

ELECTRONIC LETTER

Cancer surveillance is often inadequate in people at high risk for colorectal cancer

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J Med Genet 2003;40:e54(<http://www.jmedgenet.com/cgi/content/full/40/5/e54>)

Hereditary colorectal cancer syndromes account for about 6% of cases of colorectal cancer. People with gene mutations associated with hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) have a lifetime risk of colorectal cancer of 80%–100% and should undergo more frequent colorectal screening, as well as additional surveillance for associated extracolonic tumours. Despite the proven benefit of cancer screening and the recent publication of guidelines for genetic testing in hereditary colorectal cancer,¹ there is little information about the prevalence of appropriate cancer surveillance among people at risk for HNPCC or FAP.

The HNPCC syndrome is inherited as an autosomal dominant trait in which affected people have a greater than 80% risk of developing colorectal cancer, which is often right sided and appears at an early age (4th and 5th decades).² Although mutations in DNA mismatch repair genes (*hMLH1* and *hMSH2*) have been identified in 30%–64% of these families,³ genetic testing is not informative in many cases and most people are diagnosed with HNPCC on the basis of clinical criteria and family cancer history. Colonoscopy with polypectomy at intervals of one to three years has been shown to be effective in reducing the incidence of colorectal cancer among people at risk of HNPCC.⁴ Because of accelerated tumour growth associated with HNPCC, newer recommendations advocate colonoscopy every one to two years, beginning at age 20–25.⁵ As HNPCC confers a risk of endometrial cancer of 40%–60%,⁶ expert panels currently recommend annual transvaginal ultrasound or endometrial aspirate for women at risk for HNPCC beginning at age 25–35.^{3,7}

The FAP syndrome is also inherited as an autosomal dominant trait, and is characterised by the development of hundreds to thousands of adenomatous polyps in the colon. The risk of colorectal cancer is 100% if the affected person does not undergo colectomy. Although polyps usually appear in the second or third decade, attenuated phenotypes have been described in which people develop polyps later in life.⁸ Mutations in the *APC* gene are identifiable in most people manifesting the characteristic polyposis phenotype; however, commercially available tests fail to show abnormalities in up to 20% of affected families.^{3,9} In the absence of definitive genetic testing, it is recommended that all people with a family history of FAP undergo frequent colorectal surveillance with yearly sigmoidoscopy starting at 12 years of age. Screening intervals may be lengthened if no polyps are detected; however, surveillance should be continued given the possibility of late onset disease or attenuated phenotypes.^{3,10} People who are found to have polyps should undergo complete surgical resection of the colon followed by continued lower tract surveillance based on the type of colectomy. As affected people are at risk of adenocarcinoma of the ampulla and duodenum and may develop polyps in the upper gastrointestinal tract, they should also undergo periodic surveillance with upper endoscopy (EGD) with ampullary biopsy every six months to four years, depending on the number of polyps.^{3,10}

The published recommendations for cancer screening in HNPCC and FAP are summarised in table 1. The objective of

Key points

- HNPCC and FAP convey a lifetime risk of colorectal cancer of 80%–100% and people at risk should undergo frequent cancer surveillance which is different from the screening indicated for people at average risk.
- Examination of cancer screening practices of people at risk of hereditary colorectal cancer syndromes showed that although 95% had undergone colorectal screening, only 64% had screening which was appropriate for their high risk. People who did not have an affected phenotype were less likely to undergo appropriate colorectal cancer surveillance than those who had developed clinical manifestations of neoplasia ($p < 0.003$).
- Surveillance for extracolonic cancers associated with hereditary colorectal cancer is often overlooked.

the present study was to determine whether people at highest risk for colorectal cancer because of a personal or family history of HNPCC or FAP undergo screening for cancer in accordance with the guidelines recommended for these syndromes.

METHODS

Subjects were identified through their visits to a cancer genetics clinic at a specialised cancer centre. Potential study participants had referred themselves or been referred by their physicians for genetic evaluation because of a family history of colorectal cancer which might indicate a hereditary cancer syndrome or because of a polyposis phenotype in themselves or a first degree relative. People with a personal or family history fulfilling clinical criteria for HNPCC or FAP interested in undergoing genetic testing were invited to participate in a research protocol to test for mutations in genes associated with HNPCC (mismatch repair genes *hMSH2* and *hMLH1*) or FAP (*APC* gene).

Study participants completed questionnaires eliciting information about demographics, general health and health behaviours, cancer screening practices, knowledge of heredity and cancer genetics, and attitudes towards genetic testing. Subjects were asked specifically whether they had ever undergone sigmoidoscopy, colonoscopy, or upper endoscopy and at what frequency. Women were asked whether they had ever undergone endometrial biopsy or pelvic ultrasound and at what frequency. Options for frequency of screening procedures were provided in a multiple choice format: once a year, once every 2–3 years, every 5 years, less often than every 5 years, or only if there is a problem. These choices of colorectal

Abbreviations: HNPCC, hereditary non-polyposis colorectal cancer; FAP, familial adenomatous polyposis

Table 1 Cancer screening recommendations for those with a family history suggestive of a hereditary colorectal cancer syndrome

Syndrome	Cancer surveillance	Screening recommendations	Considered "appropriate" surveillance (for the purpose of this study)
HNPCC	Colorectal	Colonoscopy every 1–2 years beginning at age 25	Colonoscopy every 1–3 years beginning at age 25
	Endometrial (women only)	Transvaginal ultrasound ± endometrial biopsy every 1 year beginning at age 25–35	Endometrial ultrasound or biopsy every year beginning at age 35
FAP	Colorectal	Flexible sigmoidoscopy* every 1 year beginning at age 12	Flexible sigmoidoscopy or colonoscopy every 1–3 years
People without polyps		Flexible sigmoidoscopy* Every 1 years, ages 12–25 Every 2 years, ages 26–35 Every 3 years, ages 36–50 After age 50 resume "average risk" screening	
People with polyps	Upper tract	Upper endoscopy with ampullary biopsy every 6 months to 4 years depending on polyp burden	EGD every 1–5 years
	Colorectal	Surgical colectomy with continued upper and lower tract surveillance	
Subtotal colectomy or total colectomy with ileorectal anastomosis	Rectal remnant	Flexible sigmoidoscopy every 6 months–1 year with polypectomies as needed	Flexible sigmoidoscopy every 1 year
Total colectomy with ileoanal anastomosis	Pouch	Endoscopic surveillance of pouch every 3–5 years (increase frequency if polyps are found)	Flexible sigmoidoscopy every 3–5 years

*If polyps are found, assessment of indications for colectomy. If genetic testing is performed and APC gene mutation (–), flexible sigmoidoscopy at age 25.^{3,7,10}

screening intervals were chosen to distinguish those who underwent screening at least annually (recommended for FAP) or every 1–3 years (which was recommended for HNPCC at the time the study was initiated⁷) from those who underwent screening at less frequent intervals considered inadequate for high risk syndromes. This study was approved by the Office for Protection of Research Subjects of the Dana-Farber/Harvard Cancer Centre.

Self reports of surveillance practices were classified as appropriate if they were consistent with the published recommendations for cancer surveillance in people with personal or family history of HNPCC⁷ or FAP^{3, 10} (table 1). Subjects who did not report having had the recommended tests, or had undergone the tests less often than is recommended by published guidelines were classified as having had inappropriate screening. Proportions of people undergoing appropriate versus inappropriate cancer screening were compared with Fisher's exact test.

RESULTS

Table 2 shows the characteristics of the study participants. A total of 44 subjects from 26 families were enrolled from a possible 49 people who underwent testing during the study period. Twenty-six people met published clinical criteria for HNPCC (Amsterdam I and II=16, modified Amsterdam=4, Bethesda 1–3=6) and 18 had a personal or family history of FAP. Subjects lived in the north eastern United States with ages ranging from 17 to 68 (mean age 40). Women comprised 64% of the cohort. Forty-three of 44 subjects (98%) reported having medical insurance. Forty-one subjects (93%) reported having visited their primary care doctor at least once in the preceding 12 months and 27 (61%) had seen a gastroenterologist in the past year. Eleven subjects (25%) had a previous diagnosis of colorectal cancer.

Overall, 40 of 44 (91%) subjects reported having at least one endoscopic screening test for colorectal cancer (flexible sigmoidoscopy or colonoscopy). However, only 27 of 42 (64%)

Table 2 Characteristics of study participants

	HNPCC	FAP	Total
Subjects	26	18	44
Families	14	12	26
Women (No (%))	16 (62)	12 (63)	28 (64)
Age (median (range)) y	41 (17–68)	35 (17–53)	40 (17–68)
Phenotype (No (%)):			
Affected*	7 (27)	12 (67)	19 (43)
Unaffected	19 (73)	6 (33)	25 (57)
Personal history of colorectal cancer (No (%))	7 (27)	4 (21)	11 (25)
History of colectomy (No (%))	6 (23)	12 (27)	18 (41)
Total	1	4	5
Subtotal	2	7	9
Partial	3	1	4
Visited doctor in past 12 months (No (%)):			
Primary care	24 (92)	17 (94)	41 (93)
Gastroenterologist	15 (58)	12 (67)	27 (61)
Oncologist	9 (35)	7 (39)	16 (36)
Gynaecologist (women only)	10 (63)	7 (58)	17 (61)

*Affected corresponds to history of colon cancer for HNPCC, or history of multiple colonic adenomas for FAP.

Table 3 Colorectal cancer screening in HNPCC and FAP by phenotype of neoplasia

Subjects	Appropriate colorectal screening (all) (No (%))	Appropriate colorectal screening among (No (%))		
		Affected‡	Unaffected	p value*
Total (n=42†)	27/42 (64)	17/19 (89)	10/23 (43)	0.0003
HNPCC (n=24)	14/24 (58)	6/7 (86)	8/17 (47)	0.17
FAP (n=18)	13/18 (72)	11/12 (92)	2/6 (33)	0.02

*p value comparing affected and unaffected is two tailed from Fisher's exact test; †two of 26 people at risk for HNPCC were not considered eligible for colorectal cancer surveillance because of age <20; ‡affected corresponds to history of colon cancer for HNPCC, or history of multiple colonic adenomas for FAP.

people eligible for colorectal cancer screening had colorectal surveillance appropriate for their hereditary colorectal cancer syndrome. When examining surveillance by syndrome, 14 of 24 (58%) subjects at risk for HNPCC and 13 of 18 (72%) of those with a personal or family history of FAP reported colorectal cancer screening practices which were in accordance with the recommendations for their respective syndrome.

HNPCC

Colorectal surveillance

Twenty-six subjects representing 14 families had a personal or family history fulfilling clinical criteria of HNPCC. Two subjects were under 20 years of age, and were not considered eligible for colorectal cancer screening. Of the 24 people who were eligible for screening, 22 (92%) reported having undergone colorectal cancer screening at least once. However, only 14 (58%) subjects had appropriate colorectal cancer surveillance (defined as endoscopic examination of the entire colon every one to three years). Ten (42%) reported colorectal screening which was inappropriate for HNPCC. Two of these patients had had no colorectal cancer screening; another two had undergone screening with flexible sigmoidoscopy rather than colonoscopy; and six had surveillance at intervals longer than every three years. Six of seven (86%) subjects who had a previous diagnosis of colorectal cancer reported having appropriate colorectal cancer surveillance since their diagnosis of cancer. By contrast, only eight of 17 (47%) people without a diagnosis of cancer had undergone appropriate colorectal surveillance. Although 15 of 26 subjects at risk of HNPCC reported seeing a gastroenterologist in the past year, only six of these 15 people (40%) had had appropriate colorectal cancer screening.

Endometrial surveillance

Of the 16 women with a personal or family history of HNPCC, three were younger than 35 years of age and one other subject had previously undergone a hysterectomy, leaving 12 women eligible for HNPCC associated endometrial cancer screening. Only three of 12 (25%) women reported undergoing appropriate endometrial surveillance with either yearly ultrasound or yearly endometrial biopsy. Two of the women who had not had screening had a first degree relative with endometrial cancer. Of the 10 subjects who had seen a gynaecologist in the preceding year, five (50%) had had inadequate endometrial cancer screening.

FAP

Colorectal surveillance

Eighteen people representing 12 families had a personal or family history of FAP. All 18 subjects (100%) reported undergoing at least one endoscopic procedure for colorectal surveillance. Overall, 13 of 18 (72%) subjects had appropriate colorectal surveillance based on their clinical status.

Twelve of 18 (63%) subjects were known to be affected with the FAP syndrome (affected phenotype), while six of 18 (33%) subjects in the FAP cohort did not have a personal history of polyps (unaffected phenotype). All of the 12 affected people

had undergone or were scheduled to undergo colectomy. Eleven of 12 affected people (92% of affected) reported appropriate colorectal surveillance based on the presence or absence of the rectal remnant. By contrast, of the people without a history of polyps (unaffected phenotype), only two of six (33%) reported continuing lower endoscopy at the one to three year interval recommended for people at risk of developing FAP. Compared with people with an affected phenotype, subjects who were presumed to be unaffected were significantly less likely to have had appropriate colorectal surveillance ($p=0.02$).

Upper tract surveillance

Ten of 12 (83%) people known to be affected with FAP had had upper endoscopy at least once; however, it was not specified whether the procedure had been performed with a side viewing endoscope. The two affected people who had not yet undergone an upper endoscopy had been diagnosed within the previous year. Of note, one affected person reported that upper tract surveillance was not initiated until 16 years after the discovery of colonic polyps.

Colorectal surveillance by phenotype of neoplasia

History of colorectal cancer or the presence of numerous adenomatous polyps in a person at risk of a hereditary colorectal cancer syndrome establish that person as having an affected phenotype. In this cohort of people at risk of HNPCC or FAP the prevalence of appropriate colorectal cancer surveillance among affected people was 17/19 (89%) compared with 10/23 (43%) among those with an unaffected phenotype. People with a previous diagnosis which identified them as affected were significantly more likely to undergo cancer surveillance in accordance with guidelines for their high risk syndrome than were people without previous evidence of colonic neoplasia ($p=0.003$, table 3).

DISCUSSION

Although 40 of 42 (95%) subjects presenting for genetic testing for a hereditary colon cancer syndrome reported having had some form of surveillance of colorectal cancer, only 27 of 42 (64%) had undergone colorectal surveillance appropriate for their high risk syndrome. There are many potential factors which may contribute to the low prevalence of appropriate cancer screening even among patients at highest risk. Historically, poor patient compliance has been invoked as a major reason for low rates of participation in colorectal screening.^{11 12} Denial, low perceived risk of cancer, fear of discrimination by insurance providers or employers, patients' dislike of endoscopic tests, and issues of reimbursement for screening procedures may also adversely affect patient participation in cancer surveillance.¹³ However, the fact that 95% of subjects in our study had undergone colorectal screening suggests that there must be other contributing factors in this population. Despite being recognised as high risk and referred for genetic evaluation because of their striking family history of cancer, most people with an unaffected phenotype underwent colorectal cancer screening which was inadequate

given their high risk. Lack of familiarity with appropriate surveillance tests and screening intervals for HNPCC and FAP may be an important contributor to inadequate screening practices. In our cohort, most people with a family history of HNPCC who had inappropriate colorectal surveillance had actually had colorectal screening, albeit with the wrong procedure (sigmoidoscopy instead of colonoscopy) or the wrong screening interval (every five years instead of one to two years). Two thirds of the people at risk for FAP with an unaffected phenotype did not have continued surveillance after an initial clear lower tract evaluation, despite guidelines which recommend continued endoscopic screening of people without polyps owing to the possibility of late onset of polyps in some people. It is possible that in the absence of genetic testing, patients (and perhaps their doctors) may have been falsely reassured because of a negative initial endoscopic examination.

Surveillance for extracolonic malignancies which can accompany hereditary colorectal cancer syndromes is also often overlooked. Fewer than one quarter of women in this cohort who were at risk for HNPCC associated endometrial cancer indicated that they had undergone annual endometrial surveillance. Although there has been debate about the merits of endometrial screening in the absence of data supporting effectiveness, screening in this population is currently recommended by expert opinion and is included in practice guidelines.^{3,7} Possible reasons for the low prevalence of endometrial screening may include lack of evidence that it affects outcomes as well as physicians' oversight of the potential link between colorectal and endometrial cancers. In our own survey of gastroenterologists at a national meeting, only 40% mentioned endometrial cancer when asked what other cancers should be screened for in women at risk for HNPCC (unpublished data).

Despite the finding that only 64% of the people in our study received appropriate surveillance for colorectal cancer, this may be an overestimation of the prevalence of appropriate screening among those at highest risk of colorectal cancer. We used a very broad definition of appropriate colorectal screening. At the time our study questionnaire was designed, colonoscopy at one to three year intervals was considered appropriate for HNPCC,⁷ whereas more recent recommendations for HNPCC define appropriate surveillance as every one to two years.^{3,5} Subjects were evaluated based on their current surveillance regimen, although it is likely that previous inappropriate screening contributed to the diagnosis of cancer among affected people who subsequently received appropriate screening for their syndrome. Several people in our study reported having unscreened sibs not enrolled in our study, suggesting that the true prevalence of appropriate cancer surveillance among people at risk of hereditary colorectal cancer may be substantially lower than our results suggest. Although our study is limited by its size and its reliance on self-reported screening practices, we think that the low prevalence of appropriate screening among this "ideal" screening population is an important finding which merits further exploration.

In 2001 the American Gastroenterological Association published a medical position statement on hereditary colorectal cancer and genetic testing, emphasising the need for genetic evaluation and specialised cancer surveillance for people with a family history suggestive of HNPCC or FAP.¹ As genetic testing becomes more widespread, the challenge of cancer

prevention in people with hereditary predisposition to cancer lies not only in detecting the presence of a gene mutation, but also in identifying people who are at risk and implementing the cancer surveillance appropriate for these syndromes even when genetic testing is unavailable or uninformative. Increased awareness of hereditary colorectal cancer is essential for the identification of high risk patients, for whom surveillance guidelines differ markedly from those of people at average or moderate risk.

ACKNOWLEDGEMENTS

This study was funded in part by grant CA85453, National Cancer Institute, Bethesda, Maryland.

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