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Increased colorectal cancer risk in first-degree relatives of patients with hyperplastic polyposis syndrome

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► An additional table is published online only. To view this file please visit the journal online (<http://gut.bmj.com>).

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ABSTRACT

Introduction Hyperplastic polyposis syndrome (HPS) is characterised by the presence of multiple colorectal hyperplastic polyps and is associated with an increased colorectal cancer (CRC) risk. For first-degree relatives of HPS patients (FDRs) this has not been adequately quantified. Reliable evidence concerning the magnitude of a possible excess risk is necessary to determine whether preventive measures, like screening colonoscopies, in FDRs are justified.

Aims and methods We analysed the incidence rate of CRC in FDRs and compared this with the general population through person-year analysis after adjustment for demographic characteristics. Population-based incidence data from the Eindhoven Cancer Registry during the period 1970–2006 were used to compare observed numbers of CRC cases in FDRs with expected numbers based on the incidence in the general population.

Results A total of 347 FDRs (41% male) from 57 pedigrees were included, contributing 11 053 person-years of follow-up. During the study period, a total of 27 CRC cases occurred among FDRs compared to five expected CRC cases ($p < 0.001$). The RR of CRC in FDRs compared to the general population was 5.4 (95% CI 3.7 to 7.8). Four FDRs satisfied the criteria for HPS. Based on the estimated HPS prevalence of 1:3000 in the general population the projected RR of HPS in FDRs was 39 (95% CI 13 to 121).

Conclusions FDRs of HPS patients have an increased risk for both CRC and HPS compared to the general population. Hence, as long as no genetic substrate has been identified, screening colonoscopies for FDRs seem justified but this needs to be prospectively evaluated.

INTRODUCTION

Hyperplastic polyposis syndrome (HPS) is a condition characterised by the presence of multiple hyperplastic polyps (HPs) spread throughout the colon and is associated with an increased colorectal cancer risk.^{1–5} Because of this increased risk of malignant progression, HPS patients undergo endoscopic surveillance with removal of polyps or surgical colonic resection. Although an increased risk of colorectal cancer (CRC) for these patients has been established, it is uncertain whether an increased risk of CRC and/or HPS for first-degree relatives (FDRs) exists and consequently whether preventive measures, like screening colonoscopies, should be performed in this group.

Significance of this study

What is already known about this subject?

- Patients with hyperplastic polyposis syndrome (HPS) have an increased risk of developing colorectal cancer (CRC)
- First-degree relatives (FDRs) of patients with HPS are also believed to have an increased risk of CRC
- It is, however, unknown what proportion of all FDRs is at risk of developing CRC
- Reliable evidence concerning the magnitude of this possible excess risk is necessary to adequately inform FDRs regarding their risk of CRC

What are the new findings?

- In this study, the CRC incidence rate in FDRs was compared with the general population through person-year analysis with adjustment for demographics
- During the study period, a total of 27 CRC cases occurred among 347 FDRs compared to five expected CRC cases ($p < 0.001$) resulting in a RR of 5.4 (95% CI 3.7 to 7.8)
- Four FDRs satisfied the criteria for HPS. Based on the estimated HPS prevalence in the general population the projected RR of HPS in FDRs was 39 (95% CI 13 to 121)

How might it impact on clinical practice in the foreseeable future?

- Based on these findings we conclude that FDRs have an increased risk for both CRC and HPS compared to the general population
- As long as no genetic substrate has been identified screening colonoscopies for FDRs seem justified

Although HPS was initially considered to be non-familial, previously published case series report that up to 50% of HPS patients have a FDR with CRC.^{2–6} In addition, the presence of HPS has been described in multiple family members.^{2–3, 7–9} Based on these reports, a yet unidentified underlying genetic defect seems to play a role in at least some HPS cases.

Concordantly, previous studies have shown that HPS is caused in a small proportion of patients by a germline mutation in the *MUTYH* gene resulting

in a phenotype of multiple conventional adenomas and serrated polyps.^{2–10} However, in the overall majority it is unclear what proportion of FDRs are at risk of developing CRC and/or HPS. Furthermore, the possible mode of inheritance is unknown. Families have been reported previously from which both an autosomal recessive and autosomal dominant inheritance could be considered.^{2–6,8,9}

Thus, to adequately inform FDRs regarding their risk of CRC and/or HPS, reliable evidence concerning the magnitude of this excess risk is necessary. The aim of this study was to estimate the incidence rate of CRC and HPS in FDRs of HPS patients and to compare this with the general population so as to determine whether preventive measures such as screening colonoscopies in this group are justified.

METHODS

Besides HPs, HPS patients often have multiple sessile serrated adenomas (SSAs), traditional serrated adenomas and conventional adenomas. HPs and SSAs have been shown to be histologically very similar and difficult to differentiate microscopically with only moderate concordance.^{11–14} For this reason HPS was defined as at least five histologically diagnosed HPs and/or SSAs proximal to the sigmoid colon, of which two are greater than 10 mm in diameter, or more than 20 HPs and/or SSAs distributed throughout the colon.¹⁵ This is a variation of the original HPS criteria defined by the WHO which only involves HPs (>30).¹ HPS patients (probands) from four medical centres in The Netherlands were included when satisfying the above mentioned diagnostic criteria for HPS. Of these patients, family history data were obtained through face-to-face and telephone interviews or by examining data from the Departments of Clinical Genetics. Patients with a known germline *APC* mutation or bi-allelic *MUTYH* mutation were excluded from the study.

Risk assessment for CRC was performed by including person-years at risk for CRC from 1 January 1970 until 1 January 2009 (censory date). FDRs were considered at risk from birth until date of CRC diagnosis, date of death or the censory date. It was presumed that from the time the proband developed CRC FDRs would have a higher chance of receiving endoscopic screening for CRC which could cause a bias when comparing with the general population. For this reason, person-years at risk also ended at the date of CRC diagnosis in the proband if applicable.

Person-years at risk were stratified according to 5-year age group, gender and calendar year using SAS software, version 9.1. Similarly stratified population-based data from the Eindhoven Cancer Registry were used to compare the incidence of CRC in FDRs with that of the general population.¹⁶ The expected CRC incidence in FDRs was calculated by applying the age-, gender- and calendar-specific incidence rates of the general population to the composition and follow-up years of the FDR cohort. The observed versus expected number of CRC cases were formally compared by calculating a RR and 95% CI. This RR is calculated by taking the ratio of observed to expected number of cases and its CI by assuming a Poisson distribution of cases. Two-sided *p* values <0.05 were considered statistically significant.

RESULTS

First-degree relatives

In this study a total of 347 FDRs (142 male) from 57 pedigrees were included, contributing 11 053 person-years of follow-up (figure 1). The median age at end of follow-up was 60 years (IQR: 44–71). These FDRs consisted of 165 (48%) siblings,

Figure 1 Flow diagram for the participants in this study.

100 (35%) parents and 82 (17%) children. In total, 27 FDRs, consisting of 14 parents, 12 siblings and one child were excluded because (1) they died before 1 January 1970 (*n*=17) or (2) information regarding that individual was unknown (*n*=10).

Colorectal cancer

During the study period, a total of 27 (8%) CRC cases occurred among FDRs. The median age of CRC occurrence was 62 years (IQR: 57–78) and 15 (56%) were of the male gender (table 1). The RR of CRC in FDRs compared to the general population was 5.4 (95% CI 3.7 to 7.8). One additional CRC case occurred outside the study period (before 1970) and was therefore not included. There were no excluded CRC cases in FDRs which developed after CRC diagnosis in the proband. Of the 27 FDRs with CRC, four probands developed CRC at a later stage. In total, 16/57 (28%) probands were diagnosed with CRC during the study period.

The difference in CRC risk between men and women within the FDR group was not statistically different (RR: 1.9, 95% CI 0.9 to 4.1, Pearson χ^2 test: *p*=0.089). Also when comparing this between siblings (brothers and sisters) and non-siblings (parents and children) within the FDR group, no significant difference was seen (RR: 1.0, 95% CI 0.4 to 2.5, Pearson χ^2 test: *p*=0.96). Other malignancies recorded in the study period included breast cancer (*n*=10), gastric cancer (*n*=2), ovarian cancer (*n*=2) and others (*n*=12).

Polyps

Conventional white-light colonoscopies were performed in 65/347 (19%) of FDRs. Reasons for endoscopy were not recorded. In this group, 35/65 (54%) individuals had colorectal lesions from whom 24 the histology was known. In seven FDRs multiple histologically confirmed HPs (≥ 5) were identified at a median age of 58 years (range: 50–75) of which six had HPs proximal to the rectosigmoid colon (supplemental table). Four of these FDRs from four different pedigrees satisfied the criteria for HPS

Table 1 Risk analysis of colorectal cancer (CRC) in first-degree relatives of patients with hyperplastic polyposis syndrome compared with population-based data from the Eindhoven Cancer Registry

Group	Person-years	Observed CRCs	Expected CRCs	RR (observed/expected)	95% CI
Males	4736	15	2.3	6.5	3.9 to 10.8
Females	6317	12	2.6	4.6	2.6 to 8.0
Combined	11053	27	5.0	5.4	3.7 to 7.8

(WHO). Based on the estimated HPS prevalence of 1:3000 in the general population,¹⁷ the projected RR of HPS in FDRs would be 39 (95% CI 13 to 121). In FDRs with CRC, 3/27 (11%) of cases had multiple HPs (two had HPS) compared to 4/320 (1%) non-CRC cases (Fisher's exact test: $p=0.012$). In three other FDRs, multiple polyps were detected of which the histology was unknown. The difference in risk of having multiple HPs between men and women within the FDR group was not statistically different (RR: 1.6, 95% CI 0.4 to 7.4, Fisher's exact test: $p=0.71$). Also when comparing this between siblings and non-siblings within the FDR group no significant difference was seen (RR: 3.1, 95% CI 0.6 to 16.1, Fisher's exact test: $p=0.252$).

DISCUSSION

This retrospective study describes the largest series of FDRs of HPS patients in which the presence of CRC and polyps was assessed and is, to our knowledge, the first to quantify the RR of CRC and/or HPS in FDRs. Our results showed that FDRs of HPS patients have an increased risk for both CRC and HPS compared to the general population warranting screening colonoscopies for this group.

A limitation of this study is that the data were collected in a retrospective manner and based on medical charts and self-reported information about family history. An important question therefore is whether our approach could have led to an over- or under-estimation of the incidence of CRC in FDRs. An over-estimation of CRC risk may cause stress,¹⁸ unneeded referrals for genetic counselling and possible unnecessary endoscopic procedures or surgery.^{19–20} However, previous studies evaluating the accuracy of patient reporting of familial CRC by comparing patient family history reports with cancer registries, showed that the specificity (ie, the proportion of CRC negatives which are correctly identified as not having CRC) was 92–99%. These findings imply that patients seldom incorrectly report CRC-negative FDRs as having CRC, which would lead to an over-estimation of CRC incidence in FDRs. Moreover, the sensitivity (ie, the proportion of CRC positives which are correctly identified as having CRC) was 53–86%. In other words, patients tend to under-report the incidence of CRC in FDRs, leading to under-estimation of CRC incidence in FDRs.^{21–23} Furthermore, the majority of probands included in this study were symptomatic patients and thus represent a selected patient population. These patients may have a more aggressive form of HPS and also a higher risk of (familial) CRC than other unidentified asymptomatic HPS cases. Therefore, our findings concerning their FDRs can not by default be extrapolated to all (including unidentified) HPS cases. However, considering that the aim of our study was to analyse the risk of CRC and polyps in FDRs of all identified patients with HPS, we believe our findings are relevant for the management of patients with HPS and their relatives in a clinical setting. Finally, in this study, 19% of FDRs received an endoscopy during follow-up for which the reason was unknown. It was unknown at what rate endoscopies were performed in the general population during the study period. However, considering that FDR follow-up time ended at the date of CRC diagnosis (if applicable) in the proband, we believe that the amount of screening endoscopies performed for familial CRC in FDRs will be comparable to the general population. Similarly, screening endoscopies for HPS in FDRs have only recently been proposed by some authorities and is to this date not standard practice of care.^{2–6, 24} For this reason it is also unlikely that FDRs in this study received more screening endoscopies for HPS than the general population.

In probands (ie, patients with HPS) a higher CRC incidence was observed (16/57: 28%) during the study period compared to FDRs (27/347: 8%). This finding was expected considering that not all FDRs also had HPS. However, of the four FDRs with HPS, two (50%) had CRC suggesting that the presence of multiple serrated polyps is associated with CRC. These findings are concordant with a previous large HPS cohort study which showed that the number of serrated polyps was positively correlated with the risk of CRC.¹⁵

In a previous flexible sigmoidoscopy screening study performed in a large cohort of asymptomatic individuals ($n=40\,673$), the true prevalence of HPS was estimated to be 1:3000 after subsequent colonoscopies.¹⁷ Colorectal polyps, particularly HPs, do not necessarily cause symptoms and thus could be left undiagnosed in individuals if an endoscopy is not performed. In this study only 19% of FDRs received an endoscopy. Consequently, although our study concluded that FDRs have an increased risk of having HPS, an under-estimation of the true prevalence of HPS in FDRs seems likely. In addition, of the FDRs with colorectal polyps the histology was unknown in 11/35 cases. Of these individuals five were reported to have multiple polyps of unknown histology. It seems possible that these individuals could potentially have HPS too but this could not be verified.

Alternatively, because the prevalence of HPS in the general population was based on a previous screening sigmoidoscopy study, a degree of uncertainty exists regarding this estimation. This uncertainty decreases the validity of our projected RR of HPS in FDRs.

With regard to the mode of inheritance, our study did not show a significant difference in CRC incidence between siblings and non-siblings (RR: 1.0, 95% CI 0.4 to 2.5, Pearson χ^2 test: $p=0.96$). These findings make it difficult to postulate a preference for either a vertical or a horizontal transmission. Also concerning polyp incidence in FDRs, although 3/4 (75%) of FDRs with HPS were siblings, these numbers are too few to make any conclusions about the mode of inheritance. These results are in concordance with previously reported FDRs with HPS (supplemental table: six siblings vs seven non-siblings). Alternatively, the presence of FDRs with an intermediate phenotype of <10 HPs, suggest that a co-dominant mode of inheritance, involvement of several low penetrance genes, high risk genes with reduced penetrance or even environmental factors may play a role.

Regarding the management of FDRs, this study suggests that as long as no underlying genetic cause has been identified, screening colonoscopies are justified for this group. In addition, this study showed that of the 27 FDRs with CRC, only four probands had CRC, implying that screening colonoscopies should be performed in all FDRs, independent of CRC presence in the proband. However, future large prospective screening studies in FDRs are required to further evaluate the incidence of CRC and HPS and the optimal screening programme in this group. Until these future data are acquired, we advise a provisional screening programme from the age of 35 years or 5 years younger than the lowest incidence age of HPS reported in the family. Subsequent surveillance colonoscopies could then be performed at 6 year intervals with shorter intervals when polyps are detected.

Competing interests None.

Ethics approval This study was conducted in accordance with the research code of our institutional medical ethical committee on human experimentation, as well as in agreement with the Helsinki Declaration of 1975, as revised in 1983.

Provenance and peer review Not commissioned; externally peer reviewed.

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Editor's quiz: GI snapshot

Diarrhoea and weight loss in an immunosuppressed patient

CLINICAL PRESENTATION

A 74-year-old Caucasian female presented with a 12 month history of non-bloody, culture-negative diarrhoea associated with weight loss of 10 kg. She denied any extragastrointestinal manifestations. She had previously undergone orthotopic liver transplantation for primary biliary cirrhosis 12 years ago. Her immunosuppression was mycophenolate mofetil 500 mg twice daily for the past 2 years. She had previously been on ciclosporin but this was discontinued due to renal impairment.

Baseline bloods revealed: haemoglobin 9.6 g/dl (mean corpuscular volume (MCV) 85 fl), C-reactive protein 76 mg/l and normal renal and liver biochemistry. She was euthyroid, and coeliac serology was negative. Colonoscopy demonstrated moderate, patchy mucosal inflammation predominantly affecting the proximal colon (figure 1). Multiple biopsies were obtained.

QUESTIONS

What is the diagnosis?

What is the best management?

See page 1302 for the answers

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Figure 1 Ascending colon.

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