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History of Cancer and Mortality in Community-Dwelling Older Adults

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Abstract

Background—The association between a history of cancer and mortality has not been studied in a propensity-matched population of community-dwelling older adults.

Methods—Of the 5795 participants in the Cardiovascular Health Study, 827 (14%) had self-reported physician-diagnosed cancer at baseline. Propensity scores for cancer were used to assemble a cohort of 789 and 3118 participants with and without cancer respectively who were balanced on 45 baseline characteristics. Cox regression models were used to determine the association between cancer and all-cause mortality among matched patients, and to identify independent predictors of mortality among unmatched cancer patients.

Results—Matched participants had a mean (SD) age of 74 (6) years, 57% were women, 10% were African Americans, and 38% died from all causes during 12 years of follow-up. All-cause mortality occurred in 41% and 37% of matched participants with and without a history of cancer respectively (hazard ratio when cancer was compared with no-cancer, 1.16; 95% confidence interval, 1.02–1.31; $P=0.019$). Among those with cancer older age, male gender, smoking, lower than college education, fair-to-poor self-reported health, coronary artery disease, diabetes mellitus, chronic kidney disease, left ventricular hypertrophy, increased heart rate, low hemoglobin and low baseline albumin were associated with increased risk of mortality

Conclusions—Among community-dwelling older adults, a history of cancer was associated with increased mortality and among those with cancer, several socio-demographic variables and morbidities predicted mortality. These findings suggest that addressing traditional risk factors for cardiovascular mortality may help improve outcomes in older adults with a history of cancer.

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Keywords

History of cancer; mortality; propensity score; older adults

Persons aged ≥ 65 years bear the disproportionate burden of cancer with regard to incidence, morbidity, and mortality (1,2). The factors that contribute to increased mortality among older adults with cancer are not well understood, especially as patients move into survivorship. Older adults are more likely to experience age-related comorbid conditions that may impact cancer prognosis, quality of life, and survival. Older adults may also be more susceptible to toxicities of cancer treatments that contribute to the emergence of new comorbidities and to increased mortality risk (3,4).

Studies have demonstrated that excess mortality related to cancer diagnosis persists even into long-term survivorship (greater than 5 years) for many cancer diagnoses (5). It is problematic, however, to make the assumption that the cause of death for cancer survivors is the cancer itself, especially among older survivors (6). An understanding of the factors that predict mortality among community-based older cancer survivors will provide meaningful information in the development of subsequent research and interventions.

In this study we sought to identify whether a baseline history of cancer was independently associated with all-cause mortality in a propensity-matched population of community-dwelling older adults, and also to identify factors associated with mortality among cancer survivors in this population. We used public-use copies of the Cardiovascular Health Study (CHS) datasets obtained from the National Heart, Lung, and Blood Institute (NHLBI) to answer these questions.

Methods

Study Design and Participants

CHS is an ongoing, prospective NHLBI-funded epidemiologic study of cardiovascular disease risk factors in older adults. Four study sites including Sacramento County, California; Washington County, Maryland; Forsyth County, North Carolina; and Allegheny County, Pennsylvania contributed 5888 community-dwelling older adults ≥ 65 years. Participants were recruited from a random sample of Medicare-eligible residents in two phases. Medicare is a single-payer insurance program run by the United States government and to be Medicare-eligible, a person must be ≥ 65 years of age or have kidney failure requiring dialysis or transplant. To be Medicare-eligible, a person or his/her spouse must have worked and paid Medicare taxes for at least 10 years. It is estimated that nearly all Medicare-eligible older adults eventually become Medicare recipients. Persons with a history of cancer could be enrolled. However, those undergoing active treatment for cancer, including radiation therapy, chemotherapy, immunotherapy and hospice treatment were excluded.

An initial cohort, recruited between 1989 and 1990, enrolled 5,201 participants and a second cohort of 687 African-Americans was recruited between 1992 and 1993 (7). Data on 5,795 of the 5,888 original CHS participants are available in the public-use copy of the datasets (93 participants did not consent to be included in the de-identified public-use copy of the data). After excluding 10 participants who had no data on self-reported physician-diagnosis of cancer, the final sample size for the current analysis consisted of 5,785 participants. Of this number, 827 reported a baseline history of cancer, including non-melanoma skin cancers. Patients with a prior diagnosis of cancer currently requiring hospice care, radiation

therapy, or chemotherapy were ineligible, thus the cohort for this study with a history of cancer had completed initial therapies.

History of Cancer and Other Baseline Measurements

Data on self report of physician diagnosis of cancer was collected during baseline home interview using a CHS questionnaire. Participants were asked whether they were told by a doctor that they currently have cancer. Participants who answered yes to these questions were further asked about the type of cancer they had. Cancer types include lung, breast, stomach, liver, colon or rectum, pancreas, esophagus, prostate and brain cancers. Others include lymphomas, leukemia, multiple myeloma, and melanoma and non-melanoma skin cancer. Data on sociodemographic, clinical, sub-clinical, and laboratory variables were collected at baseline and have been previously described in detail (7,8). Missing values for continuous variables were imputed based on values predicted by age, sex and race using regression command in SPSS.

Outcome Measures

All-cause mortality was the primary outcome for this study. Deaths were confirmed by review of medical records and death certificates, as well as the Centers for Medicare and Medicaid Services (formerly, Health Care Financing Administration) administrative data (9). Mortality data were centrally adjudicated by the events committee (10). The analysis presented here includes mortality data through to June 30, 2000. The process of adjudication for events in the CHS study and determination of cause of death has been documented in the literature (10,11).

Assembly of a Balanced Study Cohort

Differences in key baseline characteristics between participants with and without history of cancer were identified (Table 1 and Figure 1), and we used propensity score matching to assemble a population in which those with and without a history of cancer would be well-balanced in all measured baseline covariates. A propensity score for a history of cancer would be that person's conditional probability of having a history of cancer given his/her observed baseline characteristics (12,13). Propensity scores for self-reported history of cancer were estimated for each of the 5,785 CHS participants using a non-parsimonious multivariable logistic regression model (14–19). In the model, a history of cancer was the dependent variable, and 45 baseline characteristics (Figure 1) that included many prognostically important confounders were entered as covariates.

The efficacy of propensity score models was assessed by estimating post-match absolute standardized differences between baseline covariates that directly quantifies the bias in the means (or proportions) of covariates across the groups, expressed as a percentage of the pooled standard deviations and presented as Love plots (16,20,21). Because propensity score models are sample-specific adjusters and are not intended to be used for out-of-sample prediction or estimation of coefficients, measures of fitness and discrimination are not important for the assessment of the model's effectiveness (14–19). An absolute standardized difference of 0% indicate no residual bias and <10% is considered of inconsequential bias (16,20,21).

A greedy matching protocol was used to match participants with and without a history of cancer but had a similar propensity for cancer to five, four, three, two and one decimal places in five repeated steps (14–19). In the first step, the raw propensity scores were multiplied by 100,000 so that propensity scores of 0.657525761 and 0.657524839 for a pair of participants with and without a history of cancer would be converted to 65752.58 and 65752.48 respectively. Then both the numbers were rounded to the nearest value divisible

by 0.25, so that both would be 65752.50 and thus could be matched. All participants matched by propensity scores to the 5 decimal places were then removed from the file. In the second step, we multiplied the raw propensity scores by 10,000, rather than 100,000, and repeated the above process. This was then repeated three more times, each time, multiplying by 1000, 100, and finally 10. In all, we were able to match 789 (95% of the 827) participants with cancer with 3118 participants without cancer, thus assembling a matched cohort of 3907 participants.

Statistical Analysis

The baseline characteristics were compared using Pearson's chi-square and Wilcoxon's rank-sum tests for participants with a history of cancer and those without. The association between a history of cancer and mortality was determined using Kaplan–Meier analysis and Cox regression analyses. Log-minus-log scale survival plots were used to check proportional hazards assumptions. We repeated our analysis in the full pre-match cohort of 5,785 participants using three different approaches: (1) unadjusted, (2) propensity score adjusted, and (3) multivariable-adjusted, using all covariates used in the propensity score model. We conducted subgroup analyses and tested for interactions to examine if there was any heterogeneity in the association between history of cancer and all-cause mortality.

Bivariate and multivariable Cox regression models were used to determine predictors of mortality in all 827 participants with history of cancer. Covariates included in the models were age, gender, race, marital status, education, income, tobacco use, fair to poor general health, coronary artery disease, hypertension, diabetes mellitus, atrial fibrillation, left ventricular hypertrophy, transient ischemic attack, stroke, chronic kidney disease defined as estimated glomerular filtration rate <60 ml/min/1.73 m², serum uric acid, white blood cell count, serum albumin, fibrinogen, and c-reactive protein. Age, gender, and race were forced into the multivariable models using forward stepwise strategy with a $P < 0.10$ cut-off. All tests were two-tailed, and a p-value of 0.05 or less was considered statistically significant. SPSS for Windows (Version 15) was used for all data analyses.

Sensitivity Analyses

Although our matched cohort was well balanced in 45 measured baseline covariates between participants with and without history of cancer, bias due to imbalances in unmeasured covariates is possible. We completed a formal sensitivity analysis to quantify the degree of a hidden bias that would need to be present to invalidate our main conclusions (22).

Results

Baseline Characteristics

Matched participants had a mean (SD) age of 74 (6) years, 57% were women, and 10% were African Americans. Before matching, compared with participants with no history of cancer, participants with a history of cancer were more likely to be older, white, have some college education, higher income, and more likely to report fair to poor general health. Pre-match imbalances and post-match balances between participants with and without a history of cancer are displayed in Table 1 and Figure 1. After matching, absolute standardized differences for all measured covariates were $<10\%$, suggesting substantial covariate balance across the groups (Figure 1).

History of Cancer and Mortality

Overall, 1,483 (38%) participants in the matched cohort died from all causes during 11 years of follow-up. Kaplan–Meier survival curves for all-cause mortality are displayed in Figure 2. Death due to all causes occurred in 41% (rate, 492/10,000 person-years of follow-up) and

37% (rate, 427/10,000 person-years) of participants respectively with and without a history of cancer (hazard ratio when cancer was compared with no cancer, 1.16; 95% confidence interval (CI), 1.02–1.31; $P=0.019$; Table 2). In the absence of hidden bias, a sign-score test for matched data with censoring provides evidence ($P=0.017$) that participants without a history of cancer clearly outlived those with a history of cancer. However, a hidden covariate that would increase the odds of having a history of cancer by only 2% could potentially explain away this association. The association of history of cancer and all-cause mortality was homogeneous across various subgroups of participants (Figure 3).

Among 5,785 pre-match participants, 36% (2082/5785) participants died from all causes. Unadjusted, propensity-adjusted, and multivariable-adjusted hazard ratios for death were respectively 1.26 (95% CI, 1.12–1.41; $P<0.0001$), 1.12 (95% CI, 1.00–1.26; $P=0.055$) and 1.16 (95% CI, 1.03–1.30; $P=0.013$; Table 2).

Predictors of Mortality among Cancer Survivors

Among participants with history of cancer ($n=827$), baseline characteristics that had a bivariate association with mortality are displayed in Table 3. Age was a strong and independent predictor of mortality among cancer survivors. Every two years increase in age was associated with significant 9% increase in mortality. Other baseline characteristics that had significant independent associations with increased mortality were: current smoking (a 72% increase), self-reported fair to poor general health (a 66% increase), coronary artery disease (a 42% increase), diabetes mellitus (an 84% increase), left ventricular hypertrophy (an 82% increase), and chronic kidney disease (a 44% increase; Table 3). Baseline characteristics associated with reduced risk of death included female gender (a 43% reduction), college or higher education (a 21% reduction), serum albumin concentration (a 40% reduction for every gram increase in serum level; Table 3).

Discussion

The current analysis demonstrates that the prevalence of a history of cancer was relatively high among community-dwelling older adults, and that the presence of traditional socio-demographic and clinical risk factors for increased mortality also predicted mortality in cancer survivors. We also observed that when these traditional risk factors and other measured baseline characteristics were balanced after propensity score matching, compared to older adults without cancer, cancer survivors were at increased risk of death from all causes. To the best of our knowledge, this is the first report of an association between a history of cancer and mortality in a propensity-matched population of community-dwelling older adults in which participants with and without cancer that was well balanced in 45 measured baseline covariates. These findings are important as they demonstrate that a history of cancer, regardless of its type or severity is associated with increased mortality among community-dwelling older adults, and that the prognosis of cancer survivors may be improved by addressing traditional cardiovascular risk factors such as smoking and diabetes.

The observed associations between a history of cancer and all-cause mortality can be explained by a direct effect of cancer, a confounding by one or more measured covariates such as socio-demographic and other co-morbidities associated with cancer, or a confounding by an unmeasured covariate. Prior studies have demonstrated an impact of common cancer types on survival rates well into survivorship and that increased mortality in the cancer survivor may in part be explained by confounding (5,23–25). We observed that before matching, participants with a history of cancer in our study had higher mean age and a higher proportion of these patients reported fair to poor general health compared to those without a history of cancer (Table 1). However, after matching, these and other baseline characteristics were well balanced. Therefore, the increased cancer-associated mortality

observed in the present analysis may not be explained by baseline differences in socio-demographic and other risk factors. Findings from our sensitivity analysis suggest that the association between cancer and mortality observed in our study was relatively insensitive to potential imbalance in an unmeasured confounder. Therefore, the observed association between a history of cancer and mortality is likely to be independent of the measured baseline covariates in our study.

Presence of coexisting subclinical and clinical conditions such as smoking, diabetes mellitus, chronic kidney disease, and coronary artery disease strongly predicted mortality among those with a history of cancer. While the diagnosis of cancer may be associated with organ dysfunction due to metastasis, the coexistence of comorbid conditions with cancer has been reported to have a significant effect on survival outcome (26). One potential explanation for this is the overall low mortality rates among cancer survivors in our study, likely due to selection bias that excluded patients with more advanced or terminal cancer and included patients with less aggressive cancers such as prostate cancer. These may have allowed more traditional cardiovascular risk factors to compete with cancer to impact survival. For example, in patients with pancreatic cancer with an average life expectancy of less than a year, current smoking or the presence of coronary artery disease may not impact prognosis. However, in patients with prostate cancer with much longer life expectancy, traditional risk factors may play a more important role in affecting prognosis.

It is also possible that cancer treatment may contribute to a higher risk of all-cause mortality by exacerbating existing conditions or contributing to emerging comorbidities. Increased rates of cardiovascular disease are noted among cancer patients treated with anthracyclines (27), platinum-based chemotherapy (28,29), androgen deprivation, and chest-focused radiation therapy (30). Androgen and estrogen deprivation are associated with osteoporosis, and the risk of fracture. Bleomycin is associated with pulmonary fibrosis and respiratory compromise, as is radiation to the chest (31–33). Factors such as these may contribute to the increased risk of mortality observed in this analysis of a population-based sample. The development of new comorbidities in survivorship is associated with a higher risk of mortality (4). Factors such as these may contribute to the increased risk of mortality observed in this analysis of a population-based sample. The emergence of serum albumin as a strong and significant predictor of mortality suggests that it may indicate persistent underlying inflammation in cancer survivors.

Higher education attainment was associated with reduced mortality among cancer survivors. This association was supported by prior studies (23–25). This is likely mediated via factors such as higher income, better health insurance and better access to medical care. CHS participants were Medicare-eligible at the time of enrollment and although we had no data on their Medicare status, most were likely Medicare beneficiaries. Yet, it is possible that participants with higher education had a healthier life style which may have contributed to better outcomes. For example, the prevalence of smoking decreases with higher education levels (34). We observed that current smoking was a strong and significant predictor of mortality among cancer survivors. This is consistent with previous reports (35) and reinforces the need for smoking cessation among cancer survivors.

The use of propensity score matching design to assemble the study population in which those with and without a history of cancer were well-balanced in all measured baseline covariates is a strength of the current study. To the best of our knowledge this is the first study to examine the association between cancer survivorship and mortality using a propensity-matched design. As in randomized clinical trials, in propensity-matched studies, a balanced study cohort is assembled without knowledge of or access to outcomes data, thus investigators are blinded to study outcomes (13). Further, traditional regression-based risk

adjustment may not always ensure that the distribution of the confounders is balanced across exposure groups at baseline. In the absence of balance in the exposure groups with respect to the confounders, findings based on regression adjustments may not reflect true associations (36). Using propensity-matched designs, on the other hand, allows investigators to present the distribution of baseline characteristics data in a tabular form that is visually appealing to readers.

A key limitation of propensity-matched studies is that as in any non-randomized studies, it may not balance unmeasured covariates and thus the findings can be potentially confounded by unmeasured or un-measurable confounders. Although most clinical variables are highly correlated, a balance in large number of measured covariates would be expected to balance many related unmeasured covariates, this can neither be assumed nor be guaranteed. However, formal sensitivity analysis may help determine the potential impact of such a hidden or unmeasured confounder. For example, findings from our sensitivity analysis suggest that an unmeasured covariate that would increase the odds of having cancer by only 2% could potentially explain away the association between a history of cancer and mortality observed in our study suggesting that this association was rather sensitive to a potential unmeasured covariate. However, sensitivity analysis cannot determine if such an unmeasured covariate exists. Further, for an unmeasured binary covariate to become a confounder, it would also need to be a near-perfect predictor of mortality and could not be strongly correlated to any of the 45 baseline characteristic used in our study, which is an unlikely possibility.

Several other limitations of our study must be acknowledged. We defined cancer based on self-reported physician diagnosis. Self-report of a disease might under-represent the prevalence of the disease due to recall bias, or may over-represent prevalence due to a misunderstanding of the survey question (37). However, claims-based diagnosis of cancer has also been reported to introduce selection bias (38). Although self-reports of non-cardiovascular diseases including cancer were not centrally adjudicated in CHS, the results of self reports of cardiovascular disease which was centrally adjudicated in CHS suggests that self reports are relatively accurate methods (11). Although we had no data on cancer type, the frequencies of the specific cancer types in this representative sample would be expected to reflect the distribution of cancer in the population. We also had no data on specific cancer treatments that may influence survival or have deleterious adverse effect. Lack of data on cause-specific mortality is another limitation of this study. Finally, those without cancer at baseline may have developed cancer during follow-up. This phenomenon called regression dilution, may also underestimated the association observed in our study (39).

In conclusion, findings from the current analysis suggest that the presence of a history of cancer is common among community-dwelling older adults and seems to have an independent association with mortality. However, among those with a history of cancer, socio-demographic and traditional cardiovascular risk factors predicted mortality. These findings highlight the importance of proper identification, prevention and treatment of socio-demographic and traditional cardiovascular risk factors among cancer survivors.

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Figure 1. Absolute standardized differences before and after propensity score matching comparing covariate values between participants with and without cancer (ACE=angiotensin-converting enzyme; CCB=calcium channel blocker; COPD=chronic obstructive pulmonary disease; LVH=left ventricular hypertrophy; NSAID=non-steroidal anti-inflammatory drug; PS=potassium sparing; TIA=transient ischemic attack)

Figure 2.
Kaplan-Meier plot for mortality
(HR=hazard ratio; CI=confidence interval)

Figure 3.
Hazard ratio and 95% confidence interval (CI) for mortality associated with history of cancer in subgroups of patients in Cardiovascular Health Study

Table 1

Baseline characteristics of participants of Cardiovascular Heart Study (CHS), by cancer, before and after propensity score matching

n (%) or mean ($\pm$ SD)	Before matching			After matching		
	No cancer (n = 4958)	Cancer (n = 827)	P value	No cancer (n = 3118)	Cancer (n = 789)	P value
Age, years	73 ($\pm$ 6)	74 ($\pm$ 6)	<0.0001	74 ($\pm$ 6)	74 ($\pm$ 6)	0.667
Female	2855 (58)	468 (57)	0.593	1781 (57)	447 (57)	0.813
African American	821 (17)	79 (10)	<0.0001	312 (10)	79 (10)	0.996
Married	3260 (66)	554 (67)	0.487	2094 (67)	529 (67)	0.952
Live alone	656 (13)	95 (12)	0.167	363 (12)	91 (12)	0.932
Education college or higher	2077 (42)	395 (48)	0.002	1475 (47)	368 (47)	0.738
Income $\geq$ 25k	1732 (35)	332 (40)	0.004	1224 (39)	308 (39)	0.910
Current smoker	612 (12)	85 (10)	0.091	332 (11)	85 (11)	0.919
Alcohol per week (units)	2.38 ($\pm$ 6.4)	2.7 ($\pm$ 6.0)	0.144	2.7 ($\pm$ 7)	2.7 ($\pm$ 6)	0.843
Body mass index, kg/m ²	27 ($\pm$ 4)	27 ($\pm$ 4)	0.566	27 ($\pm$ 4)	27 ($\pm$ 4)	0.909
Self-reported general health fair to poor	1235 (25)	236 (29)	0.027	832 (27)	217 (27)	0.643
Coronary artery disease	942 (19)	180 (22)	0.063	634 (20)	164 (21)	0.778
Hypertension	2216 (45)	358 (43)	0.451	1338 (43)	334 (42)	0.769
Diabetes	822 (17)	122 (15)	0.188	463 (15)	118 (15)	0.940
LVH (by ECG)	236 (5)	44 (5)	0.487	158 (5)	40 (5)	0.998
Transient ischemic attack	304 (6)	36 (4)	0.044	135 (4)	35 (4)	0.896
Stroke	216 (4)	26 (3)	0.107	99 (3)	25 (3)	0.993
COPD	612 (12)	128 (16)	0.012	452 (15)	118 (15)	0.744
Medications						
ACE inhibitors	406 (8)	52 (6)	0.061	204 (7)	50 (6)	0.834
Beta blockers	638 (13)	105 (13)	0.891	423 (14)	98 (12)	0.398
CCB	675 (14)	106 (13)	0.535	403 (13)	103 (13)	0.906
Aspirin	188 (4)	29 (4)	0.689	112 (4)	29 (4)	0.911
Loop diuretics	336 (7)	71 (9)	0.060	259 (8)	62 (8)	0.682
Thiazide diuretics	553 (11)	93 (11)	0.938	333 (11)	88 (11)	0.702

n (%) or mean ($\pm$ SD)	Before matching		After matching	
	No cancer (n = 4958)	Cancer (n = 827)	P value	P value
NSAID	628 (13)	107 (13)	0.828	0.851
Pulse rate (per minute),	68 ($\pm$ 11)	68 ($\pm$ 11)	0.133	0.592
Average DBP (mm Hg)	71 ($\pm$ 12)	70 ($\pm$ 12)	0.061	0.651
Average SBP (mm Hg)	140 ($\pm$ 21)	139 ($\pm$ 20)	0.167	0.796
Plasma glucose (mg/dL)	111 ($\pm$ 38)	109 ($\pm$ 34)	0.075	0.790
Serum creatinine (mg/dL)	0.96 ($\pm$ 0.40)	0.99 ($\pm$ 0.40)	0.053	0.952
Serum potassium (mEq/L)	4.16 ($\pm$ 0.38)	4.19 ($\pm$ 0.38)	0.076	0.957
Serum uric acid (mg/dL)	5.67 ($\pm$ 1.54)	5.83 ($\pm$ 1.54)	0.007	0.444
Hemoglobin (g/dL)	14.0 ($\pm$ 1.4)	14.0 ($\pm$ 1.4)	0.381	0.971
Total cholesterol (mg/dL)	211 ($\pm$ 39)	211 ($\pm$ 38)	0.954	0.864
Triglyceride (mg/dL)	139 ($\pm$ 75)	143 ($\pm$ 89)	0.170	0.540
Albumin (g/dL)	3.99 ($\pm$ 0.29)	4.00 ($\pm$ 0.29)	0.603	0.869
Fibrinogen (mg/dL)	320 ($\pm$ 73)	316 ($\pm$ 80)	0.153	0.569
C reactive protein (mg/dL)	4.8 ($\pm$ 8.0)	4.9 ($\pm$ 9.7)	0.602	0.982

Table 2

Association between a history of cancer and all-cause mortality

	Events (%)		Hazard ratio (95% confidence interval)	P value
	No cancer	Cancer		
Before matching	n = 4958	n = 827		
Unadjusted	1731 (35%)	351 (42%)	1.26 (1.12–1.41)	<0.0001
Multivariable-adjusted	---	---	1.16 (1.03–1.30)	0.013
Propensity-adjusted	---	---	1.12 (1.00–1.26)	0.055
After matching	n = 3118	n = 789		
Matched	1156 (37%)	327 (41%)	1.16 (1.02–1.31)	0.019

Table 3

Unadjusted and adjusted hazard ratios of predictors of mortality in older adults with history of cancer

	Unadjusted hazard ratio (95% confidence interval); P-value	Adjusted hazard ratio (95% confidence interval); P-value
Age, years	1.10 (1.08–1.12); P<0.0001	1.09 (1.07–1.11); P<0.0001
Female	0.67 (0.54–0.82); P<0.0001	0.57 (0.45–0.72); P<0.0001
African American	1.27 (0.86–1.87); P=0.238	0.88 (0.58–1.33); P=0.532
College education or higher	0.72 (0.59–0.90); P=0.003	0.79 (0.63–0.98); P=0.032
Current smoker	1.34 (0.97–1.84); P=0.073	1.72 (1.23–2.42); P=0.001
Self-reported fair-to-poor general health	2.05 (1.65–2.54); P<0.0001	1.66 (1.31–2.11); P<0.0001
Coronary artery disease	1.68 (1.33–2.18) P<0.0001	1.42 (1.10–1.81) P=0.006
Diabetes mellitus	1.85 (1.43–2.39); P<0.0001	1.84 (1.41–2.40); P<0.0001
Chronic kidney disease	1.72 (1.38–2.14); P<0.0001	1.44 (1.15–1.81); P=0.002
Left ventricular hypertrophy (by ECG)	2.47 (1.69–3.62); P<0.0001	1.82 (1.23–2.70); P=0.003
Heart rate (beats per minute)	1.02 (1.01–1.02); P<0.0001	1.02 (1.01–1.03); P<0.0001
Hemoglobin (g/dL)	0.94 (0.87–1.02); P=0.139	0.92 (0.84–1.00); P=0.047
Albumin (g/dL)	0.58 (0.40–0.84); P=0.004	0.60 (0.41–0.88); P=0.008

* Model also adjusted for marital status, living situation, education level, household income, tobacco use, alcohol use, body mass index, fair to poor general health, coronary artery disease, hypertension, diabetes mellitus, chronic kidney disease, atrial fibrillation, left ventricular hypertrophy, stroke, transient ischemic attack, chronic obstructive pulmonary disease, use of ACE inhibitors, beta blockers, calcium channel blockers, aspirin, statins, loop diuretics, thiazide diuretics, potassium sparing diuretics, NSAIDs, heart rate, systolic and diastolic blood pressure, white cell and platelet counts, serum glucose, potassium, uric acid, hemoglobin, total cholesterol, triglyceride, albumin, fibrinogen and C-reactive protein.