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 colorectal cancer and even death from colorectal cancer at a very early age.

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 (IGC-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.
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 (HNPCC, 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 HNPCC families (risk group 1) were considered to have a 70% lifetime risk.2 According to the rules applied to mendelian inheritance, untested first generation members at risk in a HNPCC 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 HNPCC 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 HNPCC families (70%).11,12 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 have 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%.11,12 OCR subjects with one relative with early age of onset (risk group 9) have a lifetime empiric risk of 20–40%.2,13

Table 1. Families included in the study

<table>
<thead>
<tr>
<th>Family type</th>
<th>Criteria</th>
<th>No of families</th>
</tr>
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<tr>
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<td>Germline mutation in hMSH2, hMLH1, or hMSH6</td>
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</tr>
<tr>
<td></td>
<td>Amsterdam HNPCC+MSI pos+negative mutation screen</td>
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</tr>
<tr>
<td></td>
<td>Amsterdam HNPCC+MSI nd+mutation screen nd</td>
<td>4</td>
</tr>
<tr>
<td>HCC</td>
<td>Non-Amsterdam hereditary CRC+MSI neg+negative mutation screen</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Amsterdam HNPCC+MSI neg+negative mutation screen</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Non-Amsterdam hereditary CRC+MSI nd+mutation screen nd</td>
<td>5</td>
</tr>
<tr>
<td>TCR</td>
<td>Two close relatives+MSI neg+negative mutation screen</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Two close relatives+MSI nd+positive mutation screen</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Two close relatives+MSI nd+mutation screen nd</td>
<td>29</td>
</tr>
<tr>
<td>OCR</td>
<td>One parent with colorectal cancer before 40 y of age</td>
<td>5</td>
</tr>
<tr>
<td>Total no families</td>
<td>111</td>
<td></td>
</tr>
</tbody>
</table>

HNPCC, hereditary non-polyposis colorectal cancer; HCC, hereditary colorectal cancer; TCR, two close relatives with colorectal cancer; OCR, one close relative with colorectal cancer; CRC, colorectal cancer; MSI, microsatellite instability; nd, not done.

Subjects

MATERIALS AND METHODS

Subjects

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

Sex had no influence on these results. RR was even higher 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

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).
sons between different risk groups, prevalence was related to relatively low risk TCR families was unexpected. To obtain a HCC (table 2). The high prevalence of adenomas in the estimated cancer risk in the various risk groups in HNPCC and Cancer risk in adenomas

The prevalence in each risk group varied in relation to the number of adenomas between family types was (3.8) than HCC subjects (2.4) and HNPCC families (1.2). The hazard ratio between TCR and HNPCC was 3.3 (CI 2.2–4.6) and between HCC and HNPCC 2.0 (CI 1.3–2.9). The hazard ratio between TCR and HCC was 1.6 (CI 1.1–2.18).

Cancer risk in adenomas

The prevalence in each risk group varied in relation to the estimated cancer risk in the expected 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 comparisons 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 relative 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. To 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://www.gutjnl.com/)

**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

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Comparison of cancer risks between different syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cancer risk (risk/prevalence)</td>
</tr>
<tr>
<td>HNPCC, subjects at 70% risk*</td>
<td>1.43 (70/49)</td>
</tr>
<tr>
<td>HNPCC, subjects at 35% risk*</td>
<td>1.84 (35/19)</td>
</tr>
<tr>
<td>HNPCC, subjects at 17% risk</td>
<td>—</td>
</tr>
<tr>
<td>HNPCC, subjects at 5% risk</td>
<td>0.38 (5/13)</td>
</tr>
<tr>
<td>HCC, subjects at 70% risk</td>
<td>1.40 (70/50)</td>
</tr>
<tr>
<td>HCC, subjects at 35% risk*</td>
<td>1.21 (35/29)</td>
</tr>
<tr>
<td>HCC, subjects at 17% risk</td>
<td>1.00 (17/17)</td>
</tr>
<tr>
<td>TCR, subjects at 15% risk*</td>
<td>0.45 (15/33)</td>
</tr>
<tr>
<td>Normal population at 5% risk</td>
<td>0.45 (5/11)</td>
</tr>
</tbody>
</table>

*Statistically significant.
95% CI, 95% confidence interval.
HNPCC, hereditary non-polyposis colorectal cancer; HCC, hereditary colorectal cancer; TCR, two close relatives with colorectal cancer.

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 can-
cer. 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. Further-
more, 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 sub-
jects 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](image-url)  
**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).

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**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>
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</thead>
<tbody>
<tr>
<td>69</td>
<td>77</td>
<td>HNPCC</td>
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<td>3rd</td>
<td>10</td>
<td>TA</td>
<td>Low</td>
<td>A</td>
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<tr>
<td>5</td>
<td>141</td>
<td>HNPCC</td>
<td>34</td>
<td>6th</td>
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<td>TA</td>
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<td>D</td>
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<tr>
<td>87</td>
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<td>HCC</td>
<td>68</td>
<td>4th</td>
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<tr>
<td>87</td>
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<td>HCC</td>
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<td>10</td>
<td>TA</td>
<td>Low</td>
<td>T</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>
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<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>
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<td>10</td>
<td>TVA</td>
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<td>R</td>
</tr>
<tr>
<td>26</td>
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<td>HCC</td>
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<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>
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</tr>
<tr>
<td>123</td>
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<td>59</td>
<td>2nd</td>
<td>10</td>
<td>TA</td>
<td>Low</td>
<td>T</td>
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</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.

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**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>
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<td>TVA</td>
<td>High</td>
<td>A</td>
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<tr>
<td>3</td>
<td>138</td>
<td>HNPCC</td>
<td>58</td>
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<td>Carcinoma Dukes’ A</td>
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<tr>
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<td>HNPCC</td>
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<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>
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<td>HCC</td>
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<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.
protocols in Sweden. The guidelines from the Swedish cancer risk of adenomas have been used to revise surveillance at onset, prevalence, location, size and degree of dysplasia, and three family types (HNPCC, HCC, and TCR) with regard to age cancer risk in distal adenomas. The differences between the low cancer risk in proximal adenomas and a relatively higher the highest number of adenomas. In TCR there seems to be a increase in initiation rate as they had carcinoma is likely to be slower than in HNPCC. TCR families proximal adenomas and the progression from adenoma to initiation rate as well as an increased progression rate were also less of location (table 4). In HCC families, an increased initiation rate was suggested in HNPCC adenomas unrelated to size. HNPCC also HNPCC it appears that there is a rapid transformation from initiation and progression are known, and a fourth syndrome, familial adenomatosis polyposis, where an increased initiation rate is well documented for adenomas.

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.66 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 low 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.

**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>HNPCC</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HCC</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>TCR</td>
<td>+++</td>
<td>++ (distal adenomas)</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.

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.

**ACKNOWLEDGMENTS**

We are indebted to Mariamne 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.

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**REFERENCES**

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 Baldas et al (Gut 2000;47:628–31). Humoral screening of CD is coming closer to reality, and 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 the only—autoantigen for antiendomysial antibodies (EMA). This finding highlights the possibility of antigen specific testing and, depending on gluten intake, a considerable decrease in the natural killer (NK)-like subset of IEL (average 4% in controls vs 25% in coeliacs, with respect to total IEL). The increase in γδ IEL (average 4% in controls vs 25% in coeliacs, with respect to total IEL) is not per se diagnostic of CD as it has been observed, although to a lesser extent, in food allergy 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 95% 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, prior to the increase in lamina propria lymphocytes or architectural changes. Many recent reviews 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 phenotyping 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 performed 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 ESPG criteria can be followed. 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.

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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. N, normal values.

www.gutjnl.com
The changing scope of colorectal cancer

We read with great interest the commentary by Boland and Savides (Gut 2001;48:849–50) on our paper “Flexible sigmoidoscopy and the changing distribution of colorectal cancer: implications for screening” (Gut 2001;48:322–5). 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 linked to a true increase in the incidence of proximal cancers or to a reduction in the incidence of distal and rectal tumours owing to the widespread use of flexible sigmoidoscopy and the consequent removal of premalignant adenomas.

We recently carried out further analysis of data from the Northern Ireland Colorectal Cancer Registry for the years 1995–97. The results of this analysis are shown in table 1 together with our previously published data for the years 1976–78. All incidences were age standardised per 100 000 for each sex using the world standard population.

Table 1 Incidence of proximal, distal, and rectal colorectal cancers in the years indicated. All incidences were age standardised per 100 000 for each sex using the world standard population.

<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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1976–78</td>
<td>4.7</td>
<td>6.1</td>
<td>12.5</td>
</tr>
<tr>
<td>1995–97</td>
<td>9.5</td>
<td>8.4</td>
<td>12.2</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1976–78</td>
<td>4.7</td>
<td>5.8</td>
<td>6.0</td>
</tr>
<tr>
<td>1995–97</td>
<td>8.2</td>
<td>6.2</td>
<td>6.6</td>
</tr>
</tbody>
</table>

These values show that the age standardised incidence of colonic carcinoma has increased in both sexes over the period studied (proximal more than distal) while the incidence of rectal cancer has remained relatively constant. These data suggest that the changing pattern of distribution of colorectal cancer which we have observed is unlikely to 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 subites, with relative sparing of the distal colon and rectum due to either the protective effect of non-steroidal anti-inflammatory drugs or endoscopic polypectomy.

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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, cryptdins, so far recorded in mice). The lysozyme rich granules in Paneth cells appears to be one of the main sources of anti-microbial 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 defensin 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.3 Thirty five years ago, Azzopardi and Evans4 found mucin containing macrophages (denominated muciphages) in the colonic mucosa. Those cells were described as normal phagocytes in an otherwise normal mucosa. The mucoprotein present in their cytoplasm stained with a variety of mucous colors (alcian blue, aldehyde fuchsin, and mucicarmine). 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 or aggregated in the lamina propria mucosa 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 in those particular macrophages (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 mucins 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 mucosa and the underlying host (fig 1)—is noteworthy. That arrangement insinuates the possibility of an organised biological hinder (a “defensive barrier”) against a factor(s) entering the host through the rectal mucosa.

The fact that muciphages also contain lysozyme may open new vistas for those previously unattended cells. It is conceivable

Figure 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×].

References
7 Ciclitira PJ. ACA technical review on celiac sprue. Gastroenterology 2001;120:1526–40
that muciphages may be an important source of antimicrobial peptides in mucosae in protracted remission from earlier inflammatory episodes.

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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- disse a young investigator submitting an experimental and/or clinical research project in the fields of hepatobilary and pancreatic disorders. The prize, awarded by an international committee, will be personally presented to the winner during the congress “Progressi in Chirurgia Epato Bilio Pancreatica” which will be held in Napoli on June 20–22, 2002. Travel expenses will be refunded to the winner. Applications, in English, should be sent to the Organising Secretariat (G.P. Pubbliche Relazioni s.r.l., Via San Pasquale a Chiala 55, 80121 Napoli. Tel: +39 081 403837/ 411450; fax: +39 081 404036; email: g.p.congress@napoli.com) by 20 May 2002 and should include:

- Curriculum vitae of the applicant
- 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 hepatopancreatic 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, scientific excellence, and originality. Early exploratory projects, scientists not currently working in IBD, and/or interdisciplinary efforts are encouraged. Further information: Marciana Poland, Research Administrator, Broad Medical Research Program, 10900 Wilshire Blvd., 12th Floor, 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 c.V., congress Division, Leinenwebersstr. 5, PO Box 6529, D-79041 Freiburg, Germany. Tel: +49 761 15 14 39; fax: +49 761 15 14 359; 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 Dep-artment, Royal College of Physicians of Edinburgh, 9 Queen Street, Edinburgh EH2 1LQ, Tel: ++44 (0)131 225 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 7521; 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 Amsterdam, 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 Endotheraphy European Workshop: XXth Anniversary
This course will be held on 17–19 June 2002 in Brussels, Belgium. Further information: Nancy Beauprez, Gastroenterology Department, Erasme Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 (0)20 555 49 00; fax: +32 (0)20 555 4901; email: beauprez@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 information: Professor Jordi Bruix, EASL Liaison Bureau, c/o Kees 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: kmoores@rfc.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