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ORIGINAL ARTICLE – COLORECTAL CANCER

# Sidedness of Colorectal Cancer Impacts Risk of Second Primary Gastrointestinal Malignancy

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## ABSTRACT

**Introduction.** A history of colorectal cancer (CRC) increases the risk of subsequent gastrointestinal (GI) cancer. Cancers of the right colon, left colon, and rectum differ according to molecular profiles, responses to treatment, and outcomes.

**Objective.** The purpose of this study was to determine if CRC location is associated with differential risk for secondary primary GI malignancy.

**Methods.** A retrospective cohort of adults with CRC was compiled using the Surveillance, Epidemiology, and End Results database (1973–2015). Standardized incidence ratios (SIRs) for second primary GI malignancies were compared based on location of the index CRC (right colon, left colon, or rectum).

**Results.** The cohort included 281,413 adults with CRC (30.3% right, 35.3% left, 34.3% rectum). With a median 4.9-year follow-up, 12,064 (4.3%) patients developed a second primary GI malignancy (64% CRC, 36% non-CRC). Those with CRC at any location had higher than expected incidences of small intestine, bile duct, and other CRCs, and lower incidences of liver and gallbladder cancer. The SIR for small intestinal cancer was higher after right colon cancer than after left colon or rectal cancer. The esophageal cancer SIR was higher after left colon cancer. Pancreas cancer was higher than expected for right colon cancer, but lower for left colon and rectal cancer.

**Conclusion.** The location of CRC leads to differences in the incidence and location of second primary GI malignancies and may be related to similarities in the associated carcinogenesis and molecular pathways or response to treatment. CRC location not only impacts treatment response and outcomes, but should also be considered during subsequent surveillance.

With advances in cancer treatment and increased longevity, patients with a history of cancer are at greater risk for future cancer. Second primary malignancies in cancer survivors now account for 20% of all cancer diagnoses, up from 8% four decades ago.[1] Colorectal cancer (CRC) is associated with a 65% 5-year survival, placing more people with CRC at risk for second primaries.[2] Among CRC survivors, a large proportion of second primaries (27–32%) arise from the gastrointestinal (GI) system.[3]

Genetic CRC syndromes account for a minority of second primary digestive malignancies.[4] Individuals with hereditary non-polyposis colorectal cancer (HNPCC) demonstrate higher incidences of gastric, hepatobiliary, and small intestinal malignancies. Those with familial adenomatous polyposis (FAP) are more prone to gastric, small intestinal, and peri-ampullary polyps, as well as hepatobiliary and adrenal malignancies.[5]

Among genetic CRC syndromes, variable presentations have long hinted at differences in pathogenesis based on tumor location. Adenomatous polyposis syndromes traditionally present with malignancies distal to the splenic flexure, while hereditary non-polyposis cancers are strongly associated with proximal lesions.[6,7] Differences in proximal versus distal location have also been shown to influence clinical presentation, treatment response, and outcomes in sporadic CRC.[8–13]

Sporadic CRC has similar genetic underpinnings to familial CRC syndromes and may demonstrate similar associations with other GI malignancies.[7,14] A better understanding of associated malignancies in sporadic CRC could influence treatment, surveillance, and screening for



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other GI cancers. Hence, the purpose of this study was to determine if primary CRC tumor location is associated with differential risk for second primary GI malignancy.

## METHODS

### *Data Source*

The Surveillance, Epidemiology, and End Results Program (SEER) is a National Cancer Institute initiative that collects information from population-based cancer registries on cancer incidence, treatment, and outcomes. The November 2017 release of SEER 9 was used, encompassing cancers diagnosed from 1973 through 2015.[15] This database includes patients from nine geographic regions covering approximately 9.4% of the US population, and was selected because it provides the longest duration of follow-up of the available SEER databases.

### *Study Cohort*

The cohort was assembled retrospectively and included index cases of right colon, left colon, and rectal cancer diagnosed between 1973 and 2010 to obtain at least 5 years of follow-up for index cases. Cases with a histologic diagnosis of adenocarcinoma and malignant behavior were included. The International Classification of Diseases for Oncology, Third Revision (ICD-O-3) coding scheme was used to categorize incident cases by primary site as right colon (cecum, ascending colon, hepatic flexure), left colon (splenic flexure, descending colon, sigmoid colon), or rectum (rectosigmoid, rectum). Cancers of the transverse colon were excluded from analysis, as were cases identified by death certificate or autopsy only.

### *Primary Outcome*

Cases were followed for second primary GI cancers, which were categorized as CRC or non-CRC. SEER differentiates second primary versus recurrent cancer through trained registrars' use of specific coding guidelines that consider site, histology, timing, and whether anastomotic lesions have mucosal involvement.[16]

The standardized incidence ratios (SIRs) were determined using SEER-Stat, which calculates an age-adjusted ratio of observed to expected incidence rates for each event based on a standard population, derived from United States Census data.[17] The SIRs for each second primary GI cancer were compared based on the location of the index CRC (right colon, left colon, or rectum).

### *Statistical Analysis*

Demographic variables were compared using Chi square tests for categorical data, and Wilcoxon rank-sum tests for continuous data. For each SIR, 95% upper and lower confidence intervals (CIs) were calculated to determine statistical significance and signal directionality. CIs that did not include 1 were considered significant, while $< 1$ reflected a lower than expected incidence relative to the general population and $> 1$ demonstrated a higher than expected incidence. The analysis was performed using SEER-Stat version 8.3.2 and Stata versions 13.1 and 15.1 (StataCorp LLP, College Station, TX, USA).

This study met the criteria for exemption by the Vanderbilt University Institutional Review Board, given analysis of existing, non-identifiable data.

## RESULTS

### *Patient Demographics*

During the study period, 281,413 individuals were diagnosed with cancer of the right colon (30.3%), left colon (35.3%), or rectum (34.3%). The cohort was 52% male and 84% White, with a mean age of 68 years (standard deviation [SD] 13 years). Forty-two percent had localized disease, 38% had regional disease, 16% had distant disease, and 4% were unstaged. Patients were followed until death (78%), study end (20%), or loss to follow-up (2%).

Comparing cases by sidedness, those with right colon cancer were older, with female predominance, while those with left colon and rectal cancer were younger and the majority were male. Individuals with rectal cancer more commonly presented with localized disease relative to right- or left-sided colon cancer. Patients with right-sided cancers more often presented with regional (versus localized) disease compared with left-sided cancers (Table 1).

### *Risk of Subsequent Gastrointestinal Malignancy*

During a median follow-up of 4.9 years (interquartile range [IQR] 1.4–11.2), 12,064 (4.3%) patients developed at least one second primary GI cancer. CRC accounted for 64%, while 36% were non-CRC GI cancers (Table 2). Patients with CRC at any site had a higher than expected incidence of subsequent CRC and non-CRC (Table 3).

### *Variation in Second Primaries After Colorectal Cancer*

CRC at any location was associated with a higher than expected incidence of other colorectal, small intestine, and bile duct cancer (Table 3). Overall, CRC at one site

**TABLE 1** Study cohort

| Characteristic | All [*N* = 281,413] | Right colon [*N* = 85,359] | Left colon [*N* = 99,436] | Rectum [*N* = 96,618] | *p* value |
|---|---|---|---|---|---|
| Age at diagnosis [mean ± SD] | 68 ± 13 | 71 ± 12 | 67 ± 12 | 66 ± 13 | < 0.001* |
| Sex | | | | | < 0.001* |
| Female | 136,002 (48) | 47,002 (55) | 47,244 (48) | 41,756 (43) | |
| Male | 145,411 (52) | 83,357 (45) | 52,192 (52) | 54,862 (57) | |
| Race | | | | | < 0.001* |
| White | 235,687 (84) | 72,182 (85) | 82,335 (83) | 81,170 (84) | |
| Black | 23,703 (8) | 8359 (10) | 8393 (8) | 6951 (7) | |
| Other | 21,249 (8) | 4668 (5) | 8424 (8) | 8157 (8) | |
| Unknown | 774 (< 1) | 150 (< 1) | 284 (< 1) | 340 (< 1) | |
| Tumor stage | | | | | < 0.001* |
| Localized | 118,676 (42) | 31,590 (37) | 43,106 (43) | 43,980 (46) | |
| Regional | 106,829 (38) | 36,334 (43) | 37,054 (37) | 33,441 (35) | |
| Distant | 45,927 (16) | 15,402 (18) | 16,839 (17) | 13,686 (14) | |
| Unstaged | 9981 (4) | 2033 (2) | 2437 (2) | 551 (6) | |

Data are expressed as *n* (%) unless otherwise specified

*SD* standard deviation

**p* value for all pairwise comparisons of right colon, left colon, and rectal cancer

**TABLE 2** Second primary gastrointestinal malignancies after a primary colorectal cancer

| CRC location | Index CRC cases | Cases with a second GI primary |
|---|---|---|
| Right | 85,359 | 3453 (4.0) |
| Left | 99,436 | 4905 (4.9) |
| Rectum | 96,618 | 3706 (3.8) |
| All | 281,413 | 12,064 (4.2) |

*CRC* colorectal cancer, *GI* gastrointestinal

**TABLE 3** Summary of standardized incidence ratios for second gastrointestinal primaries after colorectal cancer diagnosis

| CRC location | Observed cases | Expected cases | O:E* (95% CI) |
|---|---|---|---|
| Right | 3729 | 2936 | 1.27 (1.25–1.29) |
| CRC | 2254 | 1719 | 1.31 (1.28–1.34) |
| Non-CRC | 1475 | 1216 | 1.21 (1.18–1.24) |
| Left | 5298 | 3839 | 1.38 (1.36–1.40) |
| CRC | 3541 | 2239 | 1.58 (1.56–1.61) |
| Non-CRC | 1757 | 1605 | 1.09 (1.07–1.12) |
| Rectum | 3939 | 3202 | 1.23 (1.21–1.25) |
| CRC | 2598 | 1855 | 1.40 (1.37–1.43) |
| Non-CRC | 1341 | 1354 | 0.99 (0.96–1.02) |
| All | 12,966 | 9977 | 1.30 (1.29–1.31) |
| CRC | 8393 | 5822 | 1.44 (1.42–1.46) |
| Non-CRC | 4573 | 4187 | 1.09 (1.07–1.11) |

*O:E* ratio of observed-to-expected cases based on age-adjusted standardized population, *CRC* colorectal cancer, *CI* confidence interval

decreased the likelihood of a subsequent cancer at the same site, presumably due to surgical resection. Specifically, patients with right colon cancer were less likely to have subsequent cecal, ascending colon, or hepatic flexure cancer, while patients with left colon cancer were less likely to develop sigmoid cancer. Those with rectal cancer were less likely to have sigmoid or rectosigmoid cancer. Exceptions to this included a higher than expected incidence of splenic flexure and descending colon cancer after a diagnosis of left-sided colon cancer, and a higher than expected incidence of rectal cancer after a diagnosis of rectal cancer (Table 4).

The incidence of small intestinal cancer was higher in those with a history of right-sided CRC compared with left-sided CRC or rectal cancer, while the incidence of anal cancer was higher than expected after right colon and rectal cancer, relative to left colon cancer. The incidence of esophageal cancer was higher than expected after left colon cancer diagnosis, and gastric cancer was more common than expected after right and left colon cancer, but not rectal cancer. The incidence of pancreas cancer was higher than expected for patients with right colon cancer, but lower with left colon and rectal cancer. CRC at any site was associated with a lower than expected incidence of liver and gallbladder cancer (Table 4).

**TABLE 4** Incidence of second primary gastrointestinal cancer after primary colorectal cancer relative to expected age-adjusted rates in the general population

| All | Right | Left | Rectum |
|---|---|---|---|
| Higher than expected | | | |
| Non-CRC | | | |
| Stomach: 1.12 (1.09–1.15) | Stomach: 1.21 (1.15–1.28) | Esophagus: 1.16 (1.08–1.24) | Small intestine: 2.36 (2.16–2.58) |
| Small intestine: 2.95 (2.82–3.08) | Small intestine: 4.06 (3.78–4.36) | Stomach: 1.17 (1.12–1.23) | Anus: 2.03 (1.79–2.30) |
| Anus: 1.47 (1.35–1.60) | Anus: 1.29 (1.09–1.52) | Small intestine: 2.61 (2.42–2.82) | Bile duct: 1.20 (1.09–1.32) |
| Bile duct: 1.29 (1.22–1.36) | Bile duct: 1.46 (1.33–1.60) | Bile duct: 1.24 (1.14–1.35) | |
| | Pancreas: 1.14 (1.09–1.19) | | |
| CRC | | | |
| Cecum: 1.29 (1.26–1.33) | Transverse colon: 3.95 (3.78–4.13) | Cecum: 1.78 (1.72–1.85) | Cecum: 1.71 (1.64–1.78) |
| Ascending colon: 1.46 (1.42–1.50) | Splenic flexure: 3.17 (2.91–3.45) | Ascending colon: 2.11 (2.03–2.20) | Ascending colon: 1.70 (1.62–1.79) |
| Hepatic flexure: 1.58 (1.50–1.66) | Descending colon: 2.97 (2.77–3.18) | Hepatic flexure: 2.19 (2.04–2.35) | Hepatic flexure: 1.73 (1.58–1.89) |
| Transverse colon: 2.91 (2.83–2.99) | Sigmoid colon: 1.67 (1.60–1.74) | Transverse colon: 2.92 (2.78–3.05) | Transverse colon: 1.90 (1.78–2.02) |
| Splenic flexure: 2.29 (2.17–2.42) | Rectosigmoid: 1.36 (1.26–1.47) | Splenic flexure: 2.07 (1.89–2.27) | Splenic flexure: 1.75 (1.57–1.96) |
| Descending colon: 2.38 (2.29–2.48) | Rectum: 1.27 (1.20–1.34) | Descending colon: 2.30 (2.15–2.46) | Descending colon: 1.96 (1.18–2.12) |
| Rectum: 1.50 (1.46–1.54) | | Rectosigmoid: 1.10 (1.02–1.18) | Rectum: 1.69 (1.62–1.76) |
| | | Rectum: 1.51 (1.45–1.57) | |
| Lower than expected | | | |
| Non-CRC | | | |
| Liver: 0.78 (0.74–0.82) | Liver: 0.83 (0.75–0.92) | Liver: 0.82 (0.75–0.89) | Liver: 0.69 (0.63–0.76) |
| Gallbladder: 0.65 (0.59–0.72) | Gallbladder: 0.54 (0.43–0.67) | Gallbladder: 0.72 (0.61–0.85) | Gallbladder: 0.69 (0.57–0.83) |
| Pancreas: 0.96 (0.93–0.99) | | Pancreas: 0.95 (0.91–0.99) | Pancreas: 0.82 (0.78–0.86) |
| CRC | | | |
| None | Cecum: 0.27 (0.24–0.30) | Sigmoid colon: 0.76 (0.72–0.80) | Sigmoid colon: 0.72 (0.68–0.76) |
| | Ascending colon: 0.42 (0.38–0.47) | | Rectosigmoid: 0.57 (0.51–0.64) |
| | Hepatic flexure: 0.67 (0.58–0.78) | | |
| Comparable with the standard population | | | |
| Non-CRC | | | |
| Esophagus: 1.04 (0.99–1.09) | Esophagus: 0.95 (0.87–1.04) | Anus: 1.14 (0.97–1.33) | Esophagus: 0.98 (0.90–1.06) |
| | | | Stomach: 0.90 (0.94–1.05) |
| CRC | | | |
| Sigmoid colon: 1.0 (0.97–1.03) | None | None | None |
| Rectosigmoid: 1.0 (0.95–1.05) | | | |

## DISCUSSION

In this study of a large population-based cohort of CRC patients, the incidence of subsequent primary GI malignancies was higher than expected compared with the general population. This was largely attributed to higher rates of other colorectal, small intestine, and bile duct cancer, while the incidences of liver and gallbladder cancer were lower than general population estimates. Furthermore, the incidence and site of secondary GI malignancies varied depending on the location of the primary CRC. Notable differences included small intestine cancer, which was more frequent among patients with CRC at any site, but significantly greater for right- versus left-sided CRC. An association between right colon cancer and pancreas cancer was also observed. Additionally, left-sided lesions were associated with future esophageal cancer, but decreased the risk of pancreas cancer.

The association between a history of cancer and second primary cancer is well-documented.[1,3] Prior work has specifically demonstrated an association between primary GI cancers and future cancers, with a large proportion also

being GI in origin.[3] Two prior studies that followed CRC patients in SEER similarly found an increased risk of certain GI cancers after CRC, but did not evaluate differences by CRC location.[3,18]

Our finding of variations in subsequent non-CRC malignancy by primary CRC location is novel but not surprising given recently appreciated differences in overall disease progression and prognosis based on primary CRC location. Large clinical trials have demonstrated that treatment response and outcomes are influenced by CRC location. Left-sided lesions portend a better prognosis than right-sided lesions regardless of stage, patient characteristics, or adjuvant chemotherapy.[8–11] Even in metastatic disease, prognosis is better for distal than proximal lesions. Furthermore, left-sided lesions demonstrate improved responsiveness to FOLFOX-based chemotherapy regimens with the addition of anti-epidermal growth factor receptor treatments.[8–12] On the contrary, right-sided lesions may respond better to anti-vascular endothelial growth factor therapy in the metastatic setting.[10,13]

Increased surveillance has been implicated as a factor in the heightened incidence of second primary malignancy after initial cancer diagnosis.[19] For CRC, guideline-concordant surveillance includes serial cross-sectional imaging of the torso and periodic endoscopy, by which other GI tumors might be found.[20] While surveillance might explain the increased incidence of second primary GI cancer, it cannot account for observed differences based on CRC location.

The proximal and distal colon have distinct embryologic origins, environment influences, and microbiomes. In the proximal colon, bile acid exposure is greater, and pH lower. Conversely, the distal colon is characterized by lower bile acid exposure, higher pH, and higher microbial load.[6,8] Some preliminary epidemiologic and clinical studies have demonstrated associations between the colon microbiome, bile acid levels, and carcinogenesis.[21]

Location-based genetic differences also exist, as first suggested by the distinct pathogenesis of HNPCC, which is characterized by proximal lesions, and FAP, which predominantly affects the distal colorectum.[7] Proximal colon lesions are more often defective in mismatch repair genes, harbor BRAF mutations, have microsatellite instability, and increased CpG island methylation. By contrast, distal lesions more commonly exhibit chromosomal instability and demonstrate p53 and KRAS mutations.[7,8,21,22]

There was a strong association between colon cancer, particularly right-sided lesions, and subsequent small bowel and pancreas cancer. The association between CRC and small bowel cancer was similarly demonstrated by McCredie et al.[18] in an Australian population, and Guan et al.[23] in a smaller SEER population, although neither demonstrated differences based on proximal versus distal location. Prior small bowel adenocarcinoma has also been found to confer an increased risk of subsequent CRC, suggesting possible common etiologic factors in the pathogenesis of these cancers.[24,25] Potential explanations for the association include the fact that small bowel adenocarcinoma develops through a similar adenoma-to-carcinoma sequence and exhibits similar mutations to CRC (k-ras, p-53, MMR genes).[26] Small bowel adenocarcinoma and CRC also share GI risk factors, including hereditary cancer syndromes, inflammatory bowel disease, and celiac disease.[26] Furthermore, dietary exposures (high fat, high cholesterol) contribute to the development of both small bowel cancer and CRC, potentially due to bile acid excess.[26–28] Our finding of an increased incidence of small bowel cancer, particularly after proximal colon cancer, supports the presence of a common carcinogenesis pathway.

The reasons for the association between right colon cancer and pancreatic cancer are less clear. It is notable that half of pancreas cancers contain mutations or deletions in the DPC gene, which encodes SMAD4. Alterations in SMAD4 are seen in a proportion of colorectal and small bowel adenocarcinomas, although the majority of SMAD4-deranged tumors do not have microsatellite instability, which is a hallmark of right-sided lesions.[29,30]

This study also demonstrated an association between left-sided colon cancer and subsequent esophageal cancer. Prior studies suggested an association between Barrett's esophagus, a precursor lesion to esophageal adenocarcinoma, and CRC, but did not identify differences based on CRC location.[31,32] To our knowledge, no prior study has demonstrated an association between left-sided colon cancer and esophageal cancer. Future case–controlled studies are needed to verify this finding and explore potential common etiologic factors.

We noted an association between CRC at all three sites and a decreased incidence of liver and gallbladder cancer. One potential explanation for fewer liver cancer cases is misclassification of primary liver tumors as colorectal metastases in patients with a history of CRC. This would probably account for a minority of clinical scenarios. Gallstone disease has been associated with various malignancies, including CRC.[33,34] The finding of lower incidence of gallbladder cancer after CRC diagnosis could be explained if common risk factors, such as obesity, resulted in both cholecystectomy and CRC. This would only be plausible if the prevalence of post-cholecystectomy status was higher in this population of CRC patients than that observed in the general population, which is not known from existing data. An alternative hypothesis is that colon resection decreases the volume of carcinogenic material delivered to the biliary system through portal flow.

Another epidemiologic factor in the association between a lower incidence of gallbladder cancer after CRC is intensity of medical care. Patients who are diagnosed with CRC and live long enough to develop a second primary malignancy may receive more medical care than those who are diagnosed late or have short survival. Increased medical contact may be associated with receipt of treatment for liver disease and/or cholecystectomy for benign indications, which could protect against future gallbladder and liver cancer.

These study findings may serve multiple purposes. They suggest directions for future case-control and cohort studies to better elucidate common risk factors. If associations are reproduced in these studies, they could be used to counsel patients regarding future cancer risk and potentially modifiable behaviors that contribute to multiple associated primaries. Additionally, they could be used to improve surveillance in cancer survivors.

For example, patients and clinicians managing patients with a history of right colon cancer can benefit from knowing that the expected incidence of small bowel cancer is fourfold that of the general population. As small bowel cancer can produce vague or no symptoms and often remains clinically occult until it is advanced in stage, this heightened awareness might prompt earlier diagnosis and treatment. Additionally, if the association between left colon cancer and esophageal cancer is verified, it could suggest a parameter for increased surveillance. Esophageal cancer is less common but deadlier than CRC. Upper endoscopy could potentially be performed concurrent with surveillance colonoscopy in patients with a history of left colon cancer if it was verified as a significant risk factor for esophageal cancer.

This study has several limitations inherent to retrospective cohort studies using large population-based databases. Given the inability to verify data accuracy within the medical record, a degree of misclassification should be assumed. Notably, there is risk for misclassification of recurrent CRC as second primaries, which would result in an overestimation of the magnitude of risk of second primary CRC. Furthermore, the SEER does not include information regarding important risk factors such as hereditary cancer syndromes, inflammatory bowel disease, or celiac disease. The database also does not provide information on how individual cases were managed, including surgical resection, radiation, and systemic therapy. Finally, while the study yielded a mean follow-up of 5 years, some CRC-associated second GI primaries may occur after a longer interval and could be underrepresented in this study.

## CONCLUSION

CRC location not only impacts treatment response and outcomes but also the risk of second primary GI cancers. With one in five new cancer diagnoses occurring in a patient with a history of cancer, the prevention of additional primaries becomes an important focus of cancer survivor care. These epidemiologic findings warrant further study in case-controlled and cohort studies. Ultimately, surveillance strategies for GI malignancies may be modified and may be more specialized based on a history of CRC and its specific location.

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