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ORIGINAL ARTICLE

Right sided colorectal cancer increases with age and screening should be tailored to reflect this: a national cancer database study

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Abstract

Background In the United States, colorectal cancer (CRC) screening and surveillance is recommended until age 75. However, rates of surgery for CRC are greatest in the elderly, questioning current guidelines. Tumor sidedness is an emerging prognostic marker that may help guide screening and treatment decisions, with specific benefit evaluating CRC anatomic distribution in the elderly. Our objective was to investigate the anatomical distribution of CRC in the elderly and factors associated with right-sidedness.

Methods The National Cancer Database (2004–2016) was used to identify elderly patients with CRC. Cases were stratified by tumor sidedness and elderly subgroups: 65–74, 75–84, and ≥ 85 years of age, and further categorized by primary site. Multivariate analysis identified factors associated with CRC right-sidedness. The outcomes were CRC sidedness in the elderly, the anatomic distribution by age group, and factors associated with right-sidedness.

Results There were 508,219 colorectal cancer patients aged over 65 years identified, 54% of whom had a right-sided cancer. The right-sided incidence rates by age group were 49% (65–74 years), 58.2% (75–84 years), and 65.9% (≥ 85 years) ($p < 0.001$). Variables associated with right-sidedness were age (OR 1.032; 95% CI 1.031–1.033; $p < 0.001$), female sex (OR 1.541; 95% CI 1.522–1.561; $p < 0.001$), Medicare (OR 1.023, 95% CI 1.003–1.043; $p = 0.027$), year of diagnosis ≥ 2010 (OR 1.133; 95% CI 1.119–1.147; $p < 0.001$), tumor size > 5 cm (OR 1.474; 95% CI 1.453–1.495; $p < 0.001$), pathologic stage IV (OR 1.036; 95% CI 1.012–1.060; $p = 0.003$).

Conclusions We found higher rates of right-sided colon cancer in the 75 and above age group. This is a population who would benefit greatly from a high-quality and complete colonoscopy for early diagnosis. As screening and surveillance for this age group are not currently recommended, our findings question the lack of universal recommendation of colonoscopy in patients over 75 years old. Guidelines for CRC screening and surveillance should consider the colon cancer right-shift in the elderly population. Based on these results, we recommend thorough assessment of the proximal colon in the elderly.

Keywords Colorectal cancer · Colonoscopy · Colorectal cancer screening · Colorectal cancer surveillance · Elderly · Tumor sidedness

Introduction

Colorectal cancer (CRC) is the third most common and deadly disease worldwide [1]. It is also the only type of cancer with the potential to be prevented by early detection through colonoscopy. Screening has been shown to be a cost-effective method to reduce the incidence and mortality of CRC [2–4]. In the United States (US) and most other countries with population screening programs, screening is based primarily on age, with separate considerations for those with a personal or family history [5]. The US Preventive Services Task Force (USPSTF) and the US Multi-Society Task Force of Colorectal Cancer (MSTF) recommend screening and

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surveillance for average-risk individuals 50–75 years old, with individualized screening for adults aged 76–85 years old, and screening discouraged after 85 years of age [6–8]. These recommendations come in the face of a rapidly aging population, with the number of Americans aged 65 and older outnumbering those less than 65 with continued exponential growth projected [9]. CRC is a disease of the elderly, with a substantially higher probability of developing CRC and increasing incidence in patients 65 and older over the past decade [1, 10–12].

There is growing evidence for personalizing CRC screening based on risk factors. While age a risk factor for surgery, it is not a contraindication to undergoing procedures [13]. Decision-making for screening and surveillance in the elderly is complex, and should depend on factors other than age, including the screening and family history, comorbidities, functional status, patient preferences, and risk factors for the disease. Using age alone could result in excluding many who would benefit from screening and subsequent treatment [14, 15]. Colon cancer sidedness (right versus left) is an emerging prognostic and predictive biomarker for outcomes in CRC [16]. There are distinct molecular, pathological, and clinical differences between right- and left-sided colon cancers for all disease stages [17–20]. These differences have been reported to affect response to chemotherapy, immunotherapy, and anti-angiogenetic agents, as well as progression-free and overall survival (OS), impacting treatment decisions [21–24]. These distinctions could also be used to help guide decision-making for screening and surveillance in the elderly. Work to date has shown that right-sided colon cancer is more likely to have poor histology, differentiation, and worse survival outcomes [25–28]. However, little work to date has looked at the distribution specifically in the elderly population. As this is the largest growing segment of the population, and population affected by CRC in the US, investigation on this topic is warranted to help guide treatment decisions for screening and surveillance.

Our goal was to investigate the anatomical distribution of colorectal cancer in the elderly and factors associated with tumor sidedness. Our hypothesis was that there are specific anatomic patterns in the elderly by age group which could be used to help guide screening, surveillance and treatment decisions in this population, and that factors associated with the tumor sidedness in the elderly could be identified.

Materials and methods

Data source

A review of the National Cancer Database Participant Use File (NCDB-PUF) was performed to identify all colorectal adenocarcinoma cases from 2004 to 2016 in elderly patients. The NCDB is a cancer registry managed by the American Cancer Society and American College of Surgeons, currently capturing over two-thirds of all newly diagnosed malignancies in the US from more than 1500 Commission on Cancer (CoC)-accredited facilities. The NCDB-PUF presents site-specific cancer data in over 120 variables, for demographics, geographic information, interventions, and outcomes [29, 30]. The database methodology has been previously described [31].

Patient population

For this study, elderly was defined as patients 65 years and older, as that is the age of senior citizenship by Medicare and the US Census Bureau. Colorectal cancer patients were identified through International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) histology codes for adenocarcinoma (8000, 8010, 8140, 8144, 8210, 8211, 8213, 8220, 8221, 8255, 8260, 8261, 8262, 8263, 8480 and 8481, Supplemental Table 1), then further selected for pathologic stage (I–IV) and topographical codes according to the primary cancer site (C180-187, C199, C209, Supplemental Table 1). We selected pathologic stage to stratify cases, as the clinical staging was missing for more than half of the cases. We excluded patients less than 65 years old, cases where pathologic stage information was missing or were pathologic stage 0, codes C188 (overlapping lesion of colon), C189 (colon, not otherwise specified), C260 (intestinal tract), or cases missing information for the outcomes of interest.

Study variables

Patients were divided into two anatomical groups according to ICD-O-3: left-sided lesions (C209, rectum; C199, rectosigmoid junction; C187, sigmoid; C186, descending colon; or C185, splenic flexure), which are tumors within reach of a flexible sigmoidoscopy, and right-sided lesions (C184, transverse colon; C183, hepatic flexure; C182, ascending colon; C180, cecum; or C181, appendix). The anatomical origin of the tumor was determined by the "Primary Site" field. The cohort was further divided into age cohorts of: 65–74, 75–84 and ≥ 85 years old. The variables evaluated included sex, age at diagnosis, race, insurance, year of diagnosis (< 2010 and ≥ 2010) Charlson-Deyo comorbidity index (0, 1, 2, 3 +), education status (higher education, ≥ 21% in the zip code of patient's area of residence with high school degree, lower education < 21%), median income per zip code, facility location, facility type (community cancer program, comprehensive community cancer program, academic/research program, integrated network cancer program), distance from home to facility in miles (≤ 10 miles and > 10 miles), population density in patient's zip code (metropolitan, urban,

rural), tumor sidedness (right, left), primary site, tumor size (≤ 5 cm, > 5 cm), and pathologic stage (I, II, III, IV). Data definitions, unless specified, were compliant with those of the NCDB-PUF data dictionary (available online at https://ncdbpuf.facs.org/?q=node/259/). Those with missing items were excluded from the analysis. The main outcome measure was the anatomical distribution of CRC in the elderly. The secondary outcomes were anatomical distribution by age group within the elderly cohort, and factors associated with tumor right-sidedness.

Statistical analysis

Variables were reported as frequencies (percentages) for categorical data and median (interquartile range) for non-normally distributed data. A chi-square (χ^2) test was used for bivariate analysis across age groups. To verify if the missing items excluded could impact the analysis, a missing data analysis was carried out via Little's MCAR (missing completely at random) test [32]. Multivariate analysis was utilized to identify factors associated with right-sided colon cancer, adjusted for all variables listed above. All comparisons were two-sided, and statistical significance was defined as $\alpha < 0.05$. All analysis was performed with SPSS version 25 (IBM Corp., Armonk, NY, USA).

Ethical statement

This study was reviewed and approved by the Columbia University Medical Center Institutional Review Board (#AAAS0160).

Results

During the study period, 508,219 colorectal adenocarcinoma cases were included in the analysis after applying exclusion criteria (Fig. 1). The demographic, provider and clinicopathologic features of the elderly cohort are shown in Table 1. The median age of diagnosis in the overall cohort was 76 years (IQR 70–82 years) and the cohort was 51.6% ($n = 262{,}327$) female. The majority ($n = 431{,}240$, 84.9%) were Medicare payers and 63.3% ($n = 321{,}583$) of the cohort had no comorbidity (CCI-0). Most patients ($n = 415{,}548$, 81.8%) lived in a metropolitan area and the median travel distance to the treatment center was less than 10 miles. The most common clinical stage at diagnosis was Stage I ($n = 67{,}196$, 34.5%). Among the included patients. the age distribution was 43.5% ($n = 221{,}314$) 65–74, 40% 75–84 ($n = 203{,}431$) and 16.5% 85 years old and greater ($n = 83{,}474$)**.** In this study of patients aged 65 and older**,** more than half of the diagnoses occurred after age 75, when colorectal cancer screening is not currently routinely recommended.

Anatomical distribution of colorectal cancer in the elderly

There were differences in sidedness by age group. In the overall cohort, there were 55.4% ($n = 281{,}762$) right-sided and 44.6% ($n = 226{,}457$) left-sided cancers. In the 65–74-year-olds, the distribution of left and right-sided cancers was nearly equivalent (51% left-sided vs. 49% right-sided). There was a shift to higher proportions of right-sided colon cancer for the 75–84 year-olds (58.2% right-sided vs. 41.8% left-sided, $p < 0.001$), and the difference became progressively more accentuated in ≥ 85-year-olds (65.9% vs. 34.1%, $p < 0.001$). In the 65–74-year-olds, clinical stage I was the most frequent ($n = 30{,}831$, 34.4%), followed by stage II ($n = 24{,}001$, 26.8%) and stage III ($n = 18{,}305$, 20.4%). In the 75–84-year-olds, clinical stage I was the most frequent ($n = 26{,}741$, 35.3%), followed by stage II ($n = 22{,}744$, 30%) and stage III (13,785, 18,2%). In the group of patients ≥ 85 year olds, clinical stage II was the most frequent ($n = 10{,}249$, 34.7%), followed by stage I ($n = 9624$, 32.6%) and stage III (5225, 17.7%). The anatomical distribution of CRC by age can be seen in Fig. 2.

The main primary anatomical sites in the 65–74-year-olds were the sigmoid colon, ($n = 43{,}758$), 19.8%), cecum ($n = 40{,}381$, 18.2%), and right colon ($n = 39{,}064$, 17.7%). In the 75–84-year olds, the main primary sites were the cecum ($n = 45{,}397$, 22.3%), right colon ($n = 43{,}085$, 21.2%), and sigmoid colon ($n = 34{,}439$, 16.9%). A similar distribution was seen in the cohort ≥ 85 years old, but with higher percentages on the right side, where the cecum was the most affected primary site ($n = 22{,}013$, 26.4%), followed by the right ($n = 19{,}550$, 23.4%), and the sigmoid colon ($n = 12{,}199$, 14.6%). The anatomic distributions by age group were seen in Fig. 3. The Little's MCAR analysis revealed the missing data at random hypothesis could not be rejected ($p = 0.111$), hence our results would not be biased by removing the missing data [32].

In the adjusted multivariate analysis, age was an independent predictor of right-sided colon cancer, with increased odds of right-sided incidence of 3.2% for every additional year of life after age 65 ($p < 0.001$). Among factors independently associated with higher odds of right-sided colon cancer were female sex, African American race, Medicare payer, year of diagnosis during or after 2010, higher education and income status, tumor size > 5 cm, and geographic location of the treatment facility (Table 2). Pathologic stage IV and II were also associated with right-sidedness. Factors associated with lower odds of right-sided colon cancer included Medicaid payers, facilities located in the Middle Atlantic region, treatment at an Integrated Network Cancer

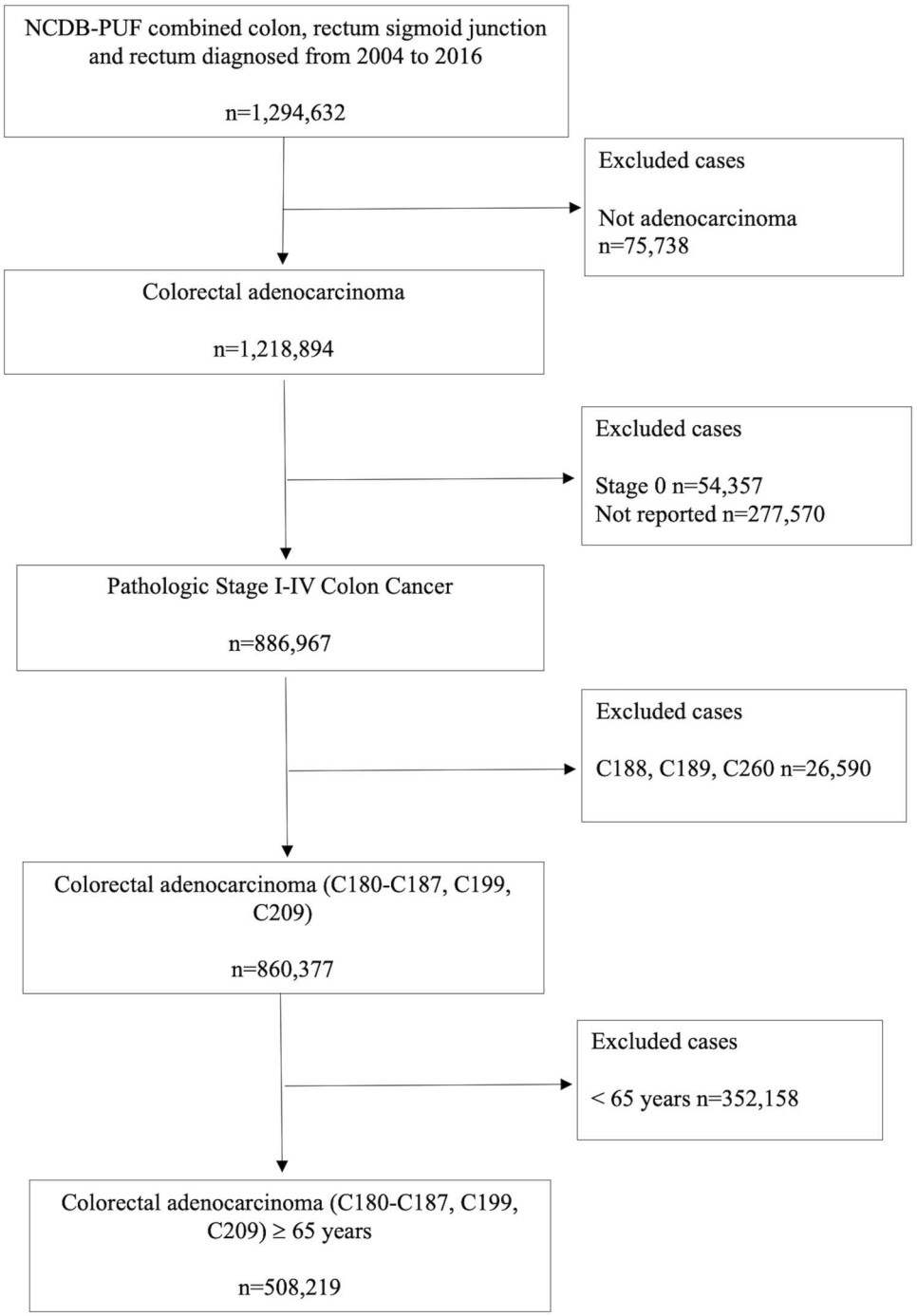

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) flow chart. C260, intestinal tract; C209, rectum; C199, rectosigmoid junction; C189, colon, not otherwise specified; C188, overlapping lesion of colon; C187, sigmoid colon; C186, descending colon; C185, splenic flexure; C184, transverse colon; C183, hepatic flexure; C182, ascending colon; C181, appendix; C180, cecum

Program or academic institution, travel distance > 10 miles to the treatment center, and residence in an urban area.

Discussion

CRC is a common cancer diagnosis and cause of cancer-related death in the elderly population [33]. Colonoscopy is the main tool used for early diagnosis, and age is a key criterion to guide decisions screening and surveillance for colonoscopy [7]. There are no specific recommendations for screening and surveillance in patients over 75 years old, which may result in inappropriate underuse or overuse of screening, or use of flexible sigmoidoscopy. We found a shift towards predominantly right-sided anatomic distribution in patients 75 years old and above. The rates of right-sided CRC increased with age, even when adjusted for confounders. Other factors associated with tumor-sidedness

Table 1 Demographic data for colorectal cancer patients in the US. 65 years and older ($n = 508,219$)

Patient characteristics	*n* (%)
Sex	
Male	245,892 (48.4)
Female	262,327 (51.6)
Age in years, median [IQR]	76 [70–82]
Race	
White	443,904 (87.3)
Black	44,521 (8.8)
Other[a]	19,794 (3.9)
Insurance	
Private Insurance	58,360 (11.5)
Medicaid	6987 (1.4)
Medicare	431,240 (84.9)
Other	11,632 (2.3)
Year of diagnosis	
Before 2010	240,651 (47.4)
2010 or Later	267,568 (52.6)
Charlson–Deyo Comorbidity Index	
0	321,583 (63.3)
1	126,712 (24.9)
2	41,089 (8.1)
3 +	18,835 (3.7)
Education status[b]	
Lower education	214,102 (42.1)
Higher education	291,887 (57.4)
Median Household Income	
Below $48,000	122,482 (24.1)
$48,000 or Greater	157,999 (31.1)
Facility location	
New England	31,171 (6.1)
Middle Atlantic	79,475 (15.6)
South Atlantic	108,182 (21.3)
East North Central	97,214 (19.1)
East South Central	34,932 (6.9)
West North Central	43,751 (8.6)
West South Central	38,828 (7.6)
Mountain	19,834 (3.9)
Pacific	54,832 (10.8)
Facility Type	
Community Cancer Program	62,598 (12.3)
Comprehensive Community Cancer Program	243,530 (47.9)
Academic/Research Program	126,468 (24.9)
Integrated Network Cancer Program	75,623 (14.9)
Travel distance home to facility (miles)	
Less than or equal to 10 miles	303,262 (59.7)
Greater than 10 miles	203,069 (40)
Population density	
Metropolitan	415,548 (81.8)
Urban	69,480 (13.7)
Rural	10,506 (2.1)
Primary Cancer Site	
Righ colon	281,762 (55.4)
Left colon	226,457 (44.6)
Tumor Size (cm)	
Less than or equal to 5 cm	294,826 (58)
Greater than 5 cm	136,222 (26.8)
Pathologic Stage	
I	133,050 (26.2)
II	163,868 (32.2)
III	147,211 (29)
IV	64,090 (12.6)

Note: if sum of items < 100%, the remaining cases were missing/unknown

[a]All other races were combined as "other"

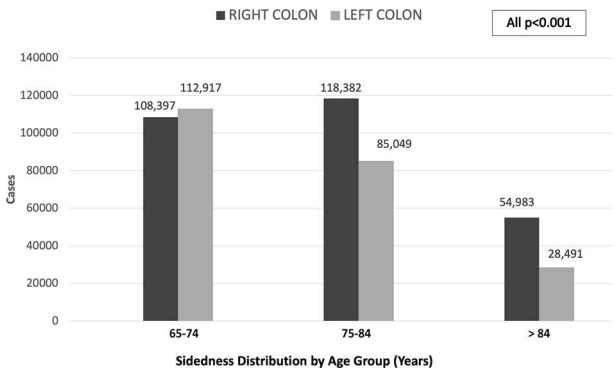

Fig. 2 Number of cases of colorectal adenocarcinoma diagnosed in the United States between 2004 and 2016 in the elderly

were female sex, Medicare payers, African American race, greater comorbidity, larger tumor size, and more advanced pathologic stage.

Studies in all age groups have shown the side of the primary tumor impacts OS across stages for colon cancer. Tumor sidedness serves as a surrogate for prognosis and chemoresponsiveness, with reports on right-sided tumors having worse OS and response to chemotherapy [16, 21, 24, 28]. Reports on OS stratified by stage found advanced stage right-sided colon cancer more aggressive than the stage equivalent left-sided tumor [23]. Besides differences in OS, epidemiologic factors associated with right and left-sided CRCs differ. Previous work investigating factors associated with tumor-sidedness in CRC found patients with right-sided cancer were more likely to be older, female and have poorly differentiated tumours with mucinous or signet-ring cell histology [16]. In comparing left-sided and right-sided CRC, other multi-center and large population reviews similarly

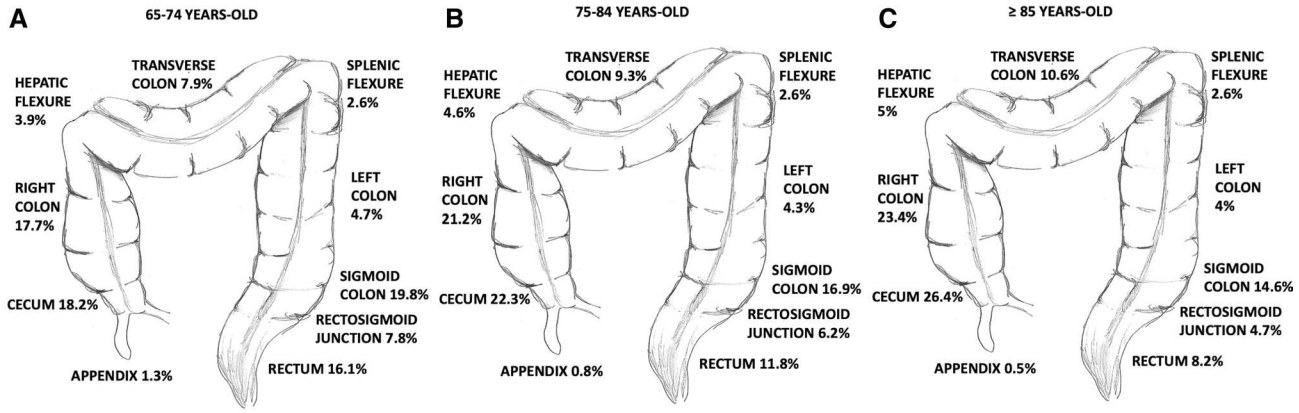

Fig. 3 Colorectal adenocarcinoma diagnosed in the United States between 2004 and 2016, stratified according to the anatomic location, in **a** patients from 65 to 74 years old, **b** patients from 75 to 84 years old, and **c** patients 85 years old and above

found that right-sided cancer was associated with older age, female sex, and worse histologic type [25, 26].

Most recent work on anatomical distribution of CRC has concentrated on early onset cancer patients. In this population under 50 years old, between 74 and 83% of malignancies were left-sided/distal to the splenic flexure [34, 35]. Flexible sigmoidoscopy could therefore be offered as a primary screening modality in average risk patients [35]. These recommendations cannot be broadly applied, as focused work on the anatomical distribution of CRC in the elderly is needed for informed decision-making. In older adults, work to date has shown a right-sided predominance and proximal migration of CRC [16, 36]. While flexible sigmoidoscopy is an accepted screening method in the younger population, it is inadequate in older adults given the comparatively higher rates of proximal cancers; this should be noted in future guidelines. In the elderly, work is evolving on the prognostic effect of right-sided tumors in both metastatic and non-metastatic colon cancer. Results for OS were mixed, with stage III colon cancers specifically having worse OS than left side tumors, but lower mortality within stage II disease and no difference in OS for the overall cohort [22].

Our work is a unique addition to the literature, analyzing CRC sidedness in the elderly population on a national scale that is stratified for primary site. In this cohort of patients aged 65 and older, we found more than half of the diagnoses occurred after age 75, and the cecum and ascending colon were the most affected sites. Together, the cecum and ascending colon comprised over 40% of the sites of CRC in the 75–84-year-olds and 50% in the over 85-year-olds. Prior work indicates that colon cancer is a disease of the elderly, with greater risk in patients over 75 than in the general population [10, 12]. The increasing age of the population has the potential to severely impact the CRC burden [9]. We hope our work provides evidence and objective recommendations for screening and surveillance specific to the older population. Among screening methods for CRC, colonoscopy remains the gold standard, as it allows examination of the entire colon and removal of pre-malignant and early stage disease [37]. However, performing a good quality and complete colonoscopy is crucial for detecting lesions. Elderly patients have higher rates of incomplete or inadequate colonoscopy, higher complications related to sedation and procedure-related complications, and electrolyte imbalances associated with bowel preparation [15, 38]. Simply excluding elderly patients with comorbidities from screening or surveillance for these higher risks would leave a whole population at greater risk of CRC unprotected. Given the benefits of early detection and treatment from colonoscopy, patient-specific pathways to accommodate the unique needs of older adults with comorbidities could help mitigate the potential complications.

We recognize the limitations in this work. The design was a retrospective review using an administrative hospital-based data source. As in any large database, there are missing data and possible data entry errors. There is an inherent possibility of confounding factors not captured by the items reported. We used Little's MCAR (missing completely at random) test to account for the impact of this on our results. Aiming to improve quality in the database, the Commission on Cancer keeps strict control for missing data, as well as setting minimal requirements to maintain accreditation status [30]. With the fields available, we were unable to distinguish between sporadic and nonsporadic CRC. Hereditary syndromes are associated with predominantly right-sided colorectal cancers, which may skew our results toward the right. However, these are assumed small numbers and hereditary syndromes not expected to be diagnosed in the elderly. We are unable to exclude patients with diagnoses of inflammatory bowel disease, familial colorectal syndromes, or family history of colorectal malignancies, all of which increase in risk of CRC development. Finally, we used

Table 2 Multivariate analysis of factors independently associated with right-side colon cancer in patients 65 years and older

Patient characteristics	Odds Ratio	95% Confidence Interval	*p* value
Female	1.541	(1.522–1.561)	< 0.001
Age at Diagnosis (Other = Reference)	1.032	(1.031–1.033)	< 0.001
White	0.687	(0.664–0.710)	< 0.001
Black	1.089	(1.064–1.114)	< 0.001
Insurance type (Other = Reference)			
Private insurance	0.960	(0.917–1.005)	0.078
Medicaid	1.023	(1.003–1.043)	0.027
Medicare	0.835	(0.789–0.884)	< 0.001
Diagnosis Year 2010 or Later	1.133	(1.119–1.147)	< 0.001
Charlson Comorbidity Index (CCI, 0 = Reference)			
CCI 3	1.309	(1.264–1.356)	< 0.001
CCI 2	1.212	(1.184–1.241)	< 0.001
CCI 1	1.110	(1.094–1.127)	< 0.001
Higher education (compared to lower education)	1.097	(1.080–1.114)	< 0.001
Income $48,000 or greater (compared to below $48,000)	1.031	(1.015–1.048)	< 0.001
Facility location (New England = Reference)			
Pacific	1.001	(0.969–1.035)	0.940
Mountain	0.993	(0.953–1.036)	0.757
West South Central	0.981	(0.947–1.016)	0.288
West North Central	1.108	(1.070–1.146)	< 0.001
East South Central	1.042	(1.005–1.081)	0.027
East North Central	1.001	(0.971–1.031)	0.972
South Atlantic	1.039	(1.008–1.071)	0.012
Middle Atlantic	0.963	(0.934–0.994)	0.018
Facility type (Community Cancer Program = Reference)			
Integrated Network Cancer Program	0.948	(0.925–0.971)	< 0.001
Academic/Research Program	0.919	(0.899–0.940)	< 0.001
Comprehensive Community Cancer Program	0.985	(0.965–1.005)	0.135
Travel Distance to facility greater than 10 miles (Reference less or equal than 10 miles)	0.913	(0.900-.926)	< 0.001
Population density (Rural = Reference)			
Metropolitan	0.996	(0.952–1.043)	0.877
Urban	0.965	(0.945–0.985)	< 0.001
Tumor size > 5 cm	1.474	(1.453–1.495)	< 0.001
Pathologic stage (I = Reference)			
IV	1.036	(1.012–1.060)	0.003
III	0.995	(0.978–1.012)	0.582
II	1.093	(1.075–1.112)	< 0.001

CCI Charlson Comorbidity Index

pathologic stage to stratify cases instead of clinical staging due to missing data; thus, patients had to have surgery to be included in the analysis. With this, there is the possibility of selection bias if right-sided lesions had surgery more often than left-sided. However, with this large national sample size we would expect this bias to have minimal impact**.** Despite any limitations from the data sources, the NCDB is the most comprehensive national cancer database with a large-scale sample that is nationally representative, increasing the generalizability of the results.

Conclusions

We found higher rates of right-sided colon cancer in the 75 and above age group. This is a population who would benefit greatly from a high-quality and complete colonoscopy for early diagnosis. As screening and surveillance for this age group are not currently recommended, our findings question the lack of universal recommendation of colonoscopy in patients over 75 years old. Guidelines for CRC screening and surveillance should consider the colon cancer right-shift

in the elderly population. Based on these results, we recommend thorough assessment of the proximal colon in the elderly.

Acknowledgments The data used in this study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator. The American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each of its Commission on Cancer accredited hospitals.

Authors Contribution Study conception and design: Reif de Paula, Simon, Profeta, Keller. Acquisition of data: Reif de Paula, Keller. Analysis and interpretation of data: Reif de Paula, Simon, Profeta, Keller. Drafting of manuscript: Reif de Paula, Keller. Critical revision: Reif de Paula, Simon, Profeta, Keller.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

Ethical approval This study was reviewed and approved by the Columbia University Medical Center Institutional Review Board (#AAAS0160). The status is not Human Subjects Research Under 45 CFR 46.

Informed consent For this type of study, no informed consent is required.

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