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Colon cancer lymph node evaluation among Military Health System beneficiaries: An analysis by race/ethnicity

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Abstract

Background—The number of lymph nodes examined during colon cancer surgery falls below nationally recommended guidelines in the general population, with blacks and Hispanics less likely to have adequate nodal evaluation in comparison to whites. The Department of Defense's (DoD's) Military Health System (MHS) provides equal access to medical care for its beneficiaries, regardless of racial/ethnic background. This study aimed to investigate whether racial/ethnic treatment differences exist in the MHS, an equal access medical care system.

Methods—Linked data from the DoD cancer registry and administrative claims databases were used and included 2,155 colon cancer cases. Multivariate logistic regression assessed the association between race/ethnicity and the number of lymph nodes examined (<12 and ≥ 12) overall and for stratified analyses.

Results—No overall racial/ethnic difference in the number of lymph nodes examined was identified. Further stratified analyses yielded similar results, except potential racial/ethnic differences were found among persons with poorly differentiated tumors, where non-Hispanic blacks (NHBs) tended to be less likely to have ≥12 lymph nodes dissected (OR: 0.34, 95% CI: 0.14-0.80, p-value: 0.01) compared to non-Hispanic whites.

Conclusion—Racial/ethnic disparities in the number of lymph nodes evaluated among patients with colon cancer were not apparent in an equal-access healthcare system. However, among poorly differentiated tumors, there might be racial/ethnic differences in nodal yield, suggesting the possible effects of factors other than access to healthcare.

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Introduction

Colorectal cancer (CRC) is the third leading cause of cancer death in the United States (US).[1] The American Cancer Society estimated that 136,830 incident cases and 50,310 deaths will occur in 2014 due to CRC, with almost three-fourths (71%) of incident cases occurring in the colon.[2] Lymph node metastasis is an important predictor of survival among colon cancer patients.[3, 4] The dissection of a sufficient number of lymph nodes is emphasized in order to predict nodal status (positive versus negative), thus assuring accurate staging of disease and the evaluation of lymph node metastasis.[5, 6] The number of lymph nodes evaluated has also been positively correlated with survival,[7-9] which is likely explained by the increasing use of adjuvant therapy upon detection of positive lymph nodes, which in turn depends on lymph node yield.[10] Therefore, the number of lymph nodes evaluated is an important clinical and prognostic factor for colon cancer.

National guidelines recommend that at least 12 lymph nodes be resected surgically and examined pathologically in patients with colon cancer.[11-13] Despite these promulgated guidelines, studies have indicated that compliance remains sub-optimal[7, 14, 15] and can vary according to patient factors (e.g., age or obesity),[16-18] tumor factors (e.g., tumor stage and site),[14, 18, 19] and physician factors (e.g., patient volume and years of experience).[15] Recent studies, although inconsistent,[20, 21] have suggested that the number of lymph nodes dissected may vary by race/ethnicity.[22-26] Among colon cancer cases diagnosed in Louisiana, blacks were less likely to have adequate number of lymph nodes dissected compared to whites.[22] Among Medicare beneficiaries, Hispanics were also found to have less adequate nodal yield in comparison to whites.[25, 26]

Previous studies might be influenced by unequal access to medical care, a health disparity in which medical care is not equivalent amongst different individuals due to factors such as race or ethnicity. Unequal access to healthcare due to insufficient health insurance affects not only the receipt of needed care but also the quality of care.[27] Individuals with less access to care are less likely to receive needed services and recommended care.[27] Minorities are more likely to have insufficient health insurance[28-30] and thus receive poorer quality health care.[30] For example, blacks are less likely to have access to high-volume hospitals or surgeons[31-33] and to receive surgeries[34-36] than whites. Therefore, it is possible that racial/ethnic differences in the extent of lymph node evaluation may at least partially be accounted for by unequal access to medical care. Such inequity between racial/ethnic groups may be reduced in an equal access system.

To the best of our knowledge, no previous studies have examined racial/ethnic disparities in lymph node retrieval in an equal-access setting; such studies in healthcare disparity help assess the potential influences of unequal access to care on the possible racial/ethnic differences as well as the possible effects of factors other than access to care. The Department of Defense's (DoD) Military Health System (MHS) provides equal access to medical care for its beneficiaries regardless of their racial/ethnic background, offering an excellent opportunity to investigate racial/ethnic differences in the number of lymph nodes resected and evaluated among colon cancer patients.

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The objective of this study was to examine the number of lymph nodes resected surgically and examined pathologically among non-Hispanic white (NHW), non-Hispanic black (NHB), Asian/Pacific Islanders (API), and Hispanic white (HW) colon cancer patients in the MHS. Furthermore, we assessed whether racial/ethnic differences in lymph node yield varied by age at diagnosis, sex, tumor stage, tumor grade, and colon cancer site.

Materials & Method

Data source

This study utilized linked and consolidated data from the DoD's Central Cancer Registry (CCR) and the MHS Data Repository (MDR). Information from DoD beneficiaries, including active duty members, retirees, Guards and Reserve members and their dependents, are contained in both data sources. For CCR, certified cancer registrars abstract demographic, health, and tumor characteristic information from the records of cancer patients diagnosed and/or treated at military treatment facilities (MTFs) according to the North American Association of Central Cancer Registries guidelines. MDR contains administrative and medical care claims information, which includes clinical diagnosis, diagnostic procedures, treatment, health conditions, and medical prescriptions, from the DoD heath care program, known as Tricare, for in-patient and out-patient services provided either at MTFs (direct care) or at civilian facilities that are paid for by the DoD (indirect care).

The data linkage project was reviewed and approved by the institutional review boards of the Walter Reed National Military Medical Center, Tricare Management Activity, and the National Institutes of Health Office of Human Subjects Research.

Study subjects

Patients diagnosed with histologically confirmed primary colon adenocarcinoma (International Classification of Diseases for Oncology Third Revision site codes (ICD-O-3) C180-189) that underwent a surgical procedure between 1998 and 2007 were eligible for this study. The initial study population included 2,939 patients aged 20 years or older. Patients with stage IV, who are probably less likely to receive colon cancer surgery, or unknown stage (n=755) and those with an unknown number of lymph nodes examined (n=29) were excluded from this study.

Study variables

Tumor characteristics, including the number of lymph nodes examined, were obtained from CCR. According to national colon cancer guidelines, a minimum of 12 lymph nodes should be dissected.[11-13] Therefore, the total number of regional lymph nodes removed and examined, which was obtained from the variable "regional nodes examined", was classified into two groups: <12 lymph nodes and ≥12 lymph nodes. Tumor stage was categorized as Stage I, Stage II, and Stage III based on the American Joint Committee on Cancer staging recommendations.[37] Tumor histologic grade was classified based on level of differentiation as well differentiated, moderately differentiated, poorly differentiated, and unknown. Colon cancer site was categorized into four categories: right (C180, 182, 183: cecum, ascending

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colon, hepatic flexure, respectively), transverse (C184), left (C185-187: splenic flexure, descending colon, and sigmoid colon, respectively), and overlapping/unknown (C188-189).

Demographic characteristics were obtained from CCR, with missing information supplemented from MDR. Race/ethnicity was categorized into four groups: NHW, NHB, API, and HW. Other demographic information included diagnosis year, age at diagnosis, sex, marital status, active duty status, military service branch, military healthcare benefit type, and military rank. Based on the release of national guidelines,[11-13] diagnostic years were divided into three periods: 1998-2000, 2001-2003 and 2004-2007. Age at diagnosis was categorized into four groups: 20-49 years, 50-59 years, 60-69 years, and 70+ years. Marital status included being never married, married, other (separated, divorced, or widowed), and unknown. Beneficiaries were classified as either active duty or non-active duty (i.e. retiree and dependents) at the time of their diagnosis. The service branch of the active duty member or sponsor was categorized as Army, Air Force, Navy/Marines, other (i.e. Coast Guard and Public Health Service), and unknown. Benefit type was classified into three categories TRICARE Prime (HMO-like component), not Prime, and unknown. The military rank of the active duty member or sponsor, which was used as a surrogate for income, included enlisted personnel, officer, other (i.e. civilian pay plan, general schedule, non-appropriated funds), and unknown.

Information on obesity was obtained from MDR. Patients who had an ICD-9 diagnostic code of 278.00 or 278.01 were identified as being obese.

Statistical analysis

As the first step of data analysis, the overall racial and ethnic differences between demographic and tumor characteristics were compared using chi-square tests of significance. We then assessed the association between race/ethnicity and the number of lymph nodes examined (<12 and ≥ 12) using multivariate logistic regression, adjusting for potential confounders that included demographic variables, tumor characteristics, and obesity. Finally, we analyzed whether the relationship between race/ethnicity and the number of lymph nodes examined varied by age at diagnosis, sex, tumor stage, tumor grade, and colon cancer site. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for overall and stratified analyses. Since the number of lymph nodes examined has been found to be associated with obesity,[16] all aforementioned analyses were rerun excluding all patients who were identified as being obese.

Tests of significance were two-tailed and conducted at an alpha of 0.05 using Statistical Analysis System (SAS) software, Version 9.3 for Windows (SAS Institute, Inc., Cary, North Carolina).

Results

This study included 2,155 beneficiaries with colon cancer who received care from the MHS (1,530 NHWs; 350NHBs; 169 APIs; and 106 HWs) (Table 1). The overall proportion of patients having at least 12 lymph nodes examined was 59%. The distributions of factors except year of diagnosis, marital status, and tumor grade varied among racial/ethnic groups

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(p<0.05). The number of lymph nodes examined also did not differ by race/ethnicity, with 57.5% NHWs, 62.3% NHBs, 57.4% APIs, and 65.1% HWs receiving an adequate lymph node evaluation (p=0.20). At the time of colon cancer diagnosis, NHWs tended to be older, an officer/having a sponsor who was an officer, and have earlier stage disease than minority groups. NHW, NHB, and HW patients were more likely to be men, while APIs were more likely to be women. NHBs were more likely to be an active duty member of the military and obese than other races/ethnicities. NHWs were more likely to be affiliated with the Air Force, whereas NHBs and HWs were more likely to be affiliated with the Army. NHBs and APIs were more likely to have Tricare Prime insurance than NHWs and HWs. While NHWs and NHBs tended to have right-sided colon cancers, APIs and HWs tended to be diagnosed with left-sided colon cancers.

After adjustment for potential confounding factors, NHBs, HWs, and APIs were not significantly different from NHWs in receiving adequate lymph node evaluation (Table 2). Racial/ethnic difference in the number of lymph nodes examined were also not observed when analyses were further stratified by age at diagnosis, sex, tumor stage, and colon cancer site (data for age at diagnosis and sex not shown). Furthermore, the number of lymph nodes examined did not differ by race/ethnicity among patients with well or moderately differentiated tumors. In contrast, among patients with poorly differentiated tumors, significant differences between NHBs and NHWs in nodal yield were observed. NHBs were less likely to have ≥12 lymph nodes examined compared to NHWs (OR: 0.34, 95% CI: 0.14-0.80, p-value: 0.01). Among APIs and HWs, no significant differences in the number of lymph nodes examined was found in comparison to NHWs (OR: 0.82, 95% CI: 0.26-2.54, p-value: 0.72; OR: 1.14, 95% CI: 0.25-5.28, p-value: 0.87; respectively).

Discussion

This study showed that the overall proportion of patients with ≥12 lymph nodes resected and examined (59%) was higher than in the general population (44% among patients in Louisiana and 38% among patients examined in SEER-Medicare).[22, 26] Unlike previous studies that found racial/ethnic differences in the number of lymph nodes examined,[22, 23, 25, 26] this study observed no overall differences in the number of lymph nodes examined among NHW, NHB, API, and HW beneficiaries with equal access to healthcare in the MHS. We also did not observe racial/ethnic differences by age at diagnosis, sex, tumor stage, or colon cancer site. However, among patients with poorly differentiated tumors, potential racial/ethnic differences in the number of lymph nodes examined were observed.

Our findings suggest that the racial/ethnic differences in the number of lymph nodes evaluated in the general population might be minimal within the DoD equal-access healthcare system. However, we cannot exclude the possibility of racial/ethnic differences among patients with poorly differentiated cancer. Larger studies within an equal access system are needed to demonstrate whether different racial/ethnic groups differ in the number of lymph nodes evaluated, particularly for certain subgroups such as poorly differentiated tumors and other potential effect modifiers (e.g., microsatellite instability/mismatch repair (MSI/MMR)[38, 39]) that could not be assessed in this data.

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It is not clear why the racial difference was observed only for poorly differentiated tumors. While it might result from chance alone, factors other than access to care might play a role. For example, obesity, which may vary between different racial/ethnic groups, has been found to be associated with lymph node yield.[16] Blacks and Hispanics tend to be more obese than NHWs.[40] The presence of fatty tissue causes the retrieval of lymph nodes to be more difficult due to technical complexity of lymph node dissection, as shown by increased surgical time,[41] among obese patients. However, obesity was adjusted for in our data analysis. Furthermore, when the analyses were confined to patients without obesity, the results remained similar (data not shown). Thus, obesity might not account for the observed racial difference among patients with poorly differentiated tumors.

Lymph node yield may also be influenced by physician factors. Adequate lymph node yield has been associated with surgeon procedure volume, with high-volume surgeons, who tend to have more experience, harvesting more lymph nodes compared to low-volume surgeons.[15, 42-44] The skill level of a pathologist may also play a role in the retrieval of more lymph nodes, particularly when lymph node harvest is performed by a staff pathologist compared to a pathology resident/technologist.[15] However, studies have found that pathology assistants, who often have more time and fewer distractions, harvest more lymph nodes than more experienced pathologists.[45, 46] It is not known if the physician factors varied between NHB and NHW patients in our study population.

This study had several strengths. First, it minimized the potential effects of unequal access to care on racial/ethnic differences. Second, to our knowledge, it is the first study that assessed racial/ethnic differences in lymph node evaluation by demographic or tumor characteristics, although other biological indicators such as MSI/MMR tumor status could not be analyzed. The study also had limitations. The numbers of patients in certain strata were comparatively small, which prevented us from having solid evidence on whether racial/ethnic differences in the number of lymph nodes evaluated existed in certain groups defined by age at diagnosis, sex, tumor stage, tumor grade, and colon cancer site. For example, for stage I cancer, the minimum detectable OR comparing NHBs and NHWs was calculated to be 1.9, given the numbers of NHBs and NHWs, a study power of 80%, and an alpha of 0.05, while our estimate was 1.29. Nevertheless, we found a significant OR for poorly differentiated tumors even with smaller numbers of NHBs and NHWs. Additionally, our data do not contain information on surgeon procedure volume and type of pathologist or person examining the resected specimen (e.g., pathologist versus technician) that may be related to lymph node retrieval and examination. Thus, we were unable to assess whether these physician factors might have affected our results. Lastly, the use of information from medical and administrative claims databases could result in coding errors and incomplete data. However, the combined use of data from the cancer registry minimized the likelihood of this limitation.

In summary, racial/ethnic disparities in the number of lymph nodes examined among NHWs, NHBs, APIs, and HWs were not apparent in an equal-access healthcare system. However, racial/ethnic differences in nodal evaluation could potentially vary by tumor grade, with a lower frequency of sufficient lymph nodes examined among NHBs with poorly differentiated tumor grade. These results suggest the possibility that other factors, in

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addition to access to healthcare, might play a role in the racial/ethnic disparities seen in the general population.

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Synopsis

Racial/ethnic disparities in the number of lymph nodes evaluated among colon cancer patients were not apparent in an equal-access healthcare system. However, potential racial/ethnic differences in nodal yield were observed among poorly differentiated tumors.

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Table1

Demographic and tumor characteristics by race/ethnicity among colon cancer patients in the MHS 1998-2007.

	Race/Ethnicity								
	Non-Hispanic White (n=1,530)		Non-Hispanic Black (n=350)		Asian/Pacific Islander (n=169)		Hispanic White (n=106)		
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	***p*-value**[a]
Year of diagnosis									0.05
1998-2000	577	37.7	119	34.0	55	32.5	26	24.5	
2001-2003	496	32.4	110	31.4	52	30.8	39	36.8	
2004-2007	457	29.9	121	34.6	62	36.7	41	38.7	
Age at diagnosis, years									<0.01
20-49	209	13.7	80	22.9	27	16.0	15	14.2	
50-59	335	21.9	90	25.7	59	34.9	33	31.1	
60-69	449	29.3	109	31.1	49	29.0	28	26.4	
70+	537	35.1	71	20.3	34	20.1	30	28.3	
Sex									<0.01
Men	923	60.3	215	61.4	45	26.6	72	67.9	
Women	607	39.7	135	38.6	124	73.4	34	32.1	
Marital status									0.51
Never married	45	2.9	17	4.9	2	1.2	5	4.7	
Married	1163	76.0	264	75.4	134	79.3	77	72.6	
Other	261	17.1	58	16.6	28	16.6	21	19.8	
Unknown	61	4.0	11	3.1	5	3.0	3	2.8	
Active duty status									<0.01
No	1413	92.4	306	87.4	163	96.4	98	92.5	
Yes	117	7.6	44	12.6	6	3.6	8	7.5	
Service branch[b]									<0.01
Army	506	33.1	180	51.4	60	35.5	43	40.6	
Air Force	540	35.3	87	24.9	38	22.5	25	23.6	
Navy/Marines	416	27.2	71	20.3	59	34.9	13	12.3	
Other	22	1.4	4	1.1	7	4.1	1	0.9	
Unknown	46	3.0	8	2.3	5	3.0	24	22.6	
Benefit type									<0.01
Prime	694	45.4	178	50.9	99	58.6	49	46.2	
Not prime	448	29.3	84	24.0	36	21.3	17	16.0	
Unknown	388	25.4	88	25.1	36	21.3	40	37.7	
Rank[b]									<0.01
Enlisted	696	45.5	228	65.1	102	60.4	56	52.8	
Officer	336	22.0	23	6.6	15	8.9	6	5.7	
Other	6	0.4	1	0.3	3	1.8	2	1.9	
Unknown	492	32.2	98	28.0	49	29.0	42	39.6	

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	Race/Ethnicity								
	Non-Hispanic White (n=1,530)		Non-Hispanic Black (n=350)		Asian/Pacific Islander (n=169)		Hispanic White (n=106)		
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	***p*-value[a]**
Obese									<0.01
No	1163	76.0	230	65.7	142	84.0	85	80.2	
Yes	367	24.0	120	34.3	27	16.0	21	19.8	
Tumor stage									0.02
Stage I	501	32.7	92	26.3	45	26.6	29	27.4	
Stage II	487	31.8	110	31.4	45	26.6	35	33.0	
Stage III	542	35.4	148	42.3	79	46.7	42	39.6	
Tumor grade									0.12
Well differentiated	267	17.5	46	13.1	28	16.6	13	12.3	
Moderately differentiated	997	65.2	249	71.1	114	67.5	69	65.1	
Poorly differentiated	197	12.9	39	11.1	25	14.8	16	15.1	
Unknown	69	4.5	16	4.6	2	1.2	8	7.5	
Subsite									0.01
Right	685	44.8	150	42.9	54	32.0	39	36.8	
Transverse	114	7.5	31	8.9	10	5.9	6	5.7	
Left	639	41.8	149	42.6	99	58.6	56	52.8	
Overlapping/unknown	92	6.0	20	5.7	6	3.6	5	4.7	
Number of lymph nodes examined									0.20
0-11	650	42.5	132	37.7	72	42.6	37	34.9	
12+	880	57.5	218	62.3	97	57.4	69	65.1	

[a] 2-sided *p*-value assessing the overall differences between race/ethnicity and demographic and tumor characteristics.

[b] Service branch or rank of active duty member or sponsor.

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Table2

Multivariate regression analysis assessing the receipt of adequate lymph node evaluation by race/ethnicity with the MHS 1998-2007, overall and by tumor characteristics.

	Number of lymph nodes					
Strata	**<12**	**12+**	**OR[a]**	**95% CI**		***p*-value[b]**
Overall						
Non-Hispanic White	650	880	1.00	((reference)		
Non-Hispanic Black	132	218	1.12	0.86	1.47	0.40
Asian/Pacific Islander	72	97	0.90	0.63	1.29	0.56
Hispanic White	37	69	1.37	0.87	2.17	0.17
Tumor stage						
Stage I						
Non-Hispanic White	282	219	1.00	(reference)		
Non-Hispanic Black	42	50	1.29	0.78	2.13	0.32
Asian/Pacific Islander	30	15	0.62	0.30	1.31	0.21
Hispanic White	13	16	1.52	0.67	3.48	0.32
Stage II						
Non-Hispanic White	193	294	1.00	(reference)		
Non-Hispanic Black	37	73	1.23	0.76	2.00	0.41
Asian/Pacific Islander	14	31	1.32	0.63	2.73	0.46
Hispanic White	10	25	1.31	0.56	3.08	0.54
Stage III						
Non-Hispanic White	175	367	1.00	(reference)		
Non-Hispanic Black	53	95	0.93	0.60	1.44	0.74
Asian/Pacific Islander	28	51	0.74	0.42	1.28	0.28
Hispanic White	14	28	0.95	0.45	1.99	0.89
Tumor grade						
Well differentiated						
Non-Hispanic White	139	128	1.00	(reference)		
Non-Hispanic Black	16	30	1.58	0.74	3.36	0.23
Asian/Pacific Islander	14	14	0.58	0.22	1.48	0.25
Hispanic White	6	7	0.75	0.20	2.79	0.67
Moderately differentiated						
Non-Hispanic White	413	584	1.00	(reference)		
Non-Hispanic Black	88	161	1.15	0.83	1.58	0.41
Asian/Pacific Islander	48	66	0.99	0.64	1.54	0.97
Hispanic White	26	43	1.32	0.76	2.31	0.33
Poorly differentiated						
Non-Hispanic White	54	143	1.00	(reference)		
Non-Hispanic Black	19	20	0.34	0.14	0.80	0.01
Asian/Pacific Islander	9	16	0.82	0.26	2.54	0.72

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Strata	Number of lymph nodes <12	Number of lymph nodes 12+	OR[a]	95% CI		p-value[b]
Hispanic White	4	12	1.14	0.25	5.28	0.87
Subsite						
Right-sided						
Non-Hispanic White	214	471	1.00	(reference)		
Non-Hispanic Black	38	112	1.07	0.68	1.69	0.76
Asian/Pacific Islander	11	43	1.48	0.71	3.09	0.29
Hispanic White	10	29	1.20	0.53	2.70	0.67
Left-sided						
Non-Hispanic White	349	290	1.00	(reference)		
Non-Hispanic Black	72	77	1.33	0.90	1.97	0.16
Asian/Pacific Islander	54	45	0.80	0.50	1.29	0.36
Hispanic White	25	31	1.30	0.71	2.41	0.40

[a]Odds ratio (OR) and 95% confidence intervals (CI) adjusting for year of diagnosis, age at diagnosis, sex, marital status, active duty status, service branch of active duty member/sponsor, benefit type, rank of active duty member/sponsor, obesity, colon cancer subsite, tumor stage, and tumor grade. The stratified variable was not included in the analysis stratified by the variable.

[b]2-sided *p*-value assessing the relationship between race/ethnicity and the number of lymph nodes examined.