Pergamon

European Journal of Cancer Vol. 31A, Nos. 7/8, pp. 1145–1148, 1995

0959-8049/95 $9.50+0.00

0959-8049(95)00249-9

Hereditary Nonpolyposis Colorectal Cancer: Results of Long-term Surveillance in 50 Families

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A surveillance programme comprising either colonoscopy or sigmoidoscopy plus barium enema every 2–3 years was instituted in 50 hereditary nonpolyposis colorectal cancer (HNPCC) families. The families included 238 patients with colorectal cancer (CRC) (mean age at diagnosis: 43.7 years; range: 16–86 years). These patients had 597 first-degree relatives of whom 493 could be traced and 388 (79%) accepted the invitation for screening. The control group were relatives (index patients) with symptomatic CRC. The average follow-up duration was 5 years (1–20 years). Screening led to the detection of adenomas in 33 patients and CRC in 11 patients. Pathological examination revealed 1 Dukes' A, 7 Dukes' B and 3 Dukes' C cancers. In contrast, among the control group 47% had advanced CRC (Dukes' C or distant metastases). The 5-year survival of the screen-detected cases was 87% versus 63% in the control group. Of the 11 CRC cases in the screening group, 4 were detected within 1–4 years after a negative colonic examination. A large proportion of the polyps found in the screening and control groups showed a villous growth pattern and/or a high degree of dysplasia. We conclude that periodic examination of HNPCC families allows the detection of cancer at an earlier stage than in patients not under surveillance. Because of the possibly more aggressive nature of polyps associated with HNPCC, we recommend a screening interval of 1–2 years.

Key words: hereditary non-polyposis colorectal cancer, Lynch syndrome, surveillance, adenomas
Eur J Cancer, Vol. 31A, Nos 7/8, pp. 1145–1148, 1995

INTRODUCTION

HEREDITARY nonpolyposis colorectal cancer (HNPCC) (Lynch syndrome) is an autosomal dominantly inherited disease associated with a marked increase in cancer susceptibility, especially cancer of the colorectum and endometrium [1, 2]. The disease is due to mutations in one of the following so-called DNA mismatch repair genes: *hMSH2, hMLH1, hPMS1, hPMS2* [3–7]. Colorectal cancer (CRC) in HNPCC differs from sporadic CRC by an early age of onset (mean age: 44 years), a proclivity (50–60%) for the proximal colon, and an excess of synchronous and metachronous CRCs (25%). A variety of extracolonic tumours may be encountered in HNPCC, including cancers of the endometrium, stomach, small bowel, urinary tract, biliary system and ovary [8–10]. HNPCC is one of the most common cancer predisposition syndromes affecting as many as 1 in 400 individuals in the Western world. Identification of HNPCC families is extremely important, because periodic examination of high-risk family members may prevent development of disease and death from cancer. The recent cloning of genes responsible for HNPCC raises the possibility of identification of gene carriers. These new developments will increase the demand for DNA testing and, with that, the demand for effective surveillance protocols. In The Netherlands, one of the largest series of HNPCC families is participating in a long-term surveillance programme. In the present report we describe the results of this programme.

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PATIENTS AND METHODS

In 1985 a registry of families with hereditary cancer (The Netherlands Foundation for the Detection of Hereditary Tumours) was set up in The Netherlands. One of the most important aims of the registry is to promote surveillance in families with hereditary cancer and also to guarantee the continuity of such a programme. The approach of the registry has been described elsewhere [11]. As of 1 June 1994, genealogical studies had been performed in up to 100 families with familial clustering of CRC. These families have been referred to the registry from all parts of The Netherlands. The genealogical studies have been performed by genetic field workers in close

cooperation with clinical and genetic centres. Medical and histological data have been collected to verify the family history. All first-degree relatives from families suspected of HNPCC were informed through their physician or general practitioner or by the clinical geneticist about the risk of developing CRC and were advised to participate in the surveillance programme.

The protocol recommended in The Netherlands includes colonoscopy or sigmoidoscopy in combination with a barium enema. The interval between examinations is 2–3 years. The programme is instituted between the ages of 20–25 years. To guarantee the continuity of the screening programme the registry sends, at regular times, reminders to the physicians, and the results of the examination are sent to the registry. The histopathological stages of screen-detected cases of CRC, including the 5-year survival rate, were compared with a control group comprising relatives with symptomatic CRC who were not under surveillance (index patients).

RESULTS

A total of 50 families met the "Amsterdam criteria" for HNPCC [12]. In these families, there were 238 patients with CRC, 47 with endometrial cancer, and 49 with another cancer associated with HNPCC. The mean age at diagnosis of symptomatic CRC was 43.7 years (range: 16–86 years). The 50 families included a total of 597 high-risk relatives, of whom 493 could be traced, and 388 accepted the invitation to participate in the suggested screening regimen. The mean follow-up duration was 5 years (range: 1–20 years). There was one patient with a severe complication due to the screening examinations, i.e., a cardiac arrest during colonoscopy (with a good response to resuscitation).

33 patients (8.5%) were found to have one or more colorectal adenomas and 11 (2.8%) CRCs. The histopathological stages of CRC including the 5-year survival of screen-detected cases compared with the control group (patients with symptomatic CRC), are shown in Table 1. The CRCs occurring in the controls showed a more advanced histopathological stage than the CRCs detected in the screening group. Of the 11 CRCs, 5 were detected after a negative screening examination 11 months to 3.5 years earlier. The relevant findings of these patients are summarised in Table 2. One patient was not investigated appropriately (i.e. by sigmoidoscopy instead of colonoscopy).

Besides the adenomas detected in 33 patients of the screening group, adenomas were found in 26 patients with CRC. The characteristics of these adenomas are shown in Table 3.

Table 1. Pathological stages of colorectal cancer, mortality and survival of screen-detected patients versus controls (index patients with symptomatic colorectal cancer)

	Control group	Screening group
No. of colorectal cancers	238	11
Mean age at diagnosis (year)	43.7	43.1
Pathological stage		
Dukes' A	10	1
Dukes' B	75	7
Dukes' C	51	3
Distant metastasis	25	0
Unknown	77	0
Mortality due to CRC	108 (45%)	1 (9%)
5-year survival rate	63%	87%

DISCUSSION

Surveillance targeted at high-risk groups such as HNPCC families is more attractive for several reasons. The compliance, which is of fundamental importance for the success of a screening study, will be greater if an individual perceives himself or herself to be at risk. Moreover, the detection rate of disease will be much higher, and a more invasive test may be justifiable.

The compliance in our families was comparable (approximately 80%) to that of follow-up studies of patients after polypectomy (National Polyp Study) [13] but was higher than that (63%) reported in a recent Finnish study on surveillance in HNPCC [14]. The excellent compliance in our study may be due to the personal approach applied in the genealogical studies during which genetic field workers visit the families at home. It is expected that the compliance will further increase in the near future after identification of gene carriers within a family by DNA analysis.

Several earlier short-term studies performed in Finland [15], The Netherlands [16], the U.S.A. [17], and New Zealand [18] have shown that the yield of surveillance of such families is indeed high. In these studies the reported detection rates were 1.5–3.7% for CRC and 7–10% for colorectal adenomas.

In the present study, we found also a high detection rate for colorectal neoplasms, and the carcinomas detected in the surveillance programme showed an earlier histopathological stage than those occurring in the control group. Moreover, we found a better 5-year survival rate in the screen-detected cases versus the control group.

A serious problem in studies evaluating the benefit of surveillance of HNPCC is that randomised controlled trials are not ethically justified, because of the extremely high risk for individuals concerned. The next best way is the approach used in a recent study from Finland [14]. In this study the incidence of CRC and the mortality during a 10-year period were compared between the screened group and a control group consisting of family members who refused participation or could not be traced. Finland is an ideal country for such a study because it has a complete cancer registry, which makes it possible to evaluate the occurrence of CRC and mortality in the control group. The results indicated that the screening programme instituted among 22 HNPCC families led to a 62% reduction of CRCs in the screening group compared with the control group. Moreover, there was no CRC mortality among the group screened.

In view of the results of the Finnish, the present, and preceding studies the appropriate question to ask about surveillance of HNPCC families is not "why surveillance" but "how to screen", i.e., "when should screening start and how often should it be done?" Recommendations on age limits for screening given so far have been based on the distribution of ages at diagnosis of CRC in a large series of patients from HNPCC families [19]. There is general agreement that surveillance should be initiated between 20 and 25 years of age [20]. When data on age at diagnosis of CRC in a large series of proven gene carriers become available, the risk of developing CRC can be calculated more accurately which may influence the appropriate age at which screening should be started. Another important issue is the appropriate interval between examinations. It seems likely that in HNPCC CRC also arises from pre-existing adenomatous polyps. In sporadic CRC, the evolution of a mucosal cell from normal through adenomatous to cancerous probably requires approximately 10 years. Based on the National Polyp Study in unselected series of patients with polyps, the likelihood of

Table 2. Patients with colorectal cancer detected after a negative screening examination

Patient number	Sex	Age at diagnosis	Location tumour	Stage (Dukes)	Previous negative examination	Interval
1	M	46	R	C	Colonoscopy	2 years, 7 months
2	F	46	R	B	Colonoscopy	2 years
3	M	66	R	B	Sigmoidoscopy	11 months
4*	F	41	R	C	Barium enema	2 years, 6 months
5	M	40	R	B	Colonoscopy	3 years, 6 months

R, rectum. *Died from colorectal cancer.

Table 3. Characteristics of the adenomas detected in the HNPCC families

No. of patients with adenomas	59
Total number of positive screening examinations	86
No. of patients with recurrent adenomas	18
Location:	
right colon	24 (28%)
left colon + rectum	50 (58%)
right + left colon	8 (9%)
unknown	4 (5%)
Type of histology:	
tubular	26 (30%)
tubulovillous	13 (15%)
villous	9 (10%)
unknown	38 (44%)
Dysplasia:	
low degree	42 (49%)
high degree	11 (13%)
unknown	33 (38%)

significant pathology (large polyp >1 cm, villous adenomas or cancer) appearing in a 3-year interval is small [21]. The risk is probably much lower in patients who have no polyps on a baseline sigmoidoscopy examination. Therefore, an interval for endoscopic screening of 5 years is recommended in unselected patients in follow-up programmes after polypectomy.

In the present study, 4 patients developed CRC within an interval of 2–4 years after a negative (colonoscopic) screening examination. Also in the Finnish series, 2 "interval" cancers were detected within 3 years. Possible explanations for this unexpected finding could be that polyps were missed during the preceding endoscopic examination or that the polyps in HNPCC need less time to become malignant. Studies by Mecklin and colleagues [22] and Jass and associates [23] reported a high incidence of adenomas in HNPCC with a villous growth pattern and a high degree of dysplasia. Also a large proportion of the polyps detected in the present study showed characteristics known to increase the risk of malignant conversion (dysplasia, villosity). On the basis of our results, we recommend an interval of 1–2 years between examinations in proven gene carriers. The preferred screening procedure is colonoscopy, because polyps can be removed at the same investigation. Because 60% of CRC in HNPCC is located in the proximal colon and all interval cancers in our series were located in this part of the colon, we would like to stress that a barium enema should be performed when the colon is not completely visualised during endoscopy.

The predominantly distal location of adenomas in our series, which is similar to that of sporadic adenomas in the general population, does not correspond with the anatomical distribution of carcinomas in HNPCC. An explanation may be that the HNPCC gene accelerates the malignant conversion of very small adenomas which are reported to be more evenly distributed along the large intestine [24]. This explanation is also in agreement with the finding of Jass that the size of adenomas in HNPCC does not differ significantly from that of adenomas in autopsy series [25]. A prophylactic subtotal colectomy may be considered in gene carriers with recurrent polyps with a high degree of dysplasia or a villous growth pattern. Because the remaining rectum is still at risk, follow-up is indicated after surgery. Prophylactic colorectal surgery of gene carriers without any abnormalities in the colorectum should probably be avoided, because of the morbidity associated with this operation and the possibility that the individuals will never develop CRC (10–20%).

Surveillance for CRC of HNPCC families does not solve all problems, because these families are also at risk for a spectrum of other tumours [8–10]. The choice of screening procedures should be based on the tumours that occur in a specific family and on the accessibility of these tumours to screening. It is unrealistic to advocate screening for the detection of the less commonly occurring malignancies. The added burden could adversely influence compliance for CRC screening. However, in HNPCC families, it is important that minor physical complaints, particularly when they involve the high-risk organs, be taken seriously by physicians.

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