Race Differences in High-Grade Carotid Artery Stenosis

Cover title: Race and carotid stenosis

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ABSTRACT

Background: Despite a higher incidence of stroke and a more adverse cardiovascular risk factor profile in blacks and Hispanics compared to whites, carotid artery revascularization to prevent stroke is performed less frequently among these sub-populations blacks and Hispanics compared to whites. We assessed whether there is a lower prevalence of high-grade (≥70% diameter-reducing) carotid stenosis in blacks, Hispanics and other minority populations compared to whites.

Methods: Consecutive subjects in a nation-wide Life Line program to screen for vascular disease, 2005-2019 were evaluated in a cross-sectional cohort study. The prevalence of high-grade stenosis, defined by a carotid ultrasound peak systolic velocity of ≥230 cm/sec, was assessed. Participants self-identified as white, black, Hispanic, Asian, Native American or other. Race/ethnic differences were assessed using Poisson regression. The number of individuals in the United States with high-grade stenosis was estimated by applying prevalence estimates to 2015 US Census population estimates.

Results: The prevalence of high-grade carotid stenosis was estimated in 6,130,481 individuals. The prevalence of high-grade stenosis was higher with increasing age in all race-sex strata. Generally, blacks and Hispanics had a lower prevalence of high-grade stenosis compared to whites, while Native Americans had higher prevalence. For example, for men aged 55-65 the relative risk of stenosis compared to whites (RR of 1) was 0.40 (95% CI: 0.29 – 0.55) and 0.61 (95% CI: 0.46 – 0.81) for blacks and Hispanics, respectively; and 1.53 (95% CI: 1.12 – 2.10) for Native Americans. When these prevalence estimates were applied to the Census estimates of the US population, an estimated 327,721 individuals have high-grade stenosis, of whom 7% are black, 7% Hispanic and 43% women.
Conclusions: Despite their having a more adverse cardiovascular risk profile, there was a lower prevalence of high-grade carotid artery stenosis for both the black and Hispanic population relative to the white population. This lower prevalence of high-grade stenosis is a potential contributor to the lower use of carotid revascularization procedures in these minority populations.
INTRODUCTION

Data from professional societies in the United States (US)\textsuperscript{1,2} and from the Centers for Medicare and Medicaid Services\textsuperscript{3} reflect that over 90\% of carotid revascularizations for extracranial carotid stenosis (either carotid endarterectomy or carotid artery stenting) are performed in the white populations, 4\% in black populations, 4\% in Hispanic populations, and the remainder in other racial groups. This racial/ethnic distribution of patients undergoing revascularization stands in stark contrast to the racial distribution of the general population. Among those in the age group most often affected by carotid stenosis (55 years of age and older), whites represented 78.0\%, blacks 9.5\%, Hispanics 7.8\%, and other races 4.6\% of the general population in 2010.\textsuperscript{4} The relative dearth of carotid revascularizations in minority populations, particularly among blacks, has been long-recognized,\textsuperscript{5-7} and exists in the context of a greater burden of stroke\textsuperscript{8} and a widely-recognized more adverse cardiovascular risk profile\textsuperscript{9} in minority populations. Despite a policy commitment by the National Institutes of Health (NIH) and the allocation of resources to address minority recruitment by NIH,\textsuperscript{10} the fewer revascularizations in black and other minority populations is reflected in their lower recruitment to NIH-funded clinical trials.\textsuperscript{11}

It is tempting to attribute the lower rates of revascularization in minority groups to a disparity in access to care,\textsuperscript{7} with racial/ethnic differences in revascularizations persisting after adjustment for patient and hospital characteristics in some,\textsuperscript{6,12} but not all,\textsuperscript{5,13} reports. Lower rates of revascularization in minority populations persist in the VA System, where access to care should not be an issue.\textsuperscript{13} In addition, the black population has been shown to be more risk-averse to the surgical management of carotid disease.\textsuperscript{7} An alternate explanation may be that despite a higher incidence of stroke in the black population,\textsuperscript{14} they may have a lower prevalence
of high-grade cervical carotid stenosis warranting consideration for revascularization, than their white counterparts.

The best approach to determine the prevalence of asymptomatic carotid stenosis while avoiding a clinical referral bias with minimal confounders is to assess race/ethnic differences in high-grade carotid stenosis in the general population. Extremely large samples would be required to assess differences among subgroups (such as race groups) given that only 1% to 2% of the general population might have high-grade (≥70%) stenosis. Life Line Screening (LLS, Independence, Ohio) is a direct-to-consumer company identifying adults at risk for vascular disease. While American Heart Association and USPSTF recommendations do not support the carotid screening of the general population, individuals have the ability to self-pay for such an assessment that they personally consider important. Since 2005 LLS has performed carotid duplex ultrasound assessments on more than 6 million participants across 49 states in the U.S. The purpose of this study was to determine the race/ethnic-specific prevalence of high-grade carotid stenosis using these unique data from LLS.

METHODS

Screening assessments conducted between 2005 and 2019 (inclusive) were used for this report. Participants were self-referred and self-paid. Demographic (age, sex, and race/ethnicity), clinical, and self-reported comorbidity information (hypertension, diabetes, dyslipidemia and smoking) was recorded. Participants self-identified as white, black, Hispanic, Asian, Native American or other races. Ultrasound testing was performed by trained and certified vascular ultrasound technologists using a standardized protocol. Quality control mechanisms included random and planned audits by sonographers and physicians, monthly reviews, and an annual
assessment of competencies. A participant was considered to have a high-grade stenosis if the peak systolic velocity in either carotid artery was $\geq 230$ cm/sec. If bilateral high-grade stenosis was identified, the artery with the highest peak systolic velocity was included in the analysis.

The population was then stratified by race/ethnicity (white, black, Hispanic, Asian, Native American or other), sex (men or women) and age (45-54, 55-64, 65-74 or 75-84 years), resulting in 48 strata. In an abundance of caution, those aged 85 and above were excluded because of the relatively small sample size and a greater potential of being non-representative in this “oldest-old” strata. For each stratum, the proportion of the population (with 95% confidence intervals [CI]) for the prevalence of high-grade stenosis was calculated. Poisson regression was used to estimate the prevalence ratio (with 95% confidence intervals) for high-grade stenosis for race/ethnicity (relative to a white reference) within strata defined by age and sex. A sensitivity analysis was also performed assessing the impact of risk factor adjustment on the prevalence ratio. The number of individuals in the US with high-grade stenosis was then predicted as the product of the prevalence estimates from LLS multiplied by the 2015 population estimates from the Census Bureau. The proportion of this population with prevalent high-grade stenosis was then tabulated by race and sex. Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC). Statistical tests used a 2-sided $\alpha$ of 0.05. No adjustments were made for multiple comparisons. The authors declare that all supporting data are available within the article.

RESULTS

Study population
Of the 10,464,670 unique visits over a 15-year period, ultrasound measurement of the peak systolic velocity was available for 10,208,978 (98%). These visits were conducted in 6,926,996 participants, and analysis was restricted to the first visit from each participant. Participants with missing information on race (171,435 or 2%), sex (135,491 or 2%), or age (129,151 or 2%) were excluded. Those aged 85 years and over were also excluded from the analysis (360,438 or 5%), resulting in an analysis data set of 6,130,481 (89%) individuals. Of the 6,130,481 unique participants, 86% were white, 4% were black, 4% were Hispanic, were 2% were Asian, 2% were Native American, and 2% were other races (Table I). The mean age of participants was 63.8 ± 9.0 years. Substantial data were available from all four US census geographical regions. Women comprised 63.2% of all participants and formed the majority in all race/ethnic groups.

The LLS cohort appears generally comparable to the general U.S. population as suggested by the similarities by race in the prevalence of major cardiovascular risk factors (Table 1). For example, 61.7% of blacks and 43.6% of whites reported hypertension, similar to the hypertension prevalence estimates from the general population in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study of 71% and 51%.\textsuperscript{21} The black-to-white prevalence ratio for hypertension was 61.7/43.6 = 1.42, while in REGARDS it was 71/51 = 1.39. Likewise, the prevalence of diabetes among blacks and whites was 21.3% and 10.9% respectively (black-to-white prevalence ratio = 1.95), again generally similar to the 31% and 16% prevalence observed in REGARDS respectively (ratio = 1.94).\textsuperscript{21} Unfortunately, smoking is missing on the majority (52%) of the respondents (data on smoking was only systematically collected by LLS for the period of May 2011 through March 2018). Given this limitation, the prevalence of smoking was also similar for blacks in the LLS and REGARDS (16.4% and 17%).
though more white participants in LLS smoked than in the REGARDS (23.0% and 13%, respectively).21

In the context of the very large LLS sample size, all 2-way the interactions between age, race and sex were all significant for the 230 cm/s threshold, specifically $p_{\text{age-by-race-by-sex}} = 0.0589$, $p_{\text{age-by-race}} < 0.0001$, $p_{\text{age-by-sex}} < 0.0001$, and $p_{\text{race-sex}} = 0.0155$. Accordingly, all subsequent analyses were performed stratified by age, race and sex.

Prevalence of high-grade carotid stenosis

The prevalence of high-grade carotid stenosis was higher with increasing age across all race/ethnic populations and across men and women (Figure 1, with numerical estimates in Supplemental Table SI). White men had a peak prevalence in the 75-84-year age group (0.96%, [95% CI 0.92% – 0.99%]) and white women had a peak prevalence in the same age group (0.58%, [0.56% – 0.60%]). Similarly, the highest prevalence among black men and women was also in the 75-84-year age group (0.70% [0.54 – 0.89] and 0.62% [0.52 – 0.74] respectively).

The prevalence of high grade carotid stenosis was significantly lower for blacks compared to whites across all age groups and across men and women with the exception of women aged 75-84 and 45-54 years where risk was similar or not significantly lower (Figure 2, with numerical estimates in Supplemental Table SII). Hispanics also had a lower relative risk for stenosis compared to whites, significantly so among 55-64-year-old men and 45-54-, 55-64- and 65-74-year-old women. Compared to whites, Asians also had significantly lower relative risk for stenosis for men in all age groups except 45-54, and in women for all age groups except 75-84. Native Americans had a higher relative risk of stenosis across all age groups compared to whites, with a peak of 1.86 [95% CI: 1.46-2.39] in women aged 55-64.
The sensitivity analysis adjusting for risk factors (hypertension, diabetes, dyslipidemia and smoking) showed it had virtually no impact on the prevalence ratio for high-grade stenosis (Supplemental Table IV).

*Estimated number of individuals with high-grade carotid stenosis in the US*

The 2015 US Census provides information on the national population by age (10-year strata between 45 and 84 years of age), race/ethnicity and sex (Supplemental Table SIII). From these Census data, it is estimated that 72\% of the population is white, with blacks and Hispanic comprising 11\% each; and women comprising 52\%. The number of individuals in the US with high-grade stenosis was estimated as the product of age-race-sex specific Census population estimates with the observed LLS prevalence of high-grade stenosis (Table II). With this approach, the total number of individuals with high-grade carotid stenosis in the US is estimated to be 327,721, with whites contributing 82\% of the population with high-grade stenosis, and blacks and Hispanics contributing 7\% each. Asians contribute 3\% and Native Americans contribute 1\%, while women contribute 43\% of the population with high-grade stenosis.

**DISCUSSION**

Using 15 years of data from a cohort of >6 million participants in a national vascular screening program, we have estimated the prevalence of high-grade carotid artery stenosis in the US by race, sex and age category. For both men and women, we found blacks (and Hispanics for half the age strata) had a significantly lower prevalence of high-grade stenosis than whites. Using Census data from 2015, we estimate that there are 327,721 individuals with high-grade carotid stenosis in the US. These estimates of the prevalence of high-grade stenosis in the
general population show that whites contribute a higher proportion with high-grade stenosis relative to their representation in the general population (82% versus 72% respectively), while blacks, Hispanics and Asians with high-grade stenosis contribute a smaller proportion (7%, 7% and 3%, respectively) compared to their representation in the general population (11%, 11% and 5%, respectively).

Our study is the first to address race/ethnic differences in the prevalence of high-grade stenosis in the general population. The previously reported 1% to 2% overall prevalence of high-grade stenosis indicates that immense sample sizes are needed to assess race/ethnic or sex differences, limiting previous investigations. For example, in a hypothetical cohort with 50% black and 50% white representation, and a prevalence of 1.5% for blacks, a study would require a sample size of 720,253 to achieve 90% power to detect a 10% higher odds of high-grade stenosis in whites. Sample sizes would need to be approximately 2.5 times higher if the representation of blacks were to reflect their 10% representation in the population. To our knowledge, only the LLS dataset exceeds the required sample size. A subset of these data have been used previously to assess race/ethnic differences in carotid atherosclerosis. However, that report used Doppler velocity thresholds of $\geq 110$ centimeters/second (cm/s) and $\geq 140$ cm/s, both of which are far below the accepted standard of $\geq 230$ cm/s associated with high-grade stenosis.

Because the LLS population was self-referred, we were concerned that the black and Hispanic populations in LLS were not representative of those populations in the U.S. Differences in financial resources available for self-pay, LLS testing locations with low proportions of blacks and Hispanics, and other barriers to testing could introduce bias. These concerns were somewhat mitigated in that both the prevalence of cardiovascular risk factors, and the black-white differences in their prevalence, reflect those from studies where the population
was chosen through random sampling of the U.S. population. **For examWhile no single study can be definitively representative of the national population, ple**, the black-white prevalence ratios for major risk factors **in the current analysis** were quite similar to other published studies. Specifically, for hypertension the black-to-white prevalence ratio in LLS was 1.42, while in REGARDS it was 1.39; and for diabetes the ratios were 1.95 versus 1.94. However, while there was a similar prevalence of smoking for blacks in LLS and REGARDS (16.4% and 17%), there does appear to be a higher prevalence of smoking among white participants in LLS (23%) than in REGARDS. We were also concerned that a more adverse risk factor profile would be observed in the self-referred LLS population (i.e., a self-referred assessment of the “worried sick”). However, the prevalence of risk factors was marginally lower in the LLS population than observed in the general population in the REGARDS study, and adjustment for risk factors had virtually no impact on the racial differences in the prevalence of high-grade stenosis. Furthermore, even if a referral bias were present, it generally appears to be having a similar effect for blacks and whites.

Many reports in the literature assess whether differences in risk factors can explain the differences in disease (in our case, the prevalence of high-grade stenosis). However, we found: 1) a lower prevalence of high-grade carotid stenosis in both blacks and Hispanics relative to whites, and 2) a generally heavier risk factor burden for blacks than for whites. Specifically, there was a substantially higher prevalence of hypertension and diabetes in blacks than whites (18.1% and 10.4% higher, respectively), and a very similar prevalence of dyslipidemia in blacks and whites (only a 0.8% difference). While smoking data are missing on the majority of the LLS participants, for the data available there was only a marginally higher prevalence of smoking in whites than blacks (6.6% higher in whites). Since the risk factor burden is generally
heavier for blacks than whites, adjustment for these risk factors would tend to make the white excess risk of high-grade stenosis even larger. That is, the higher prevalence of high-grade stenosis in whites compared to blacks exists despite the generally heavier risk factor burden in blacks. That smoking data, a major risk factor for extracranial atherosclerosis, is missing on the majority (52%) of the respondents in the LLS data is a substantial shortcoming of these data. For completeness, we nevertheless performed a sensitivity analysis assessing the impact of risk factor adjustment on the estimated prevalence ratio for high-grade stenosis in the 2,791,017 participants with complete risk factor data (including smoking), showing that adjustment for the prevalence of these risk factors had virtually no impact on the estimated racial differences in the prevalence of high-grade stenosis.

Prior clinical studies have examined black-white differences in carotid stenosis among patients presenting to a hospital with a stroke, generally showing that black stroke patients have less carotid stenosis than whites. However, patients with a stroke are not representative of the general population. Stroke subtypes may differ between blacks and whites, with whites having a preponderance of large vessel stroke and blacks more lacunar and hemorrhagic strokes. Hence, the atherogenic larger-vessel mechanisms bringing a white stroke patient to medical attention may be more closely related to high-grade stenosis than the small-vessel or hemorrhagic mechanisms for the black population. As a result of these selection disparities, observations made in patients presenting with a stroke or patients undergoing carotid revascularization cannot address the question of whether there are race/ethnic differences in the prevalence of carotid atherosclerosis in the general population.

Clinical trials have a responsibility to recruit minority populations in numbers sufficient to provide a valid analysis of race/ethnic differences. Despite major efforts to bolster recruitment
of minority patients, the percent of blacks has remained low in NIH trials related to asymptomatic carotid disease. An important goal should be recruitment proportionate to their representation among people with the disease. These data suggest that the goals for minority recruitment for studies of asymptomatic (i.e., general population) high-grade carotid stenosis should be reconsidered. This report would suggest that goals of 7% black, 7% Hispanic, and 43% women are more appropriate.

The LLS population represents both the greatest strength and weakness of this report. Only with this remarkable sample size available from the LLS data is it possible to reliably estimate racial differences in the prevalence of high-grade stenosis, a task made challenging by the low prevalence of the condition in the general population. In addition, that the LLS population is not drawn from a hospital/clinical population offers the opportunity to assess racial differences in the prevalence of high-grade stenosis in the general population. Conversely, the LLS population is self-referred and requires self-payment for the evaluation, opening the possibility for a referral bias by over representing those with a higher socio-economic status and be comprised of either the “worried sick” or the “worried well.” Admittedly, differences in socio-economic status between the race/ethnic groups may contribute to differences in the prevalence of stenosis, though we did not have this information to adjust for. Further, there is additional potential for residual confounding introduced by racial differences in the awareness-treatment-control of risk factors. To the extent that referral bias is playing a role, the biologic mechanism would likely be through a pathway of the prevalence of the cardiovascular risk factors. We are somewhat comforted that the prevalence of the (admitted self-reported) cardiovascular risk factors in the LLS cohort is similar to the prevalence seen in random samples of the general population. Further, adjustment for these risk factors had little impact on the
estimated racial differences in the prevalence of high-grade stenosis. As such, this seems to suggesting that if referral biases are playing a role, they were having a minimal and are having a similar impact across the race/ethnic groups. In the extremely small group of individuals with contralateral carotid occlusion, there may have been increased velocities in the index carotid artery. An important, but somewhat lesser shortcoming of the LLS data, is the self-reporting of race in the population.

In this first report of race/ethnic differences in the prevalence of high-grade carotid stenosis, we observed that both blacks and Hispanics contributed a lower proportion of high-grade carotid stenosis relative to their representation in the general population, despite their having a more adverse cardiovascular risk profile. This lower prevalence of high-grade stenosis is a potential contributor to the lower carotid revascularization rates in these minority populations.
SOURCES OF FUNDING

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DISCLOSURES

None

References


FIGURE LEGENDS

Figure 1. Prevalence (and 95% confidence interval) of high-grade carotid artery stenosis in men and women stratified by age (in years) and race/ethnicity. (Nat American, Native American; PSV, peak systolic velocity; sec, second)

Figure 2. Relative risk (and 95% confidence interval) of high-grade carotid artery stenosis in men and women stratified by age (in years) and race/ethnicity (compared to white as the reference). (Nat American, Native American)
### Table 1: Description of study population.

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<th>Variable</th>
<th>All</th>
<th>White</th>
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<th>Hispanic</th>
<th>Asian</th>
<th>Native American</th>
<th>Other</th>
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<td>N</td>
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<td>5,282,932</td>
<td>271,182</td>
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<td>103,763</td>
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<td>44.5</td>
<td>43.6</td>
<td>61.7</td>
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<td>15.3</td>
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<td>27.9</td>
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SD = standard deviation
* Number in parenthesis beside the variable name indicates the percent of the population with available data.
Table 2: Estimated number of individuals in the United States with high-grade (peak systolic velocity ≥230 cm/second) carotid artery stenosis

<table>
<thead>
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<th>US Population</th>
<th>Men</th>
<th>Women</th>
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<td>55-64</td>
<td>65-74</td>
<td>75-84</td>
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<td>592</td>
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<td>Sex total</td>
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<tr>
<td>Percent</td>
<td>57%</td>
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