Adenoma prevalence and cancer risk in familial non-polyposis colorectal cancer

G Lindgren, A Liljegren, E Jaramillo, C Rubio, A Lindblom

Background and aims: Polypectomy in the colon has been shown to prevent colorectal cancer in both the general population and in familial colorectal cancer. Individuals with a family history of colorectal cancer have an increased risk of the disease. Over a period of 10 years, 304 subjects at risk were included in ongoing surveillance with regular colonoscopies. To compile the medical findings and experience generated during this period, a retrospective cross sectional study was performed.

Subjects: Subjects were classified into three family groups: families with hereditary non-polyposis colorectal cancer (HNPCC); families with hereditary colorectal cancer (HCC, non-Lynch syndrome); and a third group of families with only empirical risk estimates based on a family history of two close relatives (TCR) with colorectal cancer.

Methods: The risk population was studied with regard to age at onset, prevalence, number, cancer risk, size, dysplasia, and distribution of adenomas. A comparison was made within the family groups and with a reference group representing the general population.

Results: In total, 195 adenomas and six cancers were detected among 85 individuals. The relative risk of having an adenoma in the whole risk population compared with the general population was 2.6. Subjects from TCR families had most adenomas and HNPCC subjects had the least. A shift from proximal adenomas to distal carcinomas in families with HCC and TCR suggested a higher cancer risk in distal adenomas in these syndromes. HNPCC families showed a younger age at onset and adenomas with a higher degree of dysplasia. In HNPCC, there was a similar localisation of adenomas and carcinomas, suggesting a high risk of cancer in all adenomas.

Conclusions: There was clear overrepresentation of adenomas in all three family types compared with the reference population. In HNPCC, we found earlier onset of adenomas and faster progression to cancer. Families with HCC, and even more so TCR subjects, had a later onset and lower risk of cancer from proximal adenomas. Based on these results, surveillance protocols in Sweden have been revised.

The lifetime risk of developing colorectal cancer is 5%, with an increased risk for individuals who have close relatives with colorectal cancer, especially if diagnosed at an early age. Depending on the family history and presence of an inherited mutation to colorectal cancer, the risk variability for colorectal cancer is up to 70%. Screening programmes, including colonoscopies in families with familial colorectal cancer as well as in the general population, reduce the incidence of colorectal cancer and seem to prevent mortality from colon cancer. Since 1990, families at risk have been counselled and invited to join a surveillance programme at the Karolinska Hospital with regular colonoscopy, and subjects with an increased risk of colorectal cancer of more than 10% have been offered regular colonoscopy every two years. The surveillance programme included the following types of risk syndromes: hereditary non-polyposis colorectal cancer (HNPCC); hereditary colorectal cancer (HCC); and individuals without a clear pattern of inheritance but with a family history of the disease. Patients with familial adenomatous polyposis were not included as they are usually treated with total colectomy.

HNPCC is an autosomal dominant syndrome predisposing to the development of colorectal cancer. It is caused by germ-line mutations in the DNA mismatch repair genes MSH2, MLH1, PMS1, PMS2, and MSH6. The syndrome is characterised by high penetrance, early onset, a more favourable prognosis than sporadic colorectal cancer, and right sided tumours. Tumours generally show microsatellite instability (MSI). The syndrome is also associated with a broad spectrum of extracolonic cancers, primarily in the endometrium, urinary tract, and small intestine. As the genes were cloned, more than 300 germline mutations in DNA mismatch repair genes were identified (ICG-HNPCC database).

Families not fulfilling the Amsterdam criteria for HNPCC because of older age at onset but with a family history of three or more first degree relatives with colorectal cancer are likely to segregate unknown predisposing gene mutations, causing HCC, and they have a risk similar to families with Lynch syndrome. Apart from HNPCC and HCC, some individuals have an empiric increased risk of colorectal cancer because of a family history. Individuals with one first and one second degree or two first degree relatives (here termed two close relatives (TCR)) affected by colorectal cancer have a risk estimation of 10–20% based on empirical data. Finally, individuals with colorectal cancer at a very early age are likely to have a predisposition for the disease, and their children have an empiric increased cancer risk.

A retrospective cross sectional study was performed to evaluate the surveillance programme in all subjects who had undergone regular colonoscopies for 1–10 years. An attempt was made to compare the prevalence, number, localisation, cancer risk, size, degree of dysplasia, and age at onset of adenomas between the risk groups and the general population. Sex differences were also studied.

Abbreviations: HNPCC, hereditary non-polyposis colorectal cancer; HCC, hereditary colorectal cancer; TCR, two close relatives with colorectal cancer; OCR, one close relative with colorectal cancer; MSI, microsatellite instability; RR, relative risk.

See end of article for authors’ affiliations

Correspondence to: A Lindblom, Department of Clinical Genetics, CMM LB 02, S 171 76 Stockholm, Sweden; annika.lindblom@cmm.ki.se

Accepted for publication 23 April 2001
Subjects included in this study were from the Cancer Family Clinic at Karolinska Hospital from 1990 to 1999. A medical history was given by the index patient and all diagnoses in the family were confirmed by medical records, pathological reports, or in very few cases death certificates. The general screening interval was every two years. After polypectomy of at least one adenoma, a new colonoscopy was performed the following year. Data from the colonoscopies were recorded anonymously in Stat View 5.0.1. Families were classified according to family type (HNPPCC, HCC, or TCR), or one close relative (OCR) using information available from clinical records (table 1). The information used for classifying families included family history and, if available, data on MSI tests in tumours and mutation screening in mismatch repair genes in affected members. All individuals were divided into risk groups as follows. Tested carriers in HNPPCC families (risk group 1) were considered to have a 70% lifetime risk.2,12 According to the rules applied to mendelian inheritance, untested first generation members at risk in a HNPPCC family have a 35% lifetime risk (risk group 2). Their children who sometimes were under surveillance have a 17% lifetime risk (risk group 3). Subjects in HNPPCC families who were under surveillance before testing but tested negative for mutation at the time of the study (risk group 4) were assumed to have the same risk (5%) as the normal population. Obvious gene carriers in families with HCC (risk group 5) have empiric risk values similar to HNPPCC families (70%).11,13 First generation (risk group 6) family members accordingly have a lifetime risk of 35% and the second generation (risk group 7) at risk in these families has an estimated lifetime risk of 17%. TCR subjects with a family history of colorectal cancer (risk group 8) have an empirical risk of 10–20%,11,13 OCR subjects with one relative with early age of onset (risk group 9) have a lifetime empiric risk of 20–40%.11,13

A reference group based on three published forensic autopsy studies was used for estimates of adenoma prevalence in the normal population.4,14,15 In reference group 1, 185 men and 118 women underwent forensic autopsy. Colonic biopsies were examined for prevalence, size, and degree of dysplasia of identified adenomas.14 Reference group 2 consisted of 198 men and 167 women who underwent autopsy/forensic autopsy. The study included prevalence, type, and location of adenomas.15 Reference group 3 comprised autopsies in 370 women and 310 men from areas with various incidences of colorectal cancer. Prevalence of adenomas, size, degree of dysplasia, and site of the adenomas were reported.14 In a comparison of prevalence in the study group versus the reference population, only individuals less than 54 years of age were included in the analysis. The reason was an uneven distribution of subjects in different age cohorts; in the reference group 75% of the cohort were older than 54 years while only 33% were over 54 years in the study group. Also, it was considered relevant to study the prevalence of adenomas at an early age as this is typical of a predisposition to cancer. Thus in the comparison between the study group and the general population, 338 subjects from the reference group and 204 from the study group were used.

**Statistical methods**

Differences in prevalence of adenomas between the three family types and the reference population were calculated as relative risks (RR). Differences between the family types were tested by χ² test. Logistic regression was used to test the influence of sex with respect to the risk of developing an adenoma. The number of adenomas among individual subjects with adenomas were compared using the hazard ratio. Age at first adenoma was analysed by ANOVA with two independent factors, sex and family type. The Tukey post hoc test was then used for pairwise comparisons of family types and age at onset of adenomas. Differences between the family types regarding size and degree of dysplasia were compared using the χ² test. Differences in localisation of adenomas and carcinomas in the bowel were analysed using χ² statistics, and corresponding 95% confidence intervals for differences in proportions were calculated.

**Genetic testing**

MSI tests and genetic testing were performed either as part of previous studies or as part of clinical handling and counselling after 1997, and were not part of this study. The MSI test used established methods and criteria.17–19 Methods used for mutation screening were denaturant gradient gel electrophoresis, protein truncation test, Southern blot, and direct sequencing.19

### RESULTS

In total, 304 subjects underwent 765 colonoscopies (table 2). Ten colorectal cancers were found in nine individuals before recruitment into the surveillance programme. These tumours have been included in table 2 to obtain correct values for prevalence and mean age at onset of adenomas or cancer in the different family types. History of previous adenomas was unknown, and most individuals had their first colonoscopy through this programme. Four individuals had colorectal cancer detected at their first colonoscopy, and two individuals developed a metachronous colorectal cancer during surveillance.

#### Prevalence and number of adenomas

The RR value of developing an adenoma before the age of 54 years in all risk groups (except tested non-carriers) was 2.6 compared with the general population (p=0.001) (table 3). Sex had no influence on these results. RR was even higher

### Table 1 Families included in the study

<table>
<thead>
<tr>
<th>Family type</th>
<th>Criteria</th>
<th>No of families</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNPPCC</td>
<td>1 Germline mutation in hMSH2, hMLH1, or hMSH6</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>2 Amsterdam HNPPCC+MSI pos+negative mutation screen</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>3 Amsterdam HNPPCC+MSI nd+mutation screen</td>
<td>4</td>
</tr>
<tr>
<td>HCC</td>
<td>1 Non-Amsterdam hereditary CRC+MSI neg+negative mutation screen</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>2 Amsterdam HNPPCC+MSI neg+negative mutation screen</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3 Non-Amsterdam hereditary CRC+MSI nd+mutation screen</td>
<td>5</td>
</tr>
<tr>
<td>TCR</td>
<td>1 Two close relatives+MSI neg+negative mutation screen</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>2 Two close relatives+MSI nd+negative mutation screen</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>3 Two close relatives+MSI nd+mutation screen</td>
<td>29</td>
</tr>
<tr>
<td>OCR</td>
<td>1 One parent with colorectal cancer before 40 y of age</td>
<td>5</td>
</tr>
<tr>
<td>Total no families</td>
<td></td>
<td>111</td>
</tr>
</tbody>
</table>
The estimated cancer risk (table 4). The risk values
sons between different risk groups, prevalence was related to
relative value of cancer risk which could be used for compari-
relatively low risk TCR families was unexpected. T o obtain a
HCC (table 2). The high prevalence of adenomas in the
The prevalence in each risk group varied in relation to the
one first degree relative (OCR) with colorectal cancer; 9, one first degree relative (OCR) with colorectal
cancer <40 years of age.

Cancer risk in adenomas
The prevalence in each risk group varied in relation to the
estimated cancer risk in the various risk groups in HNPCC and
HCC (table 2). The high prevalence of adenomas in the
relatively low risk TCR families was unexpected. To obtain a
relative value of cancer risk which could be used for compari-
sions between different risk groups, prevalence was related to the
estimated cancer risk (table 4). The risk values
(prevalence/estimated cancer risk) were highest in HNPCC,
lowest in TCR and in the normal population. To obtain a
lower cancer risk in each adenoma, the risk values were
divided by the number of adenomas per individual (from fig 1)
(table 4). Mean age of the families was similar (table 2), and
the risk of cancer was the same when only subjects less than
54 years of age were compared (data not shown).

Localisation of adenomas and carcinomas
Adenomas were located throughout the colon and rectum, as
depicted in fig 2. While adenomas were evenly distributed in
HNPCC, HCC, and in the general population, TCR adenomas
seemed to be mostly proximal (fig 2).

To determine if there was a difference in cancer risk
depending on location, a comparison was made between
adenoma location and carcinoma location in the different
family types (fig 2). Localisation of cancers among the total
number of family relatives was obtained from investigation of all
111 families in the study. In total, there were 81 HNPCC
cancers, 52 HCC cancers, and 51 TCR cancers. T o determine the
localisation of sporadic cancer in the general population, three
published reports were used (fig 2). There was a clear
difference in percentage of distal outcome between adenomas
and carcinomas in families with TCR (p<0.001) but also in
HCC (p<0.05) and the normal population (p<0.001) (fig 2).

Mean age at first observed adenoma
Mean age at identification of the first adenoma was 43 years in
HNPCC, 50 years in HCC, and 52 years in TCR (fig 3). There
was a statistically significant difference between age at first
adenoma in HNPCC and TCR (p=0.006). The difference

![Figure 1](https://gut.bmj.com/content/50/2/228/F1)

**Figure 1** Mean number of adenomas among individuals presenting with adenomas in the three family types (HNPCC, hereditary non-polyposis colorectal cancer; HCC, hereditary colorectal cancer; TCR, two close relatives with colorectal cancer).
between HNPCC and HCC was as expected (p=0.02) as this was defined by the inclusion criteria.

**Sex and age**
Overall, there was a difference (p<0.05) between the prevalence of adenomas in men (34%) and women (24%) (tables 2, 3). Men and women showed a systematic difference in mean age at first adenoma (fig 3). There was no interaction effects; the sex difference was assumed to be constant over family type and the difference between family types was assumed to be constant over sex.

**Histopathology**
In total, 152 tubular adenomas, 18 tubulovillous adenomas, two villous adenomas, 18 serrated adenomas, and five unclassified adenomas were removed. The vast majority (88%) were less than 5 mm. In four of the adenomas estimation of size was not done. Size and degree of dysplasia in adenomas from the second or later colonoscopies were compared. Thirteen adenomas were >5 mm in size but only three showed a high degree of dysplasia (table 5). In total, eight subjects had 11 adenomas with high dysplasia, and six of those eight subjects were from HNPCC families (table 6). There was a statistically significant difference between the number of adenomas with high degree dysplasia in the HNPCC compared with the other two family types (χ²=6.7, p<0.01).

**DISCUSSION**
In the following discussion of the results, we will use the RR of adenomas as an estimate of tumour initiation rate in individuals. When the actual cancer risk in an individual is higher

![Figure 2](http://gut.bmj.com/)

**Figure 2** Percentage distribution of adenomas in the three familial types (HNPCC, hereditary non-polyposis colorectal cancer; HCC, hereditary colorectal cancer; TCR, two close relatives with colorectal cancer) and in the reference population (A). Percentage distribution of carcinomas in the same family types and in the general population (B).
than the increase in initiation rate, this is considered to depend on an increased tumour progression rate in adenomas.

**A higher initiation rate in all risk groups**

There is much discussion as to whether the prevalence and frequency of adenomas in individuals with an increased risk of colorectal cancer are higher than in the general population. In this study, gene carriers in HNPCC had an RR of 4.5 compared with the general population of presenting with an adenoma before the age of 54 years. All risk groups combined had an RR of 2.6. The increased risk of adenomas in all groups compared with the general population indicates that in all families there is an increased initiation rate that explains, at least in part, the increased risk of colorectal cancer. The different numbers of adenomas in the family types suggests that the initiation rate is increased most in TCR families and increased least in HNPCC.

Autopsy studies to assess the number of adenomas in the general population are not optimal. However, the autopsy studies chosen for this study were specifically designed to give adenoma values representing the normal population. Furthermore, some authors found autopsies to be more reliable than colonoscopies in detecting adenomas <10 mm. Other studies have shown a missrate of 15–27% for detecting adenomas <5 mm using colonoscopies. However, as most of the study objects were included in a surveillance programme, a minute adenoma would show up at the next screening if missed at the previous one, thus giving correct values for prevalence in the study group.

**A higher rate of progression in the high risk syndromes**

The excess in cancer risk in adenomas in HNPCC and HCC compared with TCR and the general population in this study suggested that apart from increased initiation there is also an increased rate in tumour progression. As the genes for HCC are still unknown, we estimated the penetrance as equal to that of HNPCC. If this is an overestimation, the cancer risk in each adenoma in HCC is also overestimated and could be even lower. In particular, HNPCC subjects have an up to eightfold greater cancer risk in each adenoma compared with TCR subjects and the normal population (table 4). This fits well with an increased mutation rate in tumours because of deficient mismatch repair in this syndrome. The shift from proximal

![Figure 3](https://www.gutjnl.com/figures/figure3.png)

**Figure 3** Mean age at onset of adenoma or carcinoma in men and women in the three family types (HNPCC, hereditary non-polyposis colorectal cancer; HCC, hereditary colorectal cancer; TCR, two close relatives with colorectal cancer).

### Table 5 Adenomas greater than 5 mm from the second and subsequent colonoscopies

<table>
<thead>
<tr>
<th>Family</th>
<th>Patient</th>
<th>Family type</th>
<th>Age (y)</th>
<th>Screen</th>
<th>Size (mm)</th>
<th>Histology</th>
<th>Dysplasia</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>69</td>
<td>77</td>
<td>HNPCC</td>
<td>35</td>
<td>3rd</td>
<td>10</td>
<td>TA</td>
<td>Low</td>
<td>A</td>
</tr>
<tr>
<td>5</td>
<td>141</td>
<td>HNPCC</td>
<td>34</td>
<td>6th</td>
<td>9</td>
<td>TA</td>
<td>High</td>
<td>D</td>
</tr>
<tr>
<td>87</td>
<td>248</td>
<td>HCC</td>
<td>68</td>
<td>4th</td>
<td>10</td>
<td>TA</td>
<td>Low</td>
<td>DC</td>
</tr>
<tr>
<td>87</td>
<td>247</td>
<td>HCC</td>
<td>69</td>
<td>5th</td>
<td>10</td>
<td>TA</td>
<td>Low</td>
<td>T</td>
</tr>
<tr>
<td>87</td>
<td>247</td>
<td>HCC</td>
<td>44</td>
<td>3rd</td>
<td>7</td>
<td>VA</td>
<td>Low</td>
<td>A</td>
</tr>
<tr>
<td>134</td>
<td>90</td>
<td>HCC</td>
<td>46</td>
<td>2nd</td>
<td>6</td>
<td>TA</td>
<td>Low</td>
<td>R</td>
</tr>
<tr>
<td>24</td>
<td>179</td>
<td>HCC</td>
<td>70</td>
<td>2nd</td>
<td>15</td>
<td>TA</td>
<td>High</td>
<td>D</td>
</tr>
<tr>
<td>26</td>
<td>204</td>
<td>HCC</td>
<td>75</td>
<td>3rd</td>
<td>10</td>
<td>TVA</td>
<td>Low</td>
<td>R</td>
</tr>
<tr>
<td>26</td>
<td>204</td>
<td>HCC</td>
<td>76</td>
<td>4th</td>
<td>10</td>
<td>TVA</td>
<td>Low</td>
<td>R</td>
</tr>
<tr>
<td>26</td>
<td>208</td>
<td>HCC</td>
<td>42</td>
<td>3rd</td>
<td>7</td>
<td>TA</td>
<td>High</td>
<td>R</td>
</tr>
<tr>
<td>23</td>
<td>30</td>
<td>TCR</td>
<td>40</td>
<td>4th</td>
<td>6</td>
<td>TA</td>
<td>Low</td>
<td>A</td>
</tr>
<tr>
<td>23</td>
<td>30</td>
<td>TCR</td>
<td>41</td>
<td>5th</td>
<td>6</td>
<td>TA</td>
<td>Low</td>
<td>A</td>
</tr>
<tr>
<td>123</td>
<td>331</td>
<td>TCR</td>
<td>59</td>
<td>2nd</td>
<td>10</td>
<td>TA</td>
<td>Low</td>
<td>T</td>
</tr>
</tbody>
</table>

HNPCC, hereditary non-polyposis colorectal cancer; HCC, hereditary colorectal cancer; TCR, two close relatives with colorectal cancer; TA, tubular adenoma; TVA, tubulovillous adenoma; VA, villous adenoma; A, ascending colon; T, transverse colon; D, descending colon; R, rectum.

### Table 6 Adenomas with moderate and high dysplasia from second and subsequent colonoscopies

<table>
<thead>
<tr>
<th>Family</th>
<th>Patient</th>
<th>Family type</th>
<th>Age (y)</th>
<th>Screen</th>
<th>Size (mm)</th>
<th>Histology</th>
<th>Dysplasia</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>135</td>
<td>HNPCC</td>
<td>53</td>
<td>3rd</td>
<td>5</td>
<td>TVA</td>
<td>High</td>
<td>D</td>
</tr>
<tr>
<td>3</td>
<td>135</td>
<td>HNPCC</td>
<td>58</td>
<td>5th</td>
<td>Unknown</td>
<td>TVA</td>
<td>High</td>
<td>A</td>
</tr>
<tr>
<td>3</td>
<td>135</td>
<td>HNPCC</td>
<td>58</td>
<td>6th</td>
<td>24</td>
<td>Carcinoma Dukes’ A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>139</td>
<td>HNPCC</td>
<td>57</td>
<td>2nd</td>
<td>Unknown</td>
<td>Adenoma unclassified</td>
<td>High</td>
<td>D</td>
</tr>
<tr>
<td>5</td>
<td>141</td>
<td>HNPCC</td>
<td>34</td>
<td>6th</td>
<td>9</td>
<td>TA</td>
<td>High</td>
<td>D</td>
</tr>
<tr>
<td>28</td>
<td>299</td>
<td>HNPCC</td>
<td>40</td>
<td>2nd</td>
<td>Unknown</td>
<td>Carcinoma Dukes’ A</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>183</td>
<td>326</td>
<td>HNPCC</td>
<td>36</td>
<td>3rd</td>
<td>Unknown</td>
<td>TA</td>
<td>High</td>
<td>R</td>
</tr>
<tr>
<td>24</td>
<td>179</td>
<td>HCC</td>
<td>70</td>
<td>2nd</td>
<td>15</td>
<td>TA</td>
<td>High</td>
<td>D</td>
</tr>
<tr>
<td>24</td>
<td>179</td>
<td>HCC</td>
<td>71</td>
<td>3rd</td>
<td>Unknown</td>
<td>TA</td>
<td>High</td>
<td>A</td>
</tr>
<tr>
<td>100</td>
<td>265</td>
<td>TCR</td>
<td>69</td>
<td>3rd</td>
<td>3</td>
<td>TVA</td>
<td>High</td>
<td>A</td>
</tr>
<tr>
<td>100</td>
<td>265</td>
<td>TCR</td>
<td>69</td>
<td>3rd</td>
<td>1</td>
<td>TVA</td>
<td>High</td>
<td>D</td>
</tr>
</tbody>
</table>

HNPCC, hereditary non-polyposis colorectal cancer; HCC, hereditary colorectal cancer; TCR, two close relatives with colorectal cancer; TA, tubular adenoma; TVA, tubulovillous adenoma; VA, villous adenoma; A, ascending colon; T, transverse colon; D, descending colon; R, rectum.
Adenoma prevalence and cancer risk in HNPCC

Table 7  Modelling of tumour initiation rate and tumour progression rate in the three family types (HNPCC, HCC, TCR) in this study compared with sporadic colorectal cancer where no increased initiation and progression are known, and a fourth syndrome, familial adenomatosis polyposis, where an increased initiation rate is well documented for adenomas

<table>
<thead>
<tr>
<th>Family type</th>
<th>Tumour initiation</th>
<th>Tumour progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic colorectal cancer</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HNPCC</td>
<td>♦</td>
<td>♦</td>
</tr>
<tr>
<td>HCC</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>TCR</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>TCR +++ +? (distal adenomas)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAP</td>
<td>++++</td>
<td>0</td>
</tr>
</tbody>
</table>

HNPCC, hereditary non-polyposis colorectal cancer; HCC, hereditary colorectal cancer; TCR, two close relatives with colorectal cancer; FAP, familial adenomatosis polyposis.

0, no increased rate; + (1–5), various degrees of increased rates. This estimation is approximate and only chosen to present the idea of different degrees of increased tumour initiation and tumour promotion rates characterising different families with an increased risk of colorectal cancer because of an inherited predisposition.

Differences in mean age between syndromes

Mean age at first observed adenoma was 44 years in HNPCC which is in accordance with previous studies (fig 1). The higher penetrance for men in HNPCC found in this study (table 3) confirmed previous reports. A higher penetrance for men was also suggested in HNPCC and HCC in this study, while TCR subjects were not informative in this respect depending on different mean ages among men and women.

In summary, there was a clear overrepresentation of adenomas in all three family types. This seems to justify regular colonoscopy surveillance for prevention in these patients. The data support a proposed model (table 7) with increased rates of both initiation and tumour progression in HNPCC. In HNPCC it appears that there is a rapid transformation from adenoma to carcinoma as there was a higher grade of dysplasia in HNPCC adenomas unrelated to size. HNPCC also displayed the highest risk of cancer in each adenoma, regardless of location (table 4). In HCC families, an increased initiation rate as well as an increased progression rate were also found although the cancer risk in each adenoma was lower in proximal adenomas and the progression from adenoma to carcinoma is likely to be slower than in HNPCC. TCR families seem to have the highest increase in initiation rate as they had the highest number of adenomas. In TCR there seems to be a lower cancer risk in proximal adenomas and a relatively higher cancer risk in distal adenomas. The differences between the three family types (HNPCC, HCC, and TCR) with regard to age at onset, prevalence, location, size and degree of dysplasia, and cancer risk of adenomas have been used to revise surveillance protocols in Sweden. The guidelines from the Swedish National Oncogenetic Council now recommend the following: in HNPCC, regular colonoscopy every 1–2 years; in HCC, regular colonoscopy every 3–5 years; and in TCR, colonoscopy (or alternating colonoscopy/sigmoidoscopy) every 3–5 years.

ACKNOWLEDGMENTS

We are indebted to Marianne Törnblom for excellent management of the patient registry and Jan Kowalski for statistical analysis. The Swedish Cancer Society, the Stockholm County Council, and the Cancer Foundation in Stockholm supported the study.

Authors’ affiliations

G Lindgren, A Lindblom, Department of Clinical Genetics, Karolinska Hospital, S 171 76 Stockholm, Sweden

A Liljegren, Department of Clinical Genetics, Karolinska Hospital, S 171 76 Stockholm, Sweden and Department of Clinical Oncology, Danderyds Hospital, S 182 88, Stockholm, Sweden

E Jarrahi, Department of Gastroenterology, Karolinska Hospital, S 171 76 Stockholm, Sweden

C Rubie, Department of Oncology and Pathology, Karolinska Hospital, S 171 76 Stockholm, Sweden

REFERENCES


Readers' favourite

Top 10

Click on the 'Top 10' button on the homepage to see which are the best read articles each month

www.gutjnl.com
Intestinal intraepithelial lymphocytes and anti-transglutaminase in a screening algorithm for coeliac disease

We have noticed the frequent publication of important advances in the serological screening of coeliac disease (CD), such as the interesting and useful technique described by Bal-das et al (Gut 2000;47:628–31). Humoral screening of CD is coming closer than ever towards representing an affordable population wide strategy (Gut 2000;47:628–31), largely due to the identification of tissue transglutaminase (tTG) as the main—if not largely due to the identification of tissue transglutaminase (tTG) as the main—if not only—autoantigen for antiendomysial antibodies (EMA). This finding highlights the possibility of antigen specific testing and, today, determination of anti-tTG is a valid alternative to EMA.

However, we believe that the recent advances in the cellular component of the disease, particularly by flow cytometry7 has added specificity to mere histological study of the small bowel biopsy. It has been shown that CD is characterised by an important increase in the TcR-αβ IEL subset (or γδ IEL), a decrease in the natural killer (NK)-like subset and, depending on gluten intake, a considerable increase in the TcR-γδ IEL (αβ IEL) subset which constitute the majority of IEL. The increase in γδ IEL (average 4% in controls vs 25% in coeliacs, with total IEL)3 is not per se diagnostic of CD as it has been observed, although to a lower extent, in food allergy5 and occasionally in other conditions. But CD is the only entity in which γδ IEL have been described as systematically, permanently, and markedly raised. The combined study of total, γδ, and NK-like IELs, that could be termed “IEL lymphogram”, allows for nearly 94% specificity and sensitivity in the diagnosis of CD after clinical suspicion. This technique, complementary to the diagnosis of symptomatic and silent CD, shows its real value in latent and potential presentations of the disease, and offers important data for the differential diagnosis from other enteropathies. It is noteworthy that the increase in IEL is the earliest detectable alteration in the mucosa,7 prior to the increase in lamina propria lymphocytes or architectural changes.

Many recent reviews3 have commented on these characteristic serological and cellular findings of CD but their incorporation into clinical practice is very different. While tTG testing is spreading, IEL phenotyping—particularly by flow cytometry—is still regarded as a research tool rather than a diagnostic test. We consider that the easy procedure of IEL procurement and phenotyping6 could be routinely performed in many medium sized hospitals, and we propose an initial screening algorithm that takes this “IEL lymphogram” into account (Fig 1).

Screening would be based on tTG IgA determination, and seric IgA quantification if anti-tTG was negative. If there was an IgA deficiency, only IgG tests would then be performed. If serum and blood were obtained at the first visit and temporarily cryopreserved, many tests (serum IgA, AGA, EMA, HLA, IgE, other autoantibodies, etc.) could be achieved without the patient attending the clinic again.

The establishment of the putative diagnosis would be achieved by mandatory small bowel biopsy. But the IEL lymphogram would allow for serological and clinical evaluation of gluten withdrawal (and challenge) if it fitted into the coeliac pattern and histology showed a typical coeliac enteropathy. If the lymphogram shows normal values for γδ and NK-like IEL, it has a high negative predictive value of 95% against the existence of CD. If the interpretation of the immunohistological study is not straightforward, the classical ESPiGAN criteria can be followed.6 We believe that this algorithm, which can be conveniently adapted to the needs of each centre, can correctly classify the vast majority of patients, saving time and money, and avoiding morbidity.

F Leon, P Eiras, G Roy
Department of Immunology, Hospital Ramón y Cajal, Ctra Colmenar km 9, 28034 Madrid, Spain
C Camarero
Department of Paediatric Gastroenterology, Hospital Ramón y Cajal, Ctra Colmenar km 9, 28034 Madrid, Spain

Correspondence to: F Leon; immu_leon@altavista.com

Acknowledgements
Our work was financed by the Spanish Fondo de Investigaciones Sanitarias (FIS), grants Nos 00/0196 (G Roy) and 01/9417 (F León).

Figure 1 Proposal of an initial diagnostic algorithm for coeliac disease (CD). After screening with anti-transglutaminase (tTG), and taking into account the high negative predictive value of HLA typing, study of mandatory intestinal biopsy would include phenotyping of intraepithelial lymphocytes (IEL). The proportion of total IEL is calculated with respect to the cellularity of the epithelium while the proportions of γδ IEL and “natural killer” (NK)-like IEL are relative to the total IEL. The combined analysis of the pathology and the IEL lymphogram allows for a correct classification of >95% of patients after the first biopsy, reducing the need for subsequent invasive procedures.

www.gutjnl.com

If you have a burning desire to respond to a paper published in Gut, why not make use of our “rapid response” option?
Log onto our website, find the paper that interests you, and send your response via email by clicking on the “eLetters” option in the box at the top right hand corner. Providing it isn’t libellous or obscene, it will be posted within seven days. You can retrieve it by clicking on “read eLetters” on our homepage.

The editors will decide as before whether to also publish it in a future paper issue.

www.gutjnl.com
The changing scope of colorectal cancer

We read with great interest the commentary by Boland and Savides (Gut 2001;48:489–501) on our paper “Flexible sigmoidoscopy and the changing distribution of colorectal cancer: implications for screening” (Gut 2001;48:522–5). The authors make several important points about the changing pattern of distribution of colorectal cancer and the possible reasons for the changes we observed. Our data showed an increased percentage of colorectal cancers diagnosed proximal to the splenic flexure between 1976–78 and 1990–97. As Boland and Savides point out, this change may be due to a decreased incidence of distal and rectal cancers. These results may well represent a true increase in proximal colorectal cancers, although as Boland and Savides suggest, they could also be explained by a rising incidence in all subsites, with relative sparing of the distal colon and rectum due to either the protective effect of non-steroidal anti-inflammatory drugs or endoscopic polypectomy.

J S White, K Mc Callion, K R Gardiner
Department of Surgery, Royal Victoria and Belvoir Park Hospitals, the Queen’s University of Belfast, UK

R M S Mitchell, RG P Watson, J S A Collins
Department of Medicine, Royal Victoria and Belvoir Park Hospitals, the Queen’s University of Belfast, UK

R H Wilson
Department of Oncology, Royal Victoria and Belvoir Park Hospitals, the Queen’s University of Belfast, UK

F Kee
Department of Epidemiology and Public Health, Royal Victoria and Belvoir Park Hospitals, the Queen’s University of Belfast, UK

A Paneth cell surrogate?

We read with interest the article by Cunliffe et al (Gut 2001;48:176–85) on defensin 5 stored in normal Paneth cells and in metaplastic Paneth cells in inflammatory bowel disease (IBD). In recent years a great deal of interest has centred around Paneth cells as carriers of innate host defence, effective through their content of antimicrobial peptides and proteins.1 In humans, that mechanism seems to be conveyed by a complex system of proteins present in the granules of the Paneth cells: lysozyme, secretory phospholipase A, and probably α defensins (that is, cryptidins, so far recorded in mice).

The lysozyme rich granules in Paneth cells appears to be one of the main sources of antimicrobial peptide in the normal small bowel (where Paneth cells are normally present). Although such cells are not found in the normal colorectal mucosa, Paneth cell metaplasia may present in the colorectal mucosa of some (but not all) patients with longstanding IBD. Demonstration of human neutrophil defensins (HNPs 1–3) and lysozyme in epithelial cells of active IBD has fuelled interest in the molecular events behind defence mediated intestinal host defence.

Against that background, it may be of interest to point out that another source of cytoplasmic lysozyme has recently been unveiled.2 Thirty five years ago, Azzopardi and Evans3 found mucin containing macrophages (denominated muciphages) in the colonic mucosa. Those cells were described as normal phagocytes in an otherwise normal mucosa. The mucroprotein present in their cytoplasm stained with a variety of mucous colorants (alcan blue, aldehyde fuchsine, and mucarwine). Muciphages which were subsequently found to be associated with mucosal abnormalities induced by an inflammatory disruption of the crypts would officiate as scavengers to keep the lamina propria free from the liberated mucus. Until now, muciphages have been considered as a non-specific manifestation of mucosal damage.

We investigated the occurrence of those cells in rectal biopsies from patients with a variety of diseases, we found muciphages either scattered in the lamina propria or distributed in a more “organised” fashion underneath the superficial epithelium and along the base of the crypts, near the muscularis mucosae.

Immunostain (CD68) confirmed the macrophagic nature of those cells and histochemistry showed the presence of lysozyme (Lysozyme-Muramidase without counterstain, Dako A/S, Denmark) (fig 1).

At this stage it should be stressed that the mucus contained in the goblet cells of the crypts, in the mucus of mucous producing adenocarcinomas of the rectum, and in the mucus from a ruptured colon diverticulitis were lysozyme negative. Thus the cytoplasm of muciphages contains not only mucus but also the antimicrobial peptide lysozyme.

The presence of lysozyme in muciphages suggests that those particular macrophages are not an accidental happening but expression of a more targeted active biological mechanism of lysozyme dependent mucosal defence.

In some patients with IBD in remission, the topographical disposition of those lysozyme containing cells—between the mucus and the underlying host (fig 1)—is noteworthy.

Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Proximal colon</th>
<th>Distal colon</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1976–78</td>
<td>4.7</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>1995–97</td>
<td>9.5</td>
<td>8.4</td>
</tr>
<tr>
<td>Female</td>
<td>1976–78</td>
<td>4.7</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>1995–97</td>
<td>8.2</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Figure 1 Rectal mucosa in remission in a patient treated in the past for ulcerative colitis. Note the arrangement of lysozyme laden muciphages along the muscularis mucosae, both underneath the superficial epithelium and at the base of the crypts [lysozyme-Muramidase without counterstain, 25×].
that muciphages may be an important source of antimicrobial peptides in mucosae in protracted remission from earlier inflammatory episodes.

C A Rubio
Gastrointestinal and Liver Pathology, Research Laboratory, Karolinska Institute and Hospital, 171 76 Stockholm, Sweden. Carlos.Rubio@onkpat.ki.se

References

CORRECTION

NOTICES
Agostino Trapani International Prize
The Scuola Medica Ospedaliera Napoletana invites applications for the above international prize. A stipend of €7,000 (seven thousand Euros), generously offered by the Professor Trapani family, is available to subsi
dise a young investigator submitting an experimental and/or clinical research project in the fields of hepatobiliary and pancreatic disorder. The prize, awarded by an inter
national committee, will be personally pre
dared by the winner. Applications, in English, should include a curriculum vitae of the applicant. The research project (max three typewritten pages) including a financial plan to use the stipend. Covering letter inclusive of formal application. Address where an acknowledgement of the receipt of the application and any further correspondence should be mailed, including telephone, fax, and email address. Letter of nomination of a sponsor of known reputation in the field of hepato pancreatic and biliary surgery.

Broad Medical Research Program—Inflammatory Bowel Disease Grants
Funds for inflammatory bowel disease (IBD) research are available immediately from the Broad Medical Research Program of The Eli and Edythe L. Broad Foundation for innovative projects regarding etiology, therapy, or prevention. Grants totalling approximately US$100,000 per year are available for basic or clinical projects. Larger requests may be considered. Initial letter of interest (no submission deadline), simple application, rapid (60 day) peer review, and funding. Criteria for funding includes new ideas or directions, sci
entific excellence, and originality. Early exploration, projects not currently working in IBD, and/or interdisciplinary ef
forts are encouraged. Further information: Marciana Poland, Research Administrator, Broad Medical Research Program, 10090 Wilshire Blvd., Suite 1500, Los Angeles, CA 90024-6532, USA. Tel: +1 310 954 5091; email: info@broadmedical.org; website: www.broadmedical.org

Falk Symposium No 128:
Exogenous Factors in Colonic Carcinogenesis
This will be held on 2–3 May 2002 in Würzburg, Germany. Further information: Falk Foundation e.V.-congress Division, Koenigswuerter Str. 5, PO Box 6529, D-79041 Freiburg, Germany. Tel: +49 761 1514 0; fax: +49 761 1514 359; email: symposia@falkfoundation.de

Artificial Oxygen Carriers—A Clinical Future?
This conference will be held on 9 May 2002 in Edinburgh, UK. Further information: Rosemary Hector, Acting Consensus Conference Co-ordinator, Education and Standards Department, Royal College of Physicians of Edinburgh, 9 Queen Street, Edinburgh EH2 1LQ, Tel: +44 (0)131 229 7324; fax: +44 (0)131 220 3939; email: r.hector@rcpe.ac.uk

12th International Workshop of Digestive Endoscopy, Ultrasonography, and Radiology
This will be held on 30–31 May 2002 in Mar
seille, France. Further information: Nathalie Fontant, Atelier Phenix, 41 rue Docteur Morucci, 13006 Marseille, France. Tel: +33 04 91 37 50 83; fax: +33 04 91 57 15 28; email: nfontant@aphenix.com

Endoscopic Oncology: Gastrointestinal Endoscopy and Cancer Management
This ASGE Annual Postgraduate Course will be held on 22–23 May 2002 in San Francisco, USA. Further information: American Society for Gastrointestinal Endoscopy. Tel: +1 978 526 8330; fax: +1 978 526 7321; email: asge@shore.net

11th International Symposium on Hepatic Encephalopathy and Nitrogen Metabolism
This meeting will be held on 30 May to 1 June 2002 in Amstterdam, The Netherlands. Further information: Secretariat, Nicolaes Tulp Institute, Academic Medical Center, PO Box 23123, 1100 DS Amsterdam, The Netherlands. Tel: +31 20 666 8385; fax: +31 20 696 3228; email: tulpins@amc.uva.nl.

Gastroenterology and Endotherapy European Workshop: XXth Anniversary
This course will be held on 17–19 June 2002 in Brussels, Belgium. Further information: Nancy Beaufre, Gastroenterology Depart
ment, Erasme Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 (0)20 555 49 00; fax: +32 (0)20 555 4901; email: beaufre@ulb.ac.be

EASL Monothematic Conference on Vascular Function in Liver Disease
This conference will take place on 30 June to 2 July 2002 in London, UK. Further infor
mation: Professor Jordi Bruix, EASL Liaison Bureau, c/o Kones International, 17 rue du Cendrier, PO Box 1726, CH-1211 Geneva, Switzerland. Tel: +41 22 908 0486; fax: +41 22 732 2850; email: info@easl.ch; www.easl.com. Deadline for abstract submission 15 May 2002. Further information: kmoore@rific.ucl.ac.uk; tel: +44 (0)207 433 2876.

5th International Workshop on Pathogenesis and Host Response in Helicobacter Infections
This will be held on 4–7 July 2002 in Helsingør, Denmark. Further information: Dr Tina Ken Hansen, Department of Cardiology-Endocrinology E, Frederiksberg Hospital, Ndr. Fasanvej, DK-2000 Frederiksberg, Denmark. Fax: +45 3545 7708; email: helpatim@biobase.dk