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| **Supplemental Table 1:** Detailed definitions and technical information for sociodemographics, health behaviors, and chronic medical conditions. | |
| **Characteristic** | **Definition and/or Technical Information** |
| **Sociodemographics** |  |
| Age | Age in years |
| Gender | Male, female |
| Race | Black, white |
| Education | Participant reported:   * Less than high school * High school graduate * Some college * College or higher * Missing |
| Income | Participant reported:   * <$20k * $20k-$34k * $35k-$74k * ≥$75k * Missing (not reported) |
| Geographic Region | Participant residence:   * Stroke Buckle (coastal plains of North Carolina, South Carolina and Georgia) * Stroke Belt (remainder of North Carolina, South Carolina and Georgia, plus Tennessee, Mississippi, Alabama, Louisiana and Arkansas)   Non-Belt/Buckle (other states) |
| **Health Behaviors** |  |
| Smoking Status | Participant reported:   * Current * Past * Never |
| Alcohol use | Participant reported:   * None * Moderate (up to 1 drink per day for women or 2 drinks per day for men) * Heavy (>1 drink per day for women and >2 drinks per day for men).[63](#_ENREF_63) |
| **Chronic Medical Conditions** |  |
| Atrial Fibrillation | Participant reported history of atrial fibrillation. |
| Chronic Lung Disease | Participant use of pulmonary medications (beta agonists, leukotriene inhibitors, inhaled corticosteroids, combination inhalers, ipratropium, cromolyn, aminophylline and theophylline) as a surrogate for chronic lung disease. |
| Coronary Artery Disease | Participant reported history of myocardial infarction, coronary artery bypass grafting, or cardiac angioplasty or stenting, or baseline electrocardiographic evidence of myocardial infarction. |
| Chronic Kidney Disease | Defined as measured glomerular filtration rate of<60 ml/min based upon serum creatinine. |
| Diabetes | Fasting glucose ≥126 mg/L (or a glucose ≥200 mg/L for those not fasting) or participant reported use of insulin or oral hypoglycemic agents. |
| Deep Vein Thrombosis | Participant reported history of deep vein thrombosis. |
| Dyslipidemia | Low-density lipoprotein cholesterol >130 mg/dL or participant reported use of lipid lowering medications. |
| Hypertension | Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or participant reported antihypertensive agent use. |
| Myocardial Infarction | Participant reported history of myocardial infarction or baseline electrocardiographic evidence of myocardial infarction. |
| Obesity | {Waist circumference [>102 cm for males or >88 cm for females]} or {body mass index ≥30 kg/m2}. |
| Peripheral Artery Disease | Participant reported history of lower extremity arterial bypass or leg amputation. |
| Stroke | Participant reported history of stroke or transient ischemic attack. |
| **Medications** |  |
| Aspirin use | Self-reported participant chronic use of aspirin at baseline. |
| Statin use | Self-reported participant chronic use of statins at baseline. |
| Steroid use | Steroid use is the reported use of oral or injectable hydrocortisone, dexamethasone, fludrocortisone, prednisone, methyl prednisone, budesonide, and stanozolol. |
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| Albumin-to-Creatinine Ratio (ACR) | Abnormal defined as ACR ≥30 mcg/mg.  Albumin assay by nephelometry (BN ProSpec Nephelometer, Dade Behring, Siemens Healthcare, Deerfield, Illinois, USA). Urinary creatinine assay determined by rate blanked Jaffé procedure (Modular-P analyzer, Roche/Hitachi, Roche Diagnostics, Indianapolis, Indiana, USA). |
| Cystatin C | Abnormal defined as Cyst-C measurements above the fourth quartile (≥1.11 mg/dL)  Assay by particle-enhanced immunonephelometry (N Latex Cyst-C, Siemens AG, Munich, Germany). |
| High Sensitivity C-Reactive Protein (hsCRP) | Abnormal defined as hsCRP >3.0 mg/dL  Assay by particle-enhanced immunonephelometry (N High-sensitivity CRP, Siemens AG, Munich, Germany). |

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| **Supplemental Table 2: Mediating effects 1 of indicators of frailty on the association between risk of sepsis after cancer survivorship, excluding cancer deaths within 3 years. Among 27,878 REGARDS participants with 1305 first sepsis events.** | | | | | |
|  | **Mediation Analysis** | | | | |
|  | **Natural Indirect Effect2**  **(Mediation Effect)** | | **Natural Direct Effect3** | | **Percent**  **Mediated4 (%)**  **(Log Hazard Scale)** |
|  | **HR** | **95% CI5** | **HR** | **95% CI5** |  |
| **Mediators** |  |  |  |  |  |
| Weakness | 1.007 | 1.006 – 1.012 | 2.614 | 2.394 – 2.842 | 0.77% |
| Exhaustion | 1.005 | 1.002 – 1.010 | 2.632 | 2.411 – 2.861 | 0.50% |
| Low Physical Activity | 1.003 | 1.000 – 1.006 | 2.622 | 2.398 – 2.860 | 0.26% |
| Frailty | 1.009 | 1.005 – 1.016 | 2.607 | 2.389 – 2.849 | 0.92% |
| # Frailty Indicators | 1.008 | 1.004 – 1.015 | 2.628 | 2.410 – 2.861 | 0.85% |
|  | **Total Effect (Risk of Sepsis)** | | | | |
|  | **N** | **No. Sepsis Events (%)** | **Mean Survival Time**  **(95% CI)6** | | **Hazard Ratio (95% CI)** |
| **Cancer Survivors** | 25,155 | 346 (12.71) | 8.57 (8.49 – 8.65) | | 2.62 (2.31 – 2.97) |
| **No Cancer History** | 2723 | 959 (3.81) | 9.19 (9.17 – 9.20) | | Ref |
| 1 Models adjusted for age, sex, race, 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 95% Confidence intervals (CIs) estimated using 500 bootstrapped resamples.  6 Mean survival time in years. | | | | | |

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| **Supplemental Table 3: Mediating effects 1 of indicators of frailty on the association between cancer and sepsis. Among 26158 REGARDS participants with 1224 first sepsis events. Further adjusted for biomarkers and baseline medications.** | | | | | |
|  | **Mediation Analysis** | | | | |
|  | **Natural Indirect Effect2**  **(Mediation Effect)** | | **Natural Direct Effect3** | | **Percent**  **Mediated4 (%)**  **(Log Hazard Scale)** |
|  | **HR** | **95% CI5** | **HR** | **95% CI5** |  |
| **Mediators** |  |  |  |  |  |
| Weakness | 1.005 | 1.002 – 1.009 | 2.601 | 2.384 – 2.879 | 0.49% |
| Exhaustion | 1.004 | 1.001 – 1.008 | 2.613 | 2.396 – 2.890 | 0.40% |
| Low Physical Activity | 1.002 | 0.999 – 1.006 | 2.604 | 2.382 – 2.890 | 0.22% |
| Frailty | 1.006 | 1.002 – 1.012 | 2.595 | 2.383 – 2.883 | 0.65% |
| # Frailty Indicators | 1.006 | 1.002 – 1.011 | 2.595 | 2.383 – 2.883 | 0.60% |
|  | **Total Effect (Risk of Sepsis)** | | | | |
|  | **No. Sepsis Events (%)** | | **Mean Survival Time**  **(95% CI)6** | | **Hazard Ratio (95% CI)** |
| **Cancer Survivors** | 325 (12.56) | | 8.56 (8.48 – 8.64) | | 2.61 (2.29 – 2.97) |
| **No Cancer History** | 899 (3.81) | | 9.19 (9.17 – 9.21) | | Ref |
| 1 Models adjusted for age, sex, race, comorbidity score, Cystatin-C, and aspirin use.  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 95% Confidence intervals (CIs) estimated using 500 bootstrapped resamples.  6 Mean survival time in years. | | | | | |

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| **Supplemental Table 4: Mediating effects 1 of indicators of frailty on the association between cancer and sepsis. Among 10,586 Black participants with 408 first sepsis events. Further adjusted for biomarkers and baseline medications.** | | | | | |
|  | **Natural Indirect Effect2**  **(Mediation Effect)** | | **Natural Direct Effect3** | | **Percent**  **Mediated4 (%)**  **(Log Hazard Scale)** |
| **Mediators** | **HR** | **95% CI5** | **HR** | **95% CI5** |  |
| Weakness | 1.001 | 0.997 – 1.006 | 2.846 | 2.189 – 3.672 | 0.05% |
| Exhaustion | 1.003 | 0.996 – 1.008 | 2.834 | 2.183 – 3.664 | 0.27% |
| Low Physical Activity | 1.002 | 0.999 – 1.005 | 2.837 | 2.184 – 3.641 | 0.18% |
| Frailty | 1.002 | 1.000 – 1.005 | 2.834 | 2.184 – 3.641 | 0.18% |
| # Frailty Indicators | 1.002 | 1.000 – 1.005 | 2.837 | 2.184 – 3.641 | 0.17% |
|  | **Total Effect (Risk of Sepsis)** | | | | |
|  | **No. Sepsis Events (%)6** | | **Mean Survival Time**  **(95% CI)7** | | **Hazard Ratio (95% CI)8** |
| **Cancer Survivors** | 89 (11.51) | | 8.10 (7.97 – 8.24) | | 3.00 (2.36 – 3.82) |
| **No Cancer History** | 319 (3.25) | | 9.22 (9.19 – 9.24) | | Ref |
| 1 Models adjusted for age, sex, race, comorbidity score, Cystatin-C, and aspirin use.  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 95% Confidence intervals (CIs) estimated using 500 bootstrapped resamples.  6 % represents the proportion within cancer group with sepsis event.  7 Mean survival time in years.  8 Estimated from Cox proportional hazards model. | | | | | |

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| **Supplemental Table 5: Mediating effects 1 of indicators of frailty on the association between cancer and sepsis. Among 15,572 White participants with 816 first sepsis events. Further adjusted for biomarkers and baseline medications.** | | | | | |
|  | **Natural Indirect Effect2**  **(Mediation Effect)** | | **Natural Direct Effect3** | | **Percent**  **Mediated4 (%)**  **(Log Hazard Scale)** |
| **Mediators** | **HR** | **95% CI5** | **HR** | **95% CI5** |  |
| Weakness | 1.004 | 1.001 – 1.012 | 2.507 | 2.383 – 2.761 | 0.48% |
| Exhaustion | 1.002 | 1.000 – 1.007 | 2.513 | 2.392 – 2.760 | 0.26% |
| Low Physical Activity | 1.004 | 0.999 – 1.009 | 2.503 | 2.377 – 2.748 | 0.48% |
| Frailty | 1.004 | 0.999 – 1.009 | 2.503 | 2.377 – 2.748 | 0.48% |
| # Frailty Indicators | 1.004 | 0.999 – 1.009 | 2.514 | 2.389 – 2.761 | 0.48% |
|  | **Total Effect (Risk of Sepsis)** | | | | |
|  | **No. Sepsis Events (%)** | | **Mean Survival Time**  **(95% CI)7** | | **Hazard Ratio (95% CI)8** |
| **Cancer Survivors** | 236 (13.00) | | 8.54 (8.44 – 8.64) | | 2.45 (2.10 – 2.86) |
| **No Cancer History** | 580 (4.22) | | 8.82 (8.80 – 8.84) | | Ref |
| 1 Models adjusted for age, sex, race, comorbidity score, Cystatin-C, and aspirin use.  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 95% Confidence intervals (CIs) estimated using 500 bootstrapped resamples.  6 % represents the proportion within cancer group with sepsis event.  7 Mean survival time in years.  8 Estimated from Cox proportional hazards model. | | | | | |