ORIGINAL RESEARCH

Factors Associated with Advanced Presentations of Melanoma in the United States from 2004-2015: A National Cancer Database Analysis Cohort Study

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ABSTRACT

Purpose: Significant advances have been made in the diagnosis and treatment of melanoma, but mortality remains high. The primary aim of this study was to identify risk factors associated with advanced presentations of melanoma in the US.

Methods and Materials: Stage III and IV melanoma were identified in the National Cancer Database (NCDB) with appropriate staging and pathologic confirmation from 2004-2015. Patient-specific variables were analyzed using chi square and binary logistic regression multivariate analyses to elucidate factors associated with advanced stage melanoma at diagnosis.

Results: There were 477,914 patients meeting inclusion criteria, 63,291 (13.2%) presenting with advanced stage. Factors associated with advanced presentation included lower income, non-Hispanic white race, Medicaid/uninsured insurance, greater distance to treatment centers, male gender, younger age, more medical comorbidities, and southeast U.S. location (p < 0.05, each). All factors were statistically significant on multivariate analysis.

Conclusion: Age, gender, race/ethnicity, geographic location, socioeconomic factors, and distance to treatment center are associated with advanced melanoma diagnosis. Melanoma screening and education should target these groups, and more research is necessary to elucidate causes of the disparities that may preventing the early diagnosis of melanoma for these patients.

INTRODUCTION

Melanoma is the leading cause of skin cancer deaths in the United States with an estimated 100,640 new cases of melanomas and 8,290 predicted deaths in the United States in 2024.^{1,2} Over the last 30 years, the incidence of melanoma has increased and is expected to continue to rise.^{3,4} The primary risk factors for melanoma include ultraviolet rays exposure and genetic predisposition, or

both.² As treatment at an early stage is associated with a favorable prognosis, routine screening has been suggested as the primary means of detecting early stage cancers. Although melanoma detection is often successfully achieved with routine screening, many patients continue to present with advanced disease, possibly due to lack of access to screening or possibly related to more aggressive cancer biology. There is not a universal screening guideline for skin examinations, which also may contribute to delayed melanoma detection. This is especially prevalent in some minority groups, who despite having a lower incidence of melanoma compared to Caucasians. typically present with more advanced disease and a higher mortality rate.3,5-10

Early diagnosis of melanoma is essential for optimal patient outcomes and reduced morbidity from treatment. While cure can be achieved routinely in early-stage melanoma with surgery alone, stage III and IV melanoma require more involved treatment including targeted therapy, immunotherapy, radiation, and/or other systemic treatment and may often be incurable.^{11–13}Although the primary risk factors for melanoma have been well established, there is a paucity of data regarding the risk factors for advanced presentation of disease, making effective screening difficult. Identifying patient factors or disease factors associated with advanced presentation melanoma may improve provider and patient awareness to improve outcomes for these patients.

The primary aims of this study are to determine the incidence of advanced melanoma in the United States and to identify factors associated with advanced presentation to improve melanoma screening and outcomes through the early identification of at-risk individuals.

METHODS AND MATERIALS

Study Design

This retrospective observational cohort study investigated the prevalence of advanced melanoma in the United States and identifies associated with factors advanced presentation using the National Cancer Database (NCDB). The NCDB is one of the largest hospital-based cancer registries in the world and is jointly supported by the American College of Surgeons and the American Cancer Society. The database accounts for approximately 70% of patients treated in the United States for malignancy and contains a great number and variety of patient data points ranging from pathological characteristics, interventions, and overall survival to social and institutional factors.

This study identified patients of all ages diagnosed with invasive melanoma, defined as AJCC 8th edition Stage III and Stage IV, in the United States between 2004 and 2015. Available patient and disease-specific variables were collected including age at diagnosis, gender, primary body site at race/ethnicity. diagnosis. facility geographical location, insurance type/status, facility type, distance to facility center, residential population size. median Charlson/Devo household income. comorbidity score, and year of diagnosis (2004-2015). For the purposes of this study, patients with stage III or IV melanoma at presentation were defined as having "advanced disease". The factors associated with patients presenting with advanced disease were then described and analyzed. Patients were excluded if the histologic diagnosis was missing or either the clinical or pathologic staging absent. (Figure 1).

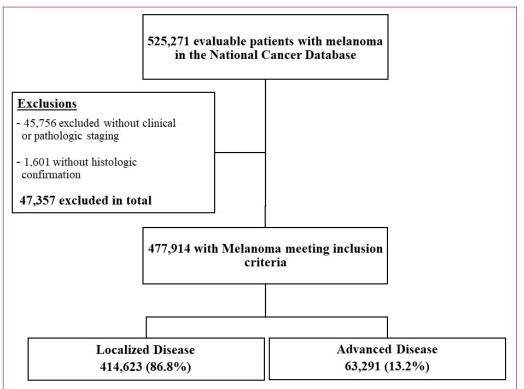


Figure 1. National Cancer Database Cohort Selection Diagram

Statistical Analyses

Descriptive statistics were used to characterize the factors associated with advanced versus localized melanoma presentation and compared using chi-square or ANOVA. Variables potentially associated with advanced presentations of melanoma were chosen through purposeful selection and univariable analyses (binary logistic regression analyses). Two-sided p < 0.05was deemed statistically significant for the analyses. multivariable All statistical analyses were performed using SPSS version 25.0, IBM Corp.

RESULTS

Clinical Characteristics

There were 477,914 patients diagnosed with melanoma from 2004 to 2015 and of them,

63,291 (13.2%) patients met inclusion criteria (Figure 1). The characteristics of those presenting with localized versus advanced melanoma are detailed in Supplemental Table 1. Factors associated with advanced melanoma presentation included younger age (17.9% age < 20 years vs. 11.4% age ≥70 years), male gender (13.6% vs. 10.4% female), black race (27.8% vs. 12.0% non-Hispanic white), cancer of the lower extremity (12.3% vs. 7.0% head/neck), comorbidities Charlson/Deyo ≥3 (26.5%) VS. 11.4% Charlson/Deyo 0), lower income status (16.3% <\$30,000 vs. 10.4% ≥\$46,000), Medicaid insurance (29.8% vs. 11.1% private insurance), West South Central United States location (AR, LA, OK, TX 15.4% vs. New England 9.0%), and distance ≥50 miles to treatment center (16.6% vs. 0-25 miles 11.2%). Multivariate analysis revealed these factors to remain statistically significant. The p-values and odds ratio of presenting with advanced disease are listed in Table 1.

Table 1. Analysis of demographic factors associated with advanced presentation of melanoma. Higher Odds Ratio represents a higher risk of presenting with advanced disease based on binary logistic regression.

Multivariate Analysis						
	Presenting with Advanced Disease					
Category	p-value	OR	Lower 95% Cl	Upper 95% Cl		
Age	<0.001	.992	.991	.993		
Sex						
Male	<0.001	Ref				
Female	<0.001	.682	.666	.697		
Median Income Quartiles 2008-2012						
<\$30,000	<0.001	Ref				
\$30,000-\$35,999	.352	.979	.937	1.023		
\$36,000-\$45,999	.010	.944	.903	.986		
≥\$46,000	<0.001	.876	.835	.919		
Race						
Non-Hispanic White	<0.001	Ref				
Hispanic White	<0.001	1.515	1.400	1.639		
Black	<0.001	1.922	1.730	2.136		
Other	<0.001	1.502	1.349	1.672		
Unknown	<0.001	.583	.523	.650		
Distance to Hospital						
0-25	<0.001	Ref				
25-50 miles	<0.001	1.191	1.155	1.228		
≥50 miles	<0.001	1.540	1.489	1.593		
Facility Type						
Community Cancer Program	<0.001	Ref				
Comprehensive Community Cancer Program	.197	.971	.928	1.015		
Academic/Research Program	.731	1.008	.963	1.054		
Integrated Network Cancer Program	.012	1.072	1.016	1.131		
Primary Site						
Head and Neck	<0.001	Ref				
Trunk	<0.001	1.808	1.754	1.863		
Upper Limb	<0.001	1.259	1.217	1.301		
Lower Limb	<0.001	2.366	2.285	2.449		
Overlapping/other	<0.001	57.825	55.282	60.485		

Cha	arlson/Deyo Sc	ore [¥]				
0	<0.001	Ref				
1	<0.001	1.548	1.501	1.595		
2	<0.001	1.791	1.678	1.912		
3	<0.001	1.831	1.638	2.047		
City Type						
Metro	<0.001	Ref				
Urban	<0.001	.914	.884	.945		
Rural	<0.001	.849	.788	.915		
Facility Location*						
New England	<0.001	Ref				
Middle Atlantic	<0.001	1.235	1.172	1.300		
South Atlantic	<0.001	1.207	1.147	1.271		
East North Central	<0.001	1.309	1.244	1.379		
East South Central	<0.001	1.195	1.123	1.271		
West North Central	<0.001	1.239	1.169	1.313		
West South Central	<0.001	1.525	1.432	1.624		
Mountain	<0.001	1.547	1.451	1.649		
Pacific	<0.001	1.209	1.144	1.277		
Percent No High School Degree Quartiles 2000						
>= 29%		Ref				
20-28.9%	<0.001	.922	.887	.958		
14-19.9%	<0.001	.838	.805	.873		
< 14%	<0.001	.715	.683	.748		
Primary Payer						
Not Insured		Ref				
Private Insurance/Managed Care	<0.001	.429	.405	.456		
Medicaid	<0.001	1.176	1.086	1.273		
Medicare	<0.001	.494	.464	.527		
Other Government	<0.001	.559	.500	.625		
Insurance Status Unknown	<0.001	.509	.466	.556		

*New England: CT, MA, ME, NH, RI, VT, Mid Atlantic: NJ, NY, PA, South Atlantic: DC, DE, FL, GA, MD, NC, SC, VA, WV, East North Central: IL, IN, MI, OH, WI, East South Central: AL, KY, MS, TN, West North Central: IA, KS, MN, MO, ND, NE, SD, West South Central: AR, LA, OK, TX, Mountain: AZ, CO, ID, MT, NM, NV, UT, WY, Pacific: AK, CA, HI, OR, WA

¥ The Charlson-Deyo value is a weighted score derived from the sum of the scores for each of the comorbid conditions listed in the Charlson Comorbidity Score Mapping Table based on International Classification of Diseases-9 or 10 (ICD-9-CM or ICD-10) coding.²⁶

The incidence of advanced melanoma was found to increase over time from 2004 to 2015, rising from 10.7% in 2004 to 13.2% in

2015. The rise in the number of advanced melanoma cases over the study period by age group is detailed in **Figure 2**.



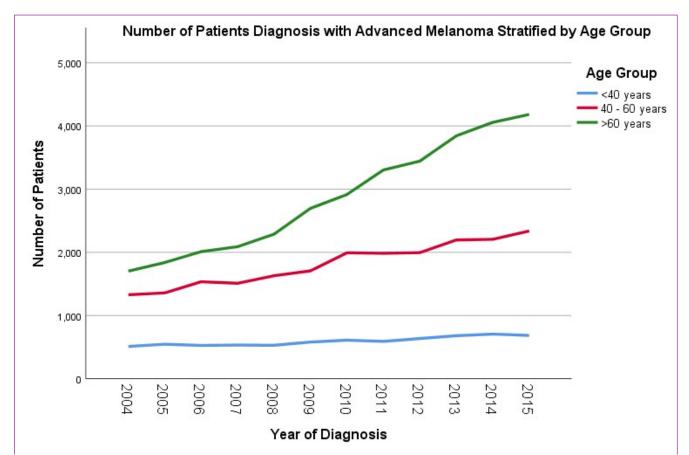


Figure 2. Number of patients diagnosed with advanced melanoma stratified by age group.

Geographic variation in advanced melanoma presentation was identified with the highest rates of advanced disease identified in the West South Central (17.6%), Mountain (15.0%), and South Atlantic (13.7%) regions while the lowest rates were identified in the New England (9.7%) and mid-Atlantic (12.0%) regions (**Figure 3**).

Several clinical factors were identified which highlight patient populations that may be at increased risk of advanced melanoma presentation. Analysis of at-risk factors in those identified by NCDB registry to have advanced disease add to what is described in existing literature. The importance of certain clinical features in the development and risk of mortality of melanoma and may suggest that these factors contribute to higher rates of mortality in some vulnerable populations. In prior studies, male gender and older age have been identified as risk factors for melanoma.^{14–16} Although older age appears to be correlated with sun exposure and thus, risk for melanoma, younger patients (age <20) presenting with melanoma were found in this study to more likely present with advanced disease. Factors contributing to children presenting with more advanced disease may be due to more aggressive tumor biology or less access to routine melanoma screening, while also considering genetic conditions (e.g., familial atypical multiple mole melanoma syndrome) that predispose children to early melanoma.

Males are more likely to have melanoma, perhaps because of occupational hazards that were more prevalent in past decades including sun exposure greater than in their female counterparts, with a likely higher

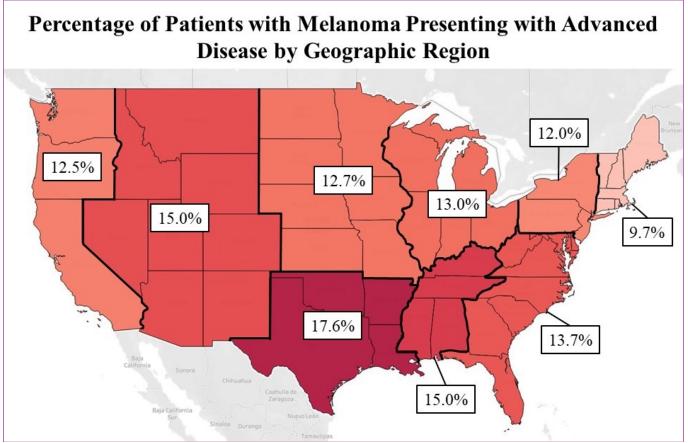


Figure 3. Percentage of patients presenting with advanced melanoma by geographic region

overall UV exposure, although the true cause is unknown.¹⁷ Another possible explanation is that males are less likely to participate in screening, which may explain the increased rate of advanced disease presentation.¹⁸

Insurance status, race, and socioeconomic factors greatly impact melanoma outcomes, all factors tied to broadly to disparities in health outcomes in the United States.^{6,11} Our study confirms that lower socioeconomic status and lack of health insurance are factors more frequently associated with advanced diseases leading to poor clinical outcomes as patients delay diagnosis until symptomatic presentations. We show initial diagnosis rates of advanced melanoma in Medicare patients to be comparable to patients with private insurance. Patients insured by Medicaid were significantly more

likely to present with advanced disease (29.8% with Medicaid vs 11.9% with Medicare). Patients with Medicaid insurance have lower acceptance rates and longer wait time for dermatology appointments when compared to Medicare patients and those privately insured. This leads to lower utilization of routine skin cancer screenings by Medicaid patients.^{19,20} Those with lower incomes are also more likely to present with advanced disease suggestive of reduced access to healthcare and unaffordable out-ofpocket costs associated with skin cancer screening, reflecting trends seen in breast cancer and prostate cancer screening in similar populations.

Race is an additional factor associated with advanced presentation.^{7,21} Although Caucasians are shown to represent most

melanoma diagnoses, African American patients had more than twice the rate of presentation with advanced disease in this study (12.0% in white vs. 27.8% in black). The reasons behind this trend are multifactorial and may be related to difficult detection of disease clinically as well as the socioeconomic differences previously discussed.²² In patients with darker skin tones, melanoma may go unnoticed and not become detected until much later in the disease's stage. Due to this fact, education to the presentation of malianant stress melanoma, how to self-screen, and severity of the disease itself is crucial in non-white groups.

In support of the hypothesis that lower access to care results in increased chances of advanced disease at presentation, geographic location was found to impact melanoma diagnoses. It was shown that states located in the South, particularly those with lower median incomes, have more advanced presentations compared to the Northeast. This could be attributed to increased sun exposure, cultural values, and lack of knowledge of risk factors, but may also be related to a reduced number of practicing dermatologists in these regions which are frequently more rural. In fact, proximity to treatment center was found to be significantly associated with advanced melanoma presentation, as well as reflecting the greater percentage of individuals in these regions lacking private health insurance or access to Medicaid. Patients living farther from treatment centers were much more likely to present with advanced melanoma (16.6% if ≥50 miles vs. 11.2% if <0-25 miles), again reflecting negative outcomes seen in rural populations in non-skin malignancies. In support of this finding, the density of dermatologists has been previously found to have an impact on survival in areas with high incidences of melanoma, while states with a

higher density of non-dermatologist physicians and a higher proportion of non-Hispanic whites have worse survival.^{23,24} Our data supports the need for improved access to dermatologic care in rural areas, which can be potentially achieved either by creating incentives for care in these areas, more intensive dermatologic training for primary care providers with partnering/referral to dermatologists willing to work with patients in the absence of insurance, poor and/or Medicaid or increasing the utilization of telemedicine. Future developments in screening leveraging smart phone technology and/or artificial intelligence may improve access and lower costs.

Advanced melanoma presentations were associated with disease of the lower extremities and trunk while head, neck, and upper extremity melanomas presented with less advanced staging. These findings are congruent with the literature, as the trunk and lower extremities typically have lower exposure to UV light, and melanomas of the head and neck are typically understood to behave much more aggressively.²⁵ However, the head and neck and upper extremities are typically visible in social interactions. Our findings could relate to difficulties associated with detecting changes on the trunk and lower extremities and argue for continued vigilance during clinical screenings.

It is crucial to note and discuss other factors, outside of our findings, that impact the incidence of advanced melanoma one of which includes family history. An estimated 5-10% of all cutaneous melanoma cases occur in families, where familial melanoma is defined as a family in which there are either 2 first-degree relative or 3 or more melanoma patients on the same side of the family.²⁷ Genetic testing and counseling are both highly recommended in high-risk melanoma patients and families due to the high mortality

rate of this disease. Unlike other cancer syndromes, melanoma is not linked to a single gene, but high penetrance genes have been recently detected. Some genetic mutations related to melanoma also seem to have a direct link with tobacco use.

Although tobacco use does seem to correlate with genetic mutations causing melanoma, there has not been concrete evidence showing a direct correlation between tobacco use and melanoma. In fact, studies have shown there may be an inverse relationship between tobacco use and prevalence of malignant melanoma.²⁸ This may be an indirect reflection of the association of indoor, sedentary life-styles in smoking populations in comparison with wealthier groups of nonsmoking patients who spend more times in leisure activities outdoors. On the other hand, there has proven to be a direct relationship between number of alcoholic beverages consumed on average per week with the incidence of malignant melanoma. In one specific article, three large prospective cohort studies were analyzed to study this risk and among a total of 1,374 cases of invasive melanoma there was a positive association between alcohol consumption and melanoma risk specifically in UV-spared sites like the trunk.²⁹ Logically speaking this makes sense because alcohol acts as a carcinogenic agent via the mechanism of acetaldehyde.

Along with alcohol consumption, ultraviolet (UV) exposure history plays a key role in the development of malignant melanoma. An estimated 60-70% of malignant melanomas are believed to be caused by UV exposure from the suppression of DNA repair that occurs during UV damage to melanoma cells. ³⁰

Comorbidities as defined by the 2015 Charlson-Deyo score are associated with advanced presentations of melanoma. This could be explained by the fact that those with health problems may neglect skin care such as applying sunscreen or that preventative services such as regular skin checks are neglected. Patients with multiple comorbidities may also have a compromised immune system, and thus more likely to develop early advanced cancer.

Targeted marketing campaigns can focus on spreading information to clinicians and patients located in rural areas, states in the Southeast, and through a medium that is accessible to those in lower socioeconomic classes. Patient education should emphasize risk factors and presentation of disease, the importance of skin protection through sunscreen and UV protective clothing, and avoidance of excessive UV exposure of unprotected skin through tanning bed use and prolonged sun exposure. New patient and annual wellness exams conducted by PCPs should necessarily involve patients disrobing and use of loose patient gowns allowing for head-to-toe skin examination and early dermatology referral to evaluate new Increasing and/or suspicious lesions. of factors awareness associated with advanced melanomas can achieve better outcomes and decrease mortality as technology and treatment options continue to improve.

The main strength of this study is the use of high-guality NCDB data and the large sample size of advanced melanoma cases. To our knowledge, this is the only study that analyzes factors associated with advanced presentation of melanoma within the period 2004-2015. Recognized confounding of variables were accounted for through use of multivariate analysis. Unmeasured confounding variables not yet recognized may exist and were not accounted for in this study. Although the NCDB reflects most cancer cases treated in the United States and

contains patients treated in both academic and community settings, no data was available from clinics not affiliated with the NCDB. In very rural populations such as in the Appalachians patient deaths due to disease presenting in a state of terminal malignancy may not undergo definitive diagnosis associated with a skin primary site when diagnosis is made at a state in which multiple internal organ systems are involved. As a result, any differences in patient populations, such as differences in early versus advanced cancers will not be reflected. Further, factors that could impact advanced melanoma presentations such as melanoma history. occupation. family and tobacco and alcohol use. UV history/severity were not included but could be in future analysis.

CONCLUSION

Age, gender, race/ethnicity, geographical location, socioeconomic factors, and facility type all contribute to differences in timing and quality of diagnosis according to our analysis of over 63,000 cases of advanced melanoma disease. Stage III/IV presentations of melanoma are associated with lower income, Medicaid insurance or the non-insured, greater distance from treatment centers, male gender. younger age, added comorbidities, southern U.S. regions, and reduced access to dermatologic care. Patients, medical providers, epidemiologists, and government organizations should be aware of the factors associated with advanced presentations of melanoma. Ultimately, patients and providers stand to benefit, always with the goal for reduced time to diagnosis and treatment and decreased mortality for this curable disease.

Conflict of Interest Disclosures: None

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	Presenting Extent of Disease				
	Localized Disease		Advance	X ²	
	n	%	n	%	
Category	414,623	86.8%	63,291	13.2%	
Age at diagnosis (years old)					<0.01
<20	2,005	0.5%	526	0.8%	
20-30	12,969	3.1%	2,201	3.5%	
30-40	27,162	6.6%	4,408	7.0%	
40-50	50,083	12.1%	8,309	13.1%	
50-60	81,756	19.7%	13,473	21.3%	
60-70	97,509	23.5%	14,288	22.6%	
≥70	143,139	34.5%	20,086	31.7%	
Sex					<0.01
Male	233,794	56.4%	40,387	63.8%	
Female	180,829	43.6%	22,904	36.2%	
Median Income Quartiles 2008-2012					<0.01
<\$30,000	27,974	7.0%	6,046	10.0%	
\$30,000-\$35,999	55,874	14.0%	10,547	17.4%	
\$36,,000-\$45,999	104,964	26.2%	17,293	28.5%	
≥\$46,000	211,225	52.8%	26,844	44.2%	
Race					<0.01
Non-Hispanic White	399,375	96.3%	59,766	94.4%	
Hispanic White	4,567	1.1%	1,461	2.3%	
Black	1,813	0.4%	817	1.3%	
Other	2,775	0.7%	692	1.1%	
Unknown	6,093	1.5%	555	0.9%	
Distance to Hospital					<0.01
0-25	299,215	72.7%	41,193	65.9%	
25-50 miles	59,794	14.5%	9,856	15.8%	
≥50 miles	52,608	12.8%	11,436	18.3%	
Facility Type					<0.01
Community Cancer Program	23,737	6.4%	3,904	7.0%	
Comprehensive Community Cancer Program	133,651	35.9%	20,280	36.1%	
Academic/Research Program	181,319	48.7%	26,304	46.8%	
Integrated Network Cancer Program	33,780	9.1%	5,668	10.1%	
Primary Site					<0.01
Head and Neck	114,680	27.7%	9,464	15.0%	

Supplemental Table 1. Advanced disease by age, sex, race, comorbidity, disease, location, insurance, income, facility geography, facility type, city type, and distance to center.

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Trunk	120,646	29.1%	16,678	26.4%	
Upper Limb	104,176	25.1%	9,553	15.1%	
Lower Limb	71,255	17.2%	11,042	17.4%	
Overlapping/other	3,866	0.9%	16,554	26.2%	
Charlson/Deyo Score					<0.01
0	367,394	88.6%	51,857	81.9%	
1	38,876	9.4%	8,792	13.9%	
2	6,389	1.5%	1,889	3.0%	
3	1,964	0.5%	753	1.2%	
City Type					<0.01
Metro	335,349	83.5%	49,064	80.5%	
Urban	58,608	14.6%	10,471	17.2%	
Rural	7,491	1.9%	1,421	2.3%	
Facility Location*					<0.01
New England	28,846	7.7%	3,099	5.5%	
Middle Atlantic	62,880	16.9%	8,600	15.3%	
South Atlantic	80,326	21.6%	12,772	22.7%	
East North Central	63,923	17.2%	9,538	17.0%	
East South Central	22,597	6.1%	3,976	7.1%	
West North Central	31,391	8.4%	4,552	8.1%	
West South Central	17,573	4.7%	3,746	6.7%	
Mountain	18,471	5.0%	3,257	5.8%	
Pacific	46,480	12.5%	6,616	11.8%	
Percent Without High School Degree Quartiles 2000					<0.01
≥ 29%	34,521	8.6%	7,613	12.5%	
20-28.9%	72,428	18.1%	13,459	22.2%	
14-19.9%	94,433	23.6%	14,908	24.6%	
< 14%	198,600	49.7%	24,745	40.7%	
Primary Payer					<0.01
Not Insured	7,509	1.8%	2,777	4.4%	
Private Insurance/Managed Care	218,148	52.6%	29,822	47.1%	
Medicaid	7,542	1.8%	3,542	5.6%	
Medicare	167,935	40.5%	24,792	39.2%	
Other Government	4,105	1.0%	877	1.4%	
Insurance Status Unknown	9,384	2.3%	1,481	2.3%	

*New England: CT, MA, ME, NH, RI, VT, Mid Atlantic: NJ, NY, PA, South Atlantic: DC, DE, FL, GA, MD, NC, SC, VA, WV, East North Central: IL, IN, MI, OH, WI, East South Central: AL, KY, MS, TN, West North Central: IA, KS, MN, MO, ND, NE, SD, West South Central: AR, LA, OK, TX, Mountain: AZ, CO, ID, MT, NM, NV, UT, WY, Pacific: AK, CA, HI, OR, WA.