SYNCHRONOUS ADENOMATOUS POLYPS: A NEW PHENOTYPIC FEATURE OF FAMILIAL COLORECTAL CANCER?

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Clinical criteria for the identification of Hereditary Non-Polyposis Colorectal Cancer (HNPPC) are not absolute. The role of polyps plays to any significant extent in this syndrome is still undefined. Purpose of the present study was to assess the frequency of adenomatous polyps synchronous to cancer (SAP), according to different levels of neoplastic familiality. In 755 (92.4%) out of 817 patients registered in the period 1984-1989 we had accurate pedigree informations about first degree relatives. They were stratified according to the presence of six clinical criteria all suggestive of an increased genetic heterozygosity at the base of the disease: a. vertical transmission of colorectal cancer; b. aggregation of malignant tumours in the sibship of the proband; c. early age of onset (less than 55 years) of colorectal cancer; d. localization of the tumour in the right colon; e. presence of multiple malignant tumours; f. mucinous histotype. We observed the presence of at least one SAP in 14 out of 41 (34.1%) patients with four or more criteria, in 12 out of 38 (20.7%) with three, in 9 out of 73 (12.3%) with two, in 30 out of 203 (14.8%) with one criterion, and in 34 out of 380 (8.9%) with no criteria (X<25.2, p<0.001). Differences were unrelated with age of patients or stage of the disease. A parallel study showed that patients with four or more criteria are significantly more likely to be HNPPC. These data show that synchronous adenomatous polyps are more frequent with increasing criteria of familiality. This might represent a further element in the clinical definition of HNPPC.

GENETIC CHANGES IN DUKE'S B COLORECTAL CARCINOMA: DO THEY HAVE PROGNOSTIC RELEVANCE?

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The Duke's classification system is the most widely used prognostic indicator in colorectal cancer (CRC). Survival of patients with early lesions is, however, by no means assured, some 55% of patients with Duke's B CRC having a recurrence of disease within five years of surgery. Recognition of this group at initial diagnosis would help target them for adjuvant therapies. The aim of this retrospective study of Duke's B CRC was to determine the frequency of a number of genetic changes thought to be characteristic of CRC progression, and to correlate these with patient survival in order to assess their prognostic relevance.

The study population consisted of 60 patients with Duke's B CRC divided into two groups based upon known outcome. Group 1–30 patients dying of their disease within 3 years of surgery and Group 2–30 patients known to be alive and well at least 5 years after surgery. Archival tumour specimens underwent polymerase chain reaction (PCR) to detect the occurrence of c-Ki-ras point mutation on chromosome 12 (detected by allele-specific PCR), c-erb B2 amplification on chromosome 17 (assessed by differential PCR) and loss of heterozygosity at the p53 locus. (assessed by PCR amplification of a polymorphic sequence in heterozygous patients).

Approximately half of the cases in each study group exhibited point mutation at codon 12 of the c-K-ras oncogene. A loss of heterozygosity at the p53 locus. Amplification of the c-erb B2 oncogene was detected to a significant extent in each group. These genetic changes, characteristic of CRC tumour progression, are not independent prognostic variables within Duke's B CRC and at present have little role in determining which patients should receive adjuvant therapies. It is possible however that, in conjunction with other genetic changes, these may form the basis of a multi-variate prognostic system for the assessment of colorectal tumours.

RECTAL CANCER: MORE STAGE A AND B, LISS C AND D

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Prognosis of colorectal cancers is closely related to the extent of spread of disease at presentation. Recently, an increasing proportion of symptomatic Duke's stages A colorectal cancers has been reported. We have investigated changes in the stage distribution of colonic and rectal cancers which have occurred over the last decade.

In a trial of screening for colorectal cancer, 155,101 subjects have been randomised to either a test or control group. The former receive a letter explaining the importance of rectal bleeding and enclosing ocula occult blood tests for completion. Those returning completed tests are designated 'acceptors'. The remainder are 'refusers'. Control group subjects are merely identified.

857 cancers have been diagnosed (see table), 438 prior to 1989 and 389 since. The proportion of stage A cancers has significantly increased with time only for the control group rectal cancers (9.9% diagnosed pre 1989, 27.5% post 89, p<0.001). Throughout the study, refusers have presented with significantly more stage B rectal than stage A colonic cancers (p<0.01).

This data suggests that the refusers have been educated re the importance of rectal bleeding by the letter of invitation to screening while the population as a whole are becoming more aware of the disease and its symptoms.
ILEAL BILE ACIDS IN FAMILIAL ADENOMATOUS POLYPOSIS

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Recent studies have suggested that an increased total biliary acid concentration, particularly chenodeoxycholic acid, may play a role in duodenal polyp formation in Familial Adenomatous Polyposis (FAP). Bile acids are promoters of colorectal neoplasia so the supply of bile acids to the colon in FAP was investigated.

Twelve ileostomists (6 with FAP and 6 controls with ulcerative colitis (UC)) were admitted to a metabolic unit after an overnight fast. A known, controlled diet was supplied for 24 hours, and ileostomy effluent collected 2 hourly and snap frozen. Samples were pooled, homogenised and freeze dried. Bile acids were extracted with ethanol and 1:1 chloroform/methanol, fractionated using Sep Pak cartridges and measured both enzymatically and by high pressure liquid chromatography.

Individuals with FAP had slightly lower 24 hour total bile acid outputs than those with UC, but this did not achieve statistical significance (0.73 ± 0.38 mmol/day, p=0.19). However those with FAP had significantly lower mean 24 hour outputs of taurochenodeoxycholic acid (0.157 ± 0.065 mmol/day, p<0.05) and mean total chenodeoxycholic acid amides (0.467 ± 0.206 mmol/day, p=0.085).

It has been suggested that individuals with FAP conserve bile acids more efficiently than the normal population and that this contributes to duodenal polyp formation. Our work supports this hypothesis but does not suggest a direct role for bile acids in colonic polyph development in FAP.

RECTAL ORNITHINE DECARBOXYLASE ACTIVITY IN FAMILIAL POLYPOSIS FOLLOWING COLON RESECTION

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Resection of the colon in patients with familial polyposis (FAP) frequently results in regression of polyphs in the remaining rectum suggesting a reduction of cellular proliferation. These patients remain at risk of developing rectal cancer but whether this risk increases with time is uncertain. Since ornithine decarboxylase (ODC) activity is associated with cellular proliferation we have measured mucosal ODC in rectal biopsies from FAP patients following ileo-rectal anastomosis (IRA) (n=36) and normal controls (n=10). We have also examined the relationship between ODC activity, age, and time from surgery.

<table>
<thead>
<tr>
<th>Years</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 25</td>
<td>507</td>
<td>41-1500</td>
</tr>
<tr>
<td>Age 26-40</td>
<td>175</td>
<td>13-794</td>
</tr>
<tr>
<td>Age &gt; 40</td>
<td>121</td>
<td>74-534</td>
</tr>
</tbody>
</table>

*p: Time from surgery

ODC activity in FAP patients following IRA (241, range 13-1500) was not different from control patients (320, 70-1000), p=0.6. However when patients were divided into three equal groups according to age, younger patients (<25yrs) had significantly higher activity than both older age groups (p<0.02). In addition patients in whom less than 10 years had elapsed since their operation had significantly higher ODC activity than those who underwent IRA more than 10 years ago (p=0.02).

These results indicate that following colon resection, ODC activity in patients with FAP are similar to normal controls and this activity appears to decrease with time. This may explain the regression of rectal polyphs following colon resection in FAP.

FACIAL BILE ACIDS IN FAMILIAL ADENOMATOUS POLYPOSIS

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Bile acids have been implicated as agents in the malignant transformation of colonic and duodenal polyphs in patients with familial adenomatous polyposis (FAP).

The faecal bile acid profile of 10 patients with FAP (6 female, 4 male; mean age 22 years) and 7 controls (4 female, 3 male; mean age 23 years) were compared. Faecal samples were collected before surgery and no subject had gallbladder or hepatic disease. Bile acids were extracted from pooled five day faecal collections and analysed by gas liquid chromatography.

There were no differences in total faecal bile acid concentration (mg g-1 dry weight) between FAP and control subjects (1.59 ± 0.94-8.1 vs 1.85, 0.22-7.77 median, range). The FAP patients, however, had increased proportions (mol%) of lithocholic acid in their faeces when compared with controls (43.6, 32.8-67 vs 19.8, 6.2-66.1; p=0.04 (Mann Whitney). Compared to control subjects patients with FAP showed a lower proportion of total primary bile acids (2.7, 0-10.3 vs 8.1, 0.5-74.7; p=0.05) and in particular a lower proportion of cholic acid (1.2, 0-6.9 vs 6, 0-16.1; p=0.05).

Preliminary results suggest an increased bacterial bio-transformation of bile acids occurs in patients with FAP. This is particularly relevant as certain secondary bile acids are capable of damaging DNA and promoting cellular proliferation.

AN ILEORECTAL ANASTOMOSIS SHOULD BE CONVERTED INTO A POLY IN MIDDLE AGED PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS

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Prophylactic surgery for patients with Familial Adenomatous Polyposis (FAP) should have a low morbidity, good functional result and significantly reduce the chance of cancer death. Currently the decision rests between a total colectomy and ileorectal anastomosis (IRA), which gives a low morbidity, good functional result and a definite cancer risk, and a restorative proctocolectomy which has a higher morbidity, reasonable functional result and an absent colorectal cancer risk.

We studied 224 patients who have undergone an IRA for FAP since 1948. The chance of developing rectal cancer was 10% by the age of 50 (95% CI 4.5% 15.5%) rising steeply and significantly to 29% by the age of 60 (95% CI 18% 40%) (life table analysis). Age at operation has no influence on the chance of developing rectal cancer, life table analysis on two separate groups (those less than 25 at IRA and those greater than or equal to 25) showed there was no significant difference, p=0.4 (log rank analysis).

<table>
<thead>
<tr>
<th>Age at rectal cancer</th>
<th>All patients</th>
<th>&lt;25 at IRA</th>
<th>&gt;25 at IRA</th>
</tr>
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<tr>
<td>40</td>
<td>5%</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>50</td>
<td>10%</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>60</td>
<td>29%</td>
<td>29%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Colectomy and IRA carries a low risk of rectal cancer until after the age of 50, when there is a steep rise in incidence. 74% of patients with rectal cancer had been sigmoidoscoped within the previous 6 months. Although most of the cancers were small, 40% already had lymph node or distant metastases. We conclude that the high cancer risk despite regular surveillance means that IRA's should be converted to pouches before the age of 50.