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A prospective study of cancer survivors and risk of sepsis within the REGARDS cohort

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ABSTRACT

Background: Hospitalized cancer patients are nearly 10 times more likely to develop sepsis when compared to patients with no cancer history. We compared the risk of sepsis between cancer survivors and no cancer history participants, and examined whether race was an effect modifier.

Methods: We performed a prospective analysis of data from the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort. We categorized participants as "cancer survivors" or "no cancer history" derived from self-reported responses of being diagnosed with any cancer, excluding non-melanoma skin cancer. We defined sepsis as hospitalization for a serious infection with ≥2 systemic inflammatory response syndrome criteria. We performed Cox proportional hazard models to examine the risk of sepsis after cancer (adjusted for socio-demographics, health behaviors, and comorbidities), and stratified by race.

Results: Among 29,693 eligible participants, 2959 (9.97%) were cancer survivors, and 26,734 (90.03%) were no cancer history participants. Among 1393 sepsis events, the risk of sepsis was higher for cancer survivors (adjusted HR: 2.61, 95% CI: 2.29–2.98) when compared to no cancer history participants. Risk of sepsis after cancer survivorship was similar for Black and White participants (p value for race and cancer interaction = 0.63).

Conclusion: In this prospective cohort of community-dwelling adults we observed that cancer survivors had more than a 2.5-fold increased risk of sepsis. Public health efforts should attempt to mitigate sepsis risk by awareness and appropriate treatment (e.g., antibiotic administration) to cancer survivors with suspected infection regardless of the number of years since cancer remission.

1. Introduction

Sepsis, characterized by a systemic inflammatory response to an infection, is a major public health problem responsible for more than 200,000 deaths and 750,000 hospitalizations annually in the United States (US) [1–3]. Among hospitalized patients, cancer patients are nearly ten times more likely to develop sepsis when compared with no cancer history patients [4]. A diagnosis of sepsis among cancer patients has been shown to increase the risk of mortality up to 2 to 3- fold, making sepsis a significant but modifiable threat to cancer survivorship [4–7]. Treatment modalities for cancer have improved in the past decades, with average 5-year survival approaching 70% [8,9]; however, there are disparities in survival rates by race and socio-economic status, a trend that mirrors disparities in sepsis rates among US adults [4,10–27].

Cancer and sepsis have a physiologically plausible association, as infections are common complications among cancer patients receiving major cancer surgeries or treatment within the hospital setting [6]. However, there exists limited epidemiologic evidence to support the mechanism of cancer survivors having long-term increased risk of sepsis years following their perspective cancers. Further, there is very limited evidence for the association between cancer and sepsis among a longitudinal cohort of participants considered community dwelling at baseline. Little attention has focused on risk of infection among cancer

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survivors living in communities as past research has focused exclusively among hospitalized cancer patients receiving surgical treatment and/or emergency care. An important and inherent limitation of prior studies was the use of hospital discharge data to identify sepsis events and the assessment of hospital-acquired rather than community acquired sepsis [4–6]. First, in hospital discharge datasets, it is difficult disentangle early (community-acquired) sepsis from later (hospital-acquired) sepsis as a result of limited availability of present-on-admission status of the sepsis diagnosis [28]. Secondly, there is often insufficient information about confounders on the association of cancer and sepsis including initial clinical presentation; chronic comorbidities such as diabetes and obesity; personal characteristics such as income, education, and body mass index; and behavioral characteristics such as smoking, alcohol use, and diet.

Modern cancer treatment and therapies have improved cancer survivorship over the past few decades, but there are inherent properties of cancer and effects of treatment that may cause cancer survivors to have reduced immune function and affect overall quality of life when compared with the general population. To date, there is limited knowledge on the risk of sepsis among cancer survivors as compared with participants with no cancer within a well-defined longitudinal cohort of community-dwelling adults [4–6]. Therefore, the objective of this study was to determine the risk of sepsis after cancer compared with no cancer history participants in the REGARDS cohort. Additionally, because there is conflicting evidence on racial differences in sepsis we aimed to determine whether risk of sepsis after cancer was modified by race [4–6,24–26,29–33]. We hypothesize that, within the REGARDS cohort, sepsis risk will be higher among cancer survivors when compared to those without a history of cancer and that there will be racial differences in the risk of sepsis after cancer.

2. Methods

2.1. Study design & data source

We performed a retrospective analysis of prospectively collected data using REGARDS, a cohort of community-dwelling adults in the US [34]. The REGARDS cohort was designed to examine risk factors for racial and geographic differences in excess stroke deaths observed among Blacks and those living in the southeastern US. 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 recruited participants between January 2003 and October 2007. At six-month intervals, REGARDS investigators have contacted the participants by telephone to identify any hospitalizations experienced by the participant in the previous six months. Further details related to REGARDS study methods are described elsewhere [34]. While the objective of REGARDS was to identify and characterize stroke events, the population of REGARDS included community-dwelling adults at healthy baseline. The REGARDS-sepsis ancillary study used the infrastructure of the parent REGARDS study to independently identify sepsis hospitalizations. Thus, the REGARDS cohort provides a unique opportunity to examine cancer survivors living in communities at baseline and future risk of community-acquired sepsis.

2.2. 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.” REGARDS investigators identified participants with self-reported history of cancer during baseline interview using the following baseline question: “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, they were excluded from participation in the study. Due to the focus on community-dwelling participants, REGARDS investigators excluded participants receiving treatment for cancer within past two years in order to study participants considered “healthy” at baseline. Therefore, participants defined as cancer survivors at baseline were those that had cancer remission for at least two years before entrance into REGARDS cohort. Further, our study excluded participants that may be undergoing cancer treatment in the hospital, leading to an increased risk of sepsis. Self-reported history of cancer in prospective cohort studies have been previously shown to have sensitivity values of 0.90 and positive predictive values of 0.75 [35].

2.3. Primary outcome of interest – community-acquired sepsis

The primary outcome of this study was first sepsis event. Our analysis focused on community-acquired sepsis; therefore, we assessed vital signs and laboratory findings within the first 28 h of hospitalization to include ED care and up to one full day of inpatient care. We included hospitalization events reported from January 1, 2003 through December 31, 2012.

In order to identify infection events among REGARDS participants, two trained abstractors independently reviewed all relevant medical records to confirm the presence of a serious infection and its pertinence to the hospitalization. Our trained abstractors reviewed emergency department physician and nursing notes, hospital admission notes, initial laboratory test and vital signs, and the discharge summary. We then identified all serious infections (i.e., all hospitalizations with a bacterial, fungal, or viral infectious process) based on the taxonomy of Angus et al for identifying severe sepsis [1]. We did not use laboratory, microbiological, or radiographic information for defining serious infections.

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 < 4000 cells/mm3 or > 10% band forms) [1].

International consensus conferences (“Sepsis-3″) have proposed new definitions for sepsis [36]. Because of its common use in prior sepsis epidemiology studies, we used the SIRS-based sepsis definition as the primary analysis. However, in a secondary analysis, we repeated the analysis using the Sepsis-3 definition of sepsis as the presence of a serious infection plus a sequential organ failure assessment (SOFA) score ≥2 [36].

2.4. Participant characteristics

Baseline demographic variables used in the analysis included self-reported age, race, sex, household income, education, and geographic region. Health behaviors included tobacco, alcohol use, and physical activity. 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 [37,67]. Baseline medical conditions included self-reported history of 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. Those with missing information for an individual medical conditions were included as having no presence of a medical condition. Biomarkers included in this analysis were high sensitivity C-reactive protein (indicator of systemic inflammation), albumin-creatinine ratio (ACR) (indicator of kidney function), and