopsies 2
years after colectomy for synchronous caecal and ascending
colon carcinoma, 1 in association with isolated adenomatous
polyps and 1 in association with intestinal spirochaetosis.
These inflammatory changes and the associated endoscopic
appearances were not suggestive of ulcerative colitis.

Discussion

Hereditary colorectal carcinomas are now thought to cause
about 5% of large-bowel cancer.2 These inherited cancers are
divided into familial adenomatous polyposis and the more
recently described and more common entity of HNPCC,3
which occurs in two forms and appears to produce no consistent
precursor lesions in the bowel. HNPCC's two forms are
Lynch syndrome I or hereditary site-specific non-polyposis
colonic cancer where only colorectal cancers are inherited, and
Lynch syndrome II or cancer family syndrome, in which
relatives also have a higher risk of other adenocarcinomas,
particularly of the endometrium and ovary.

The family reported in this study "has sufficient criteria for
the diagnosis of hereditary site-specific colorectal cancer: (i)
an autosomal dominant mode of inheritance; (ii) cancer confined
to the colon; and (iii) a younger age of onset than sporadic
colon carcinomas.

Two additional features of HNPCC are enhanced survival
compared with sporadic tumours of the same stage and an
increased prevalence of multiple primary colon carcinomas.
We did not have sufficient pathological data to examine these
possibilities in our kindred.

HNPCC kindreds characteristically show an autosomal
dominant inheritance pattern so that males and females are
equally affected.4 In contrast, this kindred contained no affected
females in the 4 generations analysed. Most data were available for the third generation, in which 10 cases were found in the 15 men with an affected parent (67%) while no cases were observed in their 8 female siblings. Both male and female family members of mine employees have similar access to health care facilities, so that an ascertainment bias is unlikely to account for the absence of female cases. It is also most unlikely to be a chance finding ($P = 0.003$; Fisher’s two-tailed exact test). We have no satisfactory explanation for this sex limitation. Male-to-male transmission of the cancer-prone genotype excludes the possibility of X-linked inheritance because males obtain their X-chromosome from their mothers. The colonoendoscopic identification of elderly unaffected male offspring of affected individuals rules out a Y-linked disorder because males obtain their Y-chromosome from their fathers. A survey of previously reported HNPCC families reveals no sex specificity for the hereditary colon cancers.

Genetic testing in HNPCC families using biomarker$^{11,14}$ and conventional linkage studies$^{13}$ has unfortunately failed to provide a reliable premorbid screening test. Recent studies on patients with sporadic colon carcinoma and families with familial adenomatous polyposis suggest that the causative gene is on the long arm of chromosome $5.15-17$ There is as yet no evidence that the HNPCC gene is allelic and we know of no molecular linkage studies on these families. If future linkage studies provide a reliable test for the gene, prophylactic surgery (as is now performed for familial adenomatous polyposis) will become appropriate.

Colonoendoscopic examinations of 3 patients after resection of carcinomas and 18 unaffected relatives showed isolated tubular adenomas in only 2 cases, one who had previously had carcinoma and one who was called up for screening. The latter patient also had a tubulovillous adenoma showing severe dysplasia. This paucity of precursor lesions for carcinoma, together with the presence of focal pre-cancerous dysplasia in macroscopically normal mucosa in one of the colonoendoscopic specimens, highlights the problem of screening for colorectal cancer in HNPCC families. The simplest conventional screening method is faecal occult blood testing but this fails to detect 20 - 30% of carcinomas.$18$ It is therefore of little value in HNPCC families, who have a 50% risk of cancer and can reasonably undergo an invasive test, since it misses very few carcinomas. We favour colonoendoscopy above a double-contrast barium enema examination because it is probably more sensitive for detecting small carcinomas. It also allows biopsy or removal of suspicious mucosal lesions or polyps. The ideal time span between colonoendoscopies is uncertain and at present we recommend a 2-year interval. If regular colonoendoscopy is possible, prophylactic surgery seems inappropriate. It would involve removal of the entire colon and regular sigmoidoscopic examination of the remaining rectum. This operation is probably not justified by a 50% risk of cancer, provided the subject undergoes regular total colonoendoscopy. If carcinoma is diagnosed and lies above the distal rectum, a colectomy with ileorectal anastomosis is indicated because regular sigmoidoscopic examination of the rectal remnant will be necessary.

A thorough population-based survey of cases of colorectal cancer in a low-incidence area suggests that inherited forms contribute 4 - 6% of cases.$2$ We know of no studies in South African patients and it is likely that many HNPCC families remain unidentified. The severity of the disorder, its easily identifiable autosomal dominant mode of inheritance and the potential for cure with early diagnosis are important reasons for recognising this disease. In the future it is to be hoped that new genetic markers will allow premorbid identification of the genotype$19$ and surgical prevention of cancer.

We are grateful to Dr Neville Polley for identifying this family, to De Beers Consolidated Mines and the Anglo American Corporation of South Africa for making it possible for us to study them, and to Sister Luzanne McAllister and Sister Barbara Powell for their help in documenting the kindred.

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**Addendum**

Continued research has documented a further affected male. In addition, examination of the hospital records of deceased family members has revealed 2 females with suspected colorectal cancer. Histological studies were not performed. Although the diagnosis cannot be confirmed in these instances, this evidence provides additional support for an autosomal dominant inheritance pattern with male predominance.

**References**


