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Mediators of Black–White inequities in cardiovascular mortality among survivors of 18 cancers in the USA

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Abstract

Background: This study aims to quantify Black–White inequities in cardiovascular disease (CVD) mortality among US survivors of 18 adult-onset cancers and the extent to which these inequities are explained by differences in socio-economic and clinical factors.

Methods: Survivors of cancers diagnosed at ages 20–64 years during 2007–16 were identified from 17 Surveillance, Epidemiology and End Results registries. Associations between race and CVD mortality were examined using proportional hazards models. Mediation analyses were performed to quantify the contributions of potential mediators, including socio-economic [health insurance, neighbourhood socio-economic status (nSES), rurality] and clinical (stage, surgery, chemotherapy, radiotherapy) factors.

Results: Among 904 995 survivors, 10 701 CVD deaths occurred (median follow-up, 43 months). Black survivors were more likely than White survivors to die from CVD for all 18 cancers with hazard ratios ranging from 1.30 (95% CI = 1.15–1.47) for lung cancer to 4.04 for brain cancer (95% CI = 2.79–5.83). The total percentage mediations (indirect effects) ranged from 24.8% for brain (95% CI=–5.2–59.6%) to 99.8% for lung (95% CI = 61.0–167%) cancers. Neighbourhood SES was identified as the strongest mediator for 14 cancers with percentage mediations varying from 25.0% for kidney cancer (95% CI = 14.1–36.3%) to 63.5% for lung cancer (95% CI = 36.5–108.7%). Insurance ranked second for 12 cancers with percentage mediations ranging from 12.3% for leukaemia (95% CI = 0.7–46.7%) to 31.3% for thyroid cancer (95% CI = 10.4–82.7%).

Conclusions: Insurance and nSES explained substantial proportions of the excess CVD mortality among Black survivors. Mitigating the effects of unequal access to care and differing opportunities for healthy living among neighbourhoods could substantially reduce racial inequities in CVD mortality among cancer survivors.

Keywords: Cancer survivorship, cardiovascular mortality, cardio-oncology, racial inequity, neighbourhood socio-economic status, health insurance

Key Messages

- This study quantifies Black–White inequities in cardiovascular disease (CVD) mortality among survivors of 18 adult-onset cancers in the USA and the extent to which these inequities are explained by differences in socio-economic factors and clinical characteristics.
- Black cancer survivors were more likely than White survivors to die from CVD for all 18 cancers, with hazard ratios ranging from 1.30 for lung cancer (95% CI = 1.15–1.47) to 4.04 for brain cancer (95% CI = 2.79–5.83).
- Substantial proportions of the excess deaths among Black vs White survivors were mediated by racial differences in health insurance status (12.3–31.3%) and neighbourhood-level socio-economic status (25.0–63.5%).
- These findings underscore the importance of neighbourhood-level interventions and equitable access to care to mitigate the racial inequities in CVD mortality among cancer survivors.

Introduction

Cancer survivors are at a higher risk of cardiovascular disease (CVD) than the general population because of cardiotoxicities of cancer treatments,[1,2] shared risk factors or both.[3,4] Most shared risk factors are influenced by social determinants of health.[5,6] Consequently, health inequities in both diseases are likely intertwined and may be exacerbated among those with both conditions.[5,7,8] Prior studies documented considerable Black–White inequities in CVD incidence or mortality among cancer survivors. These studies, however, were focused on inequities among survivors of childhood or adolescent and

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young adult cancers[9–11] or survivors of one type of adult cancer such as breast cancer[12,13] and endometrial cancer.[14,15] Further, although some of these studies have linked health insurance status, education, area-level socio-economic status, rurality and geographic region to CVD incidence or mortality among cancer survivors,[9,11] none of these studies quantified the contribution of each factor to racial inequities. This study aimed to comprehensively examine Black–White inequities in CVD mortality among survivors of 18 adult-onset cancers in the USA and quantify to what extent the effect of race on CVD mortality is mediated by socio-economic and clinical factors.

Methods

Participants included non-Hispanic Black (hereafter, Black) and non-Hispanic White (hereafter, White) persons diagnosed with a malignant cancer at ages 20–64 years during 2007–16 in 17 Surveillance, Epidemiology, and End Results (SEER) registries ($n = 1\,287\,124$), covering 28% of the US population.[16] Exclusion criteria were individuals with a final diagnosis from autopsy or death certificate only ($n = 6119$), unknown cause of death ($n = 3399$), incomplete survival dates ($n = 6476$), <2 months of follow-up ($n = 78\,319$) and missing information for mediator variables ($n = 113\,271$). Additionally, survivors of less common cancers with <20 CVD deaths in either Black or White survivors ($n = 180\,664$) were excluded to produce more stable results, leaving 904 995 survivors of 18 cancer types in the analysis (Supplementary Table S1, available as Supplementary data at *IJE* online).

Exposure

Race (Black vs White) was included as the exposure variable in our causal inference framework (Supplementary Figure S1, available as Supplementary data at *IJE* online) as a surrogate for various forms of racism (institutional, structural, interpersonal) at multiple levels (individual, residential neighbourhood, political jurisdiction, regional economy).[17] Race in SEER is abstracted from medical records, which are either self-reported or data inferred from the provider.[18]

Outcome

Death from CVDs, determined by using the International Classification of Diseases version 10, was included as the outcome. CVDs included heart disease, cerebrovascular disease, hypertension without heart disease, atherosclerosis, aortic aneurysm/dissection and other diseases of arteries, arterioles or capillaries (Supplementary Table S2, available as Supplementary data at *IJE* online).

Covariates and mediators

Demographic factors, including year and age at cancer diagnosis, sex and marital status, were treated as covariates (Supplementary methods, available as Supplementary data at *IJE* online for all variables definitions). A mediator was defined as a variable that is on the causal pathway between the exposure and the outcome. Two domains of candidate mediators considered were socio-economic factors and clinical characteristics. For the socio-economic domain, health insurance (non-Medicaid, Medicaid, uninsured), as well as census tract-level neighbourhood socio-economic status and rurality at the time of cancer diagnosis were included.[19] Neighbourhood socio-economic status (nSES) is a pre-calculated census tract-based composite index that incorporates US Census (1990, 2000) and American Community Survey (2008–12) variables on education index, percent working class, percent unemployment, median household income, median house value, median rent and percent below 150% of poverty line.[19] Each census tract was assigned to a quintile or tertile based on the nationwide distribution of the index. The census tract-level rurality measure was based on the Census Bureau's percent of the population living in non-urban areas using the Urban-Rural Indicator Code: all urban (100% urban), mostly urban (50–99% urban), mostly rural (0–49% urban) and all rural (100% rural) tracts.[20] The last two categories were collapsed due to a smaller number of cases living in mostly rural or all rural areas. For the clinical domain, we included the SEER historic stage (local, regional and distant), tumour subtype (only female breast cancer, hormone receptor subtype) and cancer-directed treatments, including the receipt of surgery (performed, no/refused), chemotherapy (yes, no/unknown) and radiation therapy (yes, none/unknown).

Statistical analysis

Differences in covariates and mediators by race were assessed by using the chi-squared test. Multivariable cause-specific Cox proportional hazards models were used to examine associations of race or each mediator with CVD mortality, adjusting for covariates. Person-years of follow-up were calculated from the date of cancer diagnosis to the date of CVD death or the censoring date of death from non-CVD causes, last vital status date or study termination (31 December 2016), whichever occurred first. Stratified analyses were performed to examine whether the effect of race on CVD death varied by subgroups stratified by mediators. Interactions between race and each mediator were tested using a likelihood ratio test by comparing models with and without an interaction term (one at a time to the model adjusted for covariates) and the strength of the evidence against the null hypothesis (no interaction) was indicated by the *P*-value.[20]

To quantify the extent to which the racial inequities in CVD mortality are mediated by racial differences in candidate mediators, we performed mediation analysis using R 4.1.3 package *mma* (R Group for Statistical Computing).[21,22] A multiple mediation model was conceptualized in which the effect of race is mediated by the association between race and candidate mediators, indirectly contributing to racial inequities in CVD mortality (Supplementary Figure S1, available as Supplementary data at *IJE* online). A separate model was constructed for each cancer type due to the varying applicability of clinical factors (Supplementary Table S3, available as Supplementary data at *IJE* online). The total effect of race, the direct effect of race and the indirect effects of mediators were expressed in absolute and relative terms using coefficients and percentage mediations, respectively, with corresponding CIs calculated from 200 bootstrap re-samplings. Percentage mediation was defined as the coefficient of (in)direct effect divided by the coefficient of the total effect.[21,22] What was estimated as an 'indirect (or mediated) effect' can be interpreted as how the CVD mortality for the Black population would decrease if distributions of potential mediators of the Black population were set to be equal to those of the White population, whereas what was estimated as the 'direct effect of race' can be interpreted as racial inequity that is not through the mediators and would still remain under alternative exposure scenarios.[23] Given the correlation among

Table 1. Characteristics of non-Hispanic Black and non-Hispanic White cancer survivors diagnosed between 2007 and 2016 in 18 Surveillance, Epidemiology, and End Results (SEER) registries

Characteristic	Total ($n = 904\,995$)	Black survivors ($n = 156\,501$)	White survivors ($n = 748\,494$)
Follow-up months, median (IQR)	43 (16–77)	36 (14–70)	44 (17–78)
Cause of death, *n* (%)			
Alive	693 180 (76.6)	110 577 (70.7)	582 603 (77.8)
Cardiovascular diseases	10 701 (1.2)	3018 (1.9)	7683 (1)
Non-cardiovascular diseases	201 114 (22.2)	42 906 (27.4)	158 208 (21.1)
Age (years) at cancer diagnosis, *n* (%)			
20–29	20 504 (2.3)	3341 (2.1)	17 163 (2.3)
30–39	53 952 (6)	9546 (6.1)	44 406 (5.9)
40–49	161 404 (17.8)	29 528 (18.9)	131 876 (17.6)
50–59	399 001 (44.1)	71 272 (45.5)	327 729 (43.8)
60–64	270 134 (29.8)	42 814 (27.4)	227 320 (30.4)
Sex, *n* (%)			
Female	471 009 (52)	77 252 (49.4)	393 757 (52.6)
Male	433 986 (48)	79 249 (50.6)	354 737 (47.4)
Cancer diagnosis years, *n* (%)			
2007–09	279 421 (30.9)	46 137 (29.5)	233 284 (31.2)
2010–12	281 754 (31.1)	48 799 (31.2)	232 955 (31.1)
2013–16	343 820 (38)	61 565 (39.3)	282 255 (37.7)
Marital status, *n* (%)			
Married	536 085 (59.2)	63 778 (40.8)	472 307 (63.1)
Single	182 710 (20.2)	55 162 (35.2)	127 548 (17)
Unmarried	44 195 (4.9)	8950 (5.7)	35 245 (4.7)
Unknown	142 005 (15.7)	28 611 (18.3)	113 394 (15.1)
Insurance, *n* (%)			
Non-Medicaid	759 378 (83.9)	111 982 (71.6)	647 396 (86.5)
Medicaid	108 667 (12)	33 389 (21.3)	75 278 (10.1)
Uninsured	36 950 (4.1)	11 130 (7.1)	25 820 (3.4)
Census tract-level nSES[a], *n* (%)			
Quintile 1 (lowest)	154 810 (17.1)	65 434 (41.8)	89 376 (11.9)
Quintile 2	168 155 (18.6)	34 812 (22.2)	133 343 (17.8)
Quintile 3	180 884 (20)	26 422 (16.9)	154 462 (20.6)
Quintile 4	194 131 (21.5)	18 904 (12.1)	175 227 (23.4)
Quintile 5 (highest)	207 015 (22.9)	10 929 (7)	196 086 (26.2)
Census tract-level rurality[b], *n* (%)			
All urban	575 260 (63.6)	119 482 (76.3)	455 778 (60.9)
Mostly urban	197 580 (21.8)	26 033 (16.6)	171 547 (22.9)
Rural	132 155 (14.6)	10 986 (7)	121 169 (16.2)
Cancer type, *n* (%)			
Female breast	204 789 (22.6)	33 273 (21.3)	171 516 (22.9)
Prostate	151 372 (16.7)	34 855 (22.3)	116 517 (15.6)
Colon and rectum	88 543 (9.8)	17 166 (11)	71 377 (9.5)
Lung and bronchus	83 909 (9.3)	15 295 (9.8)	68 614 (9.2)
Thyroid	53 572 (5.9)	5212 (3.3)	48 360 (6.5)
Head and neck	46 302 (5.1)	6634 (4.2)	39 668 (5.3)
Corpus and uterus, not otherwise specified	43 731 (4.8)	5739 (3.7)	37 992 (5.1)
Kidney and renal pelvis	40 601 (4.5)	6931 (4.4)	33 670 (4.5)
Non-Hodgkin lymphoma	40 236 (4.4)	5708 (3.6)	34 528 (4.6)
Urinary bladder	29 374 (3.2)	2482 (1.6)	26 892 (3.6)
Leukaemia	23 281 (2.6)	3096 (2)	20 185 (2.7)
Pancreas	18 425 (2)	3498 (2.2)	14 927 (2)
Brain and other nervous system	17 001 (1.9)	1504 (1)	15 497 (2.1)
Liver and intrahepatic bile duct	15 861 (1.8)	3674 (2.3)	12 187 (1.6)
Cervix uteri	14 334 (1.6)	2869 (1.8)	11 465 (1.5)
Myeloma	13 229 (1.5)	4169 (2.7)	9060 (1.2)
Stomach	10 451 (1.2)	2629 (1.7)	7822 (1)
Hodgkin lymphoma	9984 (1.1)	1767 (1.1)	8217 (1.1)
Summary stage, *n* (%)			
Localized	479 970 (53)	78 817 (50.4)	401 153 (53.6)
Regional	226 460 (25)	38 869 (24.8)	187 591 (25.1)
Distant	155 418 (17.2)	32 758 (20.9)	122 660 (16.4)
Unstaged[c]	43 147 (4.8)	6057 (3.9)	37 090 (5)
Surgery, *n* (%)			
Performed	618 740 (68.4)	93 834 (60)	524 906 (70.1)
No/refused	286 255 (31.6)	62 667 (40)	223 588 (29.9)

(continued)

Table 1. (continued)

Characteristic	Total ($n = 904\,995$)	Black survivors ($n = 156\,501$)	White survivors ($n = 748\,494$)
Radiation, *n* (%)			
Yes	332 022 (36.7)	56 711 (36.2)	275 311 (36.8)
None/unknown	572 973 (63.3)	99 790 (63.8)	473 183 (63.2)
Chemotherapy, *n* (%)			
Yes	366 622 (40.5)	65 527 (41.9)	301 095 (40.2)
No/unknown	538 373 (59.5)	90 974 (58.1)	447 399 (59.8)

IQR, interquartile range; nSES, neighbourhood socio-economic status.
[a] nSES is a composite index that incorporates US Census (1990, 2000) and American Community Survey (2008–12) variables on education index, percent working class, percent unemployment, median household income, median house value, median rent and percent below 150% of the poverty line. Each census tract was assigned to a quintile based on the nationwide distribution of the nSES index and each individual was linked via census tract of the patient's residence at cancer diagnosis.
[b] The census tract-level rurality measure was based on the Census Bureau's percent of the population living in non-urban areas using the Urban-Rural Indicator Code: all urban (100% urban), mostly urban (50–99% urban), mostly rural (0–49% urban) and all rural (100% rural) tracts. The last two categories have been collapsed due to a smaller number of cases and referred to as 'Rural'.
[c] Includes leukaemia ($n = 23\,281$) and cancers with certain site/year combinations that were not covered by SEER Historic Stage A, including 19 866 head and neck cancer cases for certain subsites from 2004 to 2013.

Table 2. Association between race and the risk of cardiovascular death among cancer survivors by cancer type

Cancer type	Deaths from cardiovascular disease/total number of survivors		Black vs White, hazard ratio (95% CI)[a]
	Black	White	
Brain and other nervous system	40/1504	114/15 497	4.04 (2.79–5.83)
Corpus and uterus, not otherwise specified	351/33 273	766/171 516	2.39 (1.86–3.06)
Female breast	49/2869	86/11 465	2.38 (2.08–2.71)
Pancreas	325/17 166	794/71 377	2.37 (1.69–3.33)
Cervix uteri	85/5739	261/37 992	2.21 (1.54–3.18)
Leukaemia	230/6634	806/39 668	2.20 (1.66–2.91)
Kidney and renal pelvis	22/1767	61/8217	2.09 (1.78–2.44)
Prostate	230/6931	541/33 670	2.08 (1.90–2.28)
Thyroid	66/3096	244/20 185	1.97 (1.36–2.86)
Head and neck	87/3674	181/12 187	1.83 (1.57–2.12)
Liver and intrahepatic bile duct	337/15 295	1166/68 614	1.80 (1.39–2.33)
Non-Hodgkin lymphoma	134/4169	172/9060	1.79 (1.42–2.25)
Myeloma	94/5708	381/34 528	1.75 (1.39–2.21)
Colon and rectum	54/3498	104/14 927	1.73 (1.51–1.97)
Urinary bladder	762/34 855	1244/116 517	1.67 (1.30–2.15)
Hodgkin lymphoma[b]	46/2629	90/7822	1.57 (0.95–2.58)
Stomach[b]	36/5212	163/48 360	1.44 (0.99–2.08)
Lung and bronchus	70/2482	509/26 892	1.30 (1.15–1.47)

[a] Cause-specific Cox proportional hazard models adjusted for sex (female, male), age (20–29, 30–39, 40–49, 50–59, 60–64 years), cancer diagnosis year (2007–09, 2010–12, 2013–16) and marital status (married, single, unmarried, unknown).
[b] Excluded in the subsequent mediation analyses due to wide CIs estimate for hazard ratios.

mediators, the indirect effect was estimated at three levels: individual mediator level, domain level and total.[21] Sensitivity analyses were conducted by calculating the mediational E-values, which provide the minimum required relative risk for the associations of unmeasured confounders with both exposure and outcome to explain away the indirect effects of mediators.[24] All analyses except mediation analysis were performed using SAS 9.4 (SAS Institute Inc.).

Results

During 43 months of median follow-up, 1.9% ($n = 3018$) of Black survivors and 1.0% ($n = 7683$) of White survivors died from CVD (Table 1). Of all survivors, Black survivors were slightly more likely to be men (50.6% vs 47.4%) and younger (20–49 years, 27.1% vs 25.8%) but less likely to be married (40.8% vs 63.1%). Black survivors were also more likely to be uninsured (7.1% vs 3.4%) or Medicaid beneficiaries (21.3% vs 10.1%), to live in socio-economically deprived neighbourhoods ($nSES_{Quintile1}$, 41.8% vs 11.9%) or 'All urban' areas (76.3% vs 60.9%) and to present with distant-stage cancer (20.9% vs 16.4%) and less likely to receive surgery (40% vs 29.9%).

Supplementary Figure S2 and Supplementary Table S4 (available as Supplementary data at *IJE* online) present associations of each socio-economic factor or clinical characteristic with CVD mortality. Adjusting for race and covariates, the risk of CVD mortality was generally higher in survivors who lacked insurance or had Medicaid coverage, resided in socio-economically deprived neighbourhoods or rural areas and were diagnosed with late-stage cancers and did not receive surgery across cancer types (Supplementary Figure S2, available as Supplementary data at *IJE* online). Associations of receipt of chemotherapy or radiotherapy with CVD mortality varied across cancer types and stages (Supplementary Table S4, available as Supplementary data at *IJE* online).

Table 2 presents associations between race and CVD mortality. Adjusting for covariates, the risk of CVD death in

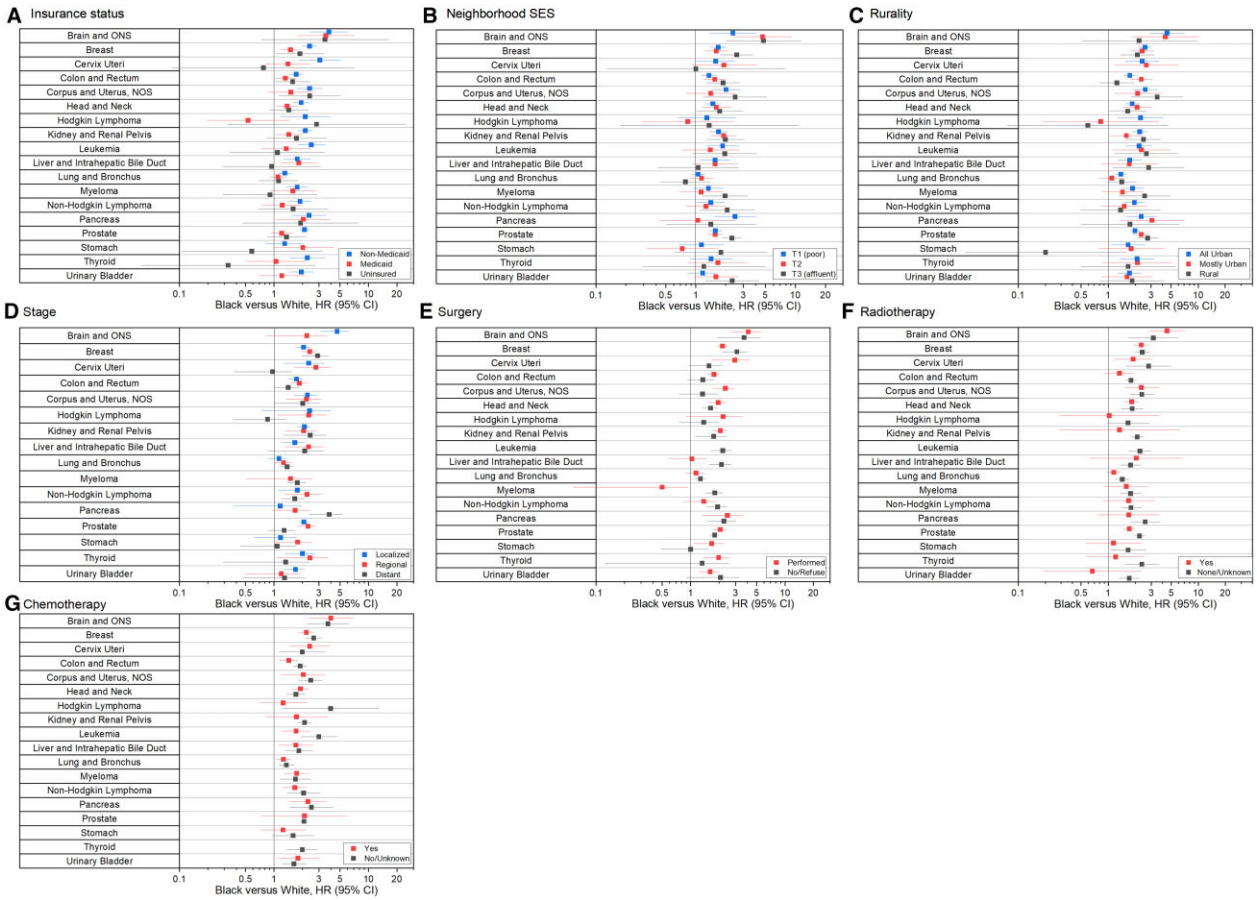

Figure 1. Associations between race and the risk of cardiovascular death among cancer survivors stratified by socio-economic and clinical factors. HR, hazard ratio; ONS, other nervous system; NOS, not otherwise specified. Cause-specific Cox proportional hazard models were adjusted for sex, age (20–29, 30–39, 40–49, 50–59, 60–64 years) and cancer diagnosis year (2007–09, 2010–12, 2013–16) and marital status (married, single, unmarried, unknown). Interactions between race and each mediator were tested using a likelihood ratio test by comparing a model with an interaction term (one at a time to the base model) vs without. For a more stable test, nSES was included as tertiles in the model

Black vs White survivors was higher for all cancers, with the hazard ratios (HRs) ranging from 1.30 (95% CI = 1.15–1.47) for lung cancer to 4.04 (95% CI = 2.79–5.83) for brain and other nervous system (brain) cancer survivors. Although the higher risks of CVD mortality among Black vs White survivors were generally consistent in strata of socio-economic and clinical factors, a few notable variations were found, with the excess risk largest among those with non-Medicaid insurance (prostate, $P_{\text{interaction}} = 0.0002$; breast, $P_{\text{interaction}} = 0.001$), those in the highest tertile of the nSES (prostate, $P_{\text{interaction}} = 0.007$), those diagnosed with a distant-stage cancer (pancreas, $P_{\text{interaction}} = 0.012$) and those who did not receive treatment [surgery (liver), $P_{\text{interaction}} = 0.012$] (Figure 1).

Table 3 and Figure 2 show results from mediation analyses decomposing the total effect of race into the direct effect of race and the indirect effects of race by mediators, expressed as percentage mediations, according to cancer type (Supplementary Table S5, available as Supplementary data at *IJE* online for coefficients). The total indirect effects ranged from 24.8% for brain (95% CI = –5.2–59.6%) to 99.8% for lung (95% CI = 61.0–167%) cancers (Table 3). The direct effect of race after considering the total indirect effects was smaller for cancers of the lung, cervix, urinary bladder, thyroid (range, 0.2–29.7%) or the estimate conferred large CIs for liver cancer, non-Hodgkin lymphoma, leukaemia and myeloma. For the remaining eight cancers, the direct effect of race on CVD mortality ranged from 34.2% (95% CI = 19.3–46.0%) for breast to 55.9% (95% CI = 36.8–67.3) for kidney and 75.2% (95% CI = 40.4–105.2%) for brain cancers.

Per domain level, the indirect effects estimated for socio-economic domain ranged from 24.8% for brain (95% CI = –5.2–59.6%) to 77.8% for lung (95% CI = 46.7–136.1%) cancers (Table 3). The indirect effects by clinical domain were relatively small (range, 2.9–46.1%) with the greatest percentage mediations estimated for cancers of the corpus uteri (46.1%, 95% CI = 34.9–65.8%), cervix (30.1%, 95% CI = 14.8–60.7%) and urinary bladder (28.4%, 95% CI = 16.9–43.2%).

Per individual mediator level, the indirect effect of the nSES ranked first for all but uterine corpus cancer with the percentage mediation ranging from 25.0% for kidney (95% CI = 14.1–36.3%) to 63.5% for lung (95% CI = 36.8–108.7%; Figure 2) cancers. The percentage mediation by insurance ranked second for all but myeloma and liver, pancreatic and cervical cancers, ranging from 12.3% for leukaemia (95% CI = 0.7–46.7%) to 26.4% for breast cancer (95% CI = 19.9–32.9%) and 31.3% for thyroid cancer (95% CI = 10.4–82.7%). Although rurality was associated with higher CVD mortality (Supplementary Figure S2, available as Supplementary data at *IJE* online), it appeared not to mediate the association between race and CVD mortality likely due to the lower likelihood of Black survivors living in rural areas.

Table 3. Relative contribution (percentage mediation, 95% CI)[a,b] of the direct effect of race and the indirect effects of mediators to Black–White inequities in cardiovascular mortality among cancer survivors

Cancer type	Indirect effect of race by mediators (mediated effects)			Direct effect of race, % (95% CI)
	Total, % (95% CI)	Socio-economic domain: insurance, neighbourhood SES, neighbourhood rurality, % (95% CI)	Clinical domain: stage, receipt of surgery, receipt of chemotherapy, receipt of radiotherapy, % (95% CI)	
Lung and bronchus	99.8 (61.0–167.0)	77.8 (46.7–136.1)	27.0 (16.9–43.2)	0.2 (–67.2–38.1)
Cervix uteri	76.1 (47.3–181.4)	59.0 (32.2–156.6)	30.1 (14.8–60.7)	23.8 (–81.5–52.7)
Urinary bladder	71.2 (42.4–142.4)	51.9 (29.1–110.2)	28.4 (11.4–54.1)	28.7 (–42.5–57.6)
Thyroid	70.0 (36.8–151.6)	71.3 (37.0–151.2)	3.5 (–17.6–28.6)	29.7 (–51.6–63.2)
Female breast	65.0 (54.0–80.7)	54.8 (43.9–67.4)	22.4 (15.4–28.7)	34.2 (19.3–46.0)
Non-Hodgkin lymphoma	63.7 (43.1–134.0)	62.1 (40.8–131.1)	2.9 (–1.2–6.8)	36.2 (–34.4–56.8)
Corpus and uterus, not otherwise specified	63.5 (44.7–84.3)	30.0 (11.1–46.1)	46.1 (34.9–65.8)	36.5 (15.7–55.3)
Prostate	59.7 (51.1–71.7)	45.2 (35.0–56.7)	22.5 (18.0–26.8)	40.3 (28.3–48.9)
Head and neck	59.1 (41.7–82.7)	49.9 (33.3–72.6)	13.5 (7.9–19.2)	40.9 (17.3–58.3)
Colon and rectum	57.6 (40.5–82.8)	49.6 (32.8–74.1)	12.6 (7.6–18.7)	42.4 (17.2–59.5)
Liver and intrahepatic bile duct	56.2 (30.9–144.7)	41.0 (13.9–111.0)	18.7 (10.8–40.8)	43.8 (–44.8–69.1)
Leukaemia	49.5 (23.7–118.5)	44.5 (20.3–106.2)	6.0 (1.4–20.7)	50.5 (–18.5–76.3)
Myeloma	48.3 (16.4–119.1)	42.8 (11.5–106.0)	6.3 (0.9–18.4)	51.7 (–19.1–83.6)
Pancreas	44.9 (24.8–83.5)	38.1 (15.5–74.7)	10.3 (3.0–22.4)	55.0 (16.4–75.2)
Kidney and renal pelvis	44.1 (32.7–63.2)	36.9 (24.9–55.1)	12.9 (5.2–22.7)	55.9 (36.8–67.3)
Brain and other nervous system	24.8 (–5.2–59.6)	22.4 (–7.9–60.4)	4.6 (–3.3–12.1)	75.2 (40.4–105.2)

SES, socio-economic status.
[a] The sum of the individual indirect effects may not equal the total indirect effect and can exceed 100% because of correlation and overlapping mediation effects. The indirect effect from one domain (a group of individual mediators) is the change in the Black–White disparity in cardiovascular mortality when the distribution of the domain is assumed to be the same between Black and White cancer survivors, whereas the distribution of the other domain is kept as observed.
[b] Percentage mediation is defined as the coefficient of (in)direct effect divided by the coefficient of the total effect of race. All coefficients and corresponding CIs can be found in Supplementary Table S5 (available as Supplementary data at *IJE* online).

Among clinical factors, >15% of percentage mediations by stage at diagnosis were estimated for cancers of the uterine corpus, urinary bladder, cervix and breast, with the largest percentage mediations for uterine corpus (24%; 95% CI = 4.5–38.1%) and urinary bladder (20.3%; 95% CI = 4.4–37.6%) cancers (Figure 2). Differences in the receipt of surgery were estimated to mediate from 5% to 41% of the racial inequity for 9 of the 16 cancers, with the largest percentage mediations for uterine corpus (41%; 95% CI = 28.0–60.3%), prostate (20.7%; 95% CI = 16.8–25.1%) and lung (17.1%; 95% CI = 11.2–30.8%) cancers. Percentage mediations by the receipt of chemotherapy or radiotherapy were relatively small for all cancer types (<12%) and only notable for lung cancer, liver cancer and leukaemia for the receipt of chemotherapy (5.3–7.4%) and myeloma and breast cancer for radiotherapy (2.5–3.8%) (Figure 2). Percentage mediation by hormone receptor status among breast cancer survivors was 5.8% (95% CI = 3.0–10.1%).

Supplementary Table S6 (available as Supplementary data at *IJE* online) presents the median (interquartile range) of E-values for each mediator, ranging from 1.21 (1.21–1.21) for radiation and 1.32 (1.25–1.48) for chemotherapy to 2.02 (1.70–2.63) for insurance and 2.79 (2.38–4.35) for nSES (Supplementary Table S5, available as Supplementary data at *IJE* online for individual values).

Discussion

In this large population-based study of cancer survivors, Black survivors were more likely than White survivors to die from CVD for all 18 cancers. Inequities in socio-economic factors and clinical characteristics mediated substantial proportions of the racial inequities in CVD mortality with the proportions considerably larger for socio-economic factors than clinical characteristics. Neighbourhood SES and health insurance were identified as the strongest mediators, indicating that social differences in these factors between populations are important mechanistic underpinnings of the observed racial inequities in CVD mortality. These findings underscore the importance of neighbourhood-level interventions and equitable access to care to mitigate the racial inequities in CVD mortality among cancer survivors.

Our findings based on a cancer-type-specific mediation analysis are somewhat different from those from prior studies based on a sequential regression among all cancer sites combined.[9,11] Previous studies concluded that race was independently associated with CVD incidence[9] or mortality[11] among cancer survivors even after adjusting for insurance, area-level SES and/or geography; however, our findings suggest that contributions of each mediator to the racial inequities in CVD mortality differ across various groups of cancer survivors and mediated effects largely explain the excess of CVD mortality among Black survivors of multiple cancers.

Neighbourhood SES was the most important mediator for all cancers but uterine corpus and explained a quarter to over half of the racial inequities in cardiovascular mortality among survivors, suggesting area-level inequalities as the underlying mechanism for the racial inequity in CVD mortality. The largest percentage mediations seen for lung cancer (64%) and cervical (49%) cancer reflect a disproportionate concentration of Black survivors of these cancers residing in the most deprived neighbourhoods compared with their White counterparts ($nSES_{quintile1}$, 53–54% vs 17–20%), which was confirmed by diminished racial inequities in each stratum of nSES, particularly among lung cancer survivors (Figure 1). However, it remains unclear which attributes captured with the nSES

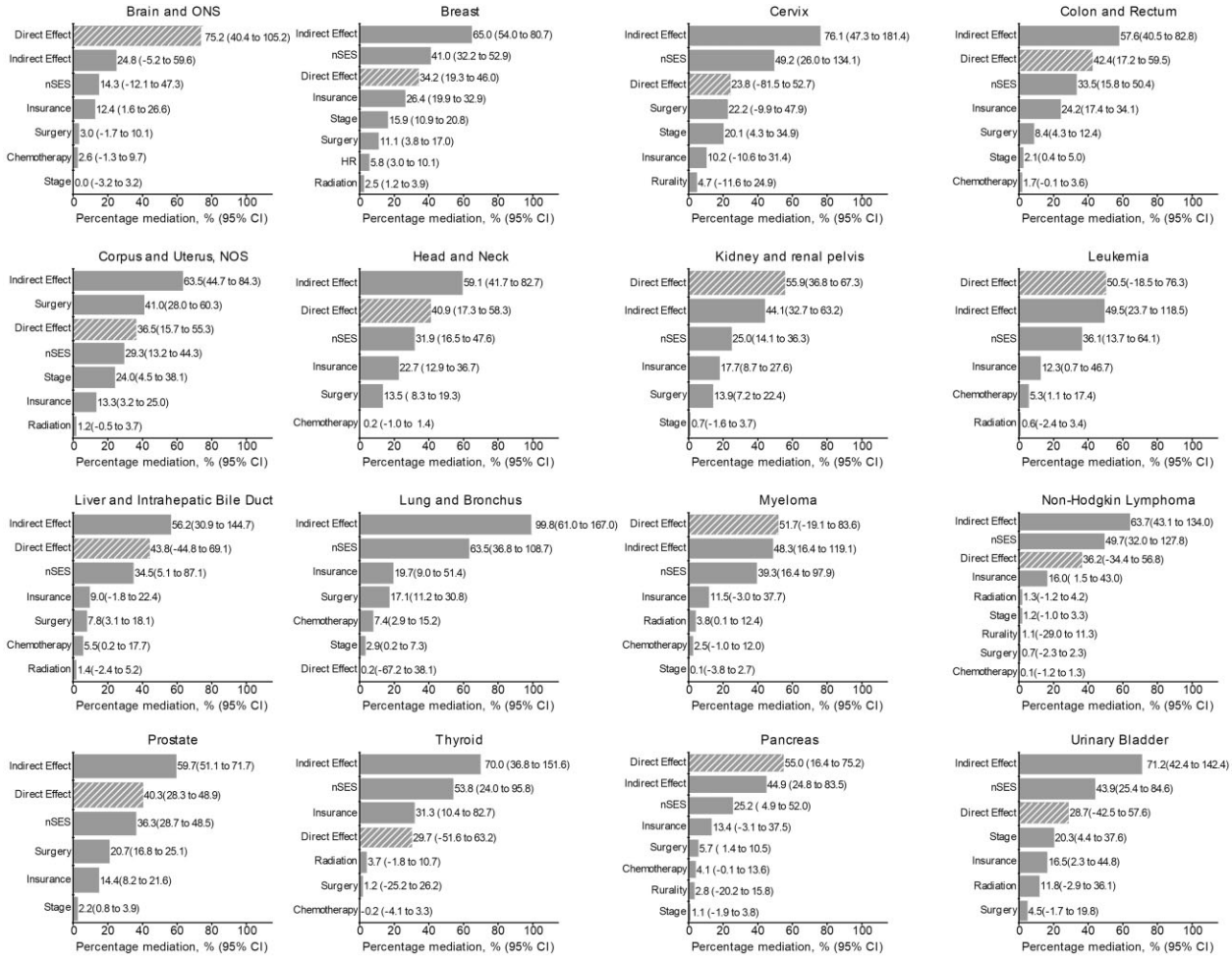

Figure 2. The direct effect of race and the indirect effects of individual mediators on Black–White inequities in cardiovascular mortality among cancer survivors, expressed as percentage mediations (95% CI). nSES, neighbourhood socio-economic status; HR, hormone receptor; ONS, other nervous system; NOS, not otherwise specified. Mediators were defined as follows: health insurance (non-Medicaid, Medicaid, uninsured), nSES (quintiles treated as continuous), rurality (all urban, mostly urban, rural), stage (localized, regional, distant), surgery (yes, no), chemotherapy (yes, no/unknown), radiotherapy (yes, none/unknown). Mediation models were adjusted for sex, age (20–29, 30–39, 40–49, 50–59, 60–64 years) and cancer diagnosis year (2007–09, 2010–12, 2013–16) and marital status (married, single, unmarried, unknown). The sum of the individual indirect effects may not equal the total indirect effect because of correlation and overlapping mediation effects among individual mediators. The indirect effect from an individual mediator is the change in the Black–White disparity in CVD mortality when the distribution of this mediator is assumed to be the same between Black and White cancer survivors, whereas distributions of all other mediators are kept as observed. Percentage mediation is defined as the coefficient of (in)direct effect divided by the coefficient of the total effect of race. All coefficients and corresponding confidence intervals can be found in Supplementary Table S5 (available as Supplementary data at *IJE* online)

measure are most influential, with possible determinants including access to general healthcare resources and specialty care, available means of transportation, built environment, access to green space, food security and environment safety.[6,25–28] Additional research is needed to elucidate the most consequential neighbourhood socio-economic mechanisms contributing to the disparate CVD mortality of cancer survivors.

Health insurance was identified as the second most important mediator, suggesting that efforts to equalize healthcare access are a likely pathway to achieving cardiovascular health equity among cancer survivors. The large percentage mediations estimated for thyroid, breast and colorectal cancers (24.2–31.3%) may reflect the stronger associations between insurance and CVD mortality ($HR_{uninsured\ versus\ non\text{-}Medicaid}$, 1.55–2.43; $HR_{Medicaid\ versus\ non\text{-}Medicaid}$, 2.43–3.66; Supplementary Figure S2, available as Supplementary data at *IJE* online) and the higher proportion of uninsured (5–10% vs 2–5%) or Medicaid beneficiaries (16–23% vs 6–11%) among Black vs White survivors of these cancers. Insurance type or coverage has been associated with the frequency and quality of cardiovascular preventive care and administration of evidence-based therapies for CVDs in various settings;[9,29–32] however, data unique to cancer survivors are limited,[32] highlighting research opportunities on the impact of health insurance on specific elements of healthcare access and delivery in the context of cardio-oncology.

Although the mediated effect by the clinical domain was generally small, it accounted for as high as 23–46% of the racial inequities in CVD mortality for some cancers, including uterine corpus, urinary bladder and prostate, with larger contributions estimated for cancer stage at diagnosis or the receipt of surgery than for the radiotherapy or chemotherapy receipt. Consistently with well-documented racial inequities in stage at diagnosis and treatment patterns,[33] Black survivors of these cancers in this study were more likely than White survivors to present with a distant stage (5.1–15.7% vs 3.2–12.5%) and also less likely to receive surgery (91.5–93.6% vs 96.5–96.9% for uterine corpus and urinary bladder; 45.9%

vs 60.9% for prostate). Reasons for the higher CVD mortality among those with advanced-stage cancers are unclear but may relate to a notion that advanced cancer biology predisposes more frequent hypercoagulable and prothrombotic events, eventually leading to cardiac events.[34] Patients who did not undergo surgery may also likely to carry elevated risks of cardiovascular mortality potentially due to a greater burden of comorbidity[35] and cardiotoxicity from non-surgical therapies.

Despite substantial indirect effects estimated for race through the examined mediators, the direct effect of race remained robust for eight cancers, including colorectum (42%), female breast (34%) and prostate (40%). These remaining proportions can be interpreted as the effect of race, not through nSES, insurance and clinical characteristics, on CVD mortality and represent missed mediations by factors not or inadequately captured by study variables. The tendency for worsening racial inequities among survivors of breast cancer or prostate cancer in privileged neighbourhoods or those with non-Medicaid insurance may also suggest additional pathways at play that can offset the impact of neighbourhood advantages or accessibility to care among Black survivors. A more nuanced and comprehensive understanding of a multitude of cardiovascular risk factors that are disproportionately prevalent among Black individuals is needed to identify means through which the racial inequities in CVD mortality among cancer survivors can be alleviated. These factors may include but are not limited to medical risk factors (e.g. hypertension, diabetes, metabolic syndrome, obesity, renal disease, sleep disorders),[26,27] sociocultural factors such as psychosocial stressors (e.g. anxiety, perceived discrimination)[36,37] and institutionalized and interpersonal racism that impacts patient–provider interactions, decision-making and healthcare utilization.[38]

Besides highlighting nSES and health insurance as mediating mechanisms that drive the racial inequity in CVD mortality among cancer survivors, the findings have implications for clinical guidelines for evaluating cardiovascular risk and prognosis among individuals with a history of cancer. Although it is well established that incorporating social determinants of health screening and interventions into cardiovascular care significantly improves patient outcomes,[6,39] current guidelines concerning cardiovascular health and risk management among cancer survivors mostly omit social determinants of health-informed approaches.[40,41] These guidelines can be updated to incorporate social determinants of health-informed practices and to help providers identify and address their patient's social needs.[6]

This study has several limitations. First, although the analysis is based on 904 995 survivors, the results are with wide CIs particularly for less common cancers because of limited statistical power. Second, causes of death, based on death certificate information, are subject to misclassification. Third, the conceptualized mediation model is inherently constrained by underlying assumptions[22,42] and missed mediations and residual confoundings are likely due to incompleteness and potential misclassification of covariates and mediators (Supplementary Figure S1, available as Supplementary data at *IJE* online). In particular, census tracts and health insurance were obtained at the time of cancer diagnosis and not over the life course, and the long-term effects of neighbourhood exposures and changing insurance coverage were not captured. Similarly, limitations inherent in SEER treatment data—under-ascertainment, lack of detailed treatment regimen and intensity, completion and information beyond the first course of treatment—may also likely result in residual mediations, particularly in consideration of the racial variation reported in subclinical or clinical cardiotoxicities after certain types of cancer treatment.[10,43–45] Furthermore, individual-level SES (e.g. education, income, occupation),[46] cardiovascular risk factors (e.g. lifestyle or behavioural factors, comorbid conditions) and healthcare utilization patterns were unavailable in SEER and their impacts on the observed racial inequities in CVD mortality could not be quantified. Nevertheless, the results from sensitivity analyses suggest that substantial confounding by unmeasured factors (median E-values, 2.02–2.79) are needed to explain away the statistically significant mediations by insurance and nSES, respectively. Of note, E-values for clinical factors were much smaller (median, 1.21–1.45, Supplementary Table S6, available as Supplementary data at *IJE* online), indicating that much less confounding is needed and some of the mediations could simply be due to unmeasured confounding. Fourth, data from SEER registries included in this study cover 28% of the US population, limiting the generalizability of our findings. Finally, this study investigated CVD mortality only among Black survivors in comparison with White survivors, given the historically rooted social stratification between populations and its long-lasting implications for health equity. Future studies are warranted to address existing inequalities in CVD mortality in more diverse populations of cancer survivors,[47] which may benefit from a rigorous causal inference framework that reflects the needs and opportunities unique to specific racial and ethnic populations in the USA.

In conclusion, the neighbourhood-level socio-economic environment, as measured by using a census tract-level composite index, and healthcare access, as measured by using insurance status, explained substantial proportions of the racial inequities in cardiovascular mortality among cancer survivors in the USA, highlighting the intersectionality of race and residential deprivation and barriers to accessing health as underlying pathways to the inequities. A broader structural approach that improves the neighbourhood environment and equalizes access to care may offer effective solutions towards advancing cardiovascular health equity among cancer survivors.

Ethics approval

This study used de-identified, publicly available data and therefore does not require institutional board review.

Data availability

The database is publicly available and can be obtained upon user authentication and request from the Surveillance, Epidemiology, and End Results (SEER) Program in National Cancer Institute (https://seer.cancer.gov/data/).

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

H.S. and A.J. contributed to the conception and design of the study. H.S. and N.H. contributed to data acquisition and analysis. H.S. drafted the article. All authors contributed to the interpretation of data, critical review and editing of the manuscript for important intellectual content and approved the final version to be published.

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Conflict of interest

None declared.

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