



Socioenvironmental adversity and risk of prostate cancer in non-Hispanic black and white men

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Abstract

Non-Hispanic black (NHB) men experience higher risk of prostate cancer than other racial/ethnic groups, and it is possible that socioenvironmental (SE) adversity and resulting stress may contribute to this disparity. Data from the Southern Community Cohort Study were used to evaluate associations between SE adversity and perceived stress in relation to prostate cancer risk, overall and by race/ethnicity and grade. Between 2002 and 2009, 26,741 men completed a questionnaire, from which an 8-item SE adversity composite was created (covering socioeconomic status, residential environment, and social support/buffers). Two items from the Perceived Stress Scale were assessed. With follow-up through 2011, 527 prostate cancer cases were diagnosed. In multivariable models, each one-unit increase in the SE adversity composite was associated with increased prostate cancer risk among non-Hispanic white (NHW) men (HR 1.23; 95% CI 1.02–1.48) and reduced risk among NHB men (HR 0.89; 95% CI 0.82–0.95) (*p* interaction: 0.001). This pattern held for low grade, but not high grade, cancers although power was limited for the latter. Perceived stress variables were associated with increased risk of prostate cancer among NHW men, but not among NHB men. Results do not support the hypothesis that SE adversity may underlay the racial disparity in prostate cancer, over and above that of covariates, including healthcare utilization.

Keywords African Americans · Life stress · Minority health · Psychological stress · Prostate cancer

Introduction

Prostate cancer (PC) is the most commonly diagnosed cancer among men in the United States [1], and risk of PC is higher among non-Hispanic black (NHB) men than other racial/ethnic groups [2]. The reasons underlying this disparity are

unknown. However, it is possible that psychological stress associated with socioenvironmental (SE) adversity, such as low socioeconomic status, adverse residential environment and low/loss of social support or buffers, may contribute to this disparity. Compared to non-Hispanic white (NHW) persons, NHB persons tend to experience more SE adversity and stressful life events, higher perceived stress and allostatic load, and altered stress hormone rhythms [3–9]. Stress signaling pathways have been linked to several

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cancer-promoting effects, such as DNA damage, compromised immunosurveillance, inhibited DNA repair and apoptosis, angiogenesis, and cell division, as well as shortened telomere length and loss of tumor suppressor protein function [10–14]. Corroborating mouse models suggests that psychological stress may contribute to the development and metastasis of PC [15]. However, no studies have evaluated the association between SE adversity and PC risk, and only limited epidemiologic research has been conducted on stress and PC, yielding mixed results [16–22].

We used data from the Southern Community Cohort Study (SCCS) to prospectively evaluate the associations between SE adversity and perceived stress, which may additionally capture individual variation in the response to SE adversity, in relation to PC risk. Results were evaluated overall, and by race/ethnicity and cancer grade.

Methods

Study population

Participants were drawn from the SCCS, an ongoing prospective cohort focused on cancer disparities [23, 24]. Participants included over 85,000 men and women recruited from 2002 to 2009 in 12 Southeastern states. English-speaking persons between ages 40–79 were eligible for inclusion if they reported no cancer in the prior year, except non-melanoma skin cancer. Approximately, 85% of SCCS participants were recruited from Community Health Centers (CHCs), which provide healthcare to low-income and under-insured individuals; remaining participants were recruited from the general population by mail. Of the 32,805 men enrolled without a history of PC prior to baseline, analyses were restricted to the 31,337 men who self-reported their race/ethnicity as NHB or NHW. We further restricted to the CHC-recruited population, as we wished to examine the association between SE adversity and PC risk, over and above that of healthcare utilization; thus, restricting to the population recruited at the point of care (CHCs) helps reduce heterogeneity in healthcare utilization (we have also adjusted for time since most recent doctor visit and screening history to also address this concern). We also wanted to eliminate potential misclassification differences resulting from different modes of data collection between CHC participants (who completed an in-person interview) and the general population (who completed a mailed questionnaire). After restricting to the CHC-recruited population, 26,741 men remained for analysis, 76% of whom were self-reported NHB ($n = 20,389$) and 24% of whom were self-reported NHW ($n = 6352$).

All study participants provided written informed consent and the study was approved by the Institutional Review

Boards of Vanderbilt University, Meharry Medical College and the Harvard T.H. Chan School of Public Health.

Exposure

SE adversity was measured using a newly developed composite, comprised of eight factors, representing three constructs previously studied in relation to health outcomes [25–37]: low socioeconomic status, as measured on the individual-level (annual household income < \$15,000; < 12 years of education with no GED; no health insurance), area-level adverse residential environment (top quartile Neighborhood Deprivation Index; [25, 26] a neighborhood crime rate $\geq 50\%$ higher than the national average) (see below for a detailed description of the area-level residential variables), and low/loss of social support or buffers (zero people they could ask for help in an emergency; being separated, divorced, or widowed; not receiving strength or comfort from religion, faith, or God). One point was given for each of these eight factors, with values potentially ranging from 0 to 8. Persons missing data on any of the variables contributing to the composite were excluded from analyses pertaining to this exposure.

Neighborhood crime was assessed using a total crime index generated by Environmental Science Research Institute (ESRI). This index was created using Applied Geographic Solutions, Inc. (AGS) and the FBI Uniform Crime Report databases to capture crimes committed within participants' census block groups between 2005 and 2010. This unweighted index includes murder, rape, robbery, assault, burglary, theft, and motor vehicle theft. The crime level within each census block group was linked to the block groups of residence at enrollment. Persons residing in a block group with a crime index ≥ 150 (representing $\geq 50\%$ higher crime than the national average) were categorized as residing in a higher crime neighborhood.

The neighborhood deprivation index (NDI) has been detailed previously [25, 26]. Briefly, the NDI was calculated using census tract-level variables (such as percentage of individuals unemployed and the percentage of households below the poverty line) from the 2000 US Census. Principal components analysis was used to derive an NDI for each participant's census tract, and participants were assigned a value corresponding to the NDI for the census tract corresponding to their residence at enrollment. The NDI was divided into quartiles, with the highest quartile representing high neighborhood deprivation.

We also investigated perceived stress, which may capture individual variation in response to SE adversity [3]. The baseline questionnaire included two items from Cohen's Perceived Stress Scale [38]. Participants were asked how often during the past month they felt "unable to control the important things in your life" and how often they felt that "difficulties were piling up so high that you could not overcome

them.” For each, those responding “none of the time” or “some of the time” were grouped, indicating low perceived stress, while those reporting feeling this way “much of the time” or “more or all of the time” were categorized as experiencing high perceived stress.

Outcome

Cases included 527 incident, invasive cancers of the prostate diagnosed between enrollment (2002–2009) and December 31, 2011, over an average of 6.1 years of follow-up. Cases were primarily identified by linkage to state cancer registries in the 12 states of SCCS enrollment, though a small number were identified by linkage to the National Death Index, which identified deaths due to PC not reported by registries ($n = 17$; 3.2%). Information on cancer grade was available from the state registries for 357 cases, 93 of which were high grade (defined by Gleason pattern 4 + 3 or Gleason score 8–10) and 264 of which were low grade (Gleason score 2–6 or Gleason pattern 3 + 4). Of those missing grade, more than half were from one state’s registry, and most were from one of four registries.

Statistical analysis

Cox proportional hazards regression was used to estimate the hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs) for associations of interest. Person-time at risk was accrued from the date of baseline interview to the earliest: PC diagnosis, date of death, or December 31st, 2011. For the 17 cases diagnosed only through the National Death Index, date of death was used as a surrogate for diagnosis date. The SE adversity composite measure was normally distributed, and modeled as a continuous linear variable. Perceived stress variables were modeled as binary variables, comparing high to low perceived stress.

In Cox models, age was the time-axis of analysis. Minimally adjusted analyses further adjusted for race/ethnicity (NHB, NHW); fully adjusted models were additionally adjusted for a priori-determined ‘core’ covariates: time since last doctor visit (≤ 3 months, 3 to ≤ 12 months, > 12 months), family history of PC (0 first-degree relatives, 1 + first-degree relatives, missing), history of digital rectal exam (DRE) screening (never, > 2 years since last screen, ≤ 2 years since last screen), and history of prostate-specific antigen (PSA) screening (never, > 2 years since last screen, ≤ 2 years since last screen). Given our interest in the stress pathway, we adjusted for healthcare utilization (time since last doctor visit and screening) to examine the association between SE adversity and PC risk, over and above that of healthcare utilization. Family history was coded with a missing category, given that this information was missing for $> 10\%$ of participants. For overall and race-stratified models of our main

exposure of interest, SE adversity, we explored additional adjustment for height, body mass index, smoking, physical activity, as well as alcohol, calcium, and lycopene consumption; their inclusion did not meaningfully change results and these variables were therefore not included in final models.

A likelihood ratio test was used to test the statistical significance of the race/ethnicity interaction. In analyses of high-grade cancer, low-grade cancers were censored at date of diagnosis, and in analyses of low-grade cancer, high-grade cancers were censored at date of diagnosis; the statistical significance of grade differences was assessed using the p value corresponding to the exposure in a case-only logistic model, comparing low-grade and high-grade cases. Analyses were conducted using Stata version 13 (College Station, TX).

Results

In this study, participants’ age at baseline ranged from 40 to 79 years, with a mean age of 51 years. Of the 25,787 men for whom an SE adversity measure was calculated, participants reported a mean of 2.8 of the 8 queried components (median = 3) (Table 1). Of these men, 4696 (18.2%) reported 0–1 SE adversities, 17,778 (68.9%) reported 2–4 SE adversities, and 3313 (12.9%) reported 5 + SE adversities. The distributions of each component factor contributing to the composite measure are provided in Supplemental Table 1 and are provided by perceived stress in Supplemental Tables 2–3.

NHB men reported more SE adversity than NHW men, with 14.3% of NHB men reporting 5 + SE adversities, as compared to 8% of NHW men (Table 1). However, NHW men reported higher perceived stress than NHB men, with 24.1% of NHW men reported feeling unable to control important things in life ‘much to all of the time,’ as compared to 16.6% of NHB men (Supplemental Table 4). Men reporting their most recent doctor visit to be more than a year prior were more likely to report 5 + SE adversities than those reporting seeing a doctor within the prior 3 months (19.7% vs 10.9%) (Table 1). Men screened within 2 years prior to study enrollment were less likely to report high SE adversity than those who had never been screened: 8.8% of those who reported receipt of PSA screening in the prior 2 years reported 5 + SE adversities, as compared to 15.4% of those who reported never having a PSA test.

Overall prostate cancer

In minimally adjusted analyses, each one-unit increase in SE adversity was associated with an 11% reduced risk of PC overall (HR 0.89; 95% CI 0.84–0.95); this association attenuated slightly with multivariable adjustment (HR 0.92; 95% CI 0.86–0.98) (Table 2). A significant interaction by

Table 1 Characteristics of the study population

| | SE adversity ^{a,b} Mean ± SD | Low SE adversity 0–1 points N (%) | Medium SE adversity 2–4 points N (%) | High SE adversity 5+ points N (%) |
|---------------------------------------|--|---|--|---|
| Total | 2.8 ± 1.4 | 4696 (18.2) | 17,778 (68.9) | 3313 (12.9) |
| Demographic | | | | |
| Age at baseline (years) | | | | |
| 40 to < 45 | 2.8 ± 1.4 | 1168 (17.3) | 4776 (70.7) | 811 (12.0) |
| 45 to < 50 | 2.9 ± 1.4 | 1059 (16.1) | 4610 (70.1) | 904 (13.8) |
| 50 to < 55 | 3.0 ± 1.4 | 858 (15.9) | 3764 (69.7) | 779 (14.4) |
| 55 to < 60 | 2.9 ± 1.5 | 582 (18.0) | 2206 (68.1) | 453 (14.0) |
| 60 to < 65 | 2.7 ± 1.5 | 467 (23.8) | 1271 (64.7) | 227 (11.6) |
| 65 to < 70 | 2.4 ± 1.5 | 305 (29.0) | 658 (62.6) | 89 (8.5) |
| 70 to < 75 | 2.2 ± 1.5 | 186 (34.6) | 320 (59.5) | 32 (6.0) |
| 75 to < 79 | 2.4 ± 1.4 | 71 (27.1) | 173 (66.0) | 18 (6.9) |
| Race/ethnicity | | | | |
| Non-Hispanic black | 3.0 ± 1.4 | 3172 (16.1) | 13,701 (69.6) | 2825 (14.3) |
| Non-Hispanic white | 2.5 ± 1.4 | 1524 (25.0) | 4077 (67.0) | 488 (8.0) |
| Preventive care/screening | | | | |
| Time since last doctor visit (months) | | | | |
| ≤ 3 | 2.7 ± 1.4 | 3234 (19.6) | 11,441 (69.5) | 1794 (10.9) |
| > 3 to ≤ 12 | 2.9 ± 1.5 | 1060 (18.4) | 3883 (67.3) | 824 (14.3) |
| > 12 | 3.2 ± 1.4 | 380 (11.2) | 2347 (69.1) | 670 (19.7) |
| Prostate-specific antigen screening | | | | |
| Never | 3.1 ± 1.4 | 1680 (12.5) | 9687 (72.1) | 2076 (15.4) |
| Ever, > 2 years since last screen | 2.8 ± 1.5 | 317 (19.7) | 1082 (67.4) | 207 (12.9) |
| Ever, ≤ 2 years since last screen | 2.5 ± 1.5 | 2385 (26.8) | 5744 (64.4) | 787 (8.8) |
| Digital rectal exam screening | | | | |
| Never | 3.0 ± 1.4 | 1632 (14.1) | 8207 (70.9) | 1744 (15.1) |
| Ever, > 2 years since last screen | 2.9 ± 1.4 | 766 (16.5) | 3256 (70.1) | 623 (13.4) |
| Ever, ≤ 2 years since last screen | 2.6 ± 1.5 | 2249 (24.5) | 6045 (65.8) | 896 (9.8) |
| Family history | | | | |
| Family history prostate cancer | | | | |
| 0 first-degree relatives | 2.8 ± 1.4 | 4036 (18.1) | 15,360 (69.0) | 2875 (12.9) |
| ≥ 1 first-degree relatives | 2.4 ± 1.5 | 323 (30.1) | 673 (62.7) | 78 (7.3) |
| Missing | 3.1 ± 1.4 | 337 (13.8) | 1745 (71.5) | 360 (14.7) |

SE socioenvironmental

^aAmong those with an SE adversity count ($n=25,787$), time since last doctor visit missing for 154, history of prostate-specific antigen screening missing for 1822 and history of digital rectal exam missing for 369

^bStressor composite ranges from 0 to 8, with 1 point given for each of the following eight SE adversities: divorced, separated, or widowed, uninsured, lack of faith or comfort from God, no one to help in an emergency, low education, low income higher crime in neighborhood, and high Neighborhood Deprivation Index; therefore, the HR for this continuous measure corresponds to the risk of prostate cancer associated with the presence of each additional SE adversity

race/ethnicity was observed (p interaction = 0.001), with an HR of 0.89 (95% CI 0.82–0.95) among NHB men and an HR of 1.23 (95% CI 1.02–1.48) among NHW men.

To better understand the role of screening on differences observed by race/ethnicity, we first explored the joint distribution of SE adversity and history of PSA screening by race/ethnicity. Among NHW men, 10.3% who had never received a PSA test reported 5+ SE adversities (high adversity), as

compared to 4.7% who had been screened in the prior 2 years. Among NHB men, 16.9% who had never received a PSA test reported high SE adversity, as compared to 10.1% who had been recently screened (Supplemental Table 5). We also conducted sensitivity analyses restricted to men aged > 50 years who reported no history of PSA screening (as men following screening guidelines would have been expected to be screened by this age). Results were comparable to those observed in the

Table 2 Associations between SE adversity, perceived stress, and any prostate cancer, overall and by race/ethnicity

| | Cohort N = 26,741 | Cases N = 527 | Age and race adjusted | | Fully adjusted ^a | | Race/ethnicity-specific results ^a | | | | p interaction | |
|---|----------------------|------------------|--------------------------|------------|-----------------------------|------------|--|------------|--------------------|------------|---------------|--|
| | | | Overall | | Overall | | Non-Hispanic black | | Non-Hispanic white | | | |
| | | | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI | | |
| SE adversity composite^b | | | | | | | | | | | | |
| SE adversity count (continuous) ^c | 2.8 ± 1.4 | 2.7 ± 1.5 | 0.89 | 0.84, 0.95 | 0.92 | 0.86, 0.98 | 0.89 | 0.82, 0.95 | 1.23 | 1.02, 1.48 | 0.001 | |
| Perceived stress | | | | | | | | | | | | |
| How often: <u>unable to control</u> important things in life ^d | | | | | | | | | | | | |
| None to some of the time | 21,482 (81.6) | 444 (86.4) | 1.00 | Ref. | 1.00 | Ref. | 1.00 | Ref. | 1.00 | Ref. | 0.03 | |
| Much to all of the time | 4844 (18.4) | 70 (13.6) | 0.96 | 0.74, 1.24 | 0.96 | 0.73, 1.26 | 0.83 | 0.61, 1.14 | 1.82 | 1.00, 3.30 | | |
| How often: <u>difficulties piling up</u> so high, unable to overcome them? ^e | | | | | | | | | | | | |
| None to some of the time | 21,659 (82.3) | 442 (86.0) | 1.00 | Ref. | 1.00 | Ref. | 1.00 | Ref. | 1.00 | Ref. | 0.009 | |
| Much to all of the time | 4667 (17.7) | 72 (14.0) | 1.12 | 0.87, 1.44 | 1.10 | 0.84, 1.44 | 0.94 | 0.69, 1.27 | 2.34 | 1.30, 4.21 | | |

HR hazard ratio, SE socioenvironmental, 95% CI 95% confidence interval

^aAdjusted for the following: age, race, time since last doctor visit, family history of prostate cancer, history of DRE, and history of PSA screening

^bSE adversity composite ranges from 0 to 8, with 1 point given for each of the following eight SE adversities: divorced, separated, or widowed, uninsured, lack of faith or comfort from God, no one to help in an emergency, low education, low income, higher crime in neighborhood, and high Neighborhood Deprivation Index; therefore, the HR for this continuous measure corresponds to the risk of prostate cancer associated with the presence of each additional SE adversity

^cAmong those with an SE adversity count (n = 25,787), 2143 further excluded from multivariable analysis due to missing covariate information (time since last doctor visit missing for 154, history of prostate-specific antigen screening missing for 1822 and history of digital rectal exam missing for 369), leaving 23,644 persons (and 456 cases) for analysis

^dAmong those with information on the unable to control variable (n = 26,326), 2220 further excluded from multivariable analysis due to missing covariate information (time since last doctor visit missing for 171, history of prostate-specific antigen screening missing for 1881, and history of digital rectal exam missing for 404), leaving 24,106 persons (and 465 cases) for analysis

^eAmong those with information on the difficulties variable (n = 26,326), 2223 further excluded from multivariable analysis due to missing covariate information (time since last doctor visit missing for 171, history of prostate-specific antigen screening missing for 1884, and history of digital rectal exam missing for 405), leaving 24,103 persons (and 465 cases) for analysis

main analysis: SE adversity was associated with decreased risk among NHB men (HR 0.90; 95% CI 0.78–1.04) and increased risk among NHW men (HR 1.40; 95% CI 1.00–1.97) (p interaction = 0.02).

Results for perceived stress generally aligned with SE adversity. There was no statistically significant association overall when comparing those who felt unable to control the important things in life ‘much to all of the time’ to those who felt this way ‘none to some of the time’ (HR 0.96; 95% CI 0.73–1.26). This association varied by race/ethnicity (p interaction = 0.03), with a non-significant HR of 0.83 (95% CI 0.61–1.14) observed among NHB men and a statistically significant HR of 1.82 (95% CI 1.00–3.30) observed among NHW men. Similarly, there was no overall association when comparing those indicating that they felt that difficulties were piling up so high that they were unable to overcome them ‘much to all of the time’ to those who indicated this statement to be true ‘none to some of the time.’ However, this association also varied significantly by race/ethnicity (p interaction = 0.009), with no association observed among NHB men (HR 0.94; 95% CI 0.69–1.27) and a statistically significant HR of 2.34 observed among NHW men (95% CI 1.30–4.21).

Results by prostate cancer grade

The association between the SE adversity and PC did not significantly vary by grade (p difference = 0.12), with a significant multivariable-adjusted HR of 0.86 (95% CI 0.79–0.95) observed for low-grade cancer and a HR 1.02 (95% CI 0.88–1.19) for high-grade cancer (Table 3). Exploratory analyses revealed that the association between SE adversity and low-grade cancer significantly varied by race/ethnicity (p interaction < 0.001), with a HR of 0.82 among NHB men (95% CI 0.74–0.90) and an HR of 1.38 among NHW men (95% CI 1.06–1.81) (Fig. 1). However, for high-grade cancer, we found no association among NHB men (HR 0.99; 95% CI 0.84–1.17) and a non-significant positive association for NHW men (HR 1.27; 95% CI 0.83–1.92) (p interaction = 0.29).

The association between perceived stress variables and PC did not vary by grade (p difference for unable to control = 0.88; p difference for difficulties = 0.72), with no significant associations observed. We did not conduct grade-specific race-stratified analyses for perceived stress variables, given limited power for these binary exposures.

Discussion

In this study, SE adversity was inversely associated with PC risk in NHB men, while a positive association was observed in NHW men. The association between perceived

stress and risk also varied significantly by race/ethnicity, with a statistically significant positive association observed among NHW men only.

A significant inverse association was observed between SE adversity and PC risk, driven by NHB men. This was unexpected, given that NHB persons experience more SE adversity and have higher risk than NHW persons; [2] we had suspected that SE adversity and subsequent stress may contribute to the excess risk among NHB men. However, our results indicate that SE adversity, as measured in this study, does not explain the excess risk among NHB men. In fact, the expected positive association between SE adversity and PC was only observed among NHW men. While no prior work has been conducted specifically on SE adversity and risk, there is limited literature on objectively measured stress/stressful life events in relation to PC risk. Our results among NHW men are consistent with a small study in Scotland ($n = 244$ cases), which found increased daily stress, as measured by the Reeder Stress Inventory, to be associated with increased PC risk [16]. However, these results stand in contrast to a small prospective study of Caucasian Danish men ($n = 157$ cases) which found no association between a stress score, representing a combination of stress intensity and stress frequency, and risk [19] and a meta-analysis of 12 European cohort studies ($n = 865$ cases) which found no association between work stress, defined as job strain or the presence of high demands and low control at work, and PC risk [20]. To our knowledge, no studies have evaluated the association between objectively measured stress/stressful life events and PC specifically among NHB men.

The reasons underlying this difference by racial/ethnic group are unclear. The impact of SE adversity on health outcomes could vary by race/ethnicity, supported by data indicating that blacks and whites may perceive adversity and stressful life events differently [3, 39]. For example, in our study, NHB men experienced more SE adversity than NHW men, yet had lower perceived stress. Furthermore, a study of women ages 35–49 found that despite a similar number of major life events, for most major life events experienced, white women tended to report higher stress than black women [3]. Similarly, a study of 11,050 adults ages 24–32 found that while black persons had higher odds of stressful life events than white persons, they did not experience higher perceived stress [39]. Research also indicates that stressful experiences may affect the health of white persons more than black persons [4, 40, 41], with some suggestion that earlier exposure and/or more frequent exposure to adversity may make black persons more accustomed to adversity, and therefore, less likely to be impacted by each additional stressor [4], consistent with the resilience hypothesis [42]. Along these lines, it may be that SE adversity has a stronger effect on mediators of the

Table 3 Associations between SE adversity composite and high-grade/low-grade prostate cancer^a

| | Cohort <i>N</i> (%) | Cases <i>N</i> (%) | Age and race adjusted | | Fully adjusted ^b | | |
|--|------------------------|-----------------------|--------------------------|------------|-----------------------------|------------|--|
| | | | HR | 95% CI | HR | 95% CI | |
| High grade^c | | | | | | | |
| SE adversity composite ^d | | | | | | | |
| SE adversity count (continuous) | 2.9 ± 1.4 | 2.9 ± 1.4 | 0.99 | 0.86, 1.14 | 1.02 | 0.88, 1.19 | |
| Perceived stress | | | | | | | |
| How often: <u>unable to control</u> important things in life | | | | | | | |
| None to some of the time | 21,338 (81.6) | 78 (86.7) | 1.00 | Ref. | 1.00 | Ref. | |
| Much to all of the time | 4824 (18.4) | 12 (13.3) | 0.96 | 0.52, 1.77 | 1.03 | 0.56 1.92 | |
| How often: <u>difficulties</u> piling up so high, unable to overcome them? | | | | | | | |
| None to some of the time | 21,512 (82.2) | 74 (82.2) | 1.00 | Ref. | 1.00 | Ref. | |
| Much to all of the time | 4650 (17.8) | 16 (17.8) | 1.50 | 0.87, 2.60 | 1.36 | 0.76, 2.44 | |
| Low grade^c | | | | | | | |
| SE adversity composite ^d | | | | | | | |
| SE adversity count (continuous) | 2.9 ± 1.4 | 2.6 ± 1.5 | 0.85 | 0.78, 0.93 | 0.86 | 0.79, 0.95 | |
| Perceived stress | | | | | | | |
| How often: <u>unable to control</u> important things in life | | | | | | | |
| None to some of the time | 21,338 (81.6) | 222 (85.4) | 1.00 | Ref. | 1.00 | Ref. | |
| Much to all of the time | 4824 (18.4) | 38 (14.6) | 1.01 | 0.71, 1.43 | 1.04 | 0.72, 1.50 | |
| How often: <u>difficulties</u> piling up so high, unable to overcome them? | | | | | | | |
| None to some of the time | 21,512 (82.2) | 221 (85.0) | 1.00 | Ref. | 1.00 | Ref. | |
| Much to all of the time | 4650 (17.8) | 39 (15.0) | 1.15 | 0.82, 1.63 | 1.19 | 0.83, 1.71 | |

HR hazard ratio, SE socioenvironmental, 95% CI 95% confidence interval

^aAnalysis further excludes those with unknown grade, leaving 26,571 men eligible for analysis, among whom 357 cases of prostate cancer occurred (93 high-grade cases and 264 low-grade cases)

^bAdjusted for the following: age, race, time since last doctor visit, family history of prostate cancer, history of digital rectal exam, and history of prostate-specific antigen screening

^c*p* difference (high grade vs low grade): SE adversity composite: 0.12; *p* difference (high grade vs low grade) unable to control: 0.88 (0.85 with further adjustment for SE adversity composite); *p* difference (high grade vs low grade) difficulties: 0.72 (0.97 with further adjustment for SE adversity composite)

^dRanges from 0 to 8, with one point given for each of the following eight SE adversities: divorced, separated or widowed, uninsured, lack of faith or comfort from God, no one to help in an emergency, low education, low income, higher crime in neighborhood, and high Neighborhood Deprivation Index; therefore, the HR for this continuous measure corresponds to the risk of prostate cancer associated with the presence of each additional SE adversity

SE adversity/stress-PC relationship for NHW men, or that SE adversity manifests into more adverse lifestyle factors for NHW men [43].

Alternatively, it is possible that there is more measurement error in the SE adversity measure among NHB men than NHW men, as the SE adversity measure may not capture adversity experienced among NHB men as well. For example, our measure does not capture discrimination or experiences of racism; [4, 44, 45] such measurement error may attenuate the association between SE adversity and PC among NHB men. It has also been shown that factors contributing to emotional distress may vary by population subgroup, which may lead to differential measurement error by racial/ethnic group [46]. Even so, while measurement error may have attenuated a true positive association among

NHB men toward the null, this would not explain the *inverse* association.

Consistent with our findings, it has been argued that the well-documented inverse association between socioeconomic status (SES) and poor health outcomes among white persons should not be generalized to black persons [47]. While national data demonstrates strong inverse associations between SES and a range of poor health indicators for this group [48], health gains linked to increasing SES are smaller for blacks than whites, and a recent study found no association between SES and multiple indicators of health among African Americans, in contrast to whites [49]. There is a clear need for future research to better understand the conditions under which indicators of SES and SE adversity are weakly related or unrelated to health outcomes among

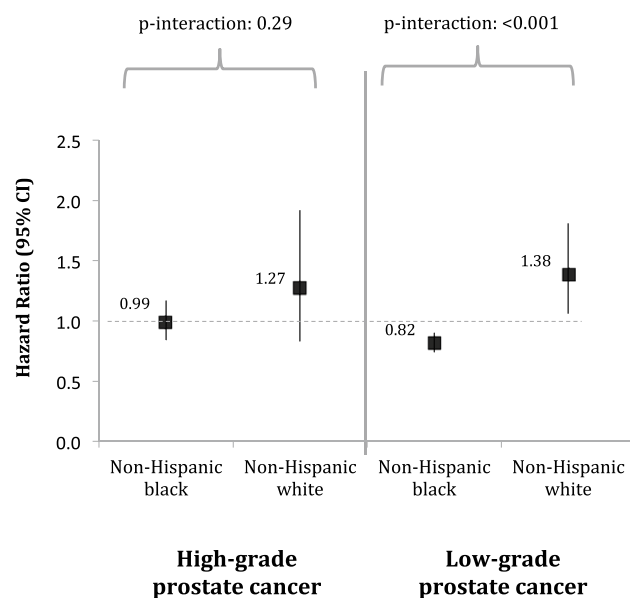


Fig. 1 Socioenvironmental (SE) adversity and risk of prostate cancer, by grade and race/ethnicity. The left side of the figure shows the hazard ratios and corresponding 95% CIs for the associations between the SE adversity composite and high-grade prostate cancer, stratified by race/ethnicity. Results are presented for low-grade prostate cancer in the right column. The SE adversity composite ranges from 0 to 8, with one point given for each of the following eight SE adversities: divorced, separated or widowed, uninsured, lack of faith or comfort from God, no one to help in an emergency, low education, low income, higher crime in neighborhood, and high Neighborhood Deprivation Index. Results are adjusted for the following: age, race, time since last doctor visit, family history of prostate cancer, history of digital rectal exam, and history of prostate-specific antigen screening

black persons, and the extent to which this pattern may vary by geographic region.

Beyond the SE adversity composite, we also evaluated perceived stress. Neither measure of perceived stress was associated with PC in the overall population, nor were any significant associations observed among NHB men. This is consistent with prior work that found no association between perceived stress and PC in African American men [18]. Taken together, these results suggest that the absence of a strong positive association between SE adversity and PC among NHB men is unlikely the result of measurement error in the SE adversity measure. However, it remains unclear why SE adversity was inversely associated with risk among NHB men, while perceived stress was not associated. Among NHW men, we observed a strong positive association between perceived stress and PC, consistent with a Canadian study, comprised largely of men of European ancestry, in which increasing duration of perceived workplace stress was associated with increased risk among men ≤ 65 years of age [21]. However, another study reported no significant associations between perceived stress and social support and risk among Caucasian men [18], and

a recently published study of Swedish men found that men with low stress resilience, as measured during compulsory military enlistment in adolescence, experienced decreased risk [22]. While associations between SE adversity and perceived stress and PC in our study are similar (indicating a strong positive association for NHW men only), SE adversity and perceived stress do differ somewhat in association among NHB men, and the distribution of the SE adversity composite did not markedly vary by perceived stress. Evaluating the interplay of SE adversity and perceived stress by racial/ethnic group in future well-powered studies may help us better understand the observed pattern of associations.

To address whether patterns held for clinically relevant cancers, we explored associations by cancer grade. The association for SE adversity varied, with an inverse association observed for low-grade cancer, and no association for high-grade cancer. Consistent with overall cancer, exploratory analyses revealed a significant interaction for low-grade cancer when stratified by race/ethnicity, with a significant inverse association observed among NHB men and a significant positive association observed among NHW men. However, for high-grade PC, the association was non-significant for both groups (although the effect estimate among NHW men was similar in magnitude to that observed for overall and low-grade cancer). As low-grade cancers are more likely to be the result of over-diagnosis than high-grade cancers, it may appear that the inverse association for low-grade cancer (and therefore total PC) among NHB men is related to screening. However, the distribution of SE adversity by screening history was comparable by race/ethnicity and sensitivity analyses revealed that the pattern of association between SE adversity and PC risk among both NHB and NHW men was unchanged when restricted to the subset of older men who have never been screened, further suggesting that screening practices are unlikely driving observed differences by race/ethnicity. Power for exploratory analyses by PC grade is limited, particularly for high-grade cancers, and further research in a larger study is needed to better understand the role of SE adversity and race in PC, and how this may vary by disease aggressiveness. This is important, given recent research indicating that stress-related signaling pathways, such as the adrenergic and glucocorticoid pathways, may be dysregulated in lethal tumors [50].

There are important limitations to this study. Given limited number of lethal cases, we were unable to examine associations for this clinically relevant outcome [51–53]. However, we examined associations by grade [54, 55], although power is still limited for this outcome. As the SE adversity composite measure covers multiple constructs, there is no clear instrument or measure to be validated against, and thus this measure has not been validated. All components of the SE adversity composite were given equal weight because without a gold standard, we determined that any sort of

pre-determined weighting would be arbitrarily-defined. Along these lines, it is also possible that some of these factors may interact to affect prostate cancer risk [56], and such interactions would not be captured by this count approach. It should also be noted that in this analysis, the components of the SE adversity composite do not perfectly correspond with regard to time period, with the NDI calculated using data from the 2000 census, baseline questionnaire data collected between 2002 and 2009, and crime data collected between 2005 and 2010. We did not have a comprehensive list of SE adversities; our composite therefore does not capture all SE adversities, such as discrimination, and it is possible that measurement error varies by race/ethnicity. It is also possible that there is error in the adversities measured. Even so, we have also examined perceived stress [38], which would not be subject to the same measurement error. SE adversity and perceived stress were measured at one time point, and it could be that SE adversity and stress at earlier life periods may be most relevant to carcinogenesis. Furthermore, we only have two items from Cohen's Perceived Stress Scale, rather than all items needed to construct validated composite measures of perceived stress; we therefore, examined the two perceived stress items separately using binary exposures, in contrast to the standard composite 4- or 10-item measures. However, results indicate that the pattern of association is comparable across these two perceived stress variables; this consistency indicates that these results merit follow-up in a population in which the validated 4-item or 10-item scales can be examined. And while patterns of association are similar for SE adversity and perceived stress variables (particularly among NHW men), we do not have statistical power to explore their interplay by race/ethnicity and grade. We do not have information on biologic measures of stress, and such measures may be informative to understanding the association between SE adversity and PC. Lastly, the majority of SCCS participants are low income, with ~62% of the population reporting a household income <\$15,000/year, and it is possible that results may not generalize to a more socioeconomically diverse cohort. This study also has several notable strengths. We leveraged a large prospective cohort to evaluate a potential contributor to PC disparities and stratified by race/ethnicity, which is not possible in most prospective cohorts due to small numbers of NHB participants. Both NHW and NHB participants were recruited from CHCs, and were relatively comparable with regard to socioeconomic status, reducing some concern about residual confounding by socioeconomic status, although this likely reduces variation in SE adversity. Further, we evaluated SE adversity using an objective construct, and evaluated the subjective construct, perceived stress, using a prospective design.

In summary, in this community health center-based population, we observed SE adversity to be positively associated

with PC risk among NHW men, but results do not support an association among NHB men. SE adversity and perceived stress do not appear to explain the racial disparity. Notably, this pattern of association held for low-grade cancer, although the number of high-grade cases was small, limiting the conclusions that can be drawn pertaining to high-grade cancer. More work in a larger study is needed to better understand these associations.

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest.

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