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 1.6) 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
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. 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. 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. 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. Race/ethnicity differences have been identified as risk factors for primary CRC development and also for CRC-specific survival beyond CRC diagnosis. Tumor subsite location within the colon has been associated with CRC-specific mortality. 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 and the cancer-type recording scheme of the Surveillance, Epidemiology, and End-Results Program of the National Cancer Institute. The order of tumors within the same patient is given by the variable *sequence number*. Stage of disease is given by the variable *sumstage*. Determination of race/ethnicity and tumor subsite location have been previously described.

**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. 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.

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,
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
with the greatest effect seen in those with the first cancer and a second primary tumor compared to the general population, Hispanics have the greatest risk of developing a second primary colorectal cancer (SPCRC) in the colon or rectum in both males and females. Additionally, of the four ethnic groups examined, Hispanics showed the greatest risk of developing a second colon cancer (SIR: 1.5; 95% CI: 1.3 to 1.7). Females also were observed to have increased risk of developing 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). 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: 1.2; 95% CI: 1.2 to 1.4).

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

| Grade | Caucasian n=49236 | African-American n=5190 | Hispanic n=8641 | Asian n=6675 | Other n=67 | Total n=69809 |
|-------|-------------------|-------------------------|----------------|--------------|------------|---------------|
| Gender |                   |                         |                |              |            |               |
| Male   | 26185 (53%)       | 2358 (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 | 28098 (57%) | 3183 (61%) | 4707 (54%) | 3023 (45%) | 35 (52%) | 39046 (56%) |
| Distal | 3221 (7%)          | 446 (9%)                | 557 (6%)       | 358 (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.

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

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

| Ethnicity       | Cases observed | Cases expected | Colon cancer | Rectal cancer |
|----------------|---------------|----------------|--------------|---------------|
| Caucasian      | 780           | 602.9          | 249          | 259.6         |
| SIR (95% CI)   | 1.3 (1.2 to 1.4) | 1.0 (0.8 to 1.1) |
| African American| 78            | 58.6           | 22           | 19.5          |
| SIR (95% CI)   | 1.3 (1.1 to 1.7) | 1.1 (0.7 to 1.7) |
| Hispanic       | 130           | 64.3           | 66           | 34.2          |
| SIR (95% CI)   | 2.0 (1.7 to 2.4) | 1.9 (1.5 to 2.5) |
| Asian          | 89            | 57.6           | 29           | 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) and Intergroup 0089 results (SIR: 1.6; 95% CI: 1.2 to 2.2). 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.[32] 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.[18] 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...
Although 56% of Hispanics were in the low socioeconomic educational status, factors such as poverty, poor access to care, and low for these observed differences range from socioeconomic 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, 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 groups. 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, and may be associated with CRC-specific mortality after CRC diagnosis, although the latter

### 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 | 239           | 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 | 34.0         | 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) |
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.\[32\] CRC patients are at increased risk for colorectal adenoma formation\[33\] 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 SPCCRCs and high-risk adenomas or for maintenance of disease-free survival among colon cancer survivors.[14-50] 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 SPCCRC 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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**REFERENCES**

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics. CA Cancer J Clin 2010;60:277-300.
2. National Center for Health Statistics. Estimates of the July 1, 2000-July 1, 2005, United States resident population from the Vintage 2005 postcensal series by year, county, age, sex, race, and Hispanic origin, prepared under a collaborative arrangement with the U.S. Census Bureau. 2006;Available on the Internet from: http://www.cdc.gov/nchs/about/major/dvs/popbridge/popbridge.htm.
3. Muller AD, Sonnenberg A. Prevention of Colorectal Cancer by Flexible Endoscopy and Polypectomy: A Case-Control Study of 32 702 Veterans. Ann Intern Med 1995;123:904-10.
4. Rex DK, Kahi CJ, Levin B, Smith RA, Bond JH, Brooks D, et al. Guidelines for Colonoscopy Surveillance after Cancer Resection: A Consensus Update by the American Cancer Society and US Multi-Society Task Force on Colorectal Cancer. CA Cancer J Clin 2006;56:160-7.
5. Winawer SJ, Zauber AG, Ho MN, O’Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of Colorectal Cancer by Colonscopic Polypectomy. N Engl J Med 1993;329:1977-81.
6. National Comprehensive Cancer Network Practice Guidelines in Oncology, www.nccn.org. 2010. v.1.2011.
7. Enblad P. The Risk of Subsequent Primary Malignant Diseases After Cancer of the Colon and Rectum. Cancer 1990;65:2091-100.
8. Hemminki K, Li X, Dong C. Second Primary Cancers after Sporadic and Familial Colorectal Cancer. Cancer Epidemiol Biomarkers Prev 2001;10:793-8.
9. Green RJ, Metlay JP, Propert K, Catalano PJ, Macdonald JS, Mayer RJ, et al. Surveillance for second primary colorectal cancer after adjuvant chemotherapy: An analysis of Intergroup 0089. Ann Intern Med 2002;136:261-9.
10. Cunliffe WJ, Hasleton PS, Tweedle DE, Schofield PF. Incidence of synchronous and metachronous colorectal carcinoma. Br J Surg 1984;71:941-3.
11. Lockhart-Mummery HE, Heald RJ. Metachronous cancer of the large intestine. Dis Colon Rectum 1972;15:261-4.
12. Yamazaki T, Takii Y, Okamoto H, Sakai Y, Hatakeyama K. What is the risk factor for metachronous colorectal carcinoma? Dis Colon Rectum 1997;40:935-8.
13. Carlsson G, Petrelli NJ, Nava H, Herrera L, Mittelman A. The value of colonoscopic surveillance after curative resection for colorectal cancer or synchronous adenomatous polyps. Arch Surg 1987;122:1261-3.
14. Chen E, Stuart M. Colonic surveillance follow-up of colorectal maligna. Dis Colon Rectum 1994;37:568-72.
15. Olsen HW, Lawrence WA, Snook CW, Mutch WM. Review of recurrent polyps and cancer in 500 patients with initial colonoscopy for polyps. Dis Colon Rectum 1988;31:222-7.
16. Granqvist S, Karlsson T. Postoperative follow-up of patients with colorectal carcinoma by colonoscopy. Eur J Surg 1992;158:307-12.
17. Curtis FD, Ron E, Ries LA, Hacker DG, Edwards BK, Tucker MA, et al. New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000. In: National Cancer Institute. Bethesda, MD: NIH Publication; 2006.
18. Smith RA, Cokkinides V, Brawley OW. Cancer Screening in the United States, 2008: A Review of Current American Cancer Society Guidelines and Cancer Screening Issues. CA Cancer J Clin 2008;58:161-79.
19. Ward E, Jemal A, Cokkinides V, Singh GK, Cardinez C, Ghafoor A, et al. Cancer Disparities by Race/Ethnicity and Socioeconomic Status. CA Cancer J Clin 2004;54:78-93.
20. Le H, Ziegas A, Lipkin SM, Zell JA. Effects of socioeconomic status and treatment disparities in colorectal cancer survival. Cancer Epidemiol Biomarkers Prev 2008;17:1950-62.
21. Wray CM, Ziegas A, Hinojosa MW, Le H, Stamos MJ, Zell JA. Tumor subsite location within the colon is prognostic for survival after colon cancer diagnosis. Dis Colon Rectum 2009;52:1359-66.
22. Percy VH, Muir C. International Classification of Diseases for Oncology, 2nd ed. Geneva: World Health Organization; 1990.
23. Surveillance, Epidemiology, and End Results Program. SEER site recode icd-0-3 (4/15/2002) definition. Bethesda, MD: National Cancer Institute 2002.
24. California Cancer Registry. Cancer Surveillance Section. Cancer reporting in California: data standards for regional registries and California cancer registry California cancer reporting system standards, vol Ill. Sacramento, CA: California Department of Health Services 2003.
25. Taylor TH, Bringman D, Anton-Culver H. Malignancies following in situ cervical cancer in Hispanic Americans and non-Hispanic Whites. Gynecol Oncol 2006;103:1012-6.
26. Bessovaanova L, Taylor TH, Mehta RS, Zell JA, Anton-Culver H. Risk of a Second Breast Cancer Associated with Hormone-Receptor and HER2/neu Status of the First Breast Cancer: Cancer Epidemiol Biomarkers Prev 2011;20:389-96.
27. Esteve BE, Raymond L. Statistical methods in cancer research, Descriptive epidemiology. New York: Oxford University Press 1994:4.
28. National Center for Health Statistics. Bridged-race intercensal estimates of the July 1, 1990-July 1, 1999, United States resident population by county, single-year of age, sex, race, and Hispanic origin, prepared by the U.S. Census Bureau with support from the National Cancer Institute. Available from: http://www.cdc.gov/nchs/about/major/dvs/popbridge/popbridge.htm. [cited in 2004].
29. Mulder PGH. An exact method for calculating a confidence interval of a poisson parameter. Am J Epidemiol 1983;117:377.
30. Armitage P. Tests for linear trends in proportions and frequencies. Biometrics 1955;11:375-86.
31. Agresti A. An introduction to categorical data analysis. New York: Wiley; 1996.
32. Das A, Chak A, Cooper GS. Temporal trend in relative risk of second primary colorectal cancer. Am J Gastroenterol 2006;101:1342-7.
33. Weisenberger DJ, Siegmund KD, Campan M, Young J, Long TI, Faasse MA, et al. CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer. Nat Genet 2006;38:787-93.
34. Azzoni C, Bottarelli L, Campanini N, Di G, Bader G, Mazzeo A, et al. Distinct
molecular patterns based on proximal and distal sporadic colorectal cancer: Arguments for different mechanisms in the tumorgenesis. Int J Colorectal Dis 2007;22:115-6.
35. Baxter NN, Goldwasser MA, Paszat LF, Sasin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. Ann Intern Med 2009;150:1-8.
36. Ransohoff DF. How much does colonoscopy reduce colon cancer mortality? Ann Intern Med 2009;150:2.
37. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: A review and meta-analysis. Am J Med 1999;106:574-82.
38. Newcomb PA, Storer BE. Postmenopausal hormone use and risk of large-bowel cancer. J Natl Cancer Inst 1995;87:1067-71.
39. Liang W. Age, sex and the risk of grade-specific second primary colorectal cancer: Evidence for the protective effect of female hormone. Eur J Cancer 2007;43:1856-61.
40. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, Hubbell FA, Aschensel J, Rodabough RJ, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med 2005;350:991-1004.
41. Foley EF, Jazaeri AA, Shupnik MA, Jazaeri O, Rice LW. Selective loss of estrogen receptor beta in malignant human colon cancer. Cancer Res 2000;60:245-8.
42. Walsh JM, Kaplan CP, Nguyen B, Gildengorin G, McPhee SJ, Perez-Stable EJ. Barriers to colorectal cancer screening in Latino and Vietnamese Americans. Compared with non-Latino white Americans. J Gen Intern Med 2004;19:156-66.
43. Green AR, Peters-Lewis A, Percac-Lima S, Betancourt JR, Richter JM, Janairo MP, et al. Barriers to screening colonoscopy for low-income Latino and white patients in an urban community health center. J Gen Intern Med 2002;17:834-40.
44. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. N Engl J Med 1994;331:1669-74.
45. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol 2001;96:2992-3003.
46. Potter JD, Slattery ML, Bostick RM, Gapstur SM. Colon cancer: a review of the epidemiology. Epidemiol Rev 1993;15:499-545.
47. Slattery ML, Kerber RA. Family history of cancer and colon cancer risk: The Utah Population Database. J Natl Cancer Inst 1994;86:1618-26.
48. Chan JA, Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, et al. Association of family history with cancer recurrence and survival among patients with stage III colon cancer. JAMA 2008;299:2515-23.
49. Zell JA, Honda J, Ziegas A, Anton-Culver H. Survival after colorectal cancer diagnosis is associated with colorectal cancer family history. Cancer Epidemiol Biomarkers Prev 2008;17:3134-40.
50. Peel DJ, Ziegas A, Fox EA, Gildea M, Laham B, Clements E, et al. Characterization of hereditary nonpolyposis colorectal cancer families from a population-based series of cases. J Natl Cancer Inst 2000;92:1517-22.
51. Ganz PA. A teachable moment for oncologists: cancer survivors, 10 million strong and growing! J Clin Oncol 2005;23:5458-60.
52. Mariotto AB, Rowland JH, Ries LA, Scoppa S, Feuer EJ. Multiple cancer prevalence: A growing challenge in long-term survivorship. Cancer Epidemiol Biomarkers Prev 2007;16:566-71.
53. Chu DZ, Chansky K, Alberts DS, Meyskens FL, Fenoglio-Preiser CM, Rivkin SE, et al. Adenoma Recurrences After Resection of Colorectal Carcinoma: Results From the Southwest Oncology Group 9041 Calcium ChemoPrevention Pilot Study. Ann Surg Oncol 2003;10:829-30.
54. S08202, “A double-blind placebo-controlled trial of efolfimethine and sulindac to prevent recurrence of high risk adenomas and second primary colorectal cancers in patients with stage 0-III colon cancer.” Southwest Oncology Group Fall 2009 Group Meeting Agenda Available from: https://swog.org/Visitors/ Fall09GpMtg/0910Agenda.pdf, page 0937. [accessed on 2010 Feb 1].
55. 80702 “A phase III trial of 6 versus 12 treatments of adjuvant FOLFOX with or without celecoxib therapy for patients with stage III colon cancer”. Cancer and Leukemia Group B Summer 2009 Agenda Book. Available from: http://www.calgb.org/Public/meetings/meeting_documents/2009/summer_group/AgendaBook_062009.pdf, page 062007 [accessed on 2010 Feb 1].
56. NSABP P-5, “Rosuvastatin in Treating Patients With Stage I or Stage II Colon Cancer That Was Removed By Surgery”. ClinicalTrials.gov website. Available from: http://clinicaltrials.gov/ct2/show/NCT01011478. [accessed on 2010 Oct 18].

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