Original study

Antibiotic Prescriptions in Lung Cancer and Melanoma Populations: Differences With Potential Clinical Implications in the Immunotherapy Era

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Abstract

Antibiotic exposure is associated with worse outcomes from immune checkpoint inhibitors (ICI). We determined antibiotic prescription patterns in lung cancer and melanoma, two malignancies in which ICI are widely used across stages. In a national cohort, antibiotics were more frequently prescribed in lung cancer, non-white individuals, patients with comorbidities, and women. These observations may have clinical and healthy policy implications.

Introduction: Antibiotic exposure is associated with worse clinical outcomes in patients receiving immune checkpoint inhibitors (ICI). We analyzed antibiotic prescription patterns in lung cancer and melanoma, two malignancies in which ICI are used broadly across stages. **Methods:** We performed a retrospective cohort study of adults in the U.S. Veterans Affairs (VA) medical system diagnosed with lung cancer or melanoma from 2003 to 2016. We defined antibiotic exposure as receipt of a prescription for a systemic antibacterial agent between 6 months before and 6 months after cancer diagnosis. Demographics, clinical variables, prescriptions, and diagnostic codes were abstracted from the VA Corporate Data Warehouse. Antibiotic exposure was compared using t tests, Chi-square, and multivariate analyses. **Results:** A total of 310,321 patients (280,068 lung cancer, 30,253 melanoma) were included in the analysis. Antibiotic exposure was more common among patients with lung cancer (42% vs. 24% for melanoma; $P < .001$). Among antibiotic-exposed patients, those with lung cancer were more likely to receive prescriptions for multiple antibiotics (47% vs. 30% for melanoma; $P < .001$). In multivariate analyses, antibiotic exposure was associated with lung cancer diagnosis (HR 1.50; 95% CI, 1.46-1.55), comorbidity score (HR 1.08; 95% CI, 1.08-1.09), non-white race (HR 1.11; 95% CI, 1.06-1.17), and female gender (HR 1.31; 95% CI, 1.24-1.37). **Conclusion:** Among cancer patients, antibiotics are prescribed frequently. Antibiotic exposure is more common in certain cancer types and patient populations. Given the negative effect antibiotic exposure has on immunotherapy outcomes, these observations may have clinical and healthy policy implications.

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Introduction

Antibiotic exposure is associated with several potential complications, including drug-specific adverse effects, drug resistance, and secondary infections.[1-4] Concerns over the apparent overuse of these agents has led to national campaigns to address antibiotic prescription patterns in both inpatient and outpatient settings.[5] Antibiotic administration occurs particularly frequently in individuals with cancer. This population faces increased infection risk for multiple reasons, including effects of the underlying malignancy (such as post-obstructive pneumonia in lung cancer), treatment-

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related immunosuppression, chronic wounds, and indwelling vascular catheters.[6,7]

In recent years, the widespread uptake of immune checkpoint inhibitors (ICI) has introduced a new concern regarding antibiotic use in oncology populations. Attributed to effects on the gut microbiome and systemic immune parameters, multiple studies have demonstrated that antibiotic exposure is associated with inferior clinical outcomes in patients receiving ICI.[8-13] Given these considerations, we determined antibiotic use patterns in patients with lung cancer and melanoma, 2 malignancies in which ICI is widely used across disease stages, in a national dataset.

Methods

This study was approved by the Institutional Review Boards of the Veterans Affairs (VA) (protocol #16-055) and Texas Tech Health Sciences Center (protocol #A19-4060). We performed a retrospective cohort study of adult patients in the United States VA health care system diagnosed with lung cancer or melanoma from January 1, 2003, and December 31, 2016. We focused on these 2 cancer types because they are commonly treated with ICI, and ICI is approved across disease stages. We selected the 2003 starting point because independently validated data was first available for the dataset at that time.

The VA is among the largest integrated health care systems in the United States, encompassing 172 medical centers and over 1000 outpatient clinics serving 9 million individuals.[14] State-of-the-art cancer care is provided at VA facilities, which have equivalent if not superior outcomes compared to non-VA facilities, including diagnosis of cancer at earlier stage, superior 5 year survival rates among common cancers, and increased likelihood of receiving appropriate treatment.[15] Relevant to the current study, due to the prescription drug benefit and comprehensiveness of the VA healthcare system, only about 15% of Veterans have medication use from non-VA sources.[16]

Patient demographics, clinical variables, pharmacy prescriptions, and diagnostic codes from electronic medical records were extracted from the VA Corporate Data Warehouse, which is the national repository of VA medical records. The Corporate Data Warehouse offers the advantage of detailed pharmacy records, although it may not have as complete cancer case information as other VA databases such as the VA Central Cancer Registry or the recently launched V16 Cancer Registry Project.[17,18] Patients with lung cancer were identified by ICD-9 codes 162.0-162.9 and ICD-10 code C34.00-34.90. Patients with melanoma were identified by ICD-9 codes 172.0-172.9 and ICD-10 codes C43.0-34.9. The timing and duration of antibiotic prescriptions was determined using the "release date" and "days of supply" variables associated with each antibiotic prescription.

We limited our analysis to antibiotics administered systemically (eg, orally or intravenously). We excluded topical, ophthalmic, and other locally administered preparations, as these routes would be expected to have limited systemic effects, including those on the gut microbiome. We used Micromedex to obtain a comprehensive listing of antibiotics that we employed as search terms in each patient's pharmacy record. Antibiotics were classified into the following categories: beta-lactam, aminoglycoside, carbapenem, macrolide, nitroimidazole, peptide (including vancomycin and linezolid), quinolone, sulfonamide, tetracycline, and other.

For our primary analyses, we focused on the 6 months leading up to and the 6 months following a cancer diagnosis for the following reasons: (1) based on current indications as first-line, consolidation, second-line, and third-line therapy for various lung cancer and melanoma scenarios, immune checkpoint inhibitors are likely to be administered within 6 months of a lung cancer or melanoma diagnosis; and (2) effects on the microbiome have been demonstrated up to 12 months after antibiotic administration.[19,20] Recognizing that, within this window, the timing of antibiotic administration may influence effects on the microbiome and therefore checkpoint inhibitor efficacy,[21] we also included analyses employing a 6 month peri-diagnosis window (from 3 months before to 3 months following cancer diagnosis). We calculated prevalence of use across patient cohorts and time periods using Chi-square tests, t tests, and multivariate analyses. For the multivariate analysis, we included all variables from the univariate analysis (cancer stage, race, gender, age, Charlson comorbidity score, and cancer type), as all were found to be statistically significant in the univariate analysis and were considered clinically meaningful. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina, USA).

Results

A total of 310,321 patients were included in the analysis. Within this population, 280,068 patients (90%) had lung cancer and 30,253 (10%) had melanoma. Among patients with lung cancer, mean age was 70 years and 98% were male; among patients diagnosed with melanoma, mean age was 66 years and 96% were male. Additional characteristics of the lung cancer and melanoma cohorts are shown in Table 1. In general, patients with lung cancer had more comorbidities than did patients with melanoma. Apart from renal disease, mild liver disease, and hemiplegia and/or paraplegia, individual comorbidities were more common in lung cancer (Supplemental Table 1). The greatest difference was observed for chronic pulmonary disease (43% vs. 13%; $P < .001$).

A total of 117,748 patients with lung cancer (42%) were prescribed antibiotics within 6 months before or after diagnosis. Among patients with melanoma, 7297 (24%) were prescribed antibiotics ($P < .001$) during this time-frame. Characteristics of patients according to receipt of antibiotics are shown in Table 2. Those receiving antibiotics were more likely to have later-stage cancer, be younger, and have more medical comorbidities. Except for dementia, individual comorbidities were more common in the antibiotic-treated population (Supplemental Table 2), with the most pronounced difference for chronic pulmonary disease. Among patients with lung cancer, for whom COPD was more than 3 times as likely as for patients with melanoma, 52% with COPD received antibiotic prescriptions, compared to 35% of patients without chronic pulmonary disease ($P < .001$).

The overwhelming majority of patients were prescribed oral rather than intravenous (IV) antibiotics. Among all patients 125,045 patients receiving antibiotics, only 1115 (0.9%) received IV antibiotics. While the rate of IV antibiotic prescription differed

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Table 1 Patient and Tumor Characteristics According to Cancer Type

	Lung Cancer n (%) or mean ± SD (N=280,068)	Melanoma n (%) or mean ± SD (N=30,253)	*P* value
Cancer Stage			<0.001
Early (I, II)	47,148 (16.8)	4,320 (14.3)	
Late (III, IV)	89,271 (31.9)	544 (1.8)	
Unknown	143,649 (51.3)	25,389 (83.9)	
Race			<0.001
White	202,509 (72.3)	26,110 (86.3)	
Black	33,365 (11.9)	607 (2.0)	
Other	8,174 (2.9)	453 (1.5)	
Unknown	36,020 (12.9)	3,083 (10.2)	
Male Gender	274,291 (97.9)	28,985 (95.8)	<0.001
Age (y)	70.3 ± 10.0	66.3 ± 13.1	<0.001
Charlson Comorbidity Index	3.3 ± 2.5	0.5 ± 0.9	<0.001

Table 2 Patient and Tumor Characteristics According to Antibiotic Prescription Receipt

	No Antibiotic Rx n (%) or mean ± SD(N=185,276)	Antibiotic Rx n (%) or mean ± SD (N=125,045)	*P* value
Cancer Stage			<0.001
Early (I, II)	23,559 (12.7)	27,909 (22.3)	
Late (III, IV)	37,464 (20.2)	52,351 (41.9)	
Unknown	124,253 (67.1)	44,785 (35.8)	
Race			<0.001
White	135,257 (73.0)	93,362 (74.7)	
Black	16,853 (9.1)	17,119 (13.7)	
Other	4,674 (2.5)	3,953 (3.2)	
Unknown	28,492 (15.4)	10,611 (8.5)	
Male Gender	181,570 (98.0)	121,706 (97.3)	<0.001
Age (y)	71.1 ± 10.4	68.3 ± 10.2	<0.001
Charlson Comorbidity Score	2.7 ± 2.3	3.5 ± 2.7	<0.001
Cancer Type			<0.001
Lung Cancer	162,320 (87.6)	117,748 (94.2)	
Melanoma	22,956 (12.4)	7,297 (5.8)	

significantly according to cancer type (0.9% for lung cancer vs. 0.5% for melanoma; $P < .001$), we did not consider this difference to be clinically meaningful.

Antibiotic exposure according to cancer stage and timing in relation to diagnosis is displayed in Supplemental Table 3. Patients with higher-stage cancer were more likely to receive antibiotics. For lung cancer, 26,165 of 47,148 early-stage (stages I and II) cases (55%) received antibiotics, compared to 52,122 of 89,271 late-stage (stages III and IV) cases (58%) ($P < .001$). For melanoma, 1744 of 4320 early-stage (stages I and II) cases (40%) received antibiotics, compared to 229 of 544 late-stage (stages III and IV) cases (42%) ($P < .001$). Notably, antibiotic prescriptions were least common among cases for which stage was unavailable: 39,461/143,649 (27%) in lung cancer; 5324/25,389 (21%) in melanoma. Antibiotics were more commonly prescribed in the 6 months following cancer diagnosis than in the 6 months preceding cancer diagnosis: 27% before, 30% after for lung cancer; 12% before, 18% after for melanoma.

Because patients in the lung cancer and melanoma groups displayed differences in key characteristics such as age, comorbidity burden, and cancer stage, we performed a multivariate analysis to identify factors independently associated with antibiotic exposure (Table 3). We found a persistent association between receipt of antibiotics and non-white race (HR 1.11), female gender (HR 1.31), comorbidity burden (HR 1.08), and lung cancer diagnosis (HR 1.50).

Table 4 displays the number of antibiotic prescriptions received by patients according to cancer type. In general, among individuals who received antibiotics, the number of distinct prescriptions was higher for patients with lung cancer, of whom 47% had 2 or more prescriptions, compared to melanoma (30% had ≥2 prescriptions) ($P < .001$).

Because different antibiotics appear to exert different effects on the gut microbiome,[22] we also examined prescription rates according to antibiotic type and category (Figure 1 and Table 5) Azithromycin was the single most prescribed antibiotic. However, as classes,

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Table 3 Multivariate Analysis of Antibiotic Prescription Receipt

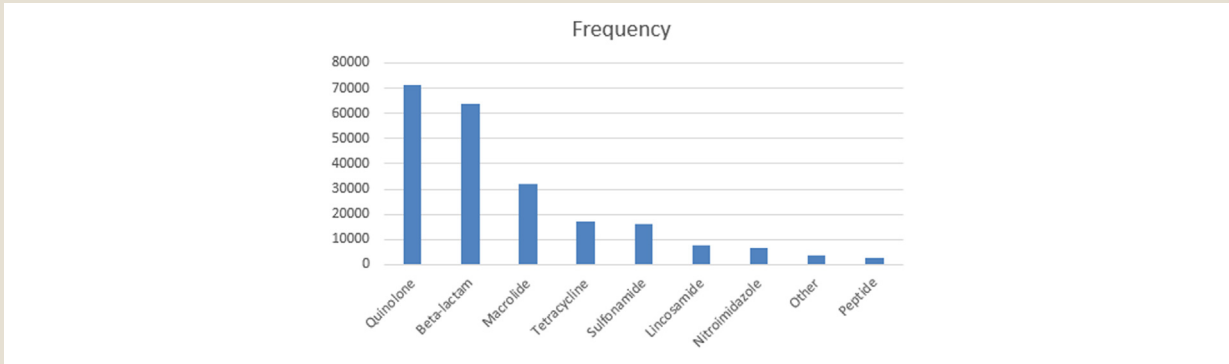
Covariate	Multivariate analysis	
	HR (95% CI)	*P* value
Stage (Late vs Early)	1.02 (1.00, 1.04)	<0.001
Race (Other vs White)	1.11 (1.06, 1.17)	
Gender (Female vs Male)	1.31 (1.24, 1.37)	<0.001
Age (continuous variable)	0.98 (0.98, 0.98)	<0.001
Charlson Comorbidity Score (continuous)	1.08 (1.08, 1.09)	<0.001
Cancer Type (Lung vs Melanoma)	1.50 (1.46, 1.55)	<0.001

Table 4 Number of Distinct Antibiotic Prescriptions According to Cancer Type

Number[a]	Lung Cancer n (%) (N=117,748)	Melanoma n (%) (N=7, 297)
1	62,479 (53.1)	5,095 (69.8)
2	32,441 (27.6)	1,550 (21.2)
3	14,410 (12.2)	467 (6.4)
4	5,645 (4.8)	132 (1.8)
≥5	2,773 (2.4)	53 (0.7)

[a] Refers to prescriptions for different antibiotics. Multiple prescriptions for a single antibiotic were counted as a single prescription.

Figure 1 Frequency of antibiotic prescriptions



fluoroquinolone and beta-lactam antibiotics were more commonly prescribed than macrolides, each accounting for more than 25% of all antibiotic prescriptions.

When we examined a shorter time interval for antibiotic exposure (within 3 months of cancer diagnosis), a total of 100,481 patients received antibiotic prescriptions, representing approximately 80% of the population receiving an antibiotic prescription within 6 months of cancer diagnosis. In these analyses, there were no meaningful differences from the corresponding analyses for the longer time interval, including patient and tumor characteristics associated with antibiotic exposure (Supplemental Table 4), multivariable analysis of antibiotic exposure (Supplemental Table 5), number of distinct antibiotic prescriptions (Supplemental Table 6), and antibiotic frequency according to cancer type, stage, and timing of prescription (Supplemental Table 7).

The proportion of patients receiving antibiotic prescriptions over time is shown in Figure 2. Over the 14 year study period, we observed little change in this parameter, which ranged from 38% to 44% and had no consistent directional trend.

Discussion

Antibiotic exposure has consistently been linked with inferior outcomes from cancer immunotherapy,[9,10,23] with such associations not observed for other types of cancer treatment.[12,24,25] To determine the potential extent of this detrimental interaction in patient populations, we analyzed antibiotic exposure in a national dataset of more than 300,000 individuals with cancer—to our knowledge, the first such study on this scale. We focused on lung cancer and melanoma because these tumor types are frequently treated with checkpoint inhibitors in both early and advanced stages of disease. Overall, we found that antibiotics were prescribed frequently to these individuals, and that most of these prescriptions occur relatively close to cancer diagnosis. However, rates differed substantially according to tumor type. Among patients with lung

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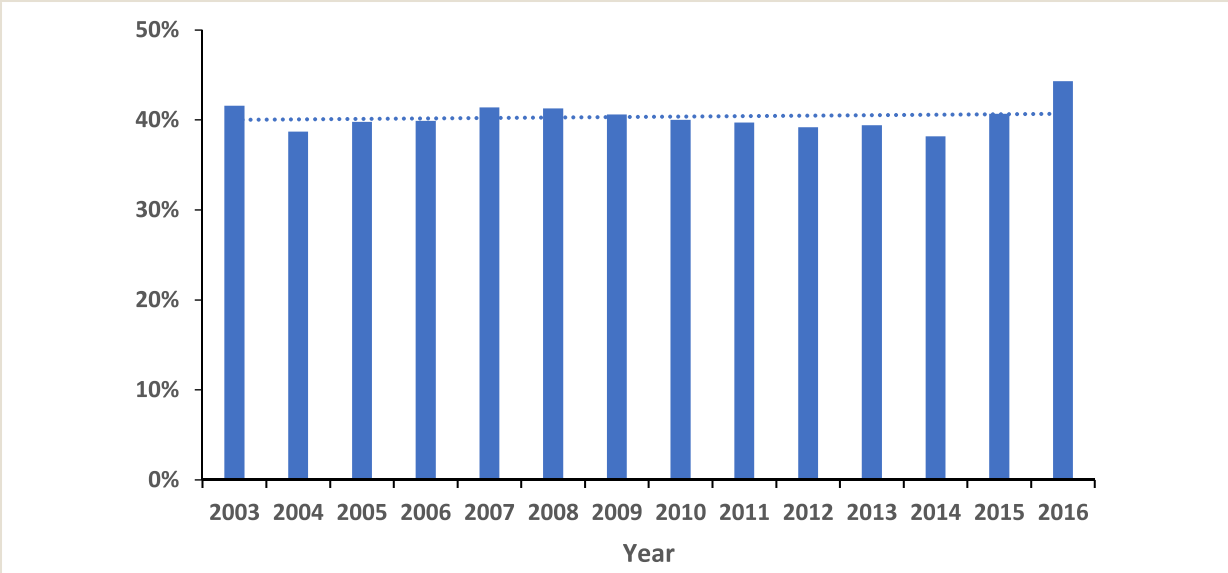
Table 5 Antibiotic Types and Categories Prescribed

Antibiotic	Antibiotic Category	Rate of Prescription (%)
AZITHROMYCIN	Macrolide	22.3
AMOXICILLIN/CLAVULANATE	Beta-lactam	20.6
CIPROFLOXACIN	Quinolone	17.3
MOXIFLOXACIN	Quinolone	16.6
LEVOFLOXACIN	Quinolone	15.4
CEPHALEXIN	Beta-lactam	12.6
SULFAMETHOXAZOLE/TRIMETHOPRIM	Sulfonamide	11.9
DOXYCYCLINE	Tetracycline	11.3
AMOXICILLIN	Beta-lactam	10.7
GATIFLOXACIN	Quinolone	7.7
CLINDAMYCIN	Lincosamide	6.0
METRONIDAZOLE	Nitroimidazole	5.2
CLARITHROMYCIN	Macrolide	2.3
CEFUROXIME	Beta-lactam	2.2
NITROFURANTOIN	Other	1.7
CEFPODOXIME PROXETIL	Beta-lactam	1.6
PENICILLIN	Beta-lactam	1.2
MINOCYCLINE	Tetracycline	1.2
TRIMETHOPRIM	Other	0.8
DEMECLOCYCLINE	Tetracycline	0.8
ERYTHROMYCIN	Macrolide	0.7
DICLOXACILLIN	Beta-lactam	0.7
VANCOMYCIN	Peptide	0.7
LINEZOLID	Peptide	0.6
TETRACYCLINE	Tetracycline	0.6
CEFTRIAXONE	Beta-lactam	0.4
NEOMYCIN	Other	0.3
CEFDINIR	Beta-lactam	0.3

Figure 2 Proportion of patients receiving antibiotic prescriptions over time



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cancer, the proportion who received antibiotic prescriptions was almost twice that among patients with melanoma, an imbalance that persisted after controlling for comorbidities, disease stage, and other factors. Patients with lung cancer were also more likely to receive multiple antibiotics, with almost half receiving prescriptions for 2 or more unique antibiotics.

The frequency of antibiotic prescriptions in our cohort—while clearly higher than in non-cancer populations—resembles that reported in other oncology cohorts, in which antibiotic usage ranges 15-55%.[12,13,24] Among these individuals, why might antibiotics be more commonly prescribed in those with lung cancer than in those with melanoma? A primary lung tumor can predispose to infection (post-obstructive pneumonia), a clinical association that would not be expected from a primary skin cancer.[26] Likewise, tumor-related symptoms and even radiographic appearance might be confused with infection in lung cancer. Consistent with disease characteristics in the U.S. population, in our study cohort, patients with lung cancer were also older, had more comorbidities, and had higher-stage cancer, all of which might predispose to antibiotic use.[27] In particular, chronic pulmonary disease, which was present in almost half of lung cancer cases but fewer than 15% of melanoma cases, was associated with higher rates of antibiotic prescriptions. However, in our multivariable model controlling for age, cancer stage, and comorbidity burden, antibiotic prescriptions were still far more common in the lung cancer population. Additionally, we note that the detrimental effects of antibiotics on immunotherapy efficacy may occur regardless of their indication. This represents a distinction from corticosteroids, for which detrimental effects on immunotherapy seem to be driven by palliative indications in poor-prognosis groups.[28]

Notably, women and non-white individuals were significantly more likely to receive antibiotic prescriptions. Earlier studies have identified gender gaps in antibiotic prescribing patterns.[29] In an analysis of UK-based primary care, adult women received twice as many antibiotic prescriptions overall as did men, and 70% more when excluding urinary tract infections.[30] In contrast to our current findings, in pediatric primary care and emergency department settings, black children receive fewer antibiotic prescriptions than nonblack children.[31,32] In adult populations, differences in antibiotic prescribing patterns also affect antimicrobial agent selection. Among individuals hospitalized with skin and soft tissue infections, white patients were more likely to receive cefazolin—a recommended first-line treatment—while black patients were more likely to receive clindamycin—which is less preferred due to dosing schedule and toxicity profile.[33]

In the present study, more than half of all antibiotic prescriptions were for fluoroquinolones or beta-lactams. This has relevance to ICI therapy because broad-spectrum antibiotics can affect the abundances of up to one-third of gut bacteria.[34] Historically, educational initiatives have been shown to decrease antibiotic substantially,[35] an important step to addressing the 30% of antibiotic prescriptions estimated to be inappropriate.[2] Indeed, from 1999 to 2012, use of prescription antibiotics declined 30% nationwide, although this decrease was limited to patients under age 60 years.[36] Furthermore, the decline in antibiotic prescription rates has been accompanied by a substantial increase in the use of broad-spectrum antibiotics,[37] which accounted for the majority of antibiotic prescriptions in our study and have greater effects on the microbiome. Although we cannot determine from the current study the frequency of appropriate versus inappropriate prescriptions, given the recent recognition of antibiotics' detrimental effects on immunotherapy outcomes, targeting antibiotic stewardship programs toward oncologists and their patients may be worthwhile. However, these efforts must consider the importance of appropriate and timely antimicrobial therapy in patients with cancer, who face a 3 times greater likelihood of fatal infection than do individuals without cancer.[38] Such clinical concerns may in part explain why we observed no decrease in antibiotics over time in our national cohort of cancer patients.

Limitations of this study include missing cancer stage information for a substantial proportion of cases and the absence of cancer treatment information. This constraint reflects selection of a VA data source rich in pharmacy records (VA Corporate Data Warehouse) but lacking the cancer case descriptors available in other sources (such as the VA Central Cancer Registry). Nevertheless, our observation that antibiotic exposure is substantially more common in lung cancer than in melanoma is likely robust because it (1) occurs in stage-specific analyses, and (2) persists in a multivariable model accounting for stage and comorbidities. Our dataset is also overwhelmingly male. This skewed gender representation could result in an underestimate of antibiotic prescriptions in the present analysis, as adult women are 40% more likely to receive antibiotics than are men.[29] It is also possible that practice patterns and availability of specific medications differ between the VA health care system and other clinical settings. Additionally, we recognize the potential difference between antibiotic *prescription* and *exposure,* as up to 30% of patients may be non-adherent to antibiotic dosing or schedule.[39] Nevertheless, it has been reported that even a single antibiotic dose may alter the microbiome.[40] Finally, our analysis does not capture antibiotic prescriptions from providers outside the VA system, which could result in underestimation of overall prescription rates. This possibility may be particularly relevant for the patients lacking cancer stage information, in whom the lower rates of antibiotic prescriptions could reflect lower rates of treatment or treatment documentation in the VA system. Key strengths of this study include a large, national patient sample in a closed medical system, and access to detailed pharmacy records.

Conclusion

In conclusion, a substantial proportion of individuals with cancer are exposed to antibiotics. Antibiotic prescription rates vary across cancer types, with more frequent and greater number of prescriptions for lung cancer than for melanoma patients. The extent to which this difference contributes to relatively better outcomes from immunotherapy in melanoma is not known. Women and non-white patients are also more likely to receive antibiotics. Based on these observations, further studies characterizing the appropriateness of antibiotic use, microbiome composition, and immunotherapy efficacy across real-world cancer populations are needed.

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Clinical Practice Points

- Antibiotic exposure has been associated with worse clinical outcomes in patients receiving immune checkpoint inhibitors (ICI)
- Antibiotics are frequently prescribed in cancer populations
- Patients with lung cancer are more likely to receive antibiotics than are patients with melanoma
- Patients with lung cancer are also more likely to receive multiple different antibiotics than are patients with melanoma
- Antibiotic prescriptions are also more common among women, non-white individuals, and patients with more comorbidities
- These observations may have clinical and healthy policy implications

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Disclosure

None of the authors report relevant conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2022.09.005.

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