Gastroenterology 2015;149:1438–1445

Incidence and Mortality of Colorectal Cancer in Individuals With a Family History of Colorectal Cancer

Robert E. Schoen,[1] Anthony Razzak,[1] Kelly J. Yu,[2] Sonja I. Berndt,[3] Kevin Firl,[3] Thomas L. Riley,[4] and Paul F. Pinsky[2]

[1]Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh, Pittsburgh, Pennsylvania; [2]Division of Cancer Prevention, National Cancer Institute, Bethesda, Maryland; [3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; and [4]Information Management Services, Inc., Rockville, Maryland

CLINICAL AT

See editorial on page 1321.

BACKGROUND & AIMS: Little is known about the change in risk conferred by family history of colorectal cancer (CRC) as a person ages. We evaluated the effect of family history on CRC incidence and mortality after 55 years of age, when the risk of early onset cancer had passed. **METHODS:** We collected data from participants in the randomized, controlled Prostate, Lung, Colorectal and Ovarian cancer screening trial of flexible sigmoidoscopy versus usual care (55–74 years old, no history of CRC), performed at 10 US centers from 1993 to 2001. A detailed family history of colorectal cancer was obtained at enrollment, and subjects were followed for CRC incidence and mortality for up to 13 years. **RESULTS:** Among 144,768 participants, 14,961 subjects (10.3%) reported a family of CRC. Of 2090 incident cases, 273 cases (13.1%) had a family history of CRC; among 538 deaths from CRC, 71 (13.2%) had a family history of CRC. Overall, family history of CRC was associated with an increased risk of CRC incidence (hazard ratio [HR], 1.30; 95% confidence interval [CI], 1.10–1.50; $P<.0001$) and increased mortality (HR, 1.31; 95% CI, 1.02–1.69; $P = .03$). Subjects with 1 first degree relative (FDR) with CRC ($n = 238$; HR, 1.23; 95% CI, 1.07–1.42) or ≥2 FDRs with CRC ($n = 35$; HR, 2.04; 95% CI, 1.44–2.86) were at increased risk for incident CRC. However, among individuals with 1 FDR with CRC, there were no differences in risk based on age at diagnosis in the FDR (for FDR <60 years of age: HR, 1.27; 95% CI, 0.97–1.63; for FDR 60–70 years of age: HR, 1.33; 95% CI, 1.06–1.62; for FDR >70 years of age: HR, 1.14; 95% CI, 0.93–1.45; P trend = .59). **CONCLUSIONS:** After 55 years of age, subjects with 1 FDR with CRC had only a modest increase in risk for CRC incidence and death; age of onset in the FDR was not significantly associated with risk. Individuals with ≥2 FDRs with CRC had continued increased risk in older age. Guidelines and clinical practice for subjects with a family history of CRC should be modified to align CRC testing to risk. ClinicalTrials.gov number, NCT00002540.

Keywords: Adenomatous Polyps; Colon Cancer; Genetic Risk Factors; Screening.

A family history (FH) of colorectal cancer (CRC) in a first degree relative (FDR; parents, siblings, or children) has long been identified as a risk factor for CRC.[1,2] Approximately 5%–10% of the population have at least 1 affected FDR with CRC.[1,3] The increased risk of CRC conferred by having a FH is thought to be determined by the number of affected relatives, the age of disease onset in the affected relative, and the closeness or degree of relation.[4–6] The lifetime risk of CRC is approximately 2-fold increased in those with an affected FDR with CRC.[1,2,7–10] The risk increases to a greater degree in individuals with multiple affected FDRs or when the CRC is diagnosed before age 50.[2,5,7–11]

Little is known about how the risk of CRC in individuals with an affected FDR manifests as a subject ages. Current screening recommendations for CRC presume ongoing, increased risk for subjects with ≥2 affected FDRs or a FDR diagnosed before age 60. Guidelines advise these subjects to undergo colonoscopy screening at 40 years of age or 10 years before the youngest affected FDR, with indefinite, repeated colonoscopy every 5 years.[12,13]

A FH of CRC is also often used to justify more intensive screening and surveillance colonoscopy, albeit with uncertain yield.[14,15] In the Clinical Outcomes Research Initiative database for example, among subjects with no findings at baseline colonoscopy and a repeated colonoscopy examination within 1 to 5 years (N = 7372), 30.1% of examinations were performed because of a FH of CRC, and significant lesions were detected infrequently.[15]

Our aim was to evaluate the effect of FH of CRC on incidence and mortality to CRC in later age, in a cohort where the risk of early onset cancer had passed.

Methods

The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial using flexible sigmoidoscopy enrolled men and women 55 to 74 years of age with no history of CRC at 10 screening centers from 1993 to 2001. Individuals were randomized to an intervention or usual care arm. Intervention arm subjects received flexible sigmoidoscopy at baseline and again at year 3 (for those randomized before April 1995) or year 5. Intervention arm subjects also received annual chest

Abbreviations used in this paper: CRC, colorectal cancer; FDR, first degree relative; FH, family history; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening trial.

Most current article

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2015.07.055

radiograph, prostate-specific antigen tests (men only), digital rectal exam (men only), CA125 tests (women only), and transvaginal ultrasonography (women only) for 4 to 6 years. Exclusion criteria included a history of prostate, lung, colorectal, or ovarian cancer. Beginning in 1995, subjects who had undergone colonoscopy, flexible sigmoidoscopy, or barium enema within the prior 3 years were ineligible for enrollment. Details of the trial have been previously published.[16,17]

Demographics and medical history, including FH of cancer, were ascertained via baseline questionnaire administered at enrollment. With respect to FH, the questionnaire asked: "Have your parents, children, brothers, sisters, half-brothers, or half-sisters ever been diagnosed as having any type of cancer (Do not include basal-cell skin cancer)?" For those responding yes, a chart was provided to document the relationship of the relative, the type of cancer, and the age at which the relative received the diagnosis of that cancer.

Incident cancers and deaths were ascertained primarily by a mailed Annual Study Update questionnaire. Medical records pertaining to diagnosed cancers were reviewed, and data for stage, histology, and grade of cancers were abstracted by certified tumor registrars. Information on vital status was supplemented by periodic linkage to the National Death Index. Cause of death was reviewed blinded to study arm, in a formal adjudication process.[18] Subjects were followed for 13 years, until December 31, 2009, death, or loss to follow-up, whichever came first. Screening centers obtained written informed consent from each participant, and the institutional review board approved the PLCO protocol at each center.

Surveillance colonoscopy examination and outcome were assessed in a randomly selected subset of subjects in the intervention arm. Details of that investigation have been described previously.[14,19] The authors had access to the study data and reviewed and approved the final manuscript.

Statistical Analysis

Family history of CRC was defined as a FDR, that is, a parent, full sibling, or child with CRC. Subjects not completing the FH section of the baseline questionnaire were excluded. CRC incidence rates per 10,000 person-years (PY) of follow-up were computed by CRC FH status; in addition, for subjects with a FH, CRC incidence rates were computed according to the youngest age at diagnosis of CRC in the FDR (<60, 60–70, >70 years of age), and the number of FDRs with CRC. Cox proportional hazards models were used to examine the hazard ratio (HR) for incident CRC with a FH of CRC and for characteristics of the FH; covariates included trial arm, sex, age, history of lower endoscopy or fecal occult blood test in the 3 years preceding enrollment, body mass index, and use of nonsteroidal anti-inflammatory drugs or aspirin. To examine a possible interaction of FH with age (<65 or ≥65), age was treated as a time-varying covariate in the Cox model; thus, we determined whether FH had a differential HR for incident CRC diagnosed in the age range 55–64 versus incident CRC diagnosed in the age range ≥65. We also examined interactions of FH with trial arm and sex. Similar analyses were performed for mortality from CRC.

Results

A total of 154,900 subjects were enrolled in PLCO, of whom 144,768 were included on the basis of completed FH information. Of the 144,768 evaluable individuals, 14,961 (10.3%) reported a FH of CRC in at least 1 FDR. Baseline characteristics of study participants with and without a FH are shown in Table 1. Subjects reporting a FH were slightly older, more likely to be women, and more likely to have undergone endoscopic testing and fecal occult blood testing in the 3 years prior to trial enrollment. Subjects with an FH of CRC were evenly distributed into the intervention and control arms of the trial (51.1% vs 48.9%, respectively) and did not differ from subjects without a FH in other demographic

Table 1. Baseline Subject Characteristics

Characteristic	No. of subjects with no family history of CRC (n = 129,808) (%)	No. of subjects with family history of CRC (n = 14,961) (%)
Gender		
Male	64,103 (49.4)	6566 (43.9)
Female	65,705 (50.6)	8395 (56.1)
Age, *y*		
55–59	43,805 (33.8)	4525 (30.3)
60–64	39,919 (30.8)	4643 (31.0)
65–69	29,037 (22.4)	3568 (23.9)
70–74	17,047 (13.3)	2225 (14.9)
Race/ethnicity		
White (non-Hispanic)	114,660 (88.3)	13,584 (90.8)
Black (non-Hispanic)	6715 (5.2)	542 (3.6)
Hispanic	2450 (1.9)	215 (1.4)
Asian	4854 (3.7)	540 (3.6)
Other/unknown	1129 (0.9)	80 (0.5)
Education		
High school graduate or less	38,822 (29.9)	4649 (31.0)
Some college	44,555 (34.3)	5252 (35.1)
College graduate	46,202 (35.6)	5039 (33.7)
Unknown	229 (0.2)	21 (0.1)
Prior FOBT[a]		
Yes	50,865 (39.2)	6364 (42.5)
No	74,814 (57.6)	8164 (54.6)
Unknown	4129 (3.2)	433 (2.9)
Prior lower GI endoscopy[a,b]		
Yes	16,420 (12.7)	2550 (17.0)
No	111,264 (85.7)	12,209 (81.6)
Unknown	2124 (1.6)	202 (1.4)
Either prior FOBT or lower GI endoscopy[a]		
Yes	55,990 (43.1)	7116 (47.6)
No	73,333 (56.5)	7802 (52.2)
Unknown	485 (0.4)	43 (0.3)
Aspirin or NSAID intake ≥3-4 days/week		
Yes	56,687 (43.7)	6457 (43.2)
No	73,011 (56.3)	8491 (56.8)
Unknown	110 (0.08)	13 (0.09)
Trial arm		
Intervention	65,301 (50.3)	7641 (51.1)
Control	64,507 (49.7)	7320 (48.9)

CRC, colorectal cancer; FOBT, fecal occult blood test; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.
[a]Within 3 years of study enrollment.
[b]Lower GI endoscopy includes sigmoidoscopy, colonoscopy, or barium enema.

categories (age, race, education). Median length of follow-up was 12.5 and 11.8 years for those with and without FH, respectively.

During screening and follow-up, there were 2090 incident cases of CRC. Of those, 273 individuals (13.1%) had an FH of CRC. Overall, a FH of CRC, compared with those without a FH, was associated with an increased risk of CRC incidence (HR, 1.30; 95% confidence interval [CI], 1.10–1.50; $P<.0001$). CRC risk increased with a greater number of affected FDRs. Subjects with 1 FDR with CRC (n = 238; HR, 1.23; 95% CI, 1.07–1.42) or ≥2 FDRs with CRC (n = 35; HR, 2.04; 95% CI, 1.44–2.86) were at increased risk for incident CRC (Table 2). The HRs based on the age at diagnosis in the affected FDR, including subjects with ≥2 FDR with CRC, were 1.46 (95% CI, 1.17–1.81), 1.33 (95% CI, 1.09–1.63), and 1.15 (95% CI, 0.92–1.44) for subjects with an FDR receiving a diagnosis at <60, 60–70, and >70 years of age, respectively. There was no statistically significant trend ($P = .18$) toward an increasing risk of CRC with a younger age at diagnosis in the affected FDR.

There was no significant interaction of FH with subjects' age for CRC incidence; FH HRs were 1.56 for age range of 55–64 versus 1.25 for ages ≥65 ($P = .13$ for interaction).

Among 538 deaths resulting from CRC, 71 (13.2%) had a FH of CRC. As with CRC incidence, CRC mortality was similarly significantly increased among those with a FH of CRC (HR, 1.31; 95% CI, 1.02–1.69, P = .03) (Table 3). There was no statistically significantly increased risk of CRC mortality among those with ≥2 affected FDRs compared to those with only 1 (HR, 1.53; 95% CI, 0.7–3.3; P trend = 0.68), but there were only 7 deaths among subjects with ≥2 affected FDRs (Table 3). There was no statistically significant trend ($P = .81$) toward an increasing risk of mortality to CRC with younger age at diagnosis in the affected FDR.

FH of CRC was significantly associated with an increased risk of CRC in both men (RR, 1.26; 95% CI, 1.05–1.50, $P = .012$) and women (HR, 1.35; 95% CI, 1.12–1.63, $P = .002$) (Table 4). Similar point estimates, although not statistically significant for men, were observed for the association of FH and CRC mortality in men (N = 307 deaths, HR, 1.20; 95% CI, 0.8–1.7, P = .3) and women (N = 231 deaths, HR, 1.44; 95% CI, 1.01–2.0, P = .04) (Supplementary Table 1). Both men (HR, 1.79; 95% CI, 1.07–3.00) and women (RR 2.27; 95% CI, 1.44–3.57) had a significantly increased risk of CRC incidence with ≥2 affected FDRs. Men and women also had a similar increased risk of CRC with 1 affected FDR (men: HR, 1.21; 95% CI, 1.00–1.47, women: RR 1.26; 95% CI, 1.03–1.54) (Table 4). Similar trends in men and women were observed for the relationship between the age at diagnosis of the affected FDR and the risk of incident CRC (Table 4).

Among those with a FH of CRC, there were 56 cases of rectal and 217 cases of colon cancer. FH of CRC in a FDR was significantly associated with the risk of colon cancer (HR, 1.31; 95% CI, 1.41–1.50, $P = .0003$); a similar HR was observed for rectal cancer, although it was not statistically significant (HR, 1.27; 95% CI, 0.95–1.69, $P = .10$) (Supplementary Table 2). There were no differences in the association of FH with proximal (HR, 1.24; 95% CI, 1.03–1.48) as opposed to distal (HR, 1.36; 95% CI, 1.13–1.64) CRC (Supplementary Table 2).

The risk of incident CRC by the age at diagnosis in the FDR was assessed after excluding individuals with ≥2 affected FDRs, as they were at higher risk (Table 5).

Table 2. Relationship Between Family History of CRC and Incident CRC

Factor	No. of cases of CRC (n = 2090)	Person-years	Rate (per 10,000 PY)	MV adjusted hazard ratio (95% CI)[a]	*P* value
Family history of CRC[b]					
No	1817	1,423,420	12.8	1.00 (ref)	<.0001
Yes	273	165,057	16.5	1.30 (1.10–1.50)	
No. of affected FDRs					
0 (no FH)	1817	1,423,420	12.8	1.00 (ref)	.008[c]
1 FDR	238	151,995	15.7	1.23 (1.07–1.42)	
≥2 FDR	35	13,062	26.8	2.04 (1.44–2.86)	
Age at diagnosis of affected FDR[d]					
No FH	1817	1,423,420	12.8	1.00 (ref)	.18[e]
FDR diagnosed at >70	88	59,047	14.9	1.15 (0.92–1.44)	
FDR diagnosed 60–70	97	57,008	17.0	1.33 (1.09–1.63)	
FDR diagnosed <60	81	45,368	17.9	1.46 (1.17–1.81)	

FDR, first degree relative; FH, family history; CRC, colorectal cancer; PY, person-years.
[a]Multivariate (MV) adjustment including trial arm, age, sex, prior FOBT, prior lower GI endoscopy, aspirin/NSAID use, and body mass index.
[b]Defined as positive FH in a first degree relative.
[c]*P* value is *P* trend for increasing number of affected FDRs among those with a family history of CRC.
[d]When there are more than 1 affected FDRs, the age at diagnosis is the youngest affected FDR. In 7 subjects, the age at diagnosis of CRC in the FDR was unknown.
[e]*P* value is *P* trend for increasing age at diagnosis of FDR. These estimates include subjects with ≥2 FDRs with CRC.

Table 3. Relationship Between Family History of CRC and Mortality to CRC

Factor	No. of deaths to CRC (n = 538)	Person-years	Rate (per 10,000 PY)	MV adjusted hazard ratio (95% CI)[a]	*P* value
Family history of CRC[b]					
No	467	1,458,514	3.20	1.00 (ref)	.03
Yes	71	169,349	4.19	1.31 (1.02–1.69)	
No. of affected FDRs					
0 (no FH)	467	1,458,514	3.20	1.00 (ref)	.68[c]
1 FDR	64	155,967	4.10	1.29 (1.00–1.70)	
≥2 FDR	7	13,383	5.23	1.53 (0.7–3.3)	
Age at diagnosis of affected FDR[d]					
No FH	467	1,458,514	3.20	1.00 (ref)	.81[e]
FDR diagnosed at >70	28	60,443	4.6	1.50 (1.02–2.2)	
FDR diagnosed 60–70	19	58,466	3.2	1.04 (0.7–1.6)	
FDR diagnosed <60	24	46,705	5.1	1.66 (1.1–2.5)	

CRC, colorectal cancer; FDR, first degree relative; FH, family history; PY, person-years.
[a]Multivariate (MV) adjustment including trial arm, age, sex, prior fecal occult blood test, prior lower gastrointestinal endoscopy, aspirin/nonsteroidal anti-inflammatory drug use and body mass index.
[b]Defined as positive FH in a first degree relative.
[c]*P* value is *P* trend for increasing number of affected FDRs among those with a family history of CRC.
[d]When there are more than 1 affected FDR, the age at diagnosis is the youngest affected FDR.
[e]*P* value is *P* trend for increasing age at diagnosis of FDR. These estimates include subjects with ≥2 FDRs with CRC.

Among individuals with 1 FDR with CRC, there was no difference in risk based on the age at diagnosis in the FDR (HR, 1.27; 95% CI, 0.97–1.63 for subjects with a FDR diagnosed at age <60; HR, 1.33; 95% CI, 1.06–1.62 for subjects with FDR diagnosed between 60 and 70 years; HR, 1.14; 95% CI, 0.93–1.45 for subjects with FDR diagnosed at >70 years of age; *P* trend = 0.59). Figure 1 demonstrates the cumulative risk of FH-associated CRC over time, stratified by FH risk group. The absolute increase in CRC incidence was 0.33% (95% CI, 0.10–0.56%) for those with 1 affected FDR and 1.6% (95% CI, 0.6–2.6%) for those with ≥2 affected FDRs.

The FH HRs for both CRC incidence and CRC mortality were similar within each trial arm; 1.27 (95% CI, 1.04–1.5) and 1.53 (95% CI, 1.1–2.2) for incidence and mortality, respectively, in the intervention arm versus 1.33 (95% CI, 1.1–1.6) and 1.15 (95% CI, 0.8–1.6), respectively, for incidence and mortality in the usual care arm (*P* value for interaction of FH by trial arm equals 0.84 for incidence and 0.73 for mortality). Also, we did not identify a statistically significant interaction between FH of CRC and screening history prior to enrollment (fecal occult blood test or endoscopy) and CRC incidence, *P* = .16.

Because a difference in use of surveillance colonoscopy after screening in subjects with compared to those without a FH of CRC could have affected CRC incidence and mortality, use of surveillance colonoscopy was examined in a randomly selected cohort of subjects (N = 3594) in the intervention arm of the PLCO trial.[14,19] The use of surveillance colonoscopy by FH and by baseline adenoma findings is shown in Table 6. At 5 years after baseline colonoscopy, surveillance colonoscopy was used in 7.2% more subjects with a FH of CRC compared to those without a FH (53.9% vs 46.7%, respectively). At 7 years, the difference was 8.8% and 6.6% at 10 years.

Discussion

In our prospective study, we observed a modest 30% increased risk in CRC incidence and mortality in subjects over age 55 with a FH of CRC in a FDR. Subjects with 2 FDRs with CRC were identified as a high-risk group, with a 2-fold increased risk of incident CRC. Within our age cohort, after excluding subjects with ≥2 FDRs, a young age of onset in the FDR (<60 years at time of diagnosis) was not associated with a differential increased risk in CRC incidence or mortality compared to subjects with FDRs affected at older ages (Table 5). We observed no differences in risk relationships between a FH of CRC and incident CRC in men compared to women, nor did we observe a stronger relationship between a FH of colorectal cancer and proximal as opposed to distal cancer or colon as opposed to rectal cancer.

A FH of CRC is used to justify more intensive surveillance colonoscopy in subjects with adenomatous polyps, at times in excess of recommended guidelines,[14,15] although evidence of an increased yield in subjects with a FH is unproven.[20] Given that our data indicate a relatively small increase in cancer incidence or mortality in subjects after age 55 with a FH of CRC, more aggressive surveillance colonoscopy in subjects with a FH of CRC and a history of adenomatous polyps is unlikely to substantially contribute to cancer prevention.

Because CRC incidence as an outcome is potentially subject to lead time and over- diagnosis bias, we also evaluated the relationship of CRC mortality to FH of CRC. CRC mortality occurred in 25.7% of incident cases (538 of 2090), limiting statistical power relative to cancer incidence. A FH of CRC was associated with an increase in CRC mortality (HR = 1.31), similar in magnitude to the increased risk observed for CRC incidence, suggesting a limited impact of lead time or over diagnosis bias to our conclusions.

Table 4. Relationship Between Family History of CRC and Incident CRC by Sex

Factor	No. of cases (n)	Person-years	Rate (per 10,000 PY)	MV adjusted hazard ratio (95% CI)[a]	*P* value
Men (n = 1204 CRC cases)					
Family history of CRC					
No	1067	697,453	15.3	1.00 (ref)	.012
Yes	137	71,640	19.1	1.26 (1.05–1.50)	
No. of affected FDRs					
0 (no FH)	1067	697,453	15.3	1.00 (ref)	.16[b]
1	122	66,365	18.4	1.21 (1.00–1.47)	
≥2	15	5276	28.4	1.79 (1.07–3.00)	
Age at diagnosis of affected FDR[c]					
0 (no FH)	1067	697,453	15.3	1.00 (ref)	.30[b]
>70	46	24,872	18.5	1.19 (0.90–1.60)	
60–70	47	26,249	17.9	1.18 (0.87–1.59)	
<60	43	19,074	22.5	1.52 (1.11–2.08)	
Unknown age	1				
Women (n = 886 CRC cases)					
Family history of CRC					
No	750	725,967	10.3	1.00 (ref)	.002
Yes	136	93,417	14.6	1.35 (1.12–1.63)	
No. of affected FDRs					
0 (no FH)	750	72,5967	10.3	1.00 (ref)	.02[b]
1	116	85,631	13.5	1.26 (1.03–1.54)	
≥2	20	7786	25.7	2.27 (1.14–3.57)	
Age at diagnosis of affected FDR[c]					
0 (no FH)	750	725,967	10.3	1.00 (ref)	.28[b]
>70	42	34,175	12.3	1.10 (0.80–1.52)	
60–70	50	30,759	16.3	1.52 (1.14–2.04)	
<60	38	26,294	14.5	1.38 (1.00–1.92)	
Unknown age	6				

CRC, colorectal cancer; FDR, first degree relative; FH, family history; MV, multivariate; PY, person-years.
[a]MV adjustment including trial arm, age, sex, prior fecal occult blood test, prior lower gastrointestinal endoscopy, aspirin/nonsteroidal anti-inflammatory drug use and body mass index.
[b]*P* value for trend.
[c]When there are more than 1 affected FDR, the age at diagnosis is the youngest affected FDR.

These data derive from a cancer screening trial, with subsequent colonoscopy surveillance provided by local providers. Our estimates of only a modest difference in CRC incidence and mortality between subjects with a FH of CRC compared to those without could be affected if either the effectiveness of screening or surveillance, or the use of surveillance after screening were significantly different in subjects with compared to those without a FH of CRC. We did not observe a significant difference in the benefit of screening in subjects with a FH of CRC, as the hazard ratios for CRC incidence and mortality were similar in those with and without a FH. We evaluated surveillance colonoscopy in a randomly selected cohort of nearly 4000 subjects in the screening arm of the trial. In clinical practice, one would expect subjects with a FH of CRC to undergo more surveillance colonoscopy. We observed a small increase in surveillance colonoscopy among those with a FH, ranging from 6.6% to 8.2% more use at 5 to 10 years after baseline colonoscopy, an amount that is unlikely to have significantly altered the CRC incidence rates among subjects with a FH in

Table 5. Relationship Between Family History of CRC and Incident CRC Risk

Family history traits	# CRCs (N = 2090)	Person-years	Rate (per 10,000 PY)	HR (95% CI)	*P* value
No FH	1817	1,423,420	12.8	1.00 (ref)	
≥ 2 affected FDRs	35	13,062	26.8	2.04 (1.44-2.86)	<0.0001
Only 1 affected FDR, FDR < 60 yrs at diagnosis	59	38,175	15.5	1.27 (0.97-1.63)	0.07[a]
Only 1 affected FDR, FDR 60-70 yrs at diagnosis	89	52,764	16.9	1.33 (1.06-1.62)	0.009[a]
Only 1 affected FDR, FDR > 70 yrs at diagnosis	85	57,565	14.8	1.14 (0.93-1.45)	0.26[a]

CRC, colorectal cancer; FDR, first degree relative; FH, family history; HR, hazard ratio; PY, person-years.
[a]*P* trend = 0.59, for subjects with 1 affected FDR.

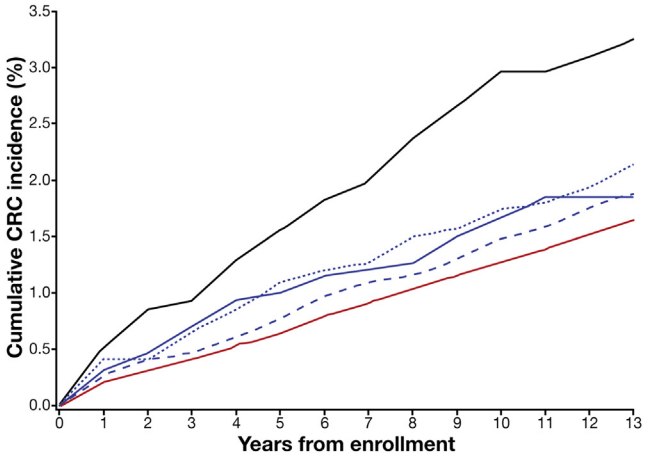

Figure 1. Cumulative CRC incidence by family history status. *Red line* indicates no family history of CRC; *black line* indicates ≥2 FDRs with a family history of CRC; *blue lines* are 1 FDR with a family history classified by the age of onset of CRC in the FDR: where age >70 is shown by the *blue dashed line*; age 60–70 is shown by the *blue dotted line*; and age <60 is shown by the *blue solid line*. CRC, colorectal cancer; FDR, first degree relative.

comparison to those without. Furthermore, the benefit of post-polypectomy surveillance colonoscopy on CRC incidence and mortality has not been determined. While randomized trials of CRC screening with stool testing or flexible sigmoidoscopy demonstrate a significant reduction in CRC incidence and mortality,[21] the contribution of surveillance colonoscopy has not been evaluated in a clinical trial.[22] It is even less certain whether post-polypectomy surveillance has a greater effect on outcome in subjects with a FH compared to those without, and in a pooled analysis of multiple trials, there was no difference in detection of advanced adenoma or cancer in subjects with compared to those without a FH.[20]

Advantages of these data compared to those previously available should be acknowledged. Most investigations exploring FH-associated CRC risk are retrospective, case-control studies.[2,8,9] In PLCO, individuals were queried about their FH at enrollment, so recall bias regarding the presence of a FH of cancer was minimized. Incident cancers in PLCO were verified by obtaining confirmatory pathologic documentation. The only other prospective study on FH and incident CRC comes from the combined Nurses' Health Study and Health Professionals Follow-up Study,[1] which followed subjects as young as 30 years old. In that cohort, a FH of CRC in a FDR was associated with a 1.7-fold increased risk of CRC. Only 73 subjects with a FH and CRC were included compared to 273 subjects evaluated here, and the former study included only 45 FH-associated CRC cases over age 55, whereas all of our cases were age 55 or more at enrollment. Thus, the PLCO cohort is by far the largest prospective study on FH associated CRC and is particularly informative of CRC risk among middle-aged and older subjects.

Our data do not address the need or utility of screening subjects prior to age 55 who have a FH of CRC, because the PLCO trial only enrolled subjects age 55 or older and excluded subjects with a history of CRC. Many studies demonstrate a higher risk of colorectal cancer at a young age in subjects with FDRs with CRC diagnosed prior to age 50.[1,2,7,8,10] Screening these subjects at young ages, such as 10 years prior to age at diagnosis in the FDR, is recommended by guidelines. In the Nurses' Health Study and Health Professionals Follow-up Study prospective cohort study[1] for example, there was a marked increase in CRC risk in younger subjects with a FH of CRC. Subjects <45 years of age with a FH of CRC had a 5-fold increased risk of CRC (N = 5, RR 5.37; 95% CI, 1.98–14.6), compared to those without a FH of CRC.

Our data do address the ongoing risk of incident CRC once the subject has reached age 55, where early onset disease, reflecting a highly penetrant genetic component, has passed. The risk estimate for incident CRC in our cohort (HR = 1.3) differs from that in the Nurses and Health Professionals study cohort (RR = 1.7) and to the preponderance of retrospective studies included in meta-analyses.[2,7] Our lower hazard ratio is likely attributable to the exclusion in our cohort of young onset cancer cases (occurring prior to age <55), and because retrospective studies may be affected by the selection of controls at lower risk of CRC compared to cases, and due to recall bias which may inflate the recollection of a FH of cancer among cases compared to controls.

A recent population-based, colonoscopy based, case control study in Utah demonstrated an overall increased risk of CRC among FDRs compared to controls (HR = 1.79) and

Table 6. Use of Surveillance Colonoscopy by Family History and Baseline Adenoma Status (N = 3954)

			% with surveillance exam after baseline colonoscopy		
Family history	Baseline adenoma status	n (%)	Within 5 years	Within 7 years	Within 10 years
No		3438	46.7	61.6	67.8
	None	1191 (34.6)	37.9	54.2	61.0
	Non-advanced	1001 (29.1)	45.2	61.9	68.4
	Advanced	1246 (36.2)	56.3	68.5	73.8
Yes		516	53.9	70.4	74.4
	None	186 (36.1)	43.0	62.9	68.3
	Non-advanced	135 (26.2)	50.4	68.9	73.3
	Advanced	195 (37.8)	66.7	78.5	81.0

noted a statistically significant difference in risk in a case-case analysis between cases with FDR's diagnosed at age <60 (HR = 2.11) versus cases with FDR's diagnosed at age >60 (HR = 1.77) (HR, 1.5; 95% CI, 1.19–1.89 for the comparison between the two).[23] Data from Samadder et al[23] also suggested the increased risk with a FH extended beyond FDR to second degree relatives and first cousins. Those data include CRC cases diagnosed at younger ages, and selection bias could also account for some of the observed difference. Our prospective results differ and suggest that, as subjects with a FH of CRC age, the likelihood of a highly penetrant, heritable cancer risk is low and that screening can be more like that of an average risk individual. A recent prospective evaluation of colonoscopy effectiveness in the Nurses' Health Study and Health Professionals Follow-up Study demonstrated a reduced incidence of CRC in subjects with a FH of CRC who underwent a colonoscopy within 5 years (n = 43, HR, 0.44; 95% CI, 0.30–0.66) compared to those with colonoscopy more than 5 years ago (n = 26, HR, 0.91; 95% CI, 0.55–1.51), and to subjects with a FH of CRC who did not undergo any prior colonoscopy.[24] However, one cannot derive recommendations for the optimal timing of colonoscopy from these findings without accounting for the number of affected FDRs, the age of the individuals, and the age of onset in the affected relatives.

Additional limitations of our study include the fact that the FH information was obtained by self-report and not verified. However, previous investigations have demonstrated accuracy in self-reported FH of CRC.[25–27] The PLCO population is generally well-educated and predominantly Caucasian, so generalization of these findings to minorities and low income groups may be limited.

In conclusion, individuals with ≥2 FDR with CRC remain at increased risk for CRC into later age. In contrast, after age 55, subjects with 1 FDR with CRC have only a modest increased risk of CRC incidence and mortality compared to those without a FH. Furthermore, after age 55, there was no difference in risk based on the age at diagnosis in the FDR. Our data suggest that increased screening and surveillance colonoscopy in subjects with a FH of CRC in 1 FDR is unlikely to contribute considerably to cancer prevention after age 55. These findings do not impact decisions on when to begin screening, but do suggest that FH-associated CRC risk is only modestly increased once the risk of early onset cancer has passed. Guidelines and clinical practice for subjects with a FH of CRC should be modified to align CRC testing to risk.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Gastroenterology at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.07.055.

References

1. Fuchs CS, Giovannucci EL, Colditz GA, et al. A prospective study of FH and the risk of colorectal cancer. N Engl J Med 1994;331:1669–1674.
2. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol 2001;96:2992–3003.
3. Ramsey SD, Yoon P, Moonesinghe R, et al. Population-based study of the prevalence of FH of cancer: implications for cancer screening and prevention. Genet Med 2006;8:571–575.
4. Kune GA, Kune S, Watson LF. The Melbourne Colorectal Cancer Study. Characterization of patients with a family history of colorectal cancer. Dis Colon Rectum 1987; 30:600–606.
5. St John DJ, McDermott FT, Hopper JL, et al. Cancer risk in relatives of patients with common colorectal cancer. Ann Intern Med 1993;118:785–790.
6. Stephenson BM, Finan PJ, Gascoyne J, et al. Frequency of familial colorectal cancer. Br J Surg 1991; 78:1162–1166.
7. Butterworth AS, Higgins JPT, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. Eur J Cancer 2006; 42:216–227.
8. Hemminki K, Li X. Familial colorectal adenocarcinoma from the Swedish Family-Cancer Database. Int J Cancer 2001;94:743–748.
9. Slattery ML, Kerber RA. Family history of cancer and colon cancer risk: the Utah population database [published erratum appears in J Natl Cancer Inst 1994 Dec 7;86(23):1802]. J Natl Cancer Inst 1994;86:1618–1626.
10. Andrieu N, Launoy G, Guillois R, et al. Familial relative risk of colorectal cancer: a population-based study. Eur J Cancer 2003;39:1904–1911.
11. Rex DK, Johnson DA, Lieberman DA, et al. Colorectal cancer prevention 2000: screening recommendations of the American College of Gastroenterology. Am J Gastroenterol 2000;95:868–877.
12. Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. [Erratum appears in Am J Gastroenterol. 2009 Jun;104(6):1613]. Am J Gastroenterol 2009;104:739–750.
13. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology 2008; 134:1570–1595.
14. Schoen RE, Pinsky PF, Weissfeld JL, et al. Utilization of surveillance colonoscopy in community practice. Gastroenterology 2010;138:73–81.
15. Lieberman DA, Holub JL, Morris CD, et al. Low rate of large polyps (>9 mm) within 10 years after an adequate baseline colonoscopy with no polyps. Gastroenterology 2014;147:343–350.
16. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012;366:2345–2357.
17. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer screening trial. Control Clin Trials 2000;21(Suppl):309S.

18. Miller AB, Yurgalevitch S, Weissfeld JL. Death review process in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. Control Clin Trials 2000; 21(Suppl):406S.
19. Pinsky PF, Schoen RE, Weissfeld JL, et al. The yield of surveillance colonoscopy by adenoma history and time to examination. Clin Gastroenterol Hepatol 2009;7:86–92.
20. Martinez ME, Baron JA, Lieberman DA, et al. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. Gastroenterology 2009; 136:832–841.
21. Weinberg DS, Schoen RE. Screening for colorectal cancer. Ann Intern Med 2014;160:6.
22. Hassan C, Quintero E, Dumonceau J-M, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2013;45:842–851.
23. Samadder NJ, Curtin K, Tuohy TMF, et al. Increased risk of colorectal neoplasia among family members of patients with colorectal cancer: a population-based study in Utah. Gastroenterology 2014;147:814–821.
24. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013;369:1095–1105.
25. Aitken J, Bain C, Ward M, Siskind V, MacLennan R. How accurate is self-reported family history of colorectal cancer? Am J Epidemiol 1995;141:863–871.
26. Kerber RA, Slattery ML. Comparison of self-reported and database-linked family history of cancer data in a case-control study. Am J Epidemiol 1997;146:244–248.
27. Ziogas A, Anton–Culver H. Validation of family history data in cancer family registries. Am J Prev Med 2003; 24:190–198.

Received April 30, 2015. Accepted July 28, 2015.

Reprint requests
Address requests for reprints to: Robert E. Schoen, MD, MPH, Division of Gastroenterology, Hepatology and Nutrition, Mezzanine Level, C Wing, PUH 200 Lothrop Street, Pittsburgh, Pennsylvania 15213-2582. e-mail: rschoen@pitt.edu.

Conflicts of interest
The authors have no conflicts of interest to disclose.

PLCO cancer screening trial registered as: NCT00002540.

Funding
This work was supported by the Division of Cancer Prevention, National Cancer Institute contract N01-CN-25511 to the University of Pittsburgh Cancer Institute.

Supplementary Table 1. Relationship Between Family History of CRC and Mortality to CRC by Sex

Factor	No. of CRC deaths	Person-years	Rate (per 10,000 PY)	MV adjusted hazard ratio (95% CI)[a]	*P* value
Men (N = 307 CRC deaths)					
Family history of CRC					
No	273	715,319	3.82	1.00 (ref)	.30
Yes	34	73,609	4.62	1.20 (0.8–1.7)	
Women (N = 231 CRC deaths)					
Family history of CRC					
No	194	743,194	2.61	1.00 (ref)	.04
Yes	37	95,741	3.86	1.44 (1.01–2.0)	

CRC, colorectal cancer; PY, person-years.
[a]Multivariate (MV) adjustment including trial arm, age, fecal occult blood test, prior lower gastrointestinal endoscopy, aspirin/nonsteroidal anti-inflammatory drug use, and body mass index.

Supplementary Table 2. Relationship Between FH of CRC and Incident CRC by Anatomic Subsite

Family history	No. of cases (n)	Person-years	Rate (per 10,000 PY)	MV adjusted hazard ratio (95% CI)[a]	*P* value
Rectal cancer (N = 462)					
No	406	1,423,420	2.9	1.00 (ref)	.10
Yes	56	165,057	3.4	1.27 (0.95-1.69)	
Colon cancer (N = 1628)					
No	1411	1,423,420	9.9	1.00 (ref)	.0003
Yes	217	165,057	13.1	1.31 (1.14-1.50)	
Distal colon cancer (N = 996)[b]					
No	865	1,423,420	6.1	1.00 (ref)	.001
Yes	131	165,057	7.9	1.36 (1.13-1.64)	
Proximal colon cancer (N = 1085)[c]					
No	945	1,423,420	6.6	1.00 (ref)	.02
Yes	140	165,057	8.5	1.24 (1.03-1.48)	

CRC, colorectal cancer; FH, family history; PY, person-years.
[a]Multivariate (MV) adjustment including trial arm, age, fecal occult blood test, prior lower gastrointestinal endoscopy, aspirin/nonsteroidal anti-inflammatory drug use, and body mass index.
[b]Distal colon cancer is defined as lesions identified in the rectum through descending colon.
[c]Proximal colon cancer is defined as lesions identified in the splenic flexure to the cecum.