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A Prospective Study of Community Mediators on the Risk of Sepsis After Cancer

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Abstract

BACKGROUND—Few studies have examined whether community factors mediate the relationship between patients surviving cancer and future development of sepsis. We determined the influence of community characteristics upon risk of sepsis after cancer, and whether there are differences by race.

METHODS—We performed a prospective analysis using data from the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort years 2003 – 2012 complemented with county-level community characteristics from the American Community Survey and County Health Rankings. We categorized those with a self-reported prior cancer diagnosis as “cancer survivors” and those without a history of cancer as “no cancer history.” We defined sepsis as hospitalization for a serious infection with ≥2 systemic inflammatory response syndrome criteria. We examined the mediation effect of community characteristics on the association between cancer survivorship and sepsis incidence using Cox Proportional hazards models adjusted for age, sex, race, and total number of comorbidities. We repeated analysis stratified by race.

RESULTS—There were 28,840 eligible participants, of which 2860 (9.92%) were cancer survivors, and 25,289 (90.08%) were no cancer history participants. The only observed community-level mediation effects were from income (% mediated 0.07%; natural indirect effect on hazard scale (NIE) = 1.001, 95%CI: 1.000 – 1.005) and prevalence of adult smoking (%

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mediated = 0.21%; NIE = 1.002, 95% CI: 1.000 – 1.004). We observed similar effects when stratified by race.

CONCLUSION—Cancer survivors are at increased risk of sepsis, however this association is weakly mediated by community poverty and smoking prevalence.

Keywords

Socioeconomic Factors; Community SES; Mediation; Sepsis; Cancer; Racial Disparities

1.1 INTRODUCTION

Sepsis is a fatal condition characterized by infection and organ dysfunction, and is more than 200,000 deaths and 750,000 hospitalizations annually.(1–3) A diagnosis of sepsis among cancer patients is associated with up to a two to three-fold risk of mortality, making sepsis a significant, but modifiable, threat to cancer survivorship.(4–6) In addition, there remain both racial and socioeconomic disparities in cancer survival rates, a pattern that resembles the disparities seen in sepsis rates among US adults.(7, 8) We previously observed that geographic and community (county-level) factors such as education, poverty, medical insurance, and unemployment rates are associated with increased mortality rates for sepsis, breast, and lung cancer.(9–11) However, few studies have attempted to examine whether community factors could play as mediators on the relationship between patients surviving cancer and future development of sepsis.

There are possible characteristics such as community-level poverty, race, and healthcare resources that may explain the association between cancer and sepsis. In addition, prior research has consistently shown that greater access to health care and geographic higher socio-economic status (SES) is associated with lower risk of cancer mortality.(12–15) For example Tannenbaum et al (2014) reported that individuals living in communities with the highest SES had a 13% reduced hazard for lung cancer mortality compared to individuals living in impoverished communities.(16) Haas et al. (2008) reported that the mediating role of racial segregation on the association between Black race and adequate breast cancer care was responsible for nearly 10% of the total effect on adequate breast cancer care.(17)

To date, there is limited knowledge on the effect of community characteristics on the association between cancer and sepsis within a well-defined longitudinal cohort of community-dwelling adults.(4–6) The purposes of this study were to identify whether community characteristics mediated the association between cancer survivors compared with participants with no cancer and future risk of sepsis. In addition, we aimed to examine whether there are differences explained by race.

2.1 METHODS

2.1.1 Ethical Statement

REGARDS executive committee and the institutional review boards of participating institutions approved this research study. All participants provided verbal consent before the telephone interview and written informed consent before the in-home study visit.

2.1.2. Study Design & Data Source

We performed a prospective cohort analysis of data obtained from the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort study years 2003 through 2012. The REGARDS cohort is one of the nation's largest ongoing cohorts of community-dwelling adults, i.e., participants considered healthy at study baseline. REGARDS recruited participants between January 2003 and October 2007. At six-month intervals until December 31 2012, REGARDS contacted the participants by telephone to identify any hospitalizations experienced by the participant in the previous six months. The REGARDS cohort includes 30,239 participants aged ≥ 45 years at baseline. The cohort is 45% male, 41% black race, and 69% >60 years old. REGARDS investigators originally designed the study to evaluate the origins for racial and geographic differences in stroke mortality, however REGARDS investigators received additionally funding to identify incident sepsis events during observation period. Further details related to REGARDS study methods are described elsewhere.(18)

2.1.3 Primary Outcome – Community Acquired Sepsis

The primary outcome of this study were first incident sepsis events. In this study we focused on community-acquired sepsis events, and not sepsis events occurring later during hospitalization. Therefore, we utilized vital signs and laboratory findings within the first 28-hours of hospitalization to include Emergency Department care and up to one full day of inpatient care. REGARDS investigators included hospitalization events reported from January 1, 2003 through December 31, 2012. Using the taxonomy of Angus et al (2001), we identified all hospitalizations (Emergency Department visits and/or hospital admission) attributed by participants to a serious infection (i.e., all hospitalizations with a bacterial, fungal, or viral infectious process).(1) We defined a sepsis event as a hospital admission for serious infection with the presence of at least two Systemic Inflammatory Response Syndrome (SIRS) criteria, including heart rate >90 beats/minute, fever (temperature >38.3°C or <36°C), tachypnea (>20 breaths/min) or PCO2<32 mmHg, and leukocytosis (white blood cells >12,000 or <4,000 cells/mm3 or >10% band forms).(1) Initial review of 1,329 hospital records reported exceptional inter-rater consensus for the presence of serious infection (kappa=0.92) and the presence of sepsis (kappa=0.90) at the time of hospital presentation.

2.1.4 Primary Exposure of Interest – Cancer Survivors

Our primary cancer exposure was defined as cancer survivorship at baseline (i.e., participants that reported a history of cancer at baseline). We classified those with a history of cancer as "cancer survivors" and those without cancer as "no cancer history." We identified participants with self-reported cancer survivorship during baseline interview using the following baseline questionnaire: "Have you ever been diagnosed with cancer?" If the participant answered "yes", then they were asked the following follow-up question regarding the date of their last treatment: "Have you been treated with chemotherapy or radiation in the past two years?" If the participant had been treated within past two years, REGARDS investigators excluded from participation in the study due to focus on community-dwelling (i.e., otherwise healthy) participants. Further, participants defined as cancer survivors at baseline were those that had cancer remission for at least two years before entrance into

REGARDS cohort. Prior studies have reported that self-reported cancer survivorship status in prospective cohort studies to have sensitivity excellent values of 0.90 and positive predictive values of 0.75.(19)

2.1.5 Mediators – County-Level Community Characteristics

We obtained county-level community characteristics from the 2014 County Health Rankings (CHR) and the 2010 American Community Survey (ACS) available through the National Historical Geographic Information System (NHGIS).(20, 21) We geocoded these data to each REGARDS participant using each participant's baseline home address Federal Information Processing Standards (FIPS) code. The ACS and CHR consist of nationally representative data collected from a sample of the total non-institutionalized population over 18 years of age living in households. The ACS 2010 provides demographic information for each county for 2006–2010.(22, 23) The CHR 2014 provides county-level characteristics for each county aggregated for years 2008 – 2012). We determined community characteristics for this study based on publicly available variables that characterize county-level socioeconomic status, healthcare availability, and health promotion. From the ACS we obtained median household income, percentage of the population completing college, percentage of the population below the poverty line, percentage of population without medical insurance coverage, percentage of urban population, and number of active medical doctors per 100,000 persons. From the CHR we included county-level proportions of adult obesity, smoking, those who could not see doctor due to cost, limited access to healthy foods, mammography screening, and access to exercise opportunities. For all statistical models for mediation analysis we standardized continuous variables by dividing by the study population standard deviation. Detailed descriptions of county-level characteristics are described in Supplemental Table 1.

2.1.6 Participant Characteristics

We analyzed self-reported baseline demographic variables that included age, race, sex, household income, education, and geographic region. Health behaviors included tobacco, and alcohol use. We defined alcohol use as moderate (one drink per day for women or two drinks per day for men) and heavy alcohol use (>1 drink per day for women and >2 drinks per day for men), per the National Institute on Alcohol Abuse and Alcoholism classification.(24) We analyzed the following self-reported medical conditions obtained during REGARDS investigators baseline interview including atrial fibrillation, chronic lung disease, coronary artery disease, deep vein thrombosis, diabetes, dyslipidemia, hypertension, myocardial infarction, obesity, peripheral artery disease, and stroke. We additionally created an individual level comorbidity score based on the sum of total number of baseline medical conditions, and those with missing information for an individual medical conditions were included as having no presence of a medical condition. We analyzed participant baseline biomarkers (high sensitivity C-reactive protein, albumin-creatinine ratio (ACR), and Cystatin-C) and medication usage (chronic use of aspirin, statins, and steroids). We additionally provide detailed information regarding participant characteristics in Supplemental Table 2.

2.1.7 Statistical Analysis

We compared differences in demographic, substance use, comorbidities, medications, biomarkers, community county-level characteristics, and sepsis incidence between cancer survivors and no cancer history participants using Chi-square, ANOVA, and Wilcoxon rank-sum tests as appropriate. We presented both the incidence rates of sepsis by cancer group and hazard for sepsis after cancer comparing cancer survivors to participants with no cancer history. We calculated the mean survival times and associated 95% confidence limits using the product-limit method of the Kaplan-Meier survival estimator. We estimated the hazard ratios (HRs) and associated 95% confidence intervals using Cox proportional hazard models. We a priori decided to adjusted models for age, sex, race, and comorbidity score. However, in additional sensitivity analysis we further adjusted all models for biomarkers and medications significant in bivariate analysis (i.e., ACR, cystatin-C, and aspirin use). In additional sensitivity, we excluded participants with cancer-related deaths within the first three years in attempt to account for REGARDS participants with diagnosis of severe and malignant cancers during early follow-up.

2.1.8 Mediation Analysis

The objective of our analysis was to test for the mediation effect of county-level community characteristics on the association between cancer and sepsis risk. We examined the mediating effects of county-level community characteristics (i.e., poverty, adult obesity prevalence, access to exercise opportunities) on the association between cancer survivorship and risk of sepsis using Cox proportional hazard models. We determined the mediating effects of community characteristics on the association between cancer and sepsis risk using SAS macros for mediation with survival data developed by Valeri and VanderWeele (2015). (25, 26) We presented results from mediation analysis as the 1) natural direct effects (NDE) (i.e., the effect of cancer on sepsis outcome not through the mediator controlling for confounders), 2) natural indirect effect (NIE) (i.e., the effect of cancer on sepsis outcome through the mediator), 3) total effects (i.e., total association between cancer and sepsis risk), 4) and proportions mediated (i.e., the percent of the total association (on the log hazard scale) that was mediated by community characteristics). We present the direct and indirect effects as the hazard ratios (HRs) and associated 95% confidence intervals, determined using bootstrapping technique with 500 resamples and with replacement.(25, 26) We calculated the proportion mediated on the log hazard scale using the formula $1 - (\ln HR_{nde}/\ln HR_{total})$ where *nde* represents the natural direct effect and total represents total effect.(25, 26) We additionally stratified mediation models by race to determine whether there are any differences in mediation possibly attributed to effect modification of race. We used Stata version 13 and SAS version 9.4 for all statistical analyses.

3.1 RESULTS

3.1.1 Baseline Participant Characteristics

Among 30,239 REGARDS participants, we excluded 1,399 due to missing exposure and outcome date, corresponding to a total of 28,840 participants included in study analysis (Supplemental Figure 1). Among the study participants 2860 (9.92%) were categorized as cancer survivors, and 25,980 (90.08%) were categorized as no cancer history participants.

We compared cancer survivors and no cancer history participants (Table 1), and cancer survivors had older age, were more likely male, more likely to have White race. Additionally, cancer survivors were more likely to have income less than $20,000 per year, reside in the Stroke Belt, and less likely to be current tobacco users. Cancer survivors had a greater prevalence of atrial fibrillation, chronic lung disease, coronary artery disease, deep vein thrombosis, hypertension, myocardial infarction, stroke, and higher total number of comorbidities when compared with participants with no cancer history (p values <0.01). Cancer survivors had higher baseline Cystatin-C, ACR levels, and more likely to be chronic users of aspirin at baseline.

When comparing distributions of community characteristics by cancer survivorship status, cancer survivors were less likely to reside in communities were the population was uninsured (18.75% vs. 18.95%, p = 0.02) and could not visit doctor in the past year due to cost (14.99% vs. 15.23%, p = 0.01). When limited to Black participants, cancer survivors resided in communities with higher median household income (Mean (SD): $43,850 (12,137) vs. $42,317 (11,079), p value <0.01, Table 2), greater proportions of adults with a college education (18.92% vs. 18.15%, p value <0.01), less poverty (16.27% vs. 17.02%, p value <0.01), lower proportion of uninsured population (18.11% vs. 18.80%, p value <0.01), greater urbanicity (50.07% vs. 47.11%, p value <0.01), and greater access to exercise activities (79.26% vs. 75.84%, p value <0.01). When limited to White participants, we observed no differences in community characteristics between cancer survivors and participants with no cancer history.

3.1.2 Mediation Results

Cancer survivors were more likely to develop sepsis (12.66% vs. 3.81%, p value <0.01) when compared to participants with no cancer history (HR: 2.63, 95% CI: 2.32 – 2.98). We examined whether community county-level characteristics mediated the association between cancer survivorship and risk of sepsis, while controlling for age, sex, race, and total number of comorbidities. We present the mediation figure in Supplemental Figure 2. Among 1351 total sepsis events from years 2003 through 2012, only median household income (percent mediated on log-hazard scale = 0.07%; natural indirect effect (NIE) = 1.001, 95% CI: 1.000 – 1.005) and prevalence of adults smoking tobacco (% mediated = 0.21%; NIE = 1.002, 95% CI: 1.000 – 1.004) were mediators on the association between cancer and sepsis risk.

Similarly, when limited to the 457 sepsis events among Blacks, only median household income (% mediated = 0.06%; NIE = 1.001, 95% CI: 1.000 – 1.004) and prevalence of adults smoking (% mediated = 0.30%; NIE = 1.003, 9%% CI: 1.001 – 1.005) were mediating effects on the association between cancer and sepsis, after adjustments for sex, age, and total number of comorbidities (Table 4). Likewise, when limited to the 894 sepsis events among White participants, only median household income (% mediated = 0.06%; NIE = 1.001, 95% CI: 1.000 – 1.004) and prevalence of adults smoking (% mediated = 0.30%; NIE = 1.003, 9%% CI: 1.001 – 1.005) were mediating effects on the association between cancer and sepsis (Table 5).

In additional analysis we performed all analyses further adjusted for baseline biomarkers and medications, and results were very similar to those derived from main analyses

(Supplemental Tables 3 through 5). Results were similar when excluding REGARDS participants that died from cancer-related causes within three years of follow-up (Supplemental Table 6).

4.1 DISCUSSION

In the REGARDS cohort, we examined whether community characteristics mediated the association between cancer survivorship and future risk of sepsis episodes. Cancer survivors were at more than a two-fold increased risk of sepsis when compared with their no cancer history counterparts even after controlling for age, sex, race, and total number of comorbidities. We observed that community-level income and adult smoking prevalence were the only potential mediators; however, they accounted for no more than a one percent of the mediation effect on the association between cancer survivorship and risk of sepsis, after controlling for confounders. We observed similar trends when stratified by race, though of note Black cancer survivors lived in communities of higher SES and access to exercise opportunities when compared to participants with no cancer history.

To our knowledge, this is first prospective analysis to examine whether community-level characteristics mediate the association between cancer survival and sepsis risk. It is biologically plausible that cancer survivors could have an elevated risk of sepsis due to two possible mechanisms; 1) underlying pathology of cancer and mutagenic cells causing a chronic inflammatory state, and/or 2) more necrotic and degraded neighboring tissues of cancerous cells due to radiation and chemotherapy. In both of these cases, it is possible that these events would lead cancer survivors to having more compromised immune functioning that would in turn increase their long-term risks for infection. While prior cross-sectional studies report infections as common complications among cancer patients, there exists limited epidemiologic evidence to support long-term sepsis risk among cancer survivors.(27, 28) We further postulated that community-level factors would have an effect on the risk of sepsis based on results from our prior study examining the association between sepsis “clusters” (hot spot areas for sepsis mortality at the county-level) and community level factors.(9) In this prior study, we observed three significant clusters of higher sepsis mortality located in the southern United States; Middle Georgia, the Mississippi Valley, and Central Appalachia.(9) Further, we discovered that these sepsis clusters were characterized by lower education, income, employment, insurance and racial demography.(9) Likewise, a large observational study performed by Mendu et al. (2012) among more than 14,000 patients observed that higher neighborhood poverty (poverty >40% vs. <5% at the census tracts level) were associated with up to a 49% increased risk of infection.(29) Nevertheless, our results did not observe that sepsis risk after cancer was mediated or associated with community-level factors to a large degree.

One of the goals of this study was to identify whether cancer survivors living in poorer communities were at higher risk of sepsis. Overall there was not much difference between cancer survivors and participants with no cancer history. However, we observed slight differences in community characteristics among Black participants. Moreover, Black cancer survivors were more likely to live in higher SES communities and within communities with greater prevalence of exercise opportunities (i.e., gymnasiums and fitness clubs within half

of a mile of residence) when compared to Black participants with no cancer history. This could be explained by three of many possible phenomena: 1) Black participants from higher SES communities were more likely to get screened for cancer and therefore became cancer survivors, 2) Black cancer survivors were more likely to relocate to higher SES communities with greater access to healthy foods, gyms, and health conscious neighbors, and/or 3) Black cancer survivors were simply more likely to live in urban areas, and thus have greater access to exercise and cancer screening due to proximity of health-associated resources.

There are conflicting reports on the effect of neighborhood and community SES on cancer survival. Both poverty and lower SES are multidimensional circumstances that are derived from multi-level factors such as personal achievements, and more importantly systematic infrastructure and availability of opportunities – also known as equity. Several studies suggest that there are varying effects of neighborhood SES, and/or access to healthcare on cancer survival.(14, 15, 30–32) For instance, Jones et al (2015) reported that among 275 Black breast cancer survivors, those living in communities with a higher number of renters were less likely to perform physical activity compared with those living in communities with higher number of home owners.(31) Further, Jones et al (2015) alluded to the notion that the potential for constant residential turnover (via rentership) decrease physical activity levels in cancer survivors even when access to exercise opportunities (i.e., gyms and fitness clubs) are available.(31) Overall, while our study results did not find many strong effects of community poverty on sepsis risk after cancer, cancer survivors were still at an increased risk of sepsis infection while living in very similar communities as participants with no cancer history, suggesting a need for primary prevention efforts for sepsis among cancer survivors.

4.1.1 Limitations

There are a few points that one must consider when interpreting these data. While we are one of the first large cohort studies to examine the risk of sepsis following cancer survival, we must note that our sample were not originally designed to survey cancer survivors or sepsis outcomes. As a result, we may have underestimated the true number of cancer survivors, sepsis events, and we were unable to disentangle specific prior cancer types. Cancer is heterogeneous and complex disease with different pathological responses and courses of treatment. However, because we categorized our cancer exposure status and sepsis outcomes using strategies independent and mutually exclusive of one another, there is no evidence to suggest that our information biases lead to differential misclassification. Secondly, we did not account for prior cancer therapies such as radiation, chemotherapy, and surgical treatments. It is likely that certain cancers such as hematological malignancies, or more intense cancer therapeutics caused greater risk of septic episodes. Nonetheless, it is because of this plausible cascade of events (i.e., cancer malignancy, treatment potency, and patient susceptibility) that we examined the association between cancer survivorship and sepsis. A future study aiming to disentangle the individual risks of specific cancers on sepsis would provide further insight to possible interventions. Further, we used county-level characteristics based on baseline home address to approximate a participant's surroundings and community environment. Thus, there is potential for information biases and misclassification as REGARDS participants could have relocated to a different address with varying community characteristics during study follow up.

4.1.2 Conclusion

In the REGARDS cohort, cancer survivors were at an increased risk of sepsis; however, community factors were not major effects along the pathway between cancer and risk sepsis. Personal and clinical factors may explain differences in sepsis risk between cancer survivors and those with a history of cancer. Nevertheless, while the current study did not observe major contributions of community factors, geographic disparities persist in both cancer and sepsis outcomes. Future efforts should take into account more granular measurements when defining a patient's community, and thus their area-level exposure to health risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Comparison of demographic, substance use, comorbidity characteristics, and sepsis incidence by cancer survivorship status. Among 28,840 REGARDS participants.

	Cancer Survivors (N = 2860)	No Cancer History (N = 25,980)	
	N (%) or Mean (SD)[1]	N (%) or Mean (SD)[1]	*p* value[2]
Age, Mean (SD)	69.61 (8.64)	64.35 (9.35)	<0.01
Male Gender	1621 (56.68)	11278 (43.41)	<0.01
Race			
Black	864 (30.21)	10920 (42.03)	<0.01
White	1996 (69.79)	15060 (57.97)	
< High School Education	370 (12.94)	3202 (12.32)	0.02
Income ≤ $20 000	524 (18.32)	4656 (17.92)	<0.01
Stroke Belt Residence	1036 (36.22)	8971 (34.53)	<0.01
Current Tobacco Use	311 (10.87)	3837 (14.77)	<0.01
Heavy Alcohol Use	103 (3.60)	1066 (4.10)	0.03
Baseline Medical Condition			
Atrial fibrillation	323 (11.52)	2140 (8.43)	<0.01
Chronic lung disease	308 (10.77)	2345 (9.03)	<0.01
Coronary artery disease	675 (24.04)	4390 (17.22)	<0.01
Chronic kidney disease	326 (11.40)	2822 (10.86)	0.38
Deep vein thrombosis	224 (7.84)	1280 (4.95)	<0.01
Diabetes	659 (23.09)	5820 (22.48)	0.46
Dyslipidemia	1691 (61.63)	14787 (59.07)	0.01
Hypertension	1801 (63.13)	15201 (58.66)	<0.01
Myocardial infarction	486 (17.31)	3125 (12.26)	<0.01
Obesity	1453 (50.88)	13917 (53.66)	0.01
Peripheral artery disease	81 (2.83)	558 (2.15)	0.02
Stroke	252 (8.85)	1578 (6.09)	<0.01
Comorbidity Score[1], Mean (SD)	2.27 (1.58)	1.97 (1.48)	<0.01
Biomarkers, Median (P25, P75)‡			
hs-CRP mg/dL	2.13 (0.97, 4.85)	2.22 (0.95, 5.05)	0.32
ACR mcg/mg	7.74 (4.83, 18.67)	7.35 (4.62, 15.68)	<0.01
Cystatin-C mg/dL	0.98 (0.85, 1.18)	0.94 (0.82, 1.11)	<0.01
Baseline Medication Use			
Aspirin	1357 (47.45)	11140 (42.88)	<0.01
Statins	942 (32.94)	8172 (31.45)	0.11
Steroids	112 (3.92)	888 (3.42)	0.17
Community Variables[1], Mean (SD)			
Median household income	42803 (11237)	42690 (11448)	0.25
% Completed college	18.65 (8.43)	18.48 (8.42)	0.24
% Below poverty line	16.78 (6.56)	16.93 (6.50)	0.13

	Cancer Survivors (N = 2860)	No Cancer History (N = 25,980)	
	N (%) or Mean (SD)[1]	N (%) or Mean (SD)[1]	*p* value[2]
% Uninsured	18.75 (4.84)	18.95 (4.55)	0.02
% Unemployed	5.41 (1.69)	5.41 (1.64)	0.62
% Urban	46.96 (29.33)	46.69 (29.15)	0.66
Medical Doctors[3]	1.49 (11.92)	1.58 (11.96)	0.98
% Adult smoking	18.95 (4.67)	18.80 (4.92)	0.08
% Adult obesity	30.08 (4.93)	30.19 (5.21)	0.14
% Mammography screening	62.89 (5.75)	62.60 (5.92)	0.11
% Exercise access	72.17 (23.63)	71.32 (24.23)	0.20
% Could not see doctor due to cost	14.99 (4.37)	15.23 (4.44)	0.01
% Limited access to healthy foods	6.79 (3.95)	6.87 (4.20)	0.80

[1] Mean (Standard deviation) or Median (interquartile range)

[2] Estimated using $\chi 2$, ANOVA, and Wilcoxon rank-sum tests.

[3] Ratio per 100,000 persons.

Biomarkers presented as median and 25^{th} and 75^{th} percentiles.

hs-CRP: high sensitivity C-reactive protein, ACR: albumin-creatinine ratio

Table 2.

Bivariate analysis of community characteristics by cancer survivorship status. Among 28,840 REGARDS participants, stratified by race/ethnicity.

	Blacks (N = 11,784)			Whites (N = 17,056)		
	Cancer Survivor (N = 864)	No Cancer History (N = 10,920)	*p* value[2]	Cancer Survivor (N = 1,996)	No Cancer History (N = 15,060)	*p* value[2]
Community Variables[1], Mean (SD)						
Median household income	43,850 (12,137)	42,317 (11,079)	<0.01	42,350 (10,796)	42,960 (11,701)	0.17
% Completed college	18.92 (8.32)	18.15 (8.05)	<0.01	18.53 (8.48)	18.72 (8.68)	0.37
% Below poverty line	16.27 (6.92)	17.02 (6.51)	<0.01	17.01 (6.39)	16.86 (6.49)	0.24
% Uninsured	18.11 (4.86)	18.80 (4.59)	<0.01	19.02 (4.80)	19.06 (4.51)	0.99
% Unemployed	5.60 (1.77)	5.52 (1.68)	0.40	5.33 (1.64)	5.33 (1.60)	0.67
% Urban	50.07 (27.99)	47.11 (28.49)	<0.01	45.61 (29.79)	46.39 (29.62)	0.28
Medical Doctors[3]	0.72 (0.19–7.07)	0.77 (0.15–8.75)	0.47	1.95 (0.36–13.38)	2.27 (0.38–3.63)	0.20
% Adult smoking	18.63 (4.32)	18.54 (4.60)	0.43	19.08 (4.81)	18.99 (5.12)	0.36
% Adult obesity	30.28 (5.28)	30.33 (5.49)	0.70	29.99 (4.77)	30.08 (4.99)	0.28
% Mammography screening	61.32 (5.02)	61.67 (5.51)	0.03	63.57 (5.92)	63.28 (6.11)	0.24
% Exercise access	79.26 (23.12)	75.84 (24.90)	<0.01	69.10 (23.19)	68.04 (23.43)	0.06
% Could not see doctor due to cost	15.49 (3.96)	15.61 (3.99)	0.57	14.78 (4.53)	14.96 (4.71)	0.13
% Limited access to healthy foods	6.42 (4.23)	6.65 (4.44)	0.25	6.95 (3.82)	7.04 (4.01)	0.78

[1]Mean (Standard deviation)

[2]Estimated using ANOVA or Wilcoxon rank-sum tests.

[3]Ratio per 100,000 persons, presented as Median (interquartile range)

Table 3:

Mediating effects [1] of community characteristics on association between cancer survivors and incidence of first sepsis event. Among 28,840 REGARDS participants with 1351 total sepsis events.

	Natural Indirect Effect[2] (Mediation Effect)		Natural Direct Effect[3]		Percent Mediated[4] (%) (Log Hazard Scale)
	HR	95% CI[5]	HR	95% CI[5]	
Mediators					
Median household income	1.001	1.000 – 1.005	2.743	2.507 – 3.082	0.07%
% Completed college	1.000	0.999 – 1.001	2.745	2.512 – 3.082	0.00%
% Below poverty line	0.999	0.998 – 1.002	2.745	2.505 – 3.089	-
% Uninsured	0.998	0.996 – 1.000	2.748	2.512 – 3.089	-
Unemployment rate	0.999	0.999 – 1.001	2.745	2.515 – 3.081	-
% Urban	0.999	0.998 – 1.002	2.747	2.508 – 3.088	-
Medical Doctors[6]	0.998	0.997 – 0.999	2.751	2.519 – 3.082	-
% Adult smoking	1.002	1.000 – 1.004	2.740	2.516 – 3.079	0.21%
% Adult obesity	1.000	0.998 – 1.002	2.745	2.522 – 3.082	0.00%
% Mammography screening	0.999	0.998 – 1.001	2.747	2.513 – 3.080	-
% Exercise access	0.997	0.993 – 0.998	2.753	2.533 – 3.079	-
% Could not see doctor due to cost	0.999	0.998 –1.000	2.746	2.510 – 3.083	-
% Limited access to healthy foods	0.999	0.995 – 1.000	2.747	2.526 – 3.081	-

	Total Effect (Risk of Sepsis)		
	No. Sepsis Events (%)	Mean Survival Time (95% CI) [7]	Hazard Ratio (95% CI) [8]
Cancer Survivors	362 (12.66)	8.56 (8.49 – 8.64)	2.63 (2.32 – 2.98)
No Cancer History	989 (3.81)	9.19 (9.17 – 9.20)	Ref

[1] Models adjusted for age, sex, race, and comorbidity score.

[3] Natural Direct Effect (i.e., the effect of the cancer on sepsis incidence *NOT through* mediator)

[4] Percent Mediated = Percent of the total association between the cancer and sepsis incidence that was mediated on the log hazard scale.

[5] Confidence intervals estimated using 500 bootstrapped resamples.

[6] Ratio per 100,000 persons.

[7] Mean survival time in years.

[8] Estimated from Cox proportional hazards model - Percent mediated calculated to be <0%

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Table 4:

Mediating effects [1] of community characteristics on association between cancer survivors and incidence of first sepsis event. Among 11,430 Blacks with 457 incident sepsis events.

	Natural Indirect Effect[2] (Mediation Effect)		**Natural Direct Effect[3]**		**Percent Mediated[4] (%) (Log Hazard Scale)**
	HR	**95% CI[5]**	**HR**	**95% CI[5]**	
Mediators					
Median household income	1.001	1.000 – 1.004	2.781	2.517 – 3.101	0.06%
% Completed college	1.000	0.999 – 1.001	2.783	2.522 – 3.102	0.01%
% Below poverty line	1.000	0.998 – 1.002	2.782	2.514 – 3.108	-
% Uninsured	0.999	0.997 – 1.000	2.785	2.522 – 3.108	-
Unemployment rate	1.000	0.999 – 1.001	2.784	2.525 – 3.100	0.00%
% Urban	0.999	0.998 – 1.002	2.785	2.518 – 3.106	-
Medical Doctors[6]	0.998	0.997 – 0.999	2.789	2.528 – 3.101	-
% Adult smoking	1.003	1.001 – 1.005	2.776	2.523 – 3.096	0.30%
% Adult obesity	0.999	0.998 – 1.002	2.783	2.532 – 3.101	-
% Mammography screening	0.999	0.996 – 1.001	2.786	2.525 – 3.097	-
% Exercise access	1.000	0.998 – 1.001	2.781	2.531 – 3.088	0.01%
% Could not see doctor due to cost	0.999	0.998 – 0.999	2.784	2.522 – 3.103	-
% Limited access to healthy foods	0.999	0.996 – 1.001	2.784	2.534 – 3.101	-

	Total Effect (Risk of Sepsis)		
	No. Sepsis Events (%)	**Mean Survival Time (95% CI) [7]**	**Hazard Ratio (95% CI) [8]**
Cancer Survivors	95 (11.00)	8.14 (8.02 – 8.26)	2.80 (2.22 – 3.53)
No Cancer History	362 (3.32)	9.21 (9.19 – 9.24)	Ref

[1] Models adjusted for age, sex, and comorbidity score.

[2] Natural Indirect Effect (i.e., the effect of the cancer on sepsis incidence *through* the mediator)

[3] Natural Direct Effect (i.e., the effect of the cancer on sepsis incidence *NOT through* mediator)

[4] Percent Mediated = Percent of the total association between the cancer and sepsis incidence that was mediated on the log hazard scale.

[5] Confidence intervals estimated using 500 bootstrapped resamples.

[6] Ratio per 100,000 persons.

[7] Mean survival time in years.

[8] Estimated from Cox proportional hazards model - Percent mediated calculated to be <0%

Table 5:

Mediating effects [1] of community characteristics on association between cancer survivors and incidence of first sepsis event. Among 16,632 White participants with 894 incident sepsis events.

	Natural Indirect Effect[2] (Mediation Effect)		Natural Direct Effect[3]		Percent Mediated[4] (%) (Log Hazard Scale)
	HR	**95% CI†**	**HR**	**95% CI†**	
Mediators					
Median household income	1.001	1.000 – 1.004	2.781	2.517 – 3.101	0.06%
% Completed college	1.000	0.999 – 1.001	2.783	2.522 – 3.102	0.01%
% Below poverty line	1.000	0.998 – 1.002	2.782	2.514 – 3.108	-
% Uninsured	0.999	0.997 – 1.000	2.785	2.522 – 3.108	-
Unemployment rate	0.999	0.999 – 1.001	2.784	2.525 – 3.100	0.00%
% Urban	0.999	0.998 – 1.002	2.785	2.518 – 3.106	-
Medical Doctors[6]	0.999	0.997 – 0.999	2.789	2.528 – 3.101	-
% Adult smoking	1.003	1.001 – 1.005	2.776	2.523 – 3.096	0.30%
% Adult obesity	0.999	0.998 – 1.002	2.783	2.532 – 3.101	-
% Mammography screening	0.999	0.996 – 1.000	2.786	2.525 – 3.097	-
% Exercise access	1.000	0.998 – 1.001	2.781	2.531 – 3.088	0.01%
% Could not see doctor due to cost	0.999	0.998 – 0.999	2.784	2.522 – 3.103	-
% Limited access to healthy foods	0.999	0.996 – 1.001	2.784	2.534 – 3.101	-

	Total Effect (Risk of Sepsis)		
	No. Sepsis Events (%)	**Mean Survival Time (95% CI)** [7]	**Hazard Ratio (95% CI)** [8]
Cancer Survivors	267 (13.38)	8.52 (8.43 – 8.62)	2.54 (2.20 – 2.95)
No Cancer History	627 (4.16)	8.82 (8.80 – 8.84)	Ref

[1] Models adjusted for age, sex, and comorbidity score.

[2] Natural Indirect Effect (i.e., the effect of the cancer on sepsis incidence *through* the mediator)

[3] Natural Direct Effect (i.e., the effect of the cancer on sepsis incidence *NOT through* mediator)

[4] Percent Mediated = Percent of the total association between the cancer and sepsis incidence that was mediated on the log hazard scale.

[5] Confidence intervals estimated using 500 bootstrapped resamples.

[6] Ratio per 100,000 persons.

[7] Mean survival time in years.

[8] Estimated from Cox proportional hazards model - Percent mediated calculated to be <0%