Characteristics of carcinoembryonic antigen-producing colorectal cancers: A population based study

Sarah Groover[1], Rashmi Kaul[1], Sarah E. Johnston[2], Yan D. Zhao[2], Asha Karippot[3], Pragatheeshwar Thirunavukarasu[3,4]

SUMMARY

Objectives: *Serum carcinoembryonic antigen is a tumor marker often found to be elevated in colorectal cancer patients. Elevated carcinoembryonic antigen has been strongly associated with poor prognosis. However, little is known about the patient and tumor characteristics between carcinoembryonic antigen-secreting and non-secreting tumors.* **Methods:** *We performed a retrospective analysis of all patients (N=164,187) in the Surveillance, Epidemiology and End Results database diagnosed with colorectal adenocarcinoma from 2010 to 2014. All patients were designated as having either positive/elevated (C1) or negative/normal (C0) pretreatment serum carcinoembryonic antigen level.* **Results:** *Of the 164,187 patients, 68,833 (57.0%) had available carcinoembryonic antigen information, and 33,412 (48.5%) had positive/elevated (C1) antigen levels. Median age was 65 years, and 36,464 (53.0%) were male. Patients with C1 cancers were more likely to be female (Odds ratio 1.06), black (Odds ratio 1.62), separated or never married (Odds ratios 1.50 and 1.49, respectively), higher grade (Odds ratios 1.35, 1.64, and 1.72 of moderately, poorly, and undifferentiated cancers, respectively), and of signet ring cell histology (Odds ratio 1.47) compared to males, whites, married participants, well differentiated grade, and adenocarcinoma histology respectively (P<0.001). Multivariate analysis showed that non-Caucasian race, female gender, unmarried status, distal to sigmoid colon location, increasing tumor invasion beyond muscular layer, increasing nodal involvement, and presence of metastases were independent factors associated with the C1 diagnosis.* **Conclusions:** *About half of all colorectal adenocarcinomas are associated with elevated pre-treatment serum carcinoembryonic antigen levels. Our study is the first nationwide population-based study quantifying the prevalence of serum carcinoembryonic antigen elevation in the colorectal cancer population, and identifying patient and tumor characteristics associated with elevated carcinoembryonic antigen.*

KEY WORDS: *Colorectal cancer; adenocarcinoma; carcinoembryonic antigen; serum; biomarkers; epidemiology; multivariate analysis; risk factors; SEER Program; United States*

INTRODUCTION

In 2018, an estimated 140,250 Americans will develop colorectal cancer (CRC) and 50,630 will die from the disease (1). Carcinoembryonic antigen (CEA) is a serum tumor marker often found in colorectal cancer patients, and elevated serum CEA has been strongly associated with poor oncological prognosis (2, 3). However, not all colorectal cancer patients produce CEA, and little is known about the patient and tumor characteristics between CEA-secreting and non-CEA-secreting tumors.

The TNM staging system of the American Joint Committee on Cancer (AJCC) utilizes the size and local extent of the primary tumor (T-stage), regional lymph node involvement (N-stage), and presence or absence of metastasis (M-stage) as core elements for staging, given the importance of these components in estimating oncological prognosis (4). With increasing evidence to show that the highest pretreatment serum CEA level is associated with poor prognosis, it has also been recommended to be included in the staging system for colorectal cancer (5-7). Incorporation of CEA into the TNM staging system has shown to significantly impact survival estimates (2, 3). However, the proportion of CRC patients who have elevated CEA levels is unknown. In this study, we aim to determine the prevalence of elevated serum CEA amongst patients with colorectal adenocarcinoma and identify the factors associated with such elevation.

PARTICIPANTS AND METHODS

Data Source and Selection of Patients

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program is a comprehensive source of US cancer data, representing 28% of the US population, through 20 population-based cancer registries, namely the Alaska Native Tumor Registry, Arizona Indians, Cherokee Nation, Connecticut, Detroit, Atlanta, Greater Georgia, Rural Georgia, San Francisco-Oakland, San Jose-Monterey, Greater California, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Jersey, New Mexico, Seattle-Puget Sound, and Utah.

We extracted all patients (N = 164,187) diagnosed with adenocarcinomatous CRC between January 1, 2010, and December 31, 2014, by accessing the database named „SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub (1973-2014 varying)" (8) (Figure 1). We used the codes „2010," „2011," „2012," „2013," and „2014" for the year of diagnosis and „Cecum," „Ascending colon," „Hepatic flexure of colon," „Transverse colon," „Splenic flexure of colon," „Descending colon," „Sigmoid colon," „Overlapping lesion of colon," „Colon, NOS," „Rectosigmoid junction," and „Rectum, NOS" for the site. Exclusion criteria included patients with lack of positive histological confirmation, lifetime occurrence of another primary malignancy, non-invasive or *in-situ* malignancies, or cases diagnosed at autopsy.

The interpretation of the highest CEA test result was recorded prior to treatment (i.e., preoperative CEA level) and was accessed using the variable „CS site-specific factor 1." Results were available as positive/elevated; negative/within normal limits; borderline/undetermined whether positive or negative; test ordered (results not in chart); test not ordered; or unknown. We grouped positive/elevated (designated C1) and negative/within normal limits (C0) as those who had CEA information available for analysis. Of the 120,536 histologically proven colorectal

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[1] Oklahoma State University Center for Health Sciences, Department of Biochemistry and Microbiology, 1111W 17th St, Tulsa, Oklahoma, USA
[2] University of Oklahoma Health Sciences Center, Department of Biostatistics and Epidemiology, 1100N Lindsay Ave, Oklahoma City, Oklahoma, USA
[3] Cancer Treatment Centers of America, 10109E 79th St, Tulsa, Oklahoma, USA
[4] Oklahoma State University Center for Health Sciences, Department of Surgery, 1111W 17th St, Tulsa, Oklahoma, USA

Correspondence to:
Pragatheeshwar Thirunavukarasu, MBBS
Oklahoma State University Center for Health Sciences, 10109E 79th Street, Suite C1155, Tulsa 74133, Oklahoma, USA
prag.t@ctca-hope.com
Office: +1-918-249-6601
Fax: +1-918-249-7514

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ABBREVIATIONS
carcinoembryonic antigen (CEA); colorectal cancer (CRC); Surveillance, Epidemiology and End Results (SEER)

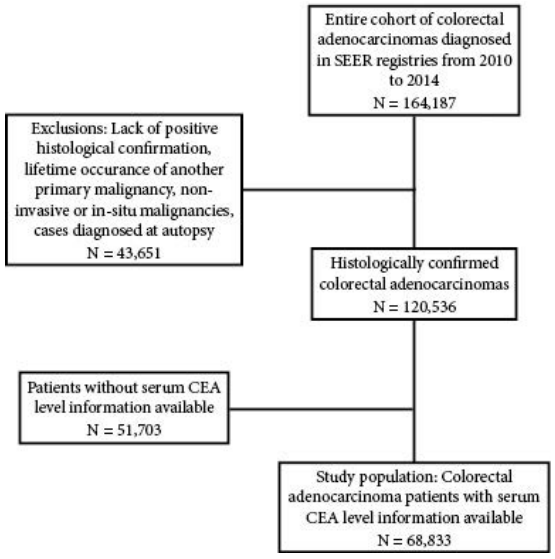

Figure 1. Flow diagram of colorectal adenocarcinoma patients selected for the study

adenocarcinomas, 68,833 patients (57.0%) had CEA information available for analysis.

Age in years, sex, and marital status when the patient was first diagnosed with cancer were obtained. Race information was available as whites; blacks; Asian or Pacific Islanders; American Indians or Alaska Natives; and unknown. Grade of primary tumor, when known, was available as well differentiated; moderately differentiated; poorly differentiated; undifferentiated; or unknown. Tumor histology was coded in the database as per the *International Classification of Diseases for Oncology, Third Edition* (ICD-O-3) and was accessed using the variable „Site and Morphology. ICD-O-3 Hist/behav, malignant."

Characteristics	All Participants (N=68,833)		OR (95% CI)	Type 3 P-value
	Normal CEA (N=35,421)	Elevated CEA (N=33,412)		
Sex				
Male	19007	17457	REF	<.001
Female	16414	15955	1.06 (1.03-1.09)	
Age at diagnosis				
Mean/Standard Deviation	64.47/13.85	64.86/13.93	1.00 (1.00-1.00)	<.001
Median/Min/Max	65/16/102	65/12/108		
Race				
White	28321	24547	REF	<.001
Black	3619	5078	1.62 (1.55-1.69)	
American Indian/Alaska Native	262	293	1.29 (1.09-1.53)	
Asian or Pacific Islander	3062	3353	1.26 (1.20-1.33)	
Unknown	157	141	1.04 (0.82-1.30)	
Hispanic				
Spanish-Hispanic-Latino	4195	4138	REF	0.029
Non-Spanish-Hispanic-Latino	31226	29274	0.95 (0.91-0.99)	
Marital Status				
Married (including common law)	19877	16183	REF	<.001
Single (never married)	5369	6500	1.49 (1.43-1.55)	
Divorced	3317	3592	1.33 (1.26-1.40)	
Widowed	4569	5058	1.36 (1.30-1.42)	
Separated	375	459	1.50 (1.31-1.73)	
Unmarried or Domestic Partner	92	47	0.63 (0.44-0.89)	
Unknown	1822	1573	1.06 (0.99-1.14)	

Table 1. Univariate analyses of patient and tumor characteristics with CEA elevation

Statistical Analysis

Categorical covariates were summarized with frequencies and percentages, and continuous covariates were summarized with means, medians, minimums, maximums, and standard deviations. We analyzed the data using univariate and multivariate logistic regression to model the odds of a patient having elevated serum CEA levels (i.e. being C1). Exponentiated maximum-likelihood estimates on model coefficients were reported along with p-values, based on the Wald test. From these models we obtained odds ratios (OR) and corresponding 95% confidence intervals (95% CI). As serum CEA elevation is strongly correlated with probability of metastatic disease at diagnosis, we performed further univariate and multivariate analyses on the subset of metastatic patients (defined as patients with stage IV CRC). Statistical analysis was performed using SAS software (9).

RESULTS

Patient and Tumor Characteristics

We performed a univariate analysis of CRC patients characterized by CEA status (C-stage) (Table 1). Of the 68,833 (57.0%) patients with available CEA information, 33,412 (48.5%) patients had positive/elevated (C1) antigen levels. Median age was 65 years and 36,464 (53.0%) patients were male. Compared to C0 cancers, patients with C1 cancers were significantly more likely (P<0.001) to be female and non-white. On analysis of the marital status, patients who were single, divorced, widowed or separated at the time of diagnosis was associated with more than 50% chance of having elevated CEA compared to married individuals. However, individuals who were unmarried but lived with their significant other were significantly less likely to be C1 compared to married individuals.

Analysis of tumor characteristics associated with CEA elevation showed that compared to C0 cancers, C1 cancers were significantly more likely (P<0.001) to be of higher grade and of more advanced stage, within each TNM category, as well as overall AJCC stage (Table 1). Signet ring cell pathology was the most common morphology associated with C1 cancers, while adenocarcinoma in preexisting adenomatous polyps and medullary histology were the most common morphologies associated with C0 cancers.

Risk Factors for CEA Secretion

We performed a multivariate analysis to identify independent factors associated with diagnosis C1 tumors (Figure 2). African-American and Asian/Pacific Islander race were more likely to have elevated CEA. Female gender was also associated with slighted higher risk of C1 tumors. Unmarried marital status variables, as described in the univariate analysis, were also associated with C1 tumors. Other factors that emerged as independent factors associated with CEA elevation included left-side tumor location (sigmoid, rectosigmoid junction, and rectum); increasing tumor invasion beyond the *muscularis propria* (T stage); increasing extent of nodal disease (N stage); and presence of metastases (M stage).

Characteristics	All Participants (N=68,833)		OR (95% CI)	Type 3 P-value
	Normal CEA (N=35,421)	Elevated CEA (N=33,412)		
SEER Site				
Alaska Natives - 1992+	69	90	REF	<.001
Atlanta (Metropolitan) - 1975+	954	978	0.79 (0.57-1.09)	
California excluding SF/SJM/LA - 2000+	8260	7005	0.65 (0.47-0.89)	
Connecticut - 1973+	1302	1480	0.87 (0.63-1.20)	
Detroit (Metropolitan) - 1973+	1754	1680	0.73 (0.53-1.01)	
Greater Georgia - 2000+	2636	2707	0.79 (0.57-1.08)	
Hawaii - 1973+	728	772	0.81 (0.58-1.13)	
Iowa - 1973+	1765	1393	0.61 (0.44-0.83)	
Kentucky - 2000+	2139	2216	0.79 (0.58-1.09)	
Los Angeles - 1992+	3612	3407	0.72 (0.53-0.99)	
Louisiana - 2000+	2293	2471	0.83 (0.60-1.14)	
New Jersey - 2000+	3515	3704	0.81 (0.59-1.11)	
New Mexico - 1973+	686	758	0.85 (0.61-1.18)	
Rural Georgia - 1992+	56	71	0.97 (0.61-1.56)	
San Francisco-Oakland SMSA - 1973+	2220	1769	0.61 (0.44-0.84)	
San Jose-Monterey - 1992+	987	824	0.64 (0.46-0.89)	
Seattle (Puget Sound) - 1974+	1657	1408	0.65 (0.47-0.90)	
Utah - 1973+	788	679	0.66 (0.47-0.92)	
Primary Site				
C18.0-Cecum	5834	5217	REF	<.001
C18.2-Ascending colon	5330	4270	0.90 (0.85-0.95)	
C18.3-Hepatic flexure of colon	1244	1051	0.94 (0.86-1.03)	
C18.4-Transverse colon	2359	2047	0.97 (0.90-1.04)	
C18.5-Splenic flexure of colon	794	766	1.08 (0.97-1.20)	
C18.6-Descending colon	1587	1420	1.00 (0.92-1.08)	
C18.7-Sigmoid colon	7106	6862	1.08 (1.03-1.14)	
C18.8-Overlapping lesion of colon	299	370	1.38 (1.18-1.62)	
C18.9-Colon, NOS	192	754	4.39 (3.73-5.17)	
C19.9-Rectosigmoid junction	2819	3015	1.20 (1.12-1.27)	
C20.9-Rectum, NOS	7857	7640	1.09 (1.04-1.14)	
Histology				
Adenocarcinoma, NOS	25036	26711	REF	<.001
Adenocarcinoma in adenomatous polyp	3254	1255	0.36 (0.34-0.39)	
Tubular adenocarcinoma	22	11	0.47 (0.23-0.97)	
Papillary adenocarcinoma, NOS	9	6	0.62 (0.22-1.76)	
Adenocarcinoma in villous adenoma	773	506	0.61 (0.55-0.69)	
Villous adenocarcinoma	19	11	0.54 (0.26-1.14)	
Adenocarcinoma in tubulovillous adenoma	3578	1685	0.44 (0.42-0.47)	
Mucinous adenocarcinoma	2059	2345	1.07 (1.00-1.14)	
Mucin-producing adenocarcinoma	227	313	1.29 (1.09-1.53)	
Signet ring cell carcinoma	327	514	1.47 (1.28-1.69)	
Medullary carcinoma, NOS	94	34	0.34 (0.23-0.50)	
Adenosquamous carcinoma	23	21	0.86 (0.47-1.55)	
Grade				
Well differentiated; Grade I	2898	1846	REF	<.001
Moderately differentiated; Grade II	24443	21001	1.35 (1.27-1.43)	
Poorly differentiated; Grade III	4988	5204	1.64 (1.53-1.76)	
Undifferentiated; anaplastic; Grade IV	798	874	1.72 (1.54-1.92)	
Unknown	2294	4487	3.07 (2.84-3.32)	

Table 1. (Continued)

Characteristics	All Participants (N=68,833)		OR (95% CI)	Type 3 P-value
	Normal CEA (N=35,421)	Elevated CEA (N=33,412)		
Overall Stage				
0	674	171	0.98 (0.82-1.16)	<.001
I	9570	2481	REF	
IIA	9106	5517	2.34 (2.21-2.47)	
IIB	646	571	3.41 (3.02-3.85)	
IIC	613	911	5.73 (5.13-6.41)	
IINOS	22	17	2.98 (1.58-5.62)	
IIIA	1713	569	1.28 (1.15-1.42)	
IIIB	7573	5739	2.92 (2.76-3.09)	
IIIC	1998	2380	4.59 (4.27-4.95)	
IIINOS	113	124	4.23 (3.27-5.48)	
IVA	1573	6877	16.86 (15.72-18.09)	
IVB	1203	6789	21.76 (20.18-23.47)	
IVNOS	137	669	18.83 (15.59-22.75)	
UNK Stage	480	597	4.80 (4.22-5.45)	
T Stage				
T1	5918	2800	REF	<.001
T2	5931	2198	0.78 (0.73-0.84)	
T3	17961	16077	1.89 (1.80-1.99)	
T4a	2283	3574	3.31 (3.09-3.55)	
T4b	1702	3917	4.86 (4.52-5.23)	
T4NOS	45	130	6.11 (4.34-8.60)	
Tis	674	171	0.54 (0.45-0.64)	
TX	907	4545	10.59 (9.73-11.52)	
N Stage				
N0	21728	14580	REF	<.001
N1a	3803	3107	1.22 (1.16-1.28)	
N1b	3589	3745	1.56 (1.48-1.64)	
N1c	470	548	1.74 (1.53-1.97)	
N1N	1302	3181	3.64 (3.40-3.90)	
N2a	2130	2835	1.98 (1.87-2.11)	
N2b	1885	3150	2.49 (2.34-2.65)	
N2N	122	263	3.21 (2.59-3.99)	
NX	392	2003	7.61 (6.82-8.50)	
M Stage				
M0	32508	19077	REF	<.001
M1a	1573	6877	7.45 (7.03-7.89)	
M1b	1203	6789	9.61 (9.02-10.25)	
M1N	137	669	8.32 (6.92-10.01)	

Table 1. (Continued)

Increased grade was not associated with diagnosis of C1 tumors on multivariate analysis.

CEA Elevation in Metastatic Cancers

Presence of metastases was strongly associated with the highest risk of C1 tumors, but all patients with metastatic disease do not have elevated serum CEA levels. Hence, we performed an analysis of the subset of patients with metastatic disease only, to identify the factors independently associated with diagnosis of C1 cancers (Figure 3). We included site of metastatic disease as a factor in the analysis. C1 patients with metastases were significantly more likely to have metastasis to liver (OR 2.86) and lungs (OR 1.53) compared to brain metastasis.

DISCUSSION AND CONCLUSIONS

Colorectal cancer is the third leading cause of cancer and cancer-related mortality in the United States. There have been multiple staging systems in the last several decades, in an attempt to categorize patients into different prognostic groups (i.e. 'stages') and streamline management options. In 1978, the AJCC published their first edition of their TNM system and today, it is the most widely used method for staging colorectal cancers, as well as all other types of cancer (10). The T stage describes the size and local extent of the primary tumor; the N stage describes regional lymph node involvement; and the M stages describes the presence or absence of metastasis (4). The overall stage is determined by combining the scores from these individual categories. By using serum CEA elevation to represent poor prognosis, we can describe the subset of people who do not have this marker and begin to uncover the environmental and genetic influences that play a protective role. Having a better understanding of the patient and tumor characteristics associated with this aggressive subset of colon cancers will help to develop more personalized treatment plans and effective management strategies. Using survival data analyses largely from the Surveillance, Epidemiology, and End Results (SEER) database, the AJCC regularly updates the text with changes to TNM categories, criteria, and prognostic stage groups, and in 2010 they published their seventh edition (11, 12). The limitation with the TNM system is that it is a purely anatomical method of assessing prognosis, without taking into consideration other biological markers associated with oncological natural history and pattern of aggressive behavior. The AJCC is beginning to incorporate non-anatomical prognostic factors into their site-specific staging guidelines (4, 13). Examples include age in thyroid cancer, histologic grade in esophageal cancer and sarcoma, mitotic rate in gastrointestinal stromal tumors, prostate-specific antigen levels and Gleason score in prostate cancer, and serum tumor markers in testicular cancer (11). Several prominent organizations, including the Colorectal Working Group of the AJCC, the American Society of Clinical Oncology (ASCO), the European group on tumor markers recommended the addition of serum carcinoembryonic antigen (CEA) levels to colorectal staging guidelines, (5-7) but the AJCC has yet to incorporate it into colorectal staging guidelines.

CEA is normally secreted on the apical side of colorectal epithelial cells and excreted with feces. However, in CRC, due to loss of polarity in cancer cells, CEA could get expressed on the whole tumor cell surface, allowing for secretion into blood vessels (14). High preoperative serum CEA levels have been well-correlated with increased recurrence and decreased survival in CRC patients (2, 15-25). Furthermore, elevated serum CEA has shown to be a more effective predictor of worse oncological prognosis than N stage (3, 26) and hence, an important factor that could potentially guide the course of treatment (27). CEA is a highly specific serum tumor marker for colorectal cancer, but it is not a sensitive tumor marker because not all colon cancer patients have elevated serum CEA levels (28, 29). While it is generally associated with larger tumor size and more

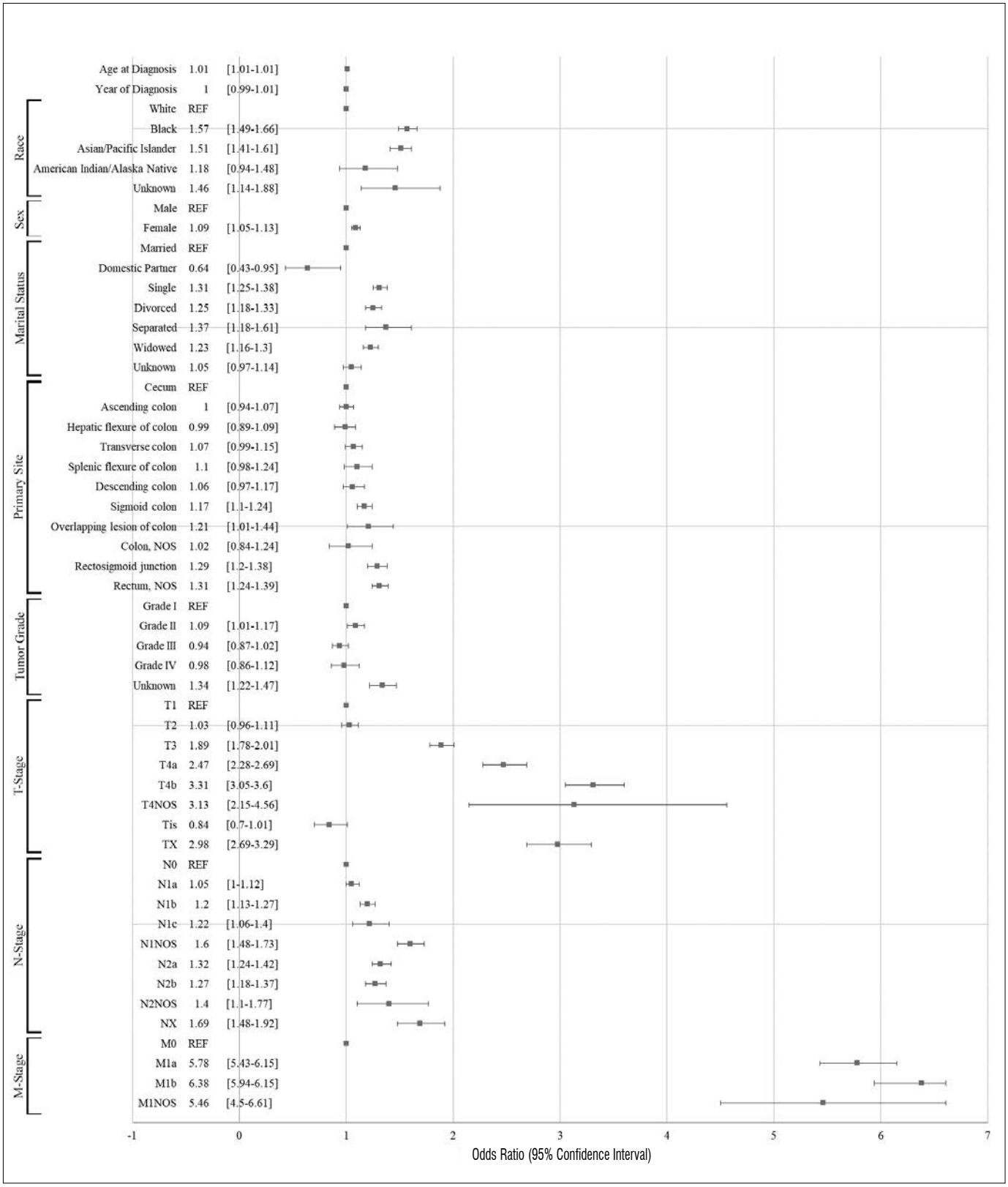

Figure 2. Flow diagram of colorectal adenocarcinoma patients selected for the study

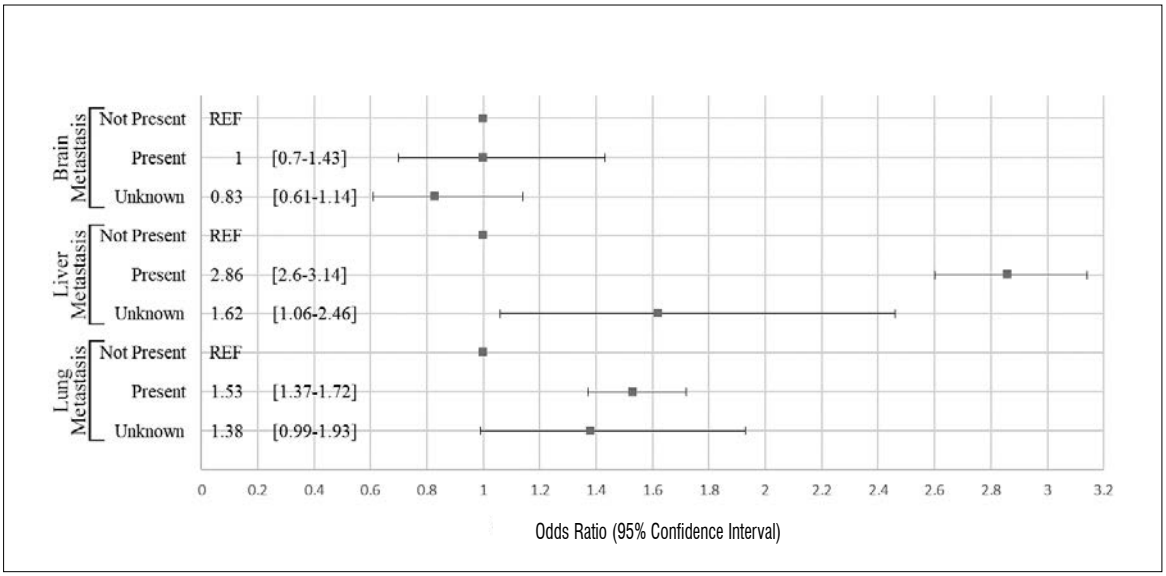

Figure 3. Multivariate analysis of site of metastasis with CEA elevation (metastatic patients only)

extensive metastasis, (30) we have shown in this study that approximately 50% of CRC cases do not have elevated CEA levels.

Another recent US study reviewing the National Cancer Database (NCDB) also reported that approximately 66% of the CRC patients had normal CEA levels (31). Their study emphasized the importance of evaluating preoperative serum CEA, as it was associated with increased hazards of mortality. However, the study did not associate these findings with any specific race or gender. In our study, African-American race was found to be an independent risk factor associated with diagnosis of colorectal cancer with elevated CEA. Supplemental data from another recent NCDB study on early onset CRC also showed that black patients were the most likely to have elevated CEA levels (32). These US population studies strongly support our findings related to elevated CEA as an important prognostic biomarker for improved disease outcome among black patients with CRC. These studies on serum CEA in the clinics can be complemented or validated by tissue CEA expression (33).

Many of the previous CRC epidemiological studies including SEER data studies have not focused on gender associations with any biomarkers in CRC. Our findings related to female gender being an independent risk factor associated with elevated CEA level are unique and need further stratification to show any association with age, race or ethnicity.

Analysis of SEER data has shown that marital status at diagnosis has been well-associated as an independent factor for poor prognosis in many types of cancers, (34-38) including colorectal cancer (39). Often, this is explained by social support mechanisms available for patients who are married at the time of diagnosis. Our study throws new light to a rather new explanation – the possibility that marital status is related to the diagnosis of biologically different cancers or other socioeconomic conditions associated with marital status may also contribute. But, such analysis or discussion is beyond the scope of this manuscript.

There are several limitations in our study, and most of them are inherent to any large population-based database retrospective analysis. The SEER database represents only 28% of the United States population via 20 different registry sites. Although such extensive coverage is appropriate for analyzing incidence and survival on a large scale, uniformity, consistency and accuracy of data entry cannot be verified by authors. Several data points have unrecorded entries, especially for race, marital status, histological grade, site of metastasis, and CEA information. However, we decided to keep all these patients and categories data-unknown patients as a variable in analysis. A drawback of our unusually large sample size is that such large sample sizes may drive even small differences to positive statistical significance, while they may not be clinically significant in daily practice.

Univariate analysis of tumor characteristics showed that C1 cancers were significantly more likely to be located in the sigmoid colon, rectosigmoid junction, or rectum and have a higher histological grade. The latter may be explained by the differences in venous drainage anatomy between colon and rectum. Colonic venous blood drains into either the inferior or superior mesenteric vein, which later drains into the portal venous system that enters the liver, where CEA is metabolized. On the other hand, rectal venous drainage enters the systemic venous system via the inferior vena cava bypassing hepatic metabolism, thereby leading to relatively higher levels of serum CEA for rectal tumors compared to colonic tumors. This is also reflected in our study results, which shows that diagnosis of C1 tumors is associated with more distal location of the primary tumor. In other words, tumors located in the ascending, transverse, and descending colon may need to produce quantitatively more CEA (i.e. to be larger in size and/or more invasive in terms of extent of the tumor) in order to demonstrate the rather equivalent levels of serum CEA as tumors located in the sigmoid colon or rectum. Further studies are needed to study this possibility in more detail.

Although CEA is a well-established marker of prognosis in CRC, about 15% of our initial patient cohort did not have the assay ordered prior to first course of treatment, and 27% were missing CEA information all together. With further accumulation of evidence to support prognostic value of CEA, we hope that the use of presence of elevation of serum CEA

on diagnosis (i.e., C-stage) would become more prevalent. This will also drive more physicians to routinely order serum CEA levels on diagnosis. In brief, serum CEA measurement on diagnosis should be considered standard of care in the initial workup of colorectal malignancies. Future studies studying the factors associated with the non-availability of serum CEA level prior to treatment might shed light on the diversity of quality of health care delivery in the USA.

This is the first and largest database-based epidemiological study quantifying the prevalence of C1 cancers in the colorectal cancer population.

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Declaration of Interests

Authors declare no conflicts of interest

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