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Risk of second primary colorectal cancer among colorectal cancer cases: A population-based analysis

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Abstract

Background: Patients with history of colorectal cancer (CRC) are at increased risk for developing a second primary colorectal cancer (SPCRC) as compared to the general population. However, the degree of risk is uncertain. Here, we attempt to quantify the risk, using data from the large population-based California Cancer Registry (CCR). **Materials and Methods:** We analyzed the CCR data for cases with surgically-treated colon and rectal cancer diagnosed during the period 1990–2005 and followed through up to January 2008. We excluded those patients diagnosed with metastatic disease and those in whom SPCRC was diagnosed within 6 months of the diagnosis of the primary CRC. Standardized incidence ratios (SIR) with 95% confidence intervals (CI) were calculated to evaluate risk as compared to the underlying population after taking into account age, sex, ethnicity, and time at risk. **Results:** The study cohort consisted of 69809 cases with colon cancer and 34448 with rectal cancer. Among these patients there were 1443 cases of SPCRCs. The SIR for developing SPCRC was higher in colon cancer survivors (SIR=1.4; 95% CI: 1.3 to 1.5) as compared to the underlying population. The incidence of SPCRC was also higher in females (SIR=1.5; 95% CI: 1.3 to 1.6) and Hispanics (SIR=2.0; 95% CI: 1.7 to 2.4) with primary colon cancer. The SIR for developing an SPCRC was higher only among those whose initial tumor was located in the descending colon (SIR=1.6; 95% CI: 1.3 to 2.0) and proximal colon (SIR=1.4; 95% CI: 1.3 to 1.6). **Conclusions:** Our results confirm that CRC patients, especially females and Hispanics, are at a higher risk of developing SPCRC than the general population. Differential SPCRC risk by colorectal tumor subsite is dependent on gender and ethnicity, underscoring the heterogeneous nature of CRC.

Keywords: Cancer registry, colon cancer, colorectal cancer, rectal cancer, second primary cancer

BACKGROUND

Colorectal cancer (CRC) is the second most common cancer in the US and the second most common cancer cause of death in the US.[1,2] Patients who have a history of localized CRC are at increased risk of developing a second primary colorectal cancer (SPCRC). In non-metastatic cases following surgical resection and adjuvant chemotherapy (e.g., in lymph node–positive or high-risk cases), surveillance colonoscopy has been the standard of care.[3-6] Despite routine colonoscopic surveillance, CRC patients have been shown to have increased risk of developing an SPCRC compared to the general population.[7,8] However, the degree of risk

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is uncertain, and clear predisposing factors for SPCRC development have not been established.

The incidence and rate of development of SPCRC have implications for appropriate surveillance methods after diagnosis of CRC, especially in view of the increasing number of CRC survivors. However, scant data are available to evaluate the effectiveness of current approaches to postoperative surveillance and for assessment of the risk of SPCRC.[9] Furthermore, available data are limited by short follow-up time. From the available literature, the incidence of SPCRC is estimated at 1.1%–3.6%, with the variation possibly related to study-specific differences in mean follow-up duration.[10-12] Also, the magnitude of risk is difficult to evaluate because of evolving CRC treatment modalities over the past decade. Current National Comprehensive Cancer Network (NCCN) guidelines recommend colonoscopy at 1 year after surgical resection and, if that is normal, to repeat the examination in 3 years and then every 5 years if no advanced adenomas are identified.[6] However, applying established surveillance recommendations from patients with colorectal polyps to patients with a personal history of CRC is potentially problematic. At the same time, it is not known whether intensive surveillance will be beneficial for decreasing the mortality from CRC-specific deaths due to SPCRCs. Hence, it is imperative to understand the risk of SPCRC among CRC cases.

Factors such as young age, female gender, prior synchronous adenoma or carcinoma, and family history of CRC have been implicated as risk factors for developing SPCRC.[8,12-17] Race/ethnicity differences have been identified as risk factors for primary CRC development[18,19] and also for CRC-specific survival beyond CRC diagnosis.[20] Tumor subsite location within the colon has been associated with CRC-specific mortality.[21] However, it is not known if race/ethnicity or tumor subsite location is predictive for SPCRC development. The purpose of this study was to identify the risk and clinical characteristics of SPCRC from the large population-based California Cancer Registry (CCR) and, more precisely, to determine whether certain intrinsic risk factors such as tumor subsite location, gender, and ethnicity play a role in the development of SPCRC. Establishing the accuracy of estimation of SPCRC risk may lead to improved recommendations for surveillance in patients with CRC and better selection of individuals who may benefit from tertiary prevention.

MATERIALS AND METHODS

Incidence data

Cancer incidence data are from the CCR Statistical Extract of January 2008. Cancer type and behavior (*in situ* or invasive disease) are as per the International Classification of Diseases for Oncology, second edition[22] and the cancer-type recording scheme of the Surveillance, Epidemiology, and End-Results Program of the National Cancer Institute.[23] The order of tumors within the same patient is given by the variable *sequence number.*[24] Stage of disease is given by the variable *sumstage*.[24] Determination of race/ethnicity and tumor subsite location have been previously described.[21]

Study cohort

The study cohort included all persons in the data set meeting all of the following conditions: a) first cancer is CRC, b) stage at diagnosis is local or regional disease, c) resident in California at diagnosis, d) diagnosed from 1990 through 2005, e) under 81 years old at diagnosis, and f) alive at diagnosis. Because of difficulties in estimating risk we excluded those: a) over age 80 at diagnosis, b) deceased at diagnosis, and c) of unknown race/ethnicity. We also excluded those diagnosed with metastatic disease and those whose second cancer was diagnosed within 6 months of the first diagnosis (to avoid synchronous tumors).

Second primary cancer ascertainment

SPCRCs were identified in the database where the *sequence number* is two, the age of diagnosis is below 85, the diagnosis period is 1990–2005, and the residence is within California. Both *in situ* and invasive disease count as second primaries as we presume the cohort is under medical surveillance. SPCRCs diagnosed over age 84 were ignored because of the difficulties of estimating risk past that age, although such cases contribute risk through age 84.

Risk of second cancer

Methods for estimating second cancer risk have been previously described.[25-27] Briefly, risk is estimated by calculating the standardized incidence ratio (SIR). Expected numbers result from summing the cumulative risk of cancer (both *in situ* and invasive disease) across the cohort, as previously described. For each individual, risk begins at diagnosis of the first cancer and ends with the earliest of the following: a) diagnosis of the second cancer, b) loss to follow-up, c) death, or d) age 84. Second primaries other than CRC are ignored. Cumulative risk is based on average annual age-, race/ethnic-, and sex-specific incidence rates estimated from the 5-year period centered on the US Census of 2000 (viz., 1998–2002), using the aforementioned CCR data set and the population data set most recently adopted by CCR.[24,28] Thus, the expected numbers of second cancers for the cohort take into account age at first diagnosis, time at risk, sex, and race/ethnicity Follow-up was extended through January 2008. Because calculations are based on age in whole years,

each patient contributes a minimum of 1 year of risk to the expected numbers of cases, which biases results towards the null hypotheses.

Statistical analysis

The SIRs are evaluated by exact Poisson 95% confidence intervals (CI).[29] Associations in contingency tables are tested by likelihood-ratio chi square (χ^2) or the Cochran-Armitage trend test (Z).[30] Strength of associations are tested with the Kappa coefficient[31] or Sakoda's adjusted contingency coefficient (C*). Interval estimates of proportions are by exact binomial methods. Cox proportional hazards regression models were performed using time from first CRC diagnosis until either incidence of second primary CRC or a censoring observation (i.e., end of study period, death from any cause, or loss to follow-up). Eight categories resulted from combining gender and race/ethnic group (Caucasian, African-American, Hispanic, Asian). Caucasian males were the referent group. All models included adjustment for age at first CRC diagnosis. Programming and analyses was accomplished with SAS/STAT® software.

Ethical considerations

This study involved analysis of existing data from the CCR database, with no subject intervention. No identifiers were linked to subjects. The study was approved by the University of California Irvine Institutional Review Board (IRB) under the category 'exempt status' (IRB# 2007-5842, and 2010-7853).

RESULTS

Clinical characteristics of primary colon and rectal cancer cases

Table 1 depicts the clinical characteristics of primary colon cancer across multiple variables. A total of 69809 cases were diagnosed with non-metastatic colon cancer and 34448 with non-metastatic rectal cancer during the study period. Among colon cancer cases there were 71% (n=49236) Caucasians, 7% (n=5190) African Americans, 12% (n=8641) Hispanics, 10% (n=6675) Asian/Pacific Islanders, and <1% (n=67) other race/ethnicities. Table 2 shows the clinical characteristics of primary rectal cancer cases. Among rectal cancer cases there were 68% (n=23446) Caucasians, 5% (n=1930) African Americans, 15% (n=5032) Hispanics, 12% (n=3991) Asian/Pacific Islanders, and less than 1% other race/ethnicities. As Table 1 shows there was no marked difference between the different ethnic groups in any of the characteristics examined, except for socioeconomic status (SES). African-Americans and Hispanics were found to be represented in greater proportions in the lower SES while Caucasians and Asians were in the higher SES quintiles. The mean age at diagnosis of the first tumor was 65.6 years ± 10.9 (SD) for colon cancer and 62.8 years ± 11.5 (SD) for rectal cancer. Mean observation time overall was 6.0 years (72.4 months ± 52.4 SD, median = 60.4 months).

Clinical characteristics of second primary colon and rectal cancer cases

In all, 1443 SPCRC cases were identified: 1077 among patients with primary colon cancer (including proximal, transverse, descending, and sigmoid colon cancers), and 366 among patients with primary rectal cancer (including rectosigmoid and rectum cancers). Among the cases with a primary diagnosis of colon cancer, 616 (58%) second primaries occurred in patients with right-sided (proximal and transverse colon) cancers, 88 (8%) in patients with descending colon cancer, and 373 (34%) in patients with sigmoid cancers. Among rectal cancer cases, SPCRCs were identified in 141 (39%) rectosigmoid cancer patients and 225 (61%) distal rectal cancer patients. Among colon cancer cases, Caucasians comprised 72% (n=780), Hispanics 12% (n=130), Asian/Pacific Islanders 8% (n=89), African-Americans 7% (n=78), and other racial/ethnic groups less than 1%. Among rectal cancer cases, Caucasians comprised 68% (n=249), Hispanics 18% (n=66), Asian/Pacific Islanders 7% (n=29), African-Americans 6% (n=22), and other racial/ethnic groups less than 1%. Mean age at diagnosis of the second tumor was 70.2 ± 10.3 years (median age = 73 years) for cases with a first diagnosis of colon cancer and 68.7 ± 11.0 years (median age = 71 years) for those with a first diagnosis of rectal cancer. Advanced stage at presentation of SPCRC was observed in 9% of primary colon cancer cases and 11% of primary rectal cancer cases. Surgical resection was performed upon diagnosis of first tumor in 98.9% of colon cancers and 95.6% of rectal cancers.

Rate of second primary colorectal cancer

We excluded tumors that were diagnosed during 0–6 months following primary diagnosis and thus 2081 colon and 669 rectal synchronous cancers were excluded. Only 13% of all SPCRCs were diagnosed within months 7–12 (i.e., the first period we examined), whereas >50% of the SPCRCs observed were diagnosed beyond 2.5 years from diagnosis of the first CRC. Also, a large proportion of SPCRC cases (~53%) developed during years 1–4 post resection. The median time from diagnosis of first tumor to development of SPCRC was 32 months.

Standardized incidence ratios

As shown in Table 3, the overall estimated standardized incidence ratio (SIR) and the 95% confidence intervals (95% CI) for an SPCRC following a prior colon cancer was elevated above the general population SIR of 1.4 (95% CI: 1.3

Table 1: Clinical characteristics of cases with a first diagnosis of colon cancer, by race/ethnicity

	Caucasian n=49236	African-American n=5190	Hispanic n=8641	Asian n=6675	Other n=67	Total n=69809
Median age* (in years, with range)	69 (14–80)	65 (15–80)	65 (12–80)	66 (17–80)	64 (30–80)	68 (12–80)
Gender						
Male	26185 (53%)	2538 (49%)	4508 (52%)	3338 (50%)	35 (52%)	36604 (52%)
Female	23051 (47%)	2652 (51%)	4133 (48%)	3337 (50%)	32 (48%)	33205 (48%)
SEER stage						
Local	22545 (46%)	2248 (43%)	3725 (43%)	2820 (42%)	26 (39%)	31364 (45%)
Regional	26691 (54%)	2942 (57%)	4916 (57%)	3855 (58%)	41 (61%)	38445 (55%)
Grade						
Well differentiated	5844 (12%)	609 (12%)	1026 (12%)	629 (9%)	8 (12%)	8116 (12%)
Moderately differentiated	31047 (63%)	3362 (65%)	5479 (63%)	4378 (66%)	42 (63%)	44308 (63%)
Poorly differentiated	8185 (17%)	707 (14%)	1367 (16%)	1144 (17%)	15 (22%)	11418 (16%)
Undifferentiated	253 (<1%)	28 (<1%)	50 (<1%)	29 (<1%)	2 (3%)	362 (<1%)
Unknown	3907 (8%)	484 (9%)	719 (8%)	495 (7%)	0 (0%)	5605 (8%)
Histological subtype						
Adenocarcinoma	43053 (87%)	4467 (86%)	7490 (87%)	5955 (89%)	64 (96%)	61029 (87%)
Mucinous adenocarcinoma	5298 (11%)	611 (12%)	964 (11%)	616 (9%)	2 (3%)	7491 (11%)
Other	885 (2%)	112 (2%)	187 (2%)	104 (2%)	1 (1%)	1289 (2%)
Colon site						
Proximal/Transverse	28098 (57%)	3183 (61%)	4707 (54%)	3023 (45%)	35 (52%)	39046 (56%)
Distal	3221 (7%)	446 (9%)	557 (6%)	558 (8%)	5 (7%)	4787 (7%)
Sigmoid	17917 (36%)	1561 (30%)	3377 (39%)	3094 (46%)	27 (40%)	25976 (37%)
Socioeconomic status**						
Lowest	4254 (9%)	1806 (35%)	2590 (30%)	811 (12%)	14 (21%)	9475 (14%)
Second lowest	8661 (18%)	1310 (25%)	2194 (25%)	1107 (17%)	25 (37%)	13297 (19%)
Middle	10970 (22%)	971 (19%)	1665 (19%)	1338 (20%)	18 (27%)	14962 (21%)
High	11948 (24%)	756 (15%)	1296 (15%)	1640 (25%)	6 (9%)	15646 (22%)
Highest	13403 (27%)	347 (7%)	896 (10%)	1779 (27%)	4 (6%)	16429 (24%)

Percentages are rounded to nearest whole number. *Age at diagnosis of first tumor; **socioeconomic status of the census tract of residence at diagnosis.

to 1.5). In all, 1433 cases of SPCRC were found over 618104 person-years. Specifically, females (SIR: 1.5; 95% CI: 1.3 to 1.6) had a greater risk than males (SIR: 1.3; 95% CI: 1.2 to 1.4). Females also were observed to have increased risk of developing a rectal cancer (SIR: 1.2; 95% CI: 1.0 to 1.4), while males showed no risk increase (SIR: 1.0; 95% CI: 0.9 to 1.1). Additionally, of the four ethnic groups examined, Hispanics showed the greatest risk of developing a second colon cancer (SIR: 2.0; 95% CI: 1.7 to 2.4), followed by Asian/Pacific Islanders (SIR: 1.5; 95% CI: 1.2 to 1.9), Caucasians (SIR: 1.3; 95% CI: 1.2- to 1.4), and African Americans (SIR: 1.3; 95% CI: 1.1 to 1.7). Similarly, Hispanics also showed elevated SPCRC risk with primary rectal cancer (SIR: 1.9; 95% CI: 1.4 to 2.5), while Asians (SIR: 1.1; 95% CI: 0.7 to 1.6), Caucasians (SIR: 0.9; 95% CI: 0.7 to 1.0), and African Americans (SIR: 1.1; 95% CI: 0.6 to 1.8) showed no statistically significant increase in risk as compared to the general population.

The estimated SPCRC risk estimates based on primary tumor subsite location are shown in Table 4. Overall, the data reveal that Hispanics have the greatest risk of developing a second primary tumor compared to the general population, with the greatest effect seen in those with the first cancer in the descending colon (SIR: 3.0; 95% CI: 1.5 to 5.2). A significantly increased risk of SPCRCs was observed among Hispanics with tumors located in the rectosigmoid colon (SIR: 2.0; 95% CI: 1.3 to 3.0) and rectum (SIR: 1.9; 95% CI: 1.4 to 2.5). Caucasians were observed to have the lowest risk of SPCRC compared to the other ethnic groups. However, among Caucasians, the greatest SPCRC risk was observed for cases with a first diagnosis of descending colon cancer (SIR: 1.6; 95% CI: 1.2 to 2.0) and proximal colon cancer (SIR: 1.4; 95% CI: 1.3 to 1.6). The data on African American population indicate no statistically significant elevated risk for SPCRC with a first diagnosis of colon or rectal cancer. Asians were observed to have an increased risk with first diagnosis of proximal colon cancer (SIR: 1.7; 95% CI: 1.2 to 2.2) but not with cancer at other sites.

Table 4 also displays the subsite-specific relative risk for developing an SPCRC in the colon and rectum in both males and females . Male subjects showed a slight increase in risk of SPCRC when the primary cancer was in the proximal colon (SIR: 1.4; 95% CI: 1.2 to 1.5) but failed to show any significant increase for cancer of the descending colon (SIR: 1.3; 95% CI: 0.7 to 1.7), sigmoid colon (SIR: 1.2; 95% CI:

Table 2: Clinical characteristics for cases with a first diagnosis of rectal cancer, by race/ethnicity

	Caucasian n=23446	African-American n=1930	Hispanic n=5032	Asian n=3991	Other n=49	Total n=34448
Median age* (years with range)	66 (15–80)	62 (14–80)	62 (14–80)	62 (14–80)	60 (40–80)	65 (14–80)
Gender						
Male	13780 (59%)	1028 (53%)	2986 (59%)	2274 (57%)	33 (67%)	20101 (58%)
Female	9666 (41%)	902 (47%)	2046 (41%)	1717 (43%)	16 (33%)	14347 (42%)
SEER stage						
Local	12862 (55%)	1079 (56%)	2607 (52%)	2097 (53%)	17 (35%)	18662 (54%)
Regional	10584 (45%)	851 (44%)	2425 (48%)	1894 (47%)	32 (65%)	15786 (46%)
Grade						
Well differentiated	2440 (10%)	174 (9%)	506 (10%)	312 (8%)	9 (18%)	3441 (10%)
Moderately differentiated	15018 (64%)	1104 (57%)	3052 (61%)	2404 (60%)	30 (61%)	21608 (63%)
Poorly differentiated	2990 (13%)	227 (12%)	617 (12%)	583 (15%)	8 (16%)	4425 (13%)
Undifferentiated	104 (<1%)	12 (<1%)	18 (<1%)	13 (<1%)	0 (0%)	147 (<1%)
Unknown	2894 (12%)	413 (21%)	839 (17%)	679 (17%)	2 (4%)	4827 (14%)
Histological subtype						
Adenocarcinoma	20670 (88%)	1461 (76%)	4144 (82%)	3336 (84%)	41 (84%)	29652 (86%)
Mucinous adenocarcinoma	1317 (6%)	129 (7%)	319 (6%)	201 (5%)	6 (12%)	1972 (6%)
Other	1459 (6%)	340 (18%)	569 (11%)	454 (11%)	2 (4%)	2824 (8%)
Colon Site						
Rectosigmoid	7715 (33%)	587 (30%)	1528 (30%)	1194 (30%)	15 (31%)	11039 (32%)
Rectum	15731 (67%)	1343 (70%)	3504 (70%)	2797 (70%)	34 (69%)	23409 (68%)
Socioeconomic status**						
Lowest	2084 (9%)	663 (34%)	1507 (30%)	462 (12%)	13 (27%)	4729 (14%)
Second lowest	4190 (18%)	461 (24%)	1309 (26%)	686 (17%)	15 (31%)	6661 (19%)
Middle	5188 (22%)	389 (20%)	1008 (20%)	828 (21%)	14 (29%)	7427 (22%)
High	5783 (25%)	252 (13%)	744 (15%)	980 (25%)	5 (10%)	7764 (23%)
Highest	6201 (26%)	165 (9%)	464 (9%)	1035 (26%)	2 (4%)	7867 (23%)

Percentages are rounded to nearest whole number. *Age at diagnosis of first tumor; **socioeconomic status of the census tract of residence at diagnosis.

1.1 to 1.4), rectosigmoid colon 1.1 (95% CI: 0.9 to 1.3), or rectum (SIR: 0.9; 95% CI: 0.8 to 1.1). Similarly, females showed the greatest increase in relative risk of developing an SPCRC with proximal colon (SIR: 1.5; 95% CI: 1.3 to 1.7) and descending colon (SIR: 2.3; 95% CI: 1.7 to 3.1) tumor locations. Among females as well as males there was no significant increase in SPCRC risk among cases with primary rectal cancer diagnosis. The distribution of SPCRC tumor subsite location by primary CRC subsite location is listed in Table 5.

Regression analysis

Regression analyses were performed using Cox proportional hazards models as described in the 'Material and Methods' section. Among cases whose primary cancer was located in the colon, after adjusting for age, Caucasian females had decreased risk of SPCRC (HR=0.84; 95% CI: 0.73 to 0.97) as compared to Caucasian men; no other significant differences were observed across the remaining categories based on race/ethnicity and gender. Among cases whose primary cancer was located in the rectum, after adjusting for age, Hispanic men showed an increased risk of SPCRC compared to Caucasian men (HR=1.77; 95% CI: 1.27 to 2.48); no other significant differences were observed across the remaining categories based on race/ethnicity and gender.

DISCUSSION

This population-based analysis confirms previous findings that CRC survivors are at increased risk of developing SPCRC compared to the general population. We have demonstrated that resected locoregional colon and rectal cancer patients have a 40% increased risk of SPCRC compared to the underlying population at risk (SIR=1.4). Our study also sheds light on four different areas. First, our results confirm earlier studies demonstrating that females are at increased risk of developing an SPCRC compared to the risk of the underlying population.[7,17] Second, in our ethnicity-specific analysis we observed that Hispanics have an approximately two-fold greater risk of developing an SPCRC than the general population. Third, we have identified an increased risk of SPCRC with proximal and descending colon tumors compared to sigmoid, rectosigmoid, and rectum tumors. Colorectal tumor subsite location also exhibited differentially increased risk of SPCRC, which was varied with gender and ethnicity, reinforcing the notion that

Table 3: Estimated standardized incidence ratios for second primary CRC among colon and rectal cancer cases

	Colon cancer	Rectal cancer
All cases		
Cases observed	1077	366
Cases expected	783.4	344.5
SIR (95% CI)	1.4 (1.3 to 1.5)	1.1 (1.0 to 1.2)
Gender		
Males		
Cases observed	612	217
Cases expected	466.0	222.4
SIR (95% CI)	1.3 (1.2 to 1.4)	1.0 (0.9 to 1.1)
Females		
Cases observed	465	149
Cases expected	317.5	122.0
SIR (95% CI)	1.5 (1.3 to 1.6)	1.2 (1.0 to 1.4)
Ethnicity		
Caucasian		
Cases observed	780	249
Cases expected	602.9	259.6
SIR (95% CI)	1.3 (1.2 to 1.4)	1.0 (0.8 to 1.1)
African American		
Cases observed	78	22
Cases expected	58.6	19.5
SIR (95% CI)	1.3 (1.1 to 1.7)	1.1 (0.7 to 1.7)
Hispanic		
Cases observed	130	66
Cases expected	64.3	34.2
SIR (95% CI)	2.0 (1.7 to 2.4)	1.9 (1.5 to 2.5)
Asian		
Cases observed	89	29
Cases expected	57.6	31.0
SIR (95% CI)	1.5 (1.2 to 1.9)	0.9 (0.6 to 1.3)

*CI: confidence interval

CRC is indeed a heterogeneous disease. Finally, we have provided information on the latency period for development of SPCRC and validated prior data showing that SPCRCs present at an early stage, which in turn provides insights into current surveillance strategies.

Our primary result of increased SPCRC risk among colon cancer cases (SIR:1.4; 95% CI:1.3 to 1.5) is consistent with previously reported SEER results (SIR: 1.36; 95% CI: 1.32 to 1.39)[32] and Intergroup 0089 results (SIR: 1.6; 95% CI: 1.2 to 2.2).[9] Similar to our study, the SEER study used 6 months as the cutoff time to exclude synchronous tumors. Our results also show an increased risk of SPCRC among colon cancer cases as compared to rectal cancer cases. The SIR for developing an SPCRC was higher in patients whose initial tumor was located in the descending colon (SIR: 1.6; 95% CI: 1.3 to 2.0) and proximal colon (SIR: 1.4; 95% CI: 1.3 to 1.6), with no significant risk when the initial tumor involved the sigmoid (SIR: 1.2; 95% CI: 1.1 to 1.4), rectosigmoid (SIR: 1.2, 95% CI: 1.0-1.4), and rectum (SIR: 1.0; 95% CI: 0.9 to 1.2). Although we acknowledge that there were only a small number of cases involving the descending colon in this study, there is a striking pattern of increased risk of SPCRC in both proximal and descending colon tumors compared to distally located tumors, e.g., tumors in the sigmoid, rectosigmoid, and rectum. It has been demonstrated that left- and right-sided sporadic CRC may arise through different embryologic, genetic, and epigenetic mechanisms. During embryological development, the right side of the colorectum originates from the midgut, whereas the left side originates from the hindgut and has a separate vascular supply. Depending upon the tumor site, there are genotypic and phenotypic differences that may influence tumorigenesis in CRC. For example, microsatellite instability (MSI) and CpG island methylator phenotype-positive have associations with proximal tumors,[33] whereas distal tumors have been associated with mutations in K-ras and P53, increased COX-2 expression, and loss of heterozygosity (LOH) at chromosome 18.[34] Recently, screening colonoscopy has been observed to be effective at reducing CRC-specific mortality from left-sided but not right-sided CRCs.[35] One potential explanation for this observation is that right-sided colorectal tumors may be more biologically aggressive.[36] Supporting this theory are the observational data demonstrating poor CRC-specific survival among colon cancer patients with proximal tumor subsite location as compared to patients with sigmoid colon cancers.[21] The variations in clinical outcomes that we see here with tumor subsite location may be explained by these biologic mechanisms.

Females are at greater risk of SPCRC than males when compared to the underlying population at risk, with the greatest risk observed for proximal and descending colon cancer cases. Previous reports on the variation in risk of subsequent malignant diseases by gender,[7] age, or extracolonic tumors.[8] However, it should be noted that the data on relative risk did not bear this out. These findings raise the question of whether postmenopausal hormonal changes influence SPCRC risk. Previous epidemiological studies have suggested that use of hormone replacement therapy (HRT) was associated with reduced risk of colon cancer among menopausal women,[37-39] that expression of estrogen receptor {beta} was much lower in colon adenocarcinoma tissue than in normal colon tissue, and that this corresponded to poorly differentiated colon tumors.[40,41] It is possible that the sharp decrease in female hormones during the menopausal ages may increase the risk of SPCRC, leading to an increased risk among elderly females. Admittedly, such associations are purely speculative.

Among Hispanics, a dramatic increase in estimated risk of SPCRC was observed for nearly all primary tumor subsite locations. Specifically, compared to the risk in the underlying population, Hispanics showed a greater than two-fold increase in relative risk for developing an SPCRC when

Table 4: Estimated standardized incidence ratios for second primary colon and rectal cancer based on tumor subsite location within the colorectum

	Colon cancer			Rectal cancer	
	Proximal	**Descending**	**Sigmoid**	**Rectosigmoid**	**Rectum**
All cases					
Cases observed	616	88	373	141	225
Cases expected	428.9	53.7	300.8	121.7	222.7
SIR (95% CI)	1.4 (1.3 to 1.6)	1.6 (1.3 to 2.0)	1.2 (1.1 to 1.4)	1.2 (1.0 to 1.4)	1.0 (0.9 to 1.2)
Gender					
Males					
Cases observed	329	43	240	84	133
Cases expected	238.1	34.3	193.6	78.6	143.8
SIR (95% CI)	1.4 (1.2 to 1.5)	1.3 (0.9 to 1.7)	1.2 (1.1 to 1.4)	1.1 (0.9 to 1.3)	0.9 (0.8 to 1.1)
Females					
Cases observed	287	45	133	57	92
Cases expected	190.8	19.4	107.2	43.1	78.9
SIR (95% CI)	1.5 (1.3 to 1.7)	2.3 (1.7 to 3.1)	1.2 (1.0 to 1.5)	1.3 (1.0 to 1.7)	1.2 (0.9 to 1.4)
Ethnicity					
Caucasian					
Cases observed	449	62	269	103	146
Cases expected	334.5	39.9	228.5	93.1	166.5
SIR (95% CI)	1.3 (1.2 to 1.5)	1.6 (1.2 to 2.0)	1.2 (1.0 to 1.3)	1.1 (0.9 to 1.3)	0.9 (0.7 to 1.0)
African American					
Cases observed	45	7	26	8	14
Cases expected	34.6	5.3	18.7	6.7	12.8
SIR (95% CI)	1.3 (0.9 to 1.7)	1.3 (0.5 to 2.7)	1.4 (0.9 to 2.0)	1.2 (0.5 to 2.4)	1.1 (0.6 to 1.8)
Hispanic					
Cases observed	80	12	38	23	43
Cases expected	34.3	4.0	25.9	11.5	22.7
SIR (95% CI)	2.3 (1.8 to 2.9)	3.0 (1.5 to 5.2)	1.5 (1.0 to 2.0)	2.0 (1.3 to 3.0)	1.9 (1.4 to 2.5)
Asian					
Cases observed	42	7	40	7	22
Cases expected	25.3	4.5	27.7	10.4	20.6
SIR (95% CI)	1.7 (1.2 to 2.2)	1.5 (0.6 to 3.2)	1.4 (1.0 to 2.0)	0.7 (0.3 to 1.4)	1.1 (0.7 to 1.6)

the primary cancer was in the proximal colon and a three-fold increase in risk of SPCRC with primary cancer of the descending colon [Table 3]. Hispanic females had the greatest overall relative risk of SPCRC, with an estimated SIR of 4.2 for first CRC tumors located in the descending colon (data not shown). Hispanics were the only ethnic group found to have an increased SPCRC risk when the primary tumor involved the rectosigmoid and rectum. Following Hispanics in overall increased risk was the Asian/Pacific Islander cohort; Caucasians and African Americans had a modestly increased risk of SPCRC compared to the general population. Tables 1 and 2 reveal that, other than the fact that a large proportion of Hispanics are from the lower socioeconomic strata, there are no substantial differences in characteristics across race/ethnic groups to explain the observed differences in risk of SPCRC.

Previous studies have reported on disparities across race/ethnic groups and socioeconomic strata in risk of developing CRC.[19] Here, we were able to quantify the difference in relative risk of SPCRC between ethnic groups. Possible causes for these observed differences range from socioeconomic factors such as poverty, poor access to care, and low educational status,[19, 42, 43] to inherent biological differences. Although 56% of Hispanics were in the low socioeconomic strata, it is worth noting that 58% of African Americans who were also found to be in the low socioeconomic strata had a lower risk of developing SPCRC (SIR: 2.0 *vs* 1.3), implying that biologic differences or other factors may exist across race/ethnicity that explain these findings. Also, determination of the etiology of health disparities requires further research to understand the range of barriers to CRC screening and to help develop multimodal interventions to improve surveillance for all patients, including minority goups.

Because of the small number of cases of CRC of the descending colon, our study has limitations of statistical power in its examination of this subsite between ethnic groups. Any errant or anomalous addition to this category could skew the estimated SIR to a higher level. The high proportion of censored observations in the time-to-event analyses make it difficult to compare one group to another directly and is beyond the scope of this manuscript. Additional large-scale epidemiological studies are needed to validate our findings. Similar to other population-based analyses, we too did not conduct any central pathologic specimen review or collect family history details. Family history has clear associations with risk of CRC,[44-47] and may be associated with CRC-specific mortality after CRC diagnosis,[48,49] although the latter

Table 5: Distribution of second primary colorectal cancer subsite location after diagnosis of first colorectal cancer

First colorectal cancer tumor location	Second colorectal cancer tumor location							
	Proximal	Transverse	Descending	Sigmoid	Rectosigmoid	Rectum	NOS*	Total
Proximal	24 (6%)	127 (29%)	41 (9%)	127 (29%)	30 (7%)	81 (19%)	5 (1%)	435
Transverse	48 (27%)	24 (13%)	21 (12%)	36 (20%)	11 (6%)	37 (20%)	4 (2%)	181
Descending	28 (32%)	15 (17%)	9 (10%)	20 (23%)	3 (3%)	9 (10%)	4 (5%)	88
Sigmoid	95 (25%)	61 (16%)	38 (10%)	45 (12%)	29 (8%)	89 (24%)	16 (4%)	373
Rectosigmoid	27 (19%)	27 (19%)	12 (9%)	21 (15%)	3 (2%)	46 (33%)	5 (4%)	141
Rectum	48 (21%)	33 (15%)	19 (8%)	28 (12%)	17 (8%)	71 (32%)	9 (4%)	225
Total	270	287	140	277	93	333	42	1443

Percentages indicate the proportion by row (i.e., the proportion among cases based on first CRC tumor location). *NOS: not otherwise specified (colorectum).

association is not uniformly represented in the literature. Without information on family history of CRC we are unable to exclude the possibility that these patients represent hereditary nonpolyposis colorectal cancer (HNPCC) or familial adenomatous polyposis or other genetic diseases. However, the incidence of HNPCC is sufficiently low (less than 1%–5%) in any given population[50] that it would account for only a negligible number of cases and so is unlikely to bias our observation. Also, we excluded cases with extracolonic tumors such as breast and endometrial cancer so as to exclude certain familial syndromes. In addition, the increased mean age at diagnosis of SPCRC (68 for males and 71 for females) suggests that most of these SPCRCs represent sporadic cancers rather than hereditary syndromes.

SPCRCs detected soon after the original CRC may represent missed synchronous rather than metachronous cancer. Previous investigators have chosen different cutoffs to distinguish synchronous from metachronous cancer. We chose 6 months as the cutoff since it is very well described in the literature; it also allows more precise estimation of the incidence risk since close to 50% of the SPCRCs have been shown to occur in less than 2 years from diagnosis of the primary CRC.[32] Some early cases of second cancers observed in our study could represent missed synchronous cancer. We excluded 2081 colon and 669 rectal synchronous cancers that were diagnosed between 0–6 months from diagnosis of the primary tumor. Additionally, we found that the median time from the diagnosis of primary CRC to the development of SPCRC was 32 months in our study. Only 13% of all SPCRCs were diagnosed within months 7–12 (i.e., the first period we examined); more than 50% of the SPCRCs observed were diagnosed 2.5 years after diagnosis of the first CRC. In addition, Table 5 shows that the second primaries are less likely to be tumors at the surgical anastomosis, given the heterogeneity of tumor site upon second primary tumor presentation. Of course, it must be acknowledged that the tumor subsite locations shown in Table 5 is based on the best available information, but may be subject to misinterpretation since the primary colorectal segment had been resected in the vast majority of cases. Our data are consistent with the earlier data from SEER, showing that the majority of SPCRCs present as early-stage tumors, with only 9%–11% presenting as stage IV cancers. This noticeable increase in early-stage SPCRC and the latency period of more than 2 years indicates inadequacies in current surveillance strategies.

Here, we have not only confirmed prior study findings by precisely estimating the increased risk of SPCRC in CRC survivors but have also identified ethnicity-specific, gender-specific, and colon subsite–specific risk factors in the development of SPCRC, confirming that differences in biologic determinants could translate into variations in risk of developing SPCRC. This has important clinical implications not for only understanding the biological differences within the tumor but also for further assessing the need for performance of intensive postoperative endoscopic surveillance to aid in tertiary prevention after the development of first primary. Current surveillance strategies may be inadequate for screening for SPCRC. A better understanding of the SPCRC risk is needed to determine whether certain patients ('high-risk' subpopulations of CRC patients) require improved approaches to surveillance or adjuvant therapy.

CONCLUSIONS

Our results demonstrate the importance of recognizing readily available clinical indicators that predict risk of developing an SPCRC after initial CRC diagnosis. Cancer survivors are steadily increasing in number[51] in part because they are living longer due to advances in prevention, screening, early detection, and therapy. Thus, there is now a critical need for effective surveillance strategies to decrease the burden of cancer in the United States.[52] CRC patients are at increased risk for colorectal adenoma formation[53] and, given the adenoma-carcinoma sequence, also at risk for SPCRC development. Clinical trials are now underway

within the National Cancer Institute–sponsored oncology cooperative groups to evaluate chemopreventive agents for prevention of SPCRCs and high-risk adenomas or for maintenance of disease-free survival among colon cancer survivors.[54-56] Diet and exercise are also being investigated as tertiary prevention strategies among CRC survivors (e.g., the CHALLENGE study, ClinicalTrials.gov Identifier NCT00578721). It is hoped that estimation of the risk of SPCRC among non-metastatic CRC cases will lead to patient-specific surveillance monitoring as well as help identify individuals who will benefit maximally from tertiary prevention strategies.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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PRIOR PRESENTATIONS

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