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Survival Differences by IDH Mutation Status Among Diffuse Astrocytoma Patients: a SEER Analysis, 2018-2020

By

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Master of Science in Public Health

Epidemiology

_____

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# Survival Differences by IDH Mutation Status Among Diffuse Astrocytoma Patients: a SEER Analysis, 2018-2020

by

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**Abstract**

Survival Differences by IDH Mutation Status Among Diffuse Astrocytoma Patients: a SEER Analysis, 2018-2020

By James Chen

**Background:** The isocitrate dehydrogenase gene encodes an enzyme that catalyzes reactions as part of the citric acid cycle. This gene is frequently mutated in gliomas, including diffuse astrocytoma. In recent years, IDH mutation has become the subject of increasing interest as studies have found that IDH mutation predicts better survival in glioma patients, as well as better response to radiation therapy and chemotherapy. This growing body of evidence lead the WHO to alter its classification of gliomas to include IDH mutation status in 2016. Due to the relative recency of these developments, there is a dearth of IDH mutation data in population level databases, and consequently most of the evidence for the association between IDH mutation and survival in glioma patients is limited to clinical data. Older studies also do not clearly differentiate between cancer subtypes according to the WHO's new classification system. This study seeks to address this gap and confirm that the association observed in clinical data can also be observed in SEER's population level data in a clearly defined sample of diffuse astrocytoma patients.

**Methods:** 246 IDH-mutant and 148 IDH-WT patients were identified using 2000-2020 brain biomarker data from the SEER database. Kaplan-Meier survival curves were generated to compare survival between IDH mutant and WT patients, and a stratified Cox model was run to calculate the hazard ratio associated with IDH mutation status, controlling for age, race, sex, radiation, chemotherapy, surgery, stage, primary site and 1p/19q co-deletion.

**Results:** Kaplan-Meier curves found that IDH mutant patients demonstrated enhanced survival over IDH wildtype patients ($p<0.0001$). Multivariable analysis using a stratified Cox model showed a statistically significant difference in survival comparing IDH wildtype to IDH mutant patients (HR: 6.73, 95% CI: 3.03 – 14.92, $p < 0.0001$).

**Conclusion:** IDH mutation predicts enhanced survival among diffuse astrocytoma patients. Further research is needed to explore the potential of IDH mutation status as a treatment guideline on diffuse astrocytoma patients via examining effect measure modification by chemotherapy. As IDH mutation is a relatively recent addition to national cancer databases such as SEER, time is needed to accumulate data for a more comprehensive and statistically powered analysis.

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## INTRODUCTION

### Background

Primary malignant brain tumors are a rare but highly fatal form of cancer, accounting for approximately 1.3% of all newly diagnosed cancers in the US and 3.1% of all cancer deaths, while having a relatively poor 5-year survival rate of 33.4% [1]. Between 2017 and 2021, the average age-standardized incidence rate of all primary malignant brain and CNS tumors was 6.2 per 100 000 person-years [1]. There are stark differences in incidence, mortality, treatment, and subtype distribution of primary malignant brain tumors between children, adolescents, and adults [2-3]. Thus, this analysis will focus on the adult population.

Primary malignant brain tumors differ in incidence and mortality by sex, race, and age [2,4]. The global age-standardized incidence rate of primary malignant brain tumors was 3.7 per 100,000 person-years among males and 2.6 per 100,000 person-years among females [2]. Non-Hispanic whites exhibited the highest incidence and mortality rates of 8.0 and 5.1 per 100,000 person-years respectively among all racial groups, while Asians and Pacific Islanders had the lowest with 3.4 and 2.3 per 100,000 person-years respectively [4]. When grouping by age, incidence rates were highest among those aged 65+ (21.3 per 100,000 person-years) and decreased with age, down to 3.4 per 100,000 person years among those aged 20-39 [4]. Survival followed the opposite trend, with the highest mortality rates observed among the oldest patients [4]. Studies into risk factors associated with primary brain malignancies are still ongoing, but thus far the validated risk factors identified are ionizing radiation and history of allergies [5].

Primary brain malignancies are highly heterogeneous and can fall into one of several categories. Of these categories, gliomas are the most common, accounting for 81% of malignant brain tumors [6]. Gliomas are tumors that arise from the glial cells of the brain or spinal cord and can be further subdivided by histology and cell type. Adult diffuse gliomas can be broadly divided into oligodendrogliomas derived from oligodendrocytes and astrocytomas derived from astrocytes, which are further subdivided according to grade [7,8]. The WHO classifies CNS tumors into grades ranging from I to IV, with increasing grade corresponding to increasing cell differentiation from normal cells, mitotic activity, and infiltration of

surrounding tissues [7]. In the case of astrocytoma, grade I tumors are classified as pilocytic astrocytomas, grade II tumors as diffuse astrocytomas, grade III tumors as anaplastic astrocytomas, and grade IV tumors as glioblastomas [7]. This study will focus on diffuse astrocytomas.

Diffuse Astrocytoma

Grade II diffuse astrocytoma is a form of low-grade astrocytoma. Diffuse astrocytoma is slow growing relative to higher grade astrocytomas, but exhibits increasing proliferative properties compared to grade I pilocytic astrocytomas [7]. Low grade astrocytomas represent the most common form of low-grade glioma, with an incidence rate of 0.43 (95% CI: 0.38-0.49) per 100,000 person-years, while also having the poorest prognoses [9]. Substantial differences in mortality risk were observed among low-grade astrocytoma patients by age ($p < 0.0001$), sex ($p < 0.0001$), race ($p = 0.0004$), ethnicity ($p < 0.0001$), and surgery type ($p < 0.0001$) [9]. 1p/19q codeletion was identified as another factor associated with survival, with patients with 1p/19q codeletion having a 63.6% reduced risk of death compared with patients without 1p/19q codeletion (SHR: 0.36, 95% CI: 0.31–0.42, $p<0.001$).

IDH Mutation

The isocitrate dehydrogenase gene encodes an enzyme that catalyzes the oxidative decarboxylation of isocitrate as part of the citric acid cycle. IDH mutations can be observed in approximately 70% of gliomas, resulting in altered metabolism [10]. IDH mutations have recently become the subject of increasing interest, as a growing body of evidence suggests that IDH mutation is associated with survival among primary brain tumors.

In a paper published in 2010, researchers from the University of Zurich identified IDH mutation status as a strong predictor of overall survival among glioblastoma and anaplastic astrocytoma patients, with IDH1 mutant patients exhibiting significantly better outcomes compared with IDH1 wildtype patients (RR 2.7; 95% CI 1.6-4.5, $p<0.0001$, sample size 382) [11]. A study published that same year confirmed that IDH mutation predicted prolonged survival via multivariate analysis ($p = 0.003$, sample size 271), and also found that IDH mutation predicted higher response rate to chemotherapy with temozolomide ($p = 0.01$) [12]. A study published in 2012 also confirmed these discoveries, finding that

IDH mutation was associated with prolonged progression-free survival in univariate and multivariate analyses ($p<0.001$, sample size 86) and correlated with a higher rate of objective response to temozolomide ($p=0.001$) [13]. Another study done in 2015 found that IDH mutation was associated with survival among grade II and III gliomas, with a hazard ratio of 2.08 (95% CI 1.22–3.57) [14]. And a more recent paper published in 2023 examining low-grade gliomas found that IDH mutant patients had an 87.9% reduced risk of death compared with IDH wildtype patients (SHR: 0.12, 95% CI: 0.01–0.31, $p < 0.001$) [9].

Taking into account this growing body of evidence, the WHO changed its classification system for diffuse gliomas in 2016. The WHO's new divides diffuse gliomas into astrocytomas and oligodendrogliomas. Astrocytomas are then subdivided into glioblastomas and diffuse and anaplastic astrocytomas. Finally, all categories are further subdivided according to IDH mutation status and 1p/19q codeletion status [8].

Taken together, these developments support the use of IDH mutation as a prognostic marker and treatment guideline for glioma patients. However, the relative recency in these developments leaves several gaps in the literature to be addressed. As most national cancer registries have only recently began tracking IDH mutation status as a variable of interest, most papers published thus far rely on clinical level data. Furthermore, several of the papers published stratified their analysis according to older glioma classification systems, which do not differentiate between pinocytic astrocytoma and diffuse astrocytoma and classify both as low grade astrocytomas. This paper will thus seek to verify that the association between IDH mutation and survival observed in clinical level data can also be observed in SEER's population level data, using a clearly defined classification of diffuse astrocytoma patients.

## METHODS

The Brain Molecular Markers variable was added to SEER in 2018 to track IDH mutation status among primary brain cancer patients. Using this variable, 246 IDH-mutant and 148 IDH wildtype diffuse astrocytoma patients (with diffuse astrocytoma defined using ICD-O-3 histology code 9400/3) who were at least 20 years old and for whom diffuse astrocytoma was their first and only cancer were identified in SEER*Stat version 8.4.3 drawing data from 2000-2020 SEER Research Plus Data, November 2022 submission including 17 registries. The outcome of interest was survival time, defined as the time, in months, from diagnosis with brain cancer to the end of the follow-up period (December 2020) or death from cancer. Patients who died of other non-cancer causes or were lost to follow-up were censored.

Age at diagnosis, sex, surgery, radiation, chemotherapy, chromosome 1p/19q codeletion, stage, and race were included as part of the analysis. Age was categorized into four intervals: 20-34 years old, 35-49 years old, 50-64 years old, and 65+ years old. Surgery, radiation, and chemotherapy were coded as binary variables dichotomized as treatment given or treatment not given. Race was categorized as non-Hispanic white, non-Hispanic black, non-Hispanic other, and Hispanic, with non-Hispanic other including non-Hispanic American Indian/Alaska Native, non-Hispanic Asian or Pacific Islander, and unknown race. All patients included in the analysis were at the localized or regional stage, with the exception of a single patient in the distant stage. That patient was dropped from the analysis due to lack of meaningful information in that stratum, and stage was modeled as a binary variable. A patient was defined as having chromosome 1p/19q codeletion if that patient exhibited deletion or loss of heterozygosity at both chromosome 1p and chromosome 19q. Otherwise, they were defined as not having 1p/19q codeletion.

Unadjusted Kaplan-Meier curves were generated to compare relative survival among IDH-mutant and wildtype diffuse astrocytoma patients. The tentative model was then assessed for collinearity issues. A Cox proportional hazards model was run and the proportional hazards assumption was assessed for all variables using log-log survival curves, goodness-of-fit testing, and the Cox model with time-dependent covariates. Assessment for effect measure modification by chemotherapy was then conducted, followed

by confounding assessment. The final gold-standard stratified Cox model was then used to calculate adjusted hazard ratios and 95% confidence intervals.

All statistical analysis was done using SAS. IRB review was not required for this study, as all data used was publicly available with a signed DUA.

## RESULTS

From 2018 to 2020, 753 cases of diffuse astrocytoma containing data on IDH mutation status were reported to the SEER database. After filtering out patients younger than 20 years old, patients for whom there was less than 1 year of follow-up, and patients for whom diffuse astrocytoma was not their primary cancer, 394 cases were included in the final analysis.

Of the 394 patients included in the final analysis, 246 (66.4%) were IDH mutant and 148 (37.6%) were IDH wildtype (Table 1). Among the IDH mutant patients, 61.0% were male and 41.0% were female, while among the IDH wildtype patients 55.4% were male and 44.6% were female. Of the covariates, age, surgery, stage, and primary site showed a statistically significant association with IDH while race, sex, radiation, chemotherapy, and chromosome 1p/19q codeletion showed no statistically significant association. IDH mutant patients tended to be younger than IDH wildtype patients, with 82.1% of IDH mutant patients being under 50 years old and 64.9% of IDH wildtype patients being 50 years or older. The most common racial group in the analysis was white non-Hispanic, accounting for 66.3% of IDH mutant patients and 72.3% of IDH wildtype patients. Clinically, the most commonly reported primary site was the frontal lobe among IDH mutant patients (48.8%) and the parietal lobe among IDH wildtype patients (26.4%). Treatment wise, 53.3% of IDH mutant and 71.0% of IDH wildtype patients received radiation therapy, 53.3% of IDH mutant and 64.9% of IDH wildtype patients received chemotherapy, and 86.6% of IDH mutant and 68.8% of IDH wildtype patients received surgery. The full demographic and clinical characteristics of the patients organized by IDH mutation status can be found in Table 1.

Sex, radiation therapy, chemotherapy and primary site failed to meet the proportional hazards assumption, so the Cox model was stratified on those variables to control for them while also directly controlling for age, race, surgery treatment, 1p/19q codeletion and stage.

Effect measure modification assessment was carried out for chemotherapy. The hazard ratio comparing IDH wildtype to IDH mutant patients among patients who received chemotherapy was 11.25 (95% CI 4.22 – 29.97) and the hazard ratio among patients who did not receive chemotherapy was 1.85

(95% CI 0.22 – 15.83). A likelihood ratio test found no evidence of effect measure modification by chemotherapy on the effect of IDH mutation on survival ($p = 0.78$).

Crude Kaplan-Meier survival curves showed a significant difference in survival by IDH mutation status over the 36 months follow-up period ($p < 0.0001$) (Figure 1). IDH mutant patients had a 94.31% survival rate, while IDH wildtype patients had a 58.78% survival rate.

Multivariable analysis using a stratified Cox model showed a significant difference in survival comparing IDH wildtype to IDH mutant patients (HR: 6.73, 95% CI: 3.03 – 14.92, $p < 0.0001$). Across age stratum, mortality was highest among patients aged 65+ (HR: 27.01, 95% CI: 8.98 – 81.26), followed by patients aged 50-64 (HR: 9.10, 95% CI: 3.03 – 27.32) and patients aged 35-49 (HR: 5.06, 95% CI: 1.38 – 18.50) comparing to patients aged 20-34 as a baseline. Across racial stratum, mortality was highest among Asians, Pacific Islanders, and other races (HR: 6.31, 95% CI: 1.06 – 37.67), followed by Black non-Hispanics (HR: 5.10, 95% CI: 1.11 – 23.38), then Hispanics (HR: 1.61, 95% CI 0.43 – 5.93) comparing to white non-Hispanics as a baseline.

## DISCUSSION

The results of the study indicate that IDH mutation is associated with survival among diffuse astrocytoma patients, with IDH wildtype patients being exposed to significantly higher hazard of mortality compared with IDH mutant patients. These results confirm that the association between IDH mutation and survival observed in previous studies using clinical data can also be observed among a clearly defined sample of diffuse astrocytoma patients using population level data from SEER. The strength of the association observed among diffuse astrocytoma patients in this study (HR 6.73) is consistent with the 87.9% reduction in risk of mortality risk among low-grade glioma patients [9] and similar to the risk ratio of 2.7 observed among glioblastoma and diffuse astrocytoma patients [11] and the hazard ratio of 2.08 observed about grade II and III glioma patients [14].

Although this study was unable to find evidence of statistically significant effect measure modification by chemotherapy on the association between IDH mutation and survival among diffuse astrocytoma patients, as other studies found among glioblastoma and diffuse astrocytoma patients [12-13], the results were still highly suggestive. The difference in point estimates stratified by chemotherapy (11.25 for chemotherapy patients vs 1.85 for non-chemotherapy patients) was not statistically significant, but the pronounced difference between strata and the relative width of the 95% confidence intervals suggest that this could be due to the smaller sample size, and that a follow-up study with a larger sample size could still find statistically significant interaction of effect measure modification by chemotherapy.

### Limitations

Studies have indicated that MGMT methylation is a potential confounder associated with survival in primary brain malignancies, as well as a potential effect measure modifier of the association between IDH mutation and survival [15]. Unfortunately, SEER has yet to make its MGMT methylation data publicly available, so this study was unable to control for confounding or test for effect measure modification by MGMT methylation.

Another limitation of this study is that SEER only began collecting data on IDH mutation status in 2018, and has published data only up until 2020, resulting in a relatively short follow-up time, an inability to produce 5-year survival estimates, and a relatively smaller sample size relative to what could be expected for a study using population level data from SEER. As IDH mutation data is a relatively recent addition to databases such as SEER, potentially more time is needed in order to accumulate data for a more robust analysis.

Finally, SEER does not contain in-depth data on chemotherapy, only tracking whether or not a patient received chemotherapy and not which drug the patient received. As a result, this greatly limits the study's ability to investigate IDH mutation's potential use in treatment guidelines.

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Figure 1: Unadjusted Kaplan-Meier survival curves of adult (>=20 years) diffuse astrocytoma patients by IDH mutation status. IDH mutant patients exhibited enhanced survival compared with IDH wildtype patients ($p<0.0001$). Data taken from 2000-2020 SEER Research Plus Data, November 2022 submission.

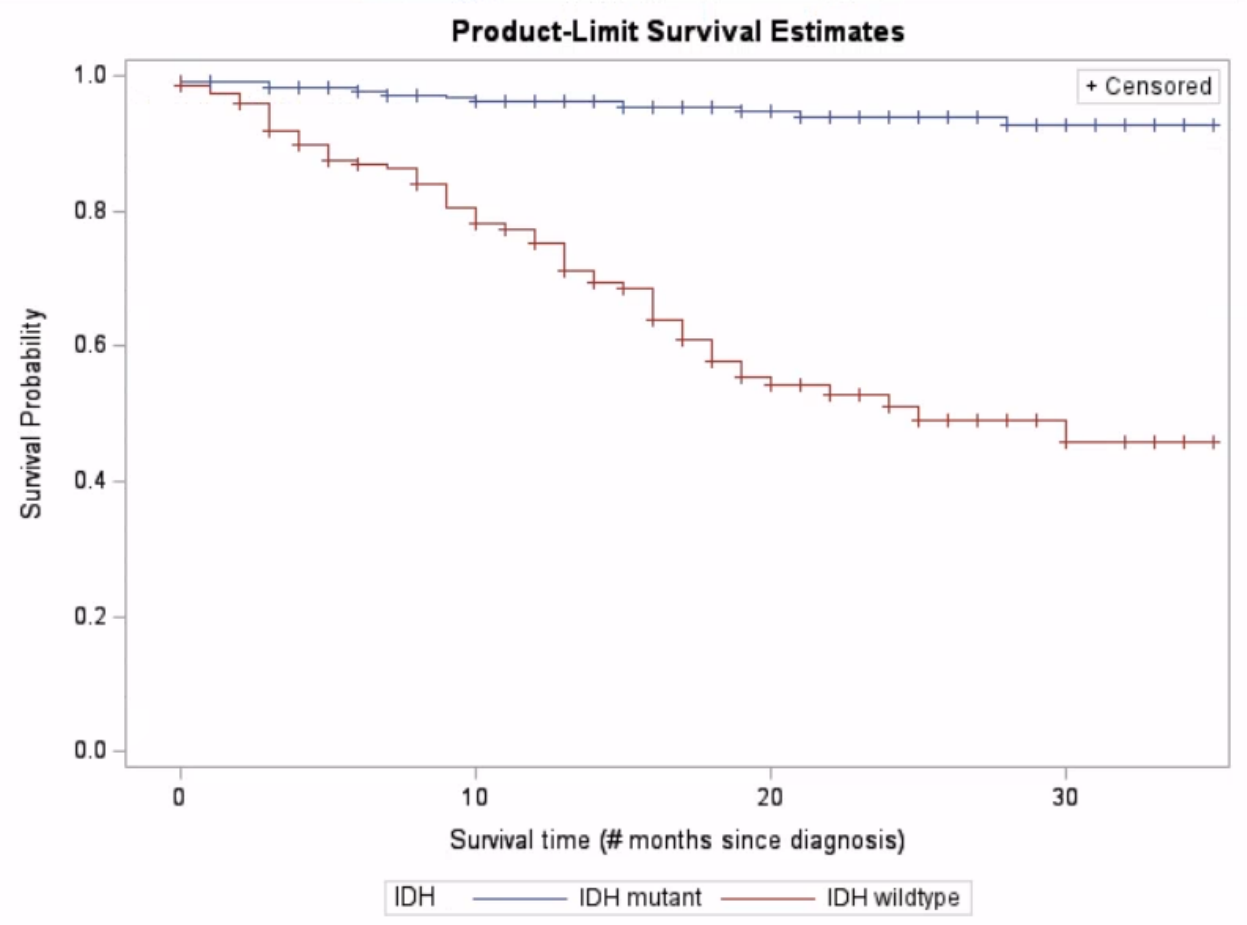

Table 1: Demographic and clinical characteristics of adult (>=20 years) diffuse astrocytoma patients by IDH mutation status. Data taken 2000-2020 SEER Research Plus Data, November 2022 submission.

| Covariate | Overall<br>n=394<br>n (%) | IDH mutant<br>n=246 (62.44%)<br>n (%) | IDH wildtype<br>n=148 (37.56%)<br>n (%) | p-value |
|---|---|---|---|---|
| **Age** | | | | |
| 20-34 years | 132 (33.50) | 105 (42.68) | 27 (18.24) | <0.0001 |
| 35-49 years | 122 (30.56) | 97 (39.43) | 25 (16.89) | |
| 50-64 years | 82 (20.81) | 32 (13.01) | 50 (33.78) | |
| 65+ years | 58 (14.72) | 12 (4.88) | 46 (41.08) | |
| **Race** | | | | |
| White non-Hispanic | 270 (68.53) | 163 (66.26) | 107 (72.30) | 0.31536 |
| Black non-Hispanic | 31 (7.87) | 19 (7.72) | 12 (8.11) | |
| Asian, Pacific Islander, or Other | 37 (9.39) | 25 (10.16) | 12 (8.11) | |
| Hispanic | 56 (14.21) | 39 (15.85) | 17 (11.49) | |
| **Sex** | | | | |
| Male | 232 (58.88) | 150 (60.98) | 82 (55.41) | 0.5654 |
| Female | 162 (41.12) | 96 (39.02) | 66 (44.59) | |
| **Treatment** | | | | |
| Surgery | 303 (76.90) | 213 (86.59) | 90 (60.81) | 0.0485 |
| No surgery/unknown | 91 (23.10) | 33 (13.41) | 58 (39.19) | |
| Radiation therapy | 236 (59.90) | 131 (53.25) | 105 (70.95) | 0.1119 |
| No radiation therapy/unknown | 158 (40.10) | 115 (46.75) | 43 (29.05) | |
| Chemotherapy | 227 (57.61) | 131 (53.25) | 96 (64.86) | 0.1366 |
| No chemotherapy/unknown | 167 (42.39) | 115 (46.75) | 52 (35.14) | |
| **Chromosome 1p/19q** | | | | |
| 1p/19q codeletion | 19 (4.82) | 12 (4.88) | 7 (4.73) | 0.2440 |
| No codeletion | 375 (95.18) | 234 (95.12) | 141 (95.27) | |
| **Stage** | | | | |
| Localized | 321 (83.81) | 214 (89.54) | 107 (74.31) | 0.0033 |
| Regional | 62 (16.19)<br>*n missing = 11* | 25 (10.46) | 37 (25.69) | |
| **Primary Site** | | | | |
| Cerebrum | 18 (4.57) | 5 (2.03) | 13 (8.78) | 0.0005 |
| Frontal lobe | 150 (38.07) | 120 (48.78) | 30 (20.27) | |
| Temporal lobe | 84 (21.32) | 45 (18.29) | 39 (26.35) | |
| Parietal lobe | 36 (9.14) | 24 (9.76) | 12 (8.11) | |
| Occipital lobe | 6 (1.52) | 3 (1.22) | 3 (2.03) | |
| Ventricle, NOS | 3 (0.76) | 0 (0.00) | 3 (2.03) | |
| Cerebellum, NOS | 5 (1.27) | 2 (0.81) | 3 (2.03) | |
| Brain stem | 7 (1.78) | 2 (0.81) | 5 (3.38) | |
| Overlapping lesion of brain | 51 (12.94) | 28 (11.38) | 23 (15.54) | |
| Brain, NOS | 30 (7.61) | 16 (6.50) | 14 (9.46) | |
| Spinal Cord | 4 (1.02) | 1 (0.41) | 3 (2.03) | |

Table 2: Stratified Cox model parameters for IDH mutation in adult (>=20 years) diffuse astrocytoma patients. Data taken from 2000-2020 SEER Research Plus Data, November 2022 submission.

| Covariate | Hazard ratio IDH wildtype vs. IDH mutant | 95% CI Lower bound | 95% CI Upper bound |
|---|---|---|---|
| **Age*** | | | |
| 35-49 years | 5.0556 | 1.3814 | 18.5027 |
| 50-64 years | 9.1029 | 3.0328 | 27.3222 |
| 65+ years | 27.0119 | 8.9789 | 81.2623 |
| **Reference group: 20-34 years* | | | |
| **Race*** | | | |
| Black non-Hispanic | 5.1035 | 1.1139 | 23.3817 |
| Asian, Pacific Islander, or Other | 6.3084 | 1.0564 | 37.6727 |
| Hispanic | 1.6062 | 0.4347 | 5.9348 |
| **Reference group: White non-Hispanic* | | | |