Association of Family History With Cancer Recurrence and Survival Among Patients With Stage III Colon Cancer

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Context A family history of colorectal cancer in a first-degree relative increases the risk of developing colorectal cancer. However, the influence of family history on cancer recurrence and survival among patients with established disease remains uncertain.

Objective To examine the association of family history of colorectal cancer with cancer recurrence and survival of patients with colon cancer.

Design, Setting, and Participants Prospective observational study of 1087 patients with stage III colon cancer enrolled in a randomized adjuvant chemotherapy trial (CALGB 89803) between April 1999 and May 2001. Patients provided data on family history at baseline and were followed up until March 2007 for disease recurrence and death (median follow-up, 5.6 years). In a subset of patients, we assessed microsatellite instability (MSI) and expression of the mismatch repair (MMR) proteins MLH1 and MSH2 in tumor specimens.

Main Outcome Measures Disease-free survival, recurrence-free survival, and overall survival according to the presence or absence of a family history of colorectal cancer.

Results Among 1087 eligible patients, 195 (17.9%) reported a family history of colorectal cancer in a first-degree relative. Cancer recurrence or death occurred in 57 of 195 patients (29%; 95% confidence interval [CI], 23%-36%) with a family history of colorectal cancer and 343 of 892 patients (38%; 95% CI, 35%-42%) without a family history. Compared with patients without a family history, the adjusted hazard ratios (HRs) among those with 1 or more affected first-degree relatives were 0.72 (95% CI, 0.54-0.96) for disease-free survival, 0.74 (95% CI, 0.55-0.99) for recurrence-free survival, and 0.75 (95% CI, 0.54-1.05) for overall survival. This reduction in risk of cancer recurrence or death associated with a family history became stronger with an increasing number of affected first-degree relatives. Compared with participants without a family history of colorectal cancer, those with 1 affected relative had a multivariate HR of 0.77 (95% CI, 0.57-1.04) for disease-free survival. For participants with 2 or more affected relatives, we observed a greater reduction in risk (multivariate HR for disease-free survival, 0.49; 95% CI, 0.23-1.04; *P* for trend with increasing number of affected relatives = .01). The improved disease-free survival associated with a family history was independent of tumoral MSI or MMR status.

Conclusion Among patients with stage III colon cancer receiving adjuvant chemotherapy, a family history of colorectal cancer is associated with a significant reduction in cancer recurrence and death.

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Approximately 16% to 20% of patients with colorectal cancer have a first-degree relative with colorectal cancer.[1] Beyond rare but highly penetrant hereditary colorectal cancer syndromes, numerous studies have demonstrated that a history of colorectal cancer in a first-degree relative increases the risk of developing the disease by approximately 2-fold.[2-5] However, the influence of family history on cancer recurrence and survival among patients with established colon cancer remains uncertain. A study of the Utah Population Database and Cancer Registry observed that family history of colon cancer had little impact on colon cancer patient survival[6]; in contrast, an analysis of a Japanese tumor registry demonstrated an improved prognosis.[7] Interpretation of these con-

For editorial comment see p 2564.

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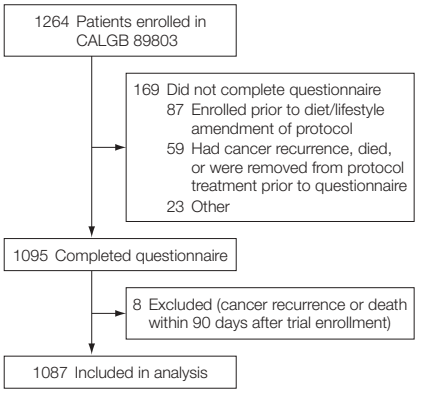
Figure 1. Derivation of Cohort Size



CALGB indicates Cancer and Leukemia Group B.

flicting data is limited by a lack of detailed information regarding tumor stage and treatment in either of these studies.

We therefore prospectively examined the influence of family history of colorectal cancer on survival of patients with stage III colon cancer who participated in a large clinical trial of adjuvant chemotherapy sponsored by the National Cancer Institute (NCI). Because detailed information about family history of colorectal cancer was assessed at study entry, we were able to prospectively analyze the influence of family history while adjusting for other predictors of cancer recurrence and survival. In addition, among a subset of subjects with archived tumor specimens, we were able to assess whether the association between family history and survival was independent of tumoral microsatellite instability (MSI) or expression of mismatch repair (MMR) proteins.

METHODS

Study Population

Patients in this study were participants in the NCI-sponsored Cancer and Leukemia Group B (CALGB) adjuvant therapy trial for stage III colon cancer (CALGB 89803). This study was a randomized trial comparing therapy with weekly fluorouracil and leucovorin to therapy with weekly irinotecan, fluorouracil, and leucovorin.[8] Between April 1999 and May 2001, 1264 patients were enrolled in the treatment trial. As part of the original randomized clinical trial protocol, we included a plan to study diet, lifestyle, and family history on patient survival. A validated self-administered questionnaire assessing diet and lifestyle habits as well as family history of colorectal cancer was administered to patients midway through their adjuvant therapy (4 months after surgical resection).[9,10]

The protocol amendment to survey family history was activated after the first 87 patients were enrolled; therefore, only the subsequent 1177 patients were offered the diet and lifestyle companion study. An additional 59 patients experienced cancer recurrence, death, or removal from the protocol before receiving the questionnaire. Thus, 1118 patients were eligible to complete the questionnaire, of whom 1095 patients (98%) completed the survey. Consistent with prior analyses, we excluded patients who experienced cancer recurrence or death within 90 days of trial enrollment to avoid potential bias in risk-factor assessment related to underlying illness,[9] thus leaving 1087 patients eligible for analysis. FIGURE 1 illustrates adherence with completion of the questionnaire and derivation of the final sample size.

Patients were eligible for the treatment trial (and thus this companion study) if they had undergone a complete surgical resection of the primary tumor within 56 days of study entry and had regional lymph node metastases but no evidence of distant metastases (stage III colon cancer). Patients were required to have a baseline Eastern Cooperative Oncology Group performance status of 0 to 2 (ambulatory) and have adequate bone marrow, renal, and hepatic function. Race or ethnicity was self-reported and recorded in the hospital database at each participating center. Classifications included white, Hispanic, black, Asian, Native Hawaiian, Native American, Indian, Filipino, other, and unknown. These data along with other demographic information were reported by each participating center to the CALGB Statistical Center. All patients provided written informed consent, approved by the institutional review board of each participating institution.

Family History Assessment

Participants were asked, "Have any of the following relatives (father, mother, 1 sibling, additional sibling) had colon or rectal cancer?" with an option for yes or no for each relative. Patients were instructed to include any deceased relative and not count half-siblings. Additionally, for each affected relative, patients provided information about the decade of the relative's age at first diagnosis (<50 years, 50-59 years, 60-69 years, ≥70 years, age unknown). No questions were asked about family size, and no attempt was made to validate reports of cancer in family members.

Measurement of MSI

Among patients with available tumor specimens, DNA was extracted from paraffin-embedded tumor and nontumor tissue. Polymerase chain reaction analysis was conducted using a panel of 10 DNA mononucleotide and dinucleotide microsatellite markers.[11] Only cases with 5 or more evaluable microsatellite markers were included. Those showing instability in at least 40% of the loci tested were classified as having high-frequency MSI (MSI-H). Cases with no evaluable markers showing instability were classed as microsatellite stable (MSS), and the remainder were classed as MSI-low (MSI-L).[11]

Immunostaining for the mismatch repair (MMR) proteins MLH1 and MSH2 was undertaken as described previously.[12] If either MLH1 or MSH2 demonstrated lack of staining, the tumor was considered to be MMR deficient. Tumors possessing staining for both MLH1 and MSH2 were considered to be MMR intact.[11]

Among the 1087 patients included in this analysis, 125 were classified as having MSI-H tumors, 614 had MSI-L or MSS tumors, and 348 did not have blocks available for genotyping analysis. Furthermore, 87 patients were clas-

sified as having tumors with deficient staining for the MMR proteins, 580 had tumors with intact MMR staining, and 420 did not have blocks available for immunohistochemical analysis. In multivariate analyses, MSI status and staining for DNA MMR proteins were coded using an indicator variable to reflect missing data.

Study End Points

For this study, the primary end point was disease-free survival (DFS), defined as time from study enrollment to tumor recurrence, occurrence of a new primary colon cancer, or death as a result of any cause. In addition, recurrence-free survival (RFS) was defined as the time from study enrollment to tumor recurrence, death with evidence of recurrence, or occurrence of a new primary colon tumor. For RFS, patients who died without known tumor recurrence were censored at the last documented evaluation by the treatment provider. Finally, overall survival was defined as the time from study enrollment to death as a result of any cause.

Statistical Methods

All 3 end points (DFS, RFS, and overall survival) were examined using Kaplan-Meier curves and the log-rank test.[13] Cox proportional hazards regression was used to determine the simultaneous impact of potential confounders.[14] The proportionality of hazards assumption for the effect of family history was tested by examining it as a time-dependent covariate in the Cox model. The time-dependent family history covariate was not statistically significant ($P=.95$), indicating that the assumption of proportional hazards was appropriate. Covariates with missing variables were coded with indicator variables in adjusted models. We tested for linear trend by entering the number of relatives (0, 1, 2 or more) affected with colorectal cancer as a continuous variable into the multivariate model. Tests of interactions between family history of colorectal cancer and potentially modifying covariates, including treatment, were assessed by entering the cross product of family history and the covariate of interest.

Statistical significance was considered at the .05 level. We used SAS version 9.1 (SAS Inc, Cary, North Carolina) for all statistical analyses. Patient registration, clinical data collection, and statistical analyses were conducted by the CALGB Statistical Center, and all analyses were based on the study database frozen on March 2, 2007. Median follow-up time was calculated among surviving patients from the time of enrollment to the time at which the study database was frozen. Using the Clark C,[15] the completeness of follow-up for this study was 83.25%. Applying the Wu modification[16] to adjust for unreported deaths, a more realistic assessment of the completeness of follow-up was 85.0%.

RESULTS

Results for the clinical trial have been previously reported. No significant differences were found between the study treatment arms in either overall survival or DFS.[8]

Baseline characteristics for the 1087 patients for whom data on family history were captured are presented in TABLE 1. Among these 1087 participants, 195 (17.9%) reported a family history of colorectal cancer in 1 or more first-degree relatives. Compared with patients without a family history, those with a family history were less likely to have presented with clinical bowel obstruction ($P=.02$). Other potentially prognostic patient and tumor characteristics did not differ significantly according to family history.

The median follow-up time from enrollment was 5.6 years (10th and 90th percentiles were 3.3 and 6.4 years, respectively). The predefined primary end point of this analysis was DFS (time to cancer recurrence or death as a result of any cause). A family history of colorectal cancer was associated with a significant reduction in the risk of cancer recurrence or mortality (FIGURE 2). This relationship remained largely unchanged after adjusting for other predictors of cancer recurrence (TABLE 2). Compared with patients without a family history, those with a family history had a multivariate hazard ratio (HR) of 0.72 (95% confidence interval [CI], 0.54-0.96) for cancer recurrence or death. Cancer recurrence or death occurred in 57 of 195 patients (29%; 95% CI, 23%-36%) with a family history of colorectal cancer compared with 343 of 892 patients (38%; 95% CI, 35%-42%) without a family history.

To isolate the influence of family history on cancer recurrences, we used the end point of RFS in secondary analyses. Compared with patients without a family history of colorectal cancer, those with a family history had a multivariate HR of 0.74 (95% CI, 0.55-0.99) for cancer recurrence (Table 2). Cancer recurrence occurred in 52 of 195 patients (27%; 95% CI, 21%-33%) with a family history of colorectal cancer and 316 of 892 patients (35%; 95% CI, 32%-39%) without a family history. Moreover, the adjusted HR for overall mortality among patients with a family history compared with patients without a family history was 0.75 (95% CI, 0.54-1.05). Death occurred in 43 of 195 patients (22%; 95% CI, 17%-28%) with a family history of colorectal cancer and 247 of 892 patients (28%; 95% CI, 25%-31%) without a family history.

The apparent benefit associated with family history was stronger with an increasing number of affected family members (FIGURE 3 and TABLE 3). Although the vast majority of patients with a family history reported 1 affected relative, there was a significant trend for improvement in DFS with an increasing number of affected family members. Compared with participants without a family history of colorectal cancer, those with 1 affected relative had a multivariate HR of 0.77 (95% CI, 0.57-1.04) for cancer recurrence or death. For participants with 2 or more affected relatives, we observed a greater reduction in risk (multivariate HR, 0.49; 95% CI, 0.23-1.04; P for trend with increasing number of affected relatives=.01). Cancer recurrence or death occurred in 50 of 165 patients (30%;

Table 1. Baseline Characteristics by Family History of Colorectal Cancer

	Family History of Colorectal Cancer, No. (%)		
	No (n=892)	Yes[a] (n=195)	*P* Value[b]
Age, median (range), y	60 (24-85)	63 (21-85)	.24[c]
Male sex	488 (55)	119 (61)	.11
Race			
White	789 (89)	171 (88)	.83
Black	61 (7)	14 (7)	
Other	39 (4)	10 (5)	
Performance status[d]			
0	658 (75)	139 (73)	.52
1-2	214 (25)	51 (27)	
Body mass index, median (range)[e]	27.3 (15.6-51.7)	26.8 (17.5-49.3)	.32[c]
Treatment arm			
Fluorouracil and leucovorin	446 (50)	102 (52)	.58
Irinotecan, fluorouracil, and leucovorin	446 (50)	93 (48)	
Tumor location			
Right colon	486 (56)	115 (61)	.26
Left colon	385 (44)	75 (39)	
Postoperative CEA[f]			
≤5	765 (92)	168 (94)	.28
>5	69 (8)	10 (6)	
Invasion through bowel wall[g]			
T1 and T2	117 (13)	25 (13)	.99
T3 and T4	753 (87)	165 (87)	
Positive lymph nodes			
1-3	553 (63)	124 (65)	.17
≥4	321 (37)	66 (35)	
Tumor differentiation			
Well	52 (6)	9 (5)	.70
Moderate	616 (71)	133 (70)	
Poor	203 (23)	49 (26)	
Clinical bowel obstruction	212 (24)	31 (16)	.02
Clinical bowel perforation	37 (4)	11 (6)	.34
Smoking status			
Current	80 (9)	27 (14)	.13
Past	393 (45)	85 (44)	
Never	408 (46)	83 (43)	
Household income in 1999, median (range), $[h]	40 542 (20 480-122 956)	41 367 (17 963-97 918)	.26
Physical activity, median (range), MET h/wk	4.9 (0-125.2)	4.5 (0-147.4)	.48
Dietary intake, median (range)			
Red meat, servings/wk	3.2 (0-22.6)	3.2 (0-15.1)	.80[c]
Processed meats, servings/wk	2.4 (0-33.0)	2.6 (0-16.0)	.15[c]
Refined grains, servings/d	3.2 (0-21.6)	2.9 (0.5-16.3)	.38[c]
Dessert, servings/d	1.2 (0-10.8)	1.1 (0-19.3)	.84[c]
Total fat, g/d	73.6 (0-127.6)	75.0 (26.8-117.2)	.50[c]

Abbreviations: CEA, carcinoembryonic antigen; MET, metabolic equivalent tasks.
[a] Percentages may not add to 100 due to rounding.
[b] By χ^2 test unless otherwise noted.
[c] By Wilcoxon rank sum.
[d] A performance status of 0 indicates the patient was fully active; 1, restricted in physically strenuous activity but ambulatory and able to carry out light work; and 2, ambulatory and capable of all self-care but unable to carry out any work activities and up and about more than 50% of waking hours. Performance status was based on patient status at initiation of chemotherapy (entry into the treatment trial).
[e] Body mass index is calculated as weight in kilograms divided by height in meters squared. Body mass index was based on patient status at initiation of chemotherapy (entry into the treatment trial).
[f] Postoperative CEA was based on patient status at initiation of chemotherapy (entry into the treatment trial).
[g] A grade of T1 or T2 indicates the level of invasion was through the bowel wall but not beyond the muscle layer; T3 or T4, the level of invasion was through the bowel wall beyond the muscle layer.
[h] Median household income was determined based on the median household income in the patient's zip code area according to the US National Census in 2000.

95% CI, 24%-38%) with 1 affected relative, 7 of 30 patients (23%; 95% CI, 12%-41%) with 2 or more affected relatives, and 343 of 892 patients (38%; 95% CI, 35%-42%) without a family history. We observed similar trends for cancer recurrence (RFS; *P* for trend = .03) and overall mortality (*P* for trend = .09) (Table 3).

We also examined whether the effect of family history varied according to the age at which the first-degree relative was diagnosed with colorectal cancer. Among patients whose relative was diagnosed with colorectal cancer at an age younger than 50 years, the adjusted HR for cancer recurrence or mortality (DFS) was 0.68 (95% CI, 0.36-1.29) compared with patients without a family history of colorectal cancer. For patients with a family member diagnosed with colorectal cancer at age 50 years or older, the adjusted HR for cancer recurrence or mortality was 0.73 (95% CI, 0.53-1.00). Cancer recurrence or death occurred in 10 of 36 patients (28%; 95% CI, 16%-44%) and 46 of 155 patients (30%; 95% CI, 23%-37%) with a history of colorectal cancer diagnosed in a family member at an age younger than 50 years and at 50 years or older, respectively.

We considered the possibility that patients with a family history of colorectal cancer might have a different prognosis related to earlier detection of their cancers. Although adjusting for depth of invasion (T stage) and nodal status (N stage) and the presence of clinical obstruction or perforation would minimize such biases, we further addressed this concern by repeating our analyses after excluding patients with earlier stage T1 and T2 tumors. However, restricting the analysis to patients with T3 and T4 tumors did not materially alter our results. Compared with patients without a family history, those with 1 or more affected first-degree relatives experienced a multivariate HR for cancer recurrence or death of 0.69 (95% CI, 0.51-0.94). Among patients with T3 and T4 tumors, cancer recurrence or death occurred in 49 of 165 patients (30%; 95%

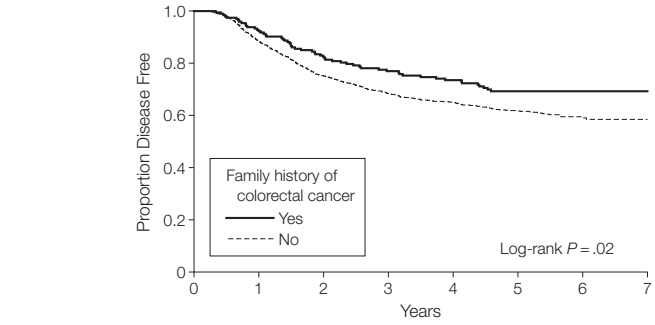
CI, 23%-37%) with a family history of colorectal cancer and 310 of 753 patients (41%; 95% CI, 38%-45%) without a family history.

We also repeated our analyses after excluding patients with a cancer detected in less than 4 positive lymph nodes (N1). Among patients with N2 disease (≥4 positive lymph nodes), our results remained largely unchanged: the adjusted HR for cancer recurrence or death among patients with a family history of colorectal cancer was 0.76 (95% CI, 0.49-1.17). Cancer recurrence or death occurred in 26 of 66 patients (39%; 95% CI, 29%-51%) with a family history of colorectal cancer and 156 of 321 patients (49%; 95% CI, 43%-54%) without a family history.

We also assessed the association between family history and DFS across strata of other potential predictors of patient outcome (FIGURE 4). The effect of family history on the risk of cancer recurrence or mortality was not significantly modified by baseline performance status, number of positive lymph nodes, or treatment arm. In contrast, the effect of family history appeared to differ according to patient age and sex. Among patients younger than 50 years, a family history of colorectal cancer was associated with an adjusted HR for cancer recurrence or death of 1.19 (95% CI, 0.61-2.31); among patients 50 years or older, the adjusted HR for family history was 0.66 (95% CI, 0.48-0.91). For patients younger than 50 years, cancer recurrence or death occurred in 14 of 40 patients (35%; 95% CI, 22%-50%) and 61 of 172 patients (35%; 95% CI, 29%-43%) with and without a family history, respectively. For patients 50 years or older, cancer recurrence or death occurred in 43 of 155 patients (28%; 95% CI, 21%-35%) and 282 of 720 patients (39%; 95% CI, 36%-43%) with and without a family history, respectively.

Among male patients, a family history of colorectal cancer was associated with an adjusted HR for cancer recurrence or death of 0.63 (95% CI, 0.44-0.91); among female patients, the adjusted HR for family history was 1.03 (95% CI, 0.64-1.63). For male patients, cancer recurrence or death occurred in 35 of 119 patients (29%; 95% CI, 22%-38%) and 202 of 488 patients (41%; 95% CI, 37%-46%) with and without a family history, respectively. For female patients, cancer recurrence or death occurred in 22 of 76 patients (29%; 95% CI, 20%-40%) and 141 of 404 patients (35%; 95% CI, 30%-40%) with and without a family history, respectively. Nonetheless, tests for interaction between patient age and the presence of a family history and patient sex and the presence of a family history did not reach statistical significance ($P = .18$ and

Figure 2. Disease-Free Survival According to Family History of Colorectal Cancer



No. at risk							
Family history of colorectal cancer							
Yes	195	179	155	137	123	104	29
No	892	786	650	572	513	405	124
No. of events							
Family history of colorectal cancer							
Yes	15	19	20	6	7	0	
No	102	118	57	28	25	12	

Table 2. Unadjusted and Multivariate Adjusted Hazard Ratios for Recurrence-Free Survival, Disease-Free Survival, and Overall Survival According to Presence of Family Member With Colorectal Cancer

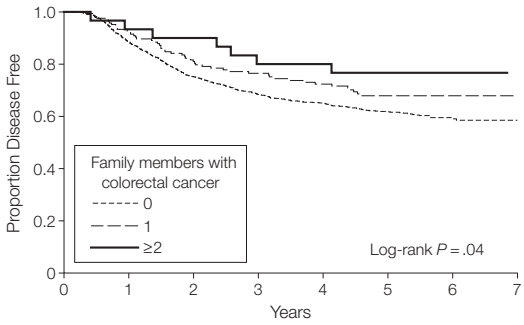
	Family Member With Colorectal Cancer	
	No	Yes
Cancer recurrence or death from any cause (disease-free survival)		
No. of events	343	57
No. at risk	892	195
Unadjusted HR (95% CI)	1 [Reference]	0.71 (0.54-0.94)
Adjusted HR (95% CI)[a]	1 [Reference]	0.72 (0.54-0.96)
Cancer recurrence (recurrence-free survival)		
No. of events	316	52
No. at risk	892	195
Unadjusted HR (95% CI)	1 [Reference]	0.71 (0.53-0.95)
Adjusted HR (95% CI)[a]	1 [Reference]	0.74 (0.55-0.99)
Overall mortality		
No. of events	247	43
No. at risk	892	195
Unadjusted HR (95% CI)	1 [Reference]	0.75 (0.54-1.03)
Adjusted HR (95% CI)[a]	1 [Reference]	0.75 (0.54-1.05)

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Multivariate HRs and 95% CIs are adjusted for age (years), sex, race, performance status (0 vs 1-2), depth of invasion (T1 and T2 vs T3 and T4), number of positive lymph nodes (1-3 vs 4 or more), presence of clinical perforation at the time of surgery, presence of bowel obstruction at the time of surgery, postoperative carcinoembryonic antigen (<5 vs ≥5), grade of tumor differentiation (undifferentiated or poorly differentiated vs well or moderately differentiated), and treatment arm. Grades for performance status and depth of invasion are explained in the footnotes to Table 1.

P=.19, respectively). In addition, the effect of family history appeared stronger when the primary tumor was located in the right colon (cecum to splenic flexure) relative to the left colon (splenic flexure to the rectosigmoid junction). Among patients with tumors located in the right colon, the adjusted HR for DFS in patients with a family history was 0.61 (95% CI, 0.41-0.90) compared with those without a family history of colorectal cancer. Among patients with tumors located in the left colon, the adjusted HR for DFS was 1.01 (95% CI, 0.65-1.56). For patients with right-sided tumors, cancer recurrence or death occurred in 32 of 115 patients (28%; 95% CI, 20%-37%) and 195 of 486 patients (40%; 95% CI, 36%-45%) with and without a family history, respectively. For patients with left-sided tumors, cancer recurrence or death occurred in 25 of 75 patients (33%; 95% CI, 24%-45%) and 138 of 385 patients (36%; 95% CI, 31%-41%) with and without a family history, respectively. Nonetheless, a test of interaction between the site of the primary tumor and the presence of a family history did not reach statistical significance (P=.16).

We also examined whether family history modified the effect of adjuvant chemotherapy assignment on DFS. Among patients with a family history of colorectal cancer, those randomized to receive irinotecan, fluorouracil, and leucovorin had an adjusted HR for cancer recurrence or death of 1.07 (95% CI, 0.60-1.92) when compared with those who received fluorouracil and leucovorin. Similarly, among patients without a family history of colorectal cancer, the adjusted HR of death or recurrence for patients treated with irinotecan, fluorouracil, and leucovorin was 1.02 (95% CI, 0.83-1.27) compared with those who received fluorouracil and leucovorin. For patients with a family history of colorectal cancer, cancer recurrence or death occurred in 27 of 93 patients (29%; 95% CI, 21%-39%) randomized to receive irinotecan, fluorouracil, and leucovorin and 30 of 102 patients (29%; 95% CI, 21%-39%) randomized to receive fluorouracil and leucovorin. For patients without a family history of colorectal cancer, cancer recurrence or death occurred in 177 of 446 patients (40%; 95% CI, 35%-44%) randomized to receive irinotecan, fluorouracil, and leucovorin and 166 of 446 patients (37%; 95% CI, 33%-42%) randomized to receive fluorouracil and leucovorin.

Figure 3. Disease-Free Survival According to Number of Family Members With History of Colorectal Cancer



No. at risk							
Family members with colorectal cancer							
0	892	786	650	572	513	405	124
1	165	151	128	113	99	83	22
≥2	30	28	27	24	24	21	8

No. of events						
Family members with colorectal cancer						
0	102	118	57	28	25	12
1	13	18	7	6	6	0
≥2	2	1	3	0	1	0

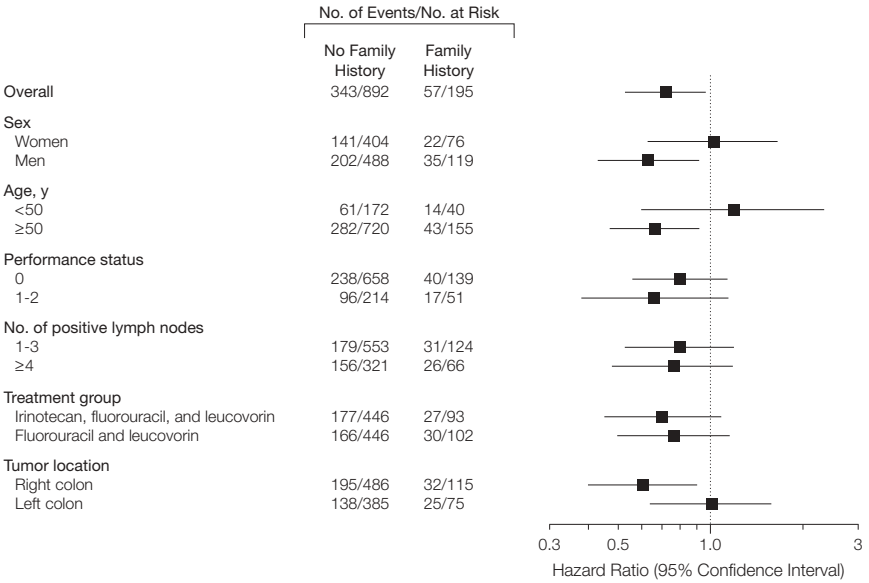
Table 3. Unadjusted and Multivariate Adjusted Hazard Ratios for Disease-Free Survival and Overall Survival According to Number of Family Members With Colorectal Cancer

	No. of Family Members With Colorectal Cancer			
	0	1	≥2	*P* Value for Trend
Cancer recurrence or death from any cause (disease-free survival)				
No. of events	343	50	7	
No. at risk	892	165	30	
Unadjusted HR (95% CI)	1 [Reference]	0.75 (0.56-1.01)	0.51 (0.24-1.09)	
Adjusted HR (95% CI)[a]	1 [Reference]	0.77 (0.57-1.04)	0.49 (0.23-1.04)	.01
Cancer recurrence (recurrence-free survival)				
No. of events	316	46	6	
No. at risk	892	165	30	
Unadjusted HR (95% CI)	1 [Reference]	0.75 (0.55-1.02)	0.49 (0.22-1.09)	
Adjusted HR (95% CI)[a]	1 [Reference]	0.79 (0.58-1.08)	0.49 (0.22-1.11)	.03
Overall mortality				
No. of events	247	36	7	
No. at risk	892	165	30	
Unadjusted HR (95% CI)	1 [Reference]	0.75 (0.53-1.06)	0.74 (0.35-1.58)	
Adjusted HR (95% CI)[a]	1 [Reference]	0.77 (0.54-1.10)	0.65 (0.30-1.40)	.09

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Multivariate HRs and 95% CIs are adjusted for age (years), sex, race, performance status (0 vs 1-2), depth of invasion (T1 and T2 vs T3 and T4), number of positive lymph nodes (1-3 vs 4 or more), presence of clinical perforation at the time of surgery, presence of bowel obstruction at the time of surgery, postoperative carcinoembryonic antigen (<5 vs ≥5), grade of tumor differentiation (undifferentiated or poorly differentiated vs well or moderately differentiated), and treatment arm. Grades for performance status and depth of invasion are explained in the footnotes to Table 1.

Finally, we considered the possibility that the association between family history and improvement in DFS might be related to MSI status. Information regarding MSI status, as determined by genotyping, was available for 739 patients; information regarding immunostaining for the DNA MMR proteins MLH1 and MSH2 was available for 667 patients. The prevalence of MSI-H tumors was 24% (30/125; 95% CI, 17%-32%) and 15% (95/614; 95% CI, 13%-19%) among patients with and without a family history of colorectal cancer, respectively. The prevalence of tumors with deficient staining for MMR proteins was 21% (24/115; 95% CI, 14%-29%) and 11% (63/552; 95% CI, 9%-14%) among patients with and without a family history of colorectal cancer, respectively. Results remained largely unchanged after adjustment for MSI status: the adjusted HR for DFS was 0.73 (95% CI, 0.55-0.97) among patients with a family history of colorectal cancer compared with those without a family history. Similarly, the adjusted HR for DFS was 0.73 (95% CI, 0.55-0.97) among patients with a family history of colorectal cancer compared with those without a family history after adjusting for MMR status. Furthermore, the effect of family history on DFS did not appear to be modified by either MSI or MMR status (*P* for interaction=.51 and .45, respectively).

Figure 4. Stratified Analysis of Disease-Free Survival (Comparison of Patients With a Family History of Colorectal Cancer With Those Without a Family History)



A performance status of 0 indicates the patient was fully active; 1, restricted in physically strenuous activity but ambulatory and able to carry out light work; and 2, ambulatory and capable of all self-care but unable to carry out any work activities and up and about more than 50% of waking hours.

COMMENT

In a cohort of patients with stage III colon cancer treated with surgery and adjuvant chemotherapy, a history of colorectal cancer in a first-degree relative was associated with a significant reduction in cancer recurrence and mortality. Moreover, the apparent benefit associated with family history increased significantly with an increasing number of affected first-degree relatives, and the effect of family history appeared to be independent of tumoral MSI or DNA MMR status.

Numerous studies have demonstrated that family history of colorectal cancer increases the risk of developing colorectal cancer.[2-5] However, few studies have examined the influence of family history of colorectal cancer on subsequent outcomes in patients with established cancer. Our findings are consistent with reports from a large registry of Japanese patients, which demonstrated improved 5-year survival among patients with colorectal cancer with a family history of the disease.[7] In contrast, Slattery and Kerber[6] found no overall effect of family history on survival of patients with colon cancer. However, the latter study was based on patients identified through a Utah cancer registry and had limited information on treatment, follow-up care, disease stage, and other prognostic factors.

Our study has several strengths because it is based on patients enrolled in an NCI-sponsored clinical trial. First, all patients had lymph node–positive cancer, reducing the impact of heterogeneity by disease stage. Second, treatment and follow-up care were standardized, and the date and nature of recurrence were recorded prospectively. Finally, extensive and detailed information on other prognostic factors was routinely collected.

Several limitations of this study deserve comment. First, because we relied on self-reported family history, misclassification of family history status may be possible. However, prior studies have demonstrated such data to be reliable.[17] Moreover, because the data on family history were collected at study baseline before cancer recurrence, any errors in recall would have attenuated rather than exaggerated a true association with patient outcome.

Additionally, we did not collect information regarding number of siblings, and the likelihood of having a family history of the disease may vary according to the number of siblings at risk for the disease. However, it is unlikely that family size independently affects survival. Moreover, less detailed information of kindred size is likely nondifferential and would only bias our results toward finding no association between family history and survival.

Our analysis sought to assess the influence of family history beyond the rare, well-characterized hereditary colorectal cancer syndromes of familial adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer (HNPCC). Beyond obtaining data on colorectal cancer in first-degree family members, our trial did not specifically elicit information about the presence of FAP or HNPCC; nonetheless, fewer than 5% of colorectal cancer cases are attributable to these syndromes. Numerous studies demonstrate that a common (ie, nonsyndromic) family history of colorectal cancer significantly increases the risk of developing colorectal cancer, and the current analysis suggests that the presence of a common (ie, nonsyndromic) family history is significantly associated with an improved cancer survival. Although we cannot exclude the possibility that patients with multiple affected relatives in our trial may have included some patients with FAP or HNPCC, the vast majority of patients reporting a family history of colorectal cancer in this study were likely to have an undefined or sporadic familial predisposition toward developing colorectal cancer. Moreover, even among patients with only 1 affected relative, we observed a 25% reduction in cancer-specific and overall mortality.

We cannot completely exclude the possibility that patients with a family history may experience an improved prognosis due to earlier detection of malignancy. However, the effect of family history persisted after adjusting for other patient and disease characteristics associated with cancer recurrence or survival. Additionally, because patients were entered into a clinical trial that was restricted to stage III cancer, pathologic stage, administration of adjuvant therapy, and follow-up care were reasonably uniform among all participants. Moreover, the benefit associated with family history remained largely unchanged across the number of positive lymph nodes as well as baseline performance status. Although the effect of family history appeared to be modified by patient age, sex, and tumor location, tests for interaction were not significant, possibly because of limited statistical power. Further investigation to explore the relationship between family history and these factors is required.

Finally, because our study was based on a well-defined cohort enrolled in a clinical trial, our results may not be generalizable to a larger population of patients with colon cancer. However, the rate of family history in this cohort is similar to the general population of patients with colon cancer, and there is no evidence that family history appreciably varies according to participation in a clinical trial.

Studies suggest the importance of genetic contributions to the development of familial colorectal cancers.[18-20] However, the relationship between family history and outcome is likely to be complex and may be influenced by a confluence of genetic and environmental factors. We considered whether shared environmental or lifestyle factors might contribute to our findings but found no significant difference in smoking, median household income, body mass index, diet, and physical activity patterns between patients with and without a family history of colorectal cancer (Table 1).

Beyond rare, well-characterized hereditary colorectal cancer syndromes (eg, FAP or HNPCC), our data support the hypothesis that a relatively common though less penetrant genetic predisposition may not only influence colorectal cancer risk but also patient survival. This finding may reflect a distinct underlying molecular and pathogenic mechanism in cancers that develop in the setting of a common (ie, sporadic) family history. For example, data suggest that family history of colorectal cancer is associated with tumors with a higher frequency of microsatellite instability (MSI-H),[21,22] which may be associated with improved prognosis compared with microsatellite stable tumors.[23-27] Consistent with the observation that MSI-H tumors are more common in the right colon,[11,28] the beneficial effect of family history in the current study appeared greater among patients with right-sided colon cancer. However, our results remained largely unchanged after adjustment for MSI or MMR status, and we found no significant interaction between family history and MSI or MMR status. This suggests that the association between a sporadic (ie, nonsyndromic) family history and reduction in risk of cancer recurrence or death may be independent of MSI or MMR status. Nonetheless, family history may influence cancer prognosis through other pathways. Further studies are needed to more fully elucidate potential mechanisms by which a common family history may influence the outcome for patients with colorectal cancer.

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