Differences in cancer survival among white and black cancer patients by presence of diabetes mellitus: Estimations based on SEER-Medicare-linked data resource

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Abstract
Diabetes prevalence and racial health disparities in the diabetic population are increasing in the US. Population-based cancer-specific survival estimates for cancer patients with diabetes have not been assessed. The Surveillance, Epidemiology, and End Results (SEER)-Medicare linkage provided data on cancer-specific deaths and diabetes prevalence among 14 separate cohorts representing 1 068 098 cancer patients ages 66+ years diagnosed between 2000 and 2011 in 17 SEER areas. Cancer-specific survival estimates were calculated by diabetes status adjusted by age, stage, comorbidities, and cancer treatment, and stratified by cancer site and sex with whites without diabetes as the reference group. Black patients had the highest diabetes prevalence particularly among women. Risks of cancer deaths were increased across most cancer sites for patients with diabetes regardless of race. Among men the largest effect of having diabetes on cancer-specific deaths were observed for black men diagnosed with Non-Hodgkin lymphoma (NHL) (HR = 1.53, 95%CI = 1.33-1.76) and prostate cancer (HR = 1.37, 95%CI = 1.32-1.42). Diabetes prevalence was higher for black females compared to white females across all 14 cancer sites and higher for most sites when compared to white and black males. Among women the largest effect of having diabetes on cancer-specific deaths were observed for black women diagnosed with corpus/uterus cancer (HR = 1.66, 95%CI = 1.54-1.79), Hodgkin lymphoma (HR = 1.62, 95%CI = 1.02-2.56) and breast ER+ (HR = 1.39, 95%CI = 1.32-1.47). The co-occurrence of diabetes and cancer significantly increases the risk of cancer death. Our study suggests that these risks may vary by cancer site, and indicates the need for future research to address racial and sex disparities and enhance understanding how prevalent diabetes may affect cancer deaths.

KEYWORDS
cancer-specific survival, diabetes, race, SEER
1 | INTRODUCTION

The prevalence of diabetes in the United States (US) has been steadily increasing over the past 25 years and appears to mirror increasing prevalence of obesity in the US. Diabetes prevalence varies by racial and ethnic groups with non-Hispanic black and Hispanic adults experiencing the highest rates. While mortality rates for many specific cancers and for cancers overall have been improving, disparities in mortality between black and white cancer patients have persisted, and in some cases, have increased. Many potential hypotheses for these differences have been proposed; however, the possible influence of the much higher prevalence of diabetes among black compared to white cancer patients has not been explored in depth.

Previous studies have investigated the association between preexisting diabetes and the incidence of selected specific cancers and with long-term, all-cause mortality. Additionally, several studies have investigated possible differences in cancer-specific survival between white and black cancer patients with and without diabetes, but these studies have been limited to examining a single cancer patient population or have been drawn from more selected patient populations that may be less representative of the overall US cancer patient populations. Furthermore, some studies were conducted outside the US or had small sample sizes.

To date, a general overview of population-based cancerspecific survival and risk of cancer death estimates for different cohorts of cancer patients with diabetes by race have not been assessed. Therefore, in this study, we used 2 unique national data resources, the Surveillance, Epidemiology, and End Results (SEER)-linked Medicare claims data to identify black and white cancer patients 66 years and older, representing more than 50% of new cancer cases, with and without prevalent diabetes to determine differences in the risk of cancer death.

2 | METHODS

2.1 | Data source

Cancer patients were identified through SEER-Medicare, a linkage of 2 large population-based data sources comprised of the National Cancer Institute funded Surveillance, Epidemiology, and End Results (SEER) registries and Medicare claims. SEER collects information on persons diagnosed with cancer in designated areas and provides specific demographic, clinical, cancer characteristics, and cause of death information. In this study, we used data from SEER-17 (November 2014 submission: Connecticut, Hawaii, Iowa, New Mexico, Utah, rural/greater Georgia, California, Kentucky, Louisiana, New Jersey, and metropolitan areas including San-Francisco-Oakland, Detroit, Seattle-Puget Sound, Atlanta, San Jose-Monterey, and Los Angeles) which cover approximately 30% of the total US population. Medicare provides federally funded health insurance for persons ages 65 years and older and comprises approximately 45 million people in the US. SEER-Medicare links 94% of SEER cancer cases diagnosed at ages 65 years and older and includes information on all Medicare covered services for beneficiaries with fee-for-service coverage.

2.2 | Study population

We selected cancer patients aged 66 years or older diagnosed with 14 specific primary only cancers between 2000 and 2011, who had continuous Medicare Part A and Part B enrollment and were not enrolled in an HMO during the year prior to diagnosis to ensure complete Medicare coverage to assess diabetes status. Cancer sites included bladder, cervix, colon/rectum, corpus/uterus, estrogen receptor (ER) positive female breast, ER negative female breast, Hodgkin lymphoma, liver, myeloma, non-Hodgkin lymphoma (NHL), ovary, pancreas, prostate, and stomach. These sites were chosen because they represent the most common cancers diagnosed among men and women in the US and because previous research has shown high diabetes prevalence and racial disparities among these cancer populations. We did not include lung cancer in our study because of our inability to assess smoking in SEER-Medicare data which would have been a major confounder in our analyses that could not be directly measured. Additionally, we wanted to focus on cancer sites that were not well represented in previous studies (due to small sample sizes) or could potentially be related to diabetes or the pathway to the development of diabetes. In addition to the 14 selected cancer cohorts, we also obtained claims information on 100,000 controls, individuals without cancer from a 5% random sample of cancer-free Medicare recipients in the SEER catchment areas. The data on individuals without cancer provided background diabetes prevalence information in the general population for comparison to the different cancer cohorts. To estimate the prevalence of diabetes for controls in each calendar year, we frequency-matched controls to cancer cases by sex and age. Controls were only sampled once in a calendar year but could be sampled repeatedly across multiple years.

2.3 | Diabetes ascertainment

Diabetes was identified from Medicare Part A hospitalization claims and Part B physician/supplier and outpatient facility claims per the International Classification of Diseases, 9th edition (ICD-9) codes. Analyses included only individuals aged 66 years and older and conditions in the physician claims were required to appear more than once in a period greater than 30 days within a 1-year period from the first
claim to be considered a diabetes claim.\textsuperscript{25-27} Diabetes (ICD-9: 250.0x-2503x, 250.7x) and diabetes with sequelae (ICD-9: 250.4x-250.6x, 250.8x-250.9x) were grouped together.\textsuperscript{25,26} For each cancer patient, diabetes status was identified in the year before first cancer diagnosis, excluding month of diagnosis, to minimize misclassification of complications potentially related to cancer diagnosis or treatment. Diabetes status for individuals without cancer was identified in the year before the birthday of the age at diagnosis of the matched case.

### 2.4 Other variables

Adjuvant cancer treatment included receipt of chemotherapy, radiotherapy, hormonal therapy, or immunotherapy as reported in SEER. Patients who received any of these therapies were classified as having received cancer treatment or as not having had treatment/unknown if had treatment if there were no reports of treatment in the SEER data. Selected comorbidities from the Charlson comorbidity index included chronic obstructive pulmonary disease, mild/moderate/severe liver disease, AIDS, peptic ulcer disease, and rheumatologic disease.\textsuperscript{25,26} Other comorbidities, namely congestive heart failure, moderate/severe renal disease, dementia, history of myocardial infarction, acute myocardial infarction, peripheral vascular disease, hemiplegia/paraplegia, and cerebrovascular disease, were not included because they have been shown to be related to obesity, may be complications of diabetes, or increase risk of death from diabetes and would have resulted in over adjustment of the risk estimates.\textsuperscript{28-41} Because of possible misclassification of causes of death from death certificate we used the SEER cause-specific death classification variable to classify deaths into cancer and noncancer categories.\textsuperscript{42} This variable uses the sequence of the cancer and causes of death that are likely to be related to the particular cancer or as a consequence of a cancer diagnosis to better classify as a death attributable to the cancer.\textsuperscript{43} Noncancer deaths or lost to follow-up were considered to be censoring events.

### 2.5 Statistical analysis

We calculated diabetes prevalence by different demographic characteristics among the cancer cases and controls. Age-adjusted 5-year cause-specific survival and 95% confidence intervals (CI) were calculated using SEER*Stat and the SEER cause-specific death classification variable.

Analyses were restricted to patients diagnosed with cancer between 2000 and 2011 to provide the survival experience of the most recently diagnosed cancer patients.\textsuperscript{44} Patients diagnosed at autopsy, on death certificates, or who had zero survival months were excluded. Cox proportional hazards regression was used to calculate hazard ratios (HR) and 95% CI to assess the effect of diabetes and race, on cancer-specific deaths.\textsuperscript{45,46} We allowed for the possibility that diabetes effects on cancer survival might be varied by race so we calculated separate hazard ratios by including a four-level variable that combined race and diabetes status, with whites without diabetes serving as the reference group. Whites without diabetes were chosen to be the referent group because they are known to have better survival compared to other groups. With an exception of Hodgkin lymphoma in males and stomach cancer in females, we found statistically significant interactions (\(P < .05\)) between race and diabetes for all other cancer sites. These analyses were stratified by cancer site and sex. Additionally, analyses were adjusted by age group (66-69 years, 70-74 years, 75-79 years, 80-84 years, 85+ years), selected comorbidities, receipt of cancer treatment, and stage at cancer diagnosis (localized, regional, distant, or unstaged/unknown). All analyses were conducted using SAS 9.3 (Cary, NC).

### 3 RESULTS

We identified 1 068 098 cancers diagnosed between 2000 and 2011, with female breast, prostate, and colorectal cancer representing the most common cancers (Table 1). The majority of cancer patients were white (91%), less than 80 years old, male, and diagnosed with earlier stage cancers. The percentage of cancer patients with diabetes did not vary substantially by age, sex, and stage at diagnoses. Patients with liver and pancreas cancers had the highest prevalence of diabetes (42.1% and 35.0%, respectively) compared to other cancer cohorts. Black patients had a higher prevalence of diabetes irrespective of cancer status. Although the matched noncancer controls had a slightly lower prevalence of diabetes than the cancer cases (20% vs 22%); the prevalence of diabetes was higher in noncancer controls among blacks than whites and did not differ greatly by age or sex.

When stratified by cancer site, black males had a higher prevalence of diabetes than white males, except for liver cancer for which diabetes was present in 44.5% of white males compared to 33.9% of black males (Table 2). Black females had higher prevalence of diabetes across all cancer sites compared to white females. White males generally had better 5-year age-adjusted cause-specific survival compared to black males. Survival rates were similar between white and black male cancer patients for pancreatic and prostate cancer and better for black compared to white male cancer patients for Hodgkin lymphoma, and myeloma. Similar to patterns observed in male cancer patients, white female cancer patients had lower diabetes prevalence, regardless of cancer site, and tended to have better 5-year age-adjusted cause-specific survival. The 5-year survival estimates were similar between white and black female cancer patients for liver, ovary, and stomach cancers and better for black compared to white
| Characteristic                | All cancers | Individuals without cancer |
|------------------------------|-------------|----------------------------|
|                              | Total       | With diabetes             | Total       | With diabetes   |
|                              | N           | N | % | N           | N | % |
| Total                        | 1 068 098   | 237 049 | 22.2 | 100 000     | 19 722 | 19.7 |
| Age, y                       |             |             |     |             |             |     |
| 66-69                        | 210 141     | 44 779 | 21.3 | 19 673      | 3 689   | 18.8 |
| 70-74                        | 267 815     | 61 610 | 23.0 | 25 076      | 5 040   | 20.1 |
| 75-79                        | 247 548     | 58 104 | 23.5 | 23 176      | 4 899   | 21.1 |
| 80-84                        | 188 056     | 42 639 | 22.7 | 17 605      | 3 651   | 20.7 |
| 85+                          | 154 538     | 29 917 | 19.4 | 14 470      | 2 443   | 16.9 |
| Race/ethnicity               |             |             |     |             |             |     |
| White                        | 973 300     | 207 537 | 21.3 | 91 121      | 17 094  | 18.8 |
| Black                        | 94 798      | 29 512 | 31.1 | 88 799      | 26 281  | 29.6 |
| Sex                          |             |             |     |             |             |     |
| Male                         | 564 980     | 127 070 | 22.5 | 52 897      | 10 984  | 20.8 |
| Female                       | 503 118     | 109 979 | 21.9 | 47 103      | 8 738   | 18.6 |
| Stage at diagnosis           |             |             |     |             |             |     |
| In situ                      | 29 588      | 7171   | 24.2 | ~           | ~       | ~   |
| Localized                    | 461 077     | 98 191 | 21.3 | ~           | ~       | ~   |
| Regional                     | 194 016     | 43 991 | 22.7 | ~           | ~       | ~   |
| Distant                      | 228 192     | 51 462 | 22.6 | ~           | ~       | ~   |
| Unknown/unstaged             | 155 225     | 36 234 | 23.3 | ~           | ~       | ~   |
| Cancer sites                 |             |             |     |             |             |     |
| Bladder                      | 60 381      | 14 199 | 23.5 | ~           | ~       | ~   |
| Cervix                       | 3,373       | 743    | 22.0 | ~           | ~       | ~   |
| Colon/Rectum                 | 125 909     | 29 531 | 23.5 | ~           | ~       | ~   |
| Corpus/Uterus                | 25 247      | 6488   | 25.7 | ~           | ~       | ~   |
| Female breast                |             |             |     |             |             |     |
| ER positive                  | 89 278      | 17 753 | 19.9 | ~           | ~       | ~   |
| ER negative                  | 16 817      | 3510   | 20.9 | ~           | ~       | ~   |
| Hodgkin lymphoma             | 1989        | 497    | 25.0 | ~           | ~       | ~   |
| Liver                        | 10 157      | 4276   | 42.1 | ~           | ~       | ~   |
| Myeloma                      | 15 890      | 3647   | 23.0 | ~           | ~       | ~   |
| Non-Hodgkin lymphoma         | 44 566      | 9781   | 21.9 | ~           | ~       | ~   |
| Ovary                        | 15 419      | 2948   | 19.1 | ~           | ~       | ~   |
| Pancreas                     | 34 058      | 11 928 | 35.0 | ~           | ~       | ~   |
| Prostate                     | 195 167     | 36 720 | 18.8 | ~           | ~       | ~   |
| Stomach                      | 18 056      | 4945   | 27.4 | ~           | ~       | ~   |
| Other                        | 411 791     | 90 083 | 21.9 | ~           | ~       | ~   |

ER, estrogen receptor.

A random sample of 100 000 individuals (controls) was chosen by frequency matching to all the sites combined cancer cohort by calendar year, age, and sex.

Controls can be sampled only once in a calendar year but can be sampled repeatedly across multiple years.

Other cancers include all reportable cancers made to SEER not individually specified as a separate cohort in this study.
female cancer patients for Hodgkin lymphoma and myeloma. In general, the magnitude of difference in the prevalence of diabetes between black and white female cancer cases is much larger (approximately 15% for most cancer sites) than the difference between black and white male cancer cases (<10% for both cancer sites).

Among both white and black males, the presence of diabetes was associated increased the risk of cancer death after controlling for age, stage, comorbidities, and treatments with an exception of Hodgkin lymphoma, liver, stomach, and bladder (in black males only) (Table 3). Blacks without or with diabetes have a higher risk of cancer death compared to whites with diabetes for most cancer sites, particularly bladder (black HR = 1.30, 1.30 compared to white HR = 1.17, $P < .0001$), colon/rectum (black HR = 1.24, 1.27, white HR = 1.16, $P < .0001$), liver (black HR = 1.23, 1.17, white HR = 1.03; $P = .0004$), NHL (black HR = 1.29, 1.53, white HR = 1.24, $P < .0001$), pancreas (black HR = 1.13, 1.17, white HR = 1.05, $P < .0001$), and stomach cancer (black HR = 1.12, 1.09, white HR = 1.04, $P = .0076$). As noted above, while males with diabetes were at slightly increased risk for mortality with most HRs less than 1.2. The highest relative increases in the risk of cancer-specific death were observed in black males with diabetes and cancers of

| Cancer site               | Males                                    |                        | Females                                    |                        |
|---------------------------|------------------------------------------|------------------------|--------------------------------------------|------------------------|
|                           | % with diabetes                          | 5-y age-adjusted cause-specific survival (%) | % with diabetes | 5-y age-adjusted cause-specific survival (%) |
|                           |                                          | 95% CI                 |                                          | 95% CI                 |
| Bladder                   | White                                    | 24.4                   | 78.6                                      | 19.0                   | 68.2                                      |
|                           | Black                                    | 31.8                   | 71.3                                      | 35.1                   | 54.5                                      |
| Cervix                    | White                                    | ~                      | ~                                        | ~                      | ~                                        |
|                           | Black                                    | ~                      | ~                                        | ~                      | ~                                        |
| Colon/Rectum              | White                                    | 24.0                   | 61.8                                      | 21.2                   | 60.4                                      |
|                           | Black                                    | 29.6                   | 53.9                                      | 34.7                   | 57.6                                      |
| Corpus/Uterus             | White                                    | ~                      | ~                                        | ~                      | ~                                        |
|                           | Black                                    | ~                      | ~                                        | ~                      | ~                                        |
| Female Breast ER-         | White                                    | ~                      | ~                                        | ~                      | ~                                        |
|                           | Black                                    | ~                      | ~                                        | ~                      | ~                                        |
| Female Breast ER+         | White                                    | ~                      | ~                                        | ~                      | ~                                        |
|                           | Black                                    | ~                      | ~                                        | ~                      | ~                                        |
| Hodgkin Lymphoma          | White                                    | 25.0                   | 54.6                                      | 23.9                   | 54.3                                      |
|                           | Black                                    | 28.3                   | 72.4                                      | 38.5                   | 57.1                                      |
| Liver                     | White                                    | 44.5                   | 10.0                                      | 39.4                   | 9.2                                       |
|                           | Black                                    | 33.9                   | 5.5                                       | 41.3                   | 10.5                                      |
| Myeloma                   | White                                    | 23.1                   | 39.7                                      | 19.5                   | 32.3                                      |
|                           | Black                                    | 30.4                   | 46.7                                      | 31.8                   | 42.1                                      |
| Non-Hodgkin Lymphoma      | White                                    | 23.4                   | 54.8                                      | 19.7                   | 55.4                                      |
|                           | Black                                    | 28.5                   | 52.1                                      | 34.4                   | 51.1                                      |
| Ovary                     | White                                    | ~                      | ~                                        | 17.8                   | 20.4                                      |
|                           | Black                                    | ~                      | ~                                        | 35.4                   | 19.2                                      |
| Pancreas                  | White                                    | 36.9                   | 3.9                                       | 3.3-4.6                | 3.15                                      |
|                           | Black                                    | 37.3                   | 4.0                                       | 2.1-6.8                | 4.89                                      |
| Prostate                  | White                                    | 17.9                   | 91.6                                      | 91.2-91.9              | ~                                         |
|                           | Black                                    | 25.7                   | 91.0                                      | 90.1-91.7              | ~                                         |
| Stomach                   | White                                    | 26.9                   | 24.4                                      | 22.4-26.5              | 25.9                                      |
|                           | Black                                    | 27.3                   | 22.7                                      | 17.7-28.1              | 37.2                                      |

CI, confidence interval; ER, estrogen receptor; SEER, Surveillance, Epidemiology, and End Results.
the bladder, colorectal, NHL, and prostate; ranging from 1.27 to 1.53.

The risks of cancer death were increased among females with diabetes across all cancer sites with the exception of stomach cancer (Table 4). Black women without or with diabetes have a higher risk of cancer death compared to white women with diabetes for some cancer sites, particularly bladder (black HR = 1.24, 1.32 compared to white HR = 1.21, \( P < .0001 \)), corpus/uterus (black HR = 1.54, 1.66, white HR = 1.26, \( P < .0001 \)), and ER negative female breast (black HR = 1.27, 1.29, white HR = 1.24, \( P < .0001 \)). Cancer death risks for white women with diabetes were higher than those

| Cancer site          | Race  | Diabetes status | N    | HR   | 95% CI | \( P \)-values |
|----------------------|-------|-----------------|------|------|--------|---------------|
| Bladder              | White | Without diabetes| 32   | 1.17 | 1.14-1.20 | <.0001        |
| Black                | With diabetes | 426 | 1.14-1.20 | <.0001        |
| Bladder              | Black  | Without diabetes| 1107| 1.30 | 1.21-1.39 | <.0001        |
| Black                | With diabetes | 515 | 1.30 | 1.17-1.44 | <.0001        |
| Colon/Rectum         | White  | Without diabetes| 39   | 1.16 | 1.13-1.19 | <.0001        |
| Black                | With diabetes | 12 | 1.16 | 1.13-1.19 | <.0001        |
| Hodgkin lymphoma     | White  | Without diabetes| 683  | 0.98 | 0.83-1.17 | <.0001        |
| Black                | With diabetes | 228 | 0.98 | 0.83-1.17 | <.0001        |
| Liver                | White  | Without diabetes| 32  | 1.03 | 0.98-1.09 | <.0001        |
| Black                | With diabetes | 2611 | 1.03 | 0.98-1.09 | <.0001        |
| Myeloma              | White  | Without diabetes| 5302| 1.10 | 1.03-1.17 | <.0001        |
| Black                | With diabetes | 1595 | 1.10 | 1.03-1.17 | <.0001        |
| Non-Hodgkin lymphoma | White  | Without diabetes| 15  | 1.11 | 1.02-1.20 | <.0001        |
| Black                | With diabetes | 784 | 1.11 | 1.02-1.20 | <.0001        |
| Pancreas             | White  | Without diabetes| 8441| 1.05 | 1.02-1.09 | <.0001        |
| Black                | With diabetes | 4944 | 1.05 | 1.02-1.09 | <.0001        |
| Prostate             | White  | Without diabetes| 141 | 1.13 | 1.05-1.22 | <.0001        |
| Black                | With diabetes | 788 | 1.13 | 1.05-1.22 | <.0001        |
| Stomach              | White  | Without diabetes| 6465| 1.17 | 1.07-1.29 | <.0001        |
| Black                | With diabetes | 2384 | 1.17 | 1.07-1.29 | <.0001        |

CI, confidence interval; HR, hazard ratio; SEER, Surveillance, Epidemiology, and End Results.
All models adjusted for age, stage, comorbidities, and treatment.
| Cancer site       | Race  | Diabetes status | N     | HR   | 95% CI   | P-values |
|------------------|-------|-----------------|-------|------|----------|----------|
| Bladder          | White | Without diabetes | 12,104 | Ref  | ~         | <.0001   |
|                  |       | With diabetes   | 2,844 | 1.21 | 1.16-1.28 |          |
|                  | Black | Without diabetes | 764   | 1.24 | 1.14-1.36 |          |
|                  |       | With diabetes   | 414   | 1.32 | 1.18-1.48 |          |
|                  | White | Without diabetes | 2,154 | Ref  | ~         | .0047    |
|                  |       | With diabetes   | 553   | 1.19 | 1.07-1.33 |          |
|                  | Black | Without diabetes | 476   | 1.08 | 0.96-1.21 |          |
|                  |       | With diabetes   | 190   | 1.18 | 1.00-1.39 |          |
| Colon/Rectum     | White | Without diabetes | 48,648| Ref  | ~         | <.0001   |
|                  |       | With diabetes   | 13,112| 1.19 | 1.16-1.22 |          |
|                  | Black | Without diabetes | 4,693 | 1.14 | 1.10-1.18 |          |
|                  |       | With diabetes   | 2,493 | 1.21 | 1.16-1.27 |          |
| Corpus/Uterus    | White | Without diabetes | 17,241| Ref  | ~         | <.0001   |
|                  |       | With diabetes   | 5,502 | 1.26 | 1.22-1.31 |          |
|                  | Black | Without diabetes | 1,518 | 1.54 | 1.44-1.63 |          |
|                  |       | With diabetes   | 986   | 1.66 | 1.54-1.79 |          |
| Female Breast ER-| White | Without diabetes | 11,905| Ref  | ~         | <.0001   |
|                  |       | With diabetes   | 2,737 | 1.24 | 1.18-1.30 |          |
|                  | Black | Without diabetes | 1,402 | 1.27 | 1.19-1.37 |          |
|                  |       | With diabetes   | 773   | 1.29 | 1.19-1.41 |          |
| Female Breast ER+| White | Without diabetes | 67,613| Ref  | ~         | <.0001   |
|                  |       | With diabetes   | 15,505| 1.24 | 1.21-1.27 |          |
|                  | Black | Without diabetes | 3,912 | 1.15 | 1.11-1.21 |          |
|                  |       | With diabetes   | 2,248 | 1.39 | 1.32-1.47 |          |
| Hodgkin Lymphoma | White | Without diabetes | 731   | Ref  | ~         | .0107    |
|                  |       | With diabetes   | 229   | 1.27 | 1.07-1.51 |          |
|                  | Black | Without diabetes | 40    | 0.94 | 0.63-1.41 |          |
|                  |       | With diabetes   | 25    | 1.62 | 1.02-2.56 |          |
| Liver            | White | Without diabetes | 1,989 | Ref  | ~         | .0099    |
|                  |       | With diabetes   | 1,293 | 1.09 | 1.02-1.18 |          |
|                  | Black | Without diabetes | 229   | 0.92 | 0.80-1.06 |          |
|                  |       | With diabetes   | 161   | 1.18 | 1.00-1.39 |          |
| Myeloma          | White | Without diabetes | 5,168 | Ref  | ~         | <.0001   |
|                  |       | With diabetes   | 1,249 | 1.20 | 1.12-1.28 |          |
|                  | Black | Without diabetes | 989   | 1.01 | 0.94-1.09 |          |
|                  |       | With diabetes   | 461   | 1.07 | 0.97-1.19 |          |
| Non-Hodgkin Lymphoma | White | Without diabetes | 18,022| Ref  | ~         | <.0001   |
|                  |       | With diabetes   | 4,415 | 1.29 | 1.24-1.34 |          |
|                  | Black | Without diabetes | 806   | 1.10 | 1.01-1.20 |          |
|                  |       | With diabetes   | 422   | 1.44 | 1.29-1.61 |          |
| Ovary            | White | Without diabetes | 11,738| Ref  | ~         | <.0001   |
|                  |       | With diabetes   | 2,547 | 1.23 | 1.17-1.29 |          |
|                  | Black | Without diabetes | 733   | 1.22 | 1.13-1.32 |          |
|                  |       | With diabetes   | 401   | 1.40 | 1.26-1.56 |          |

(Continues)
DISCUSSION

Overall, our study provides estimations of the extent to which coexisting diabetes increases risk of cancer-specific death; it appears that this increased risk is present for most cancer sites. Furthermore, compared to white patients, black patients had higher death risks, particularly in the presence of diabetes for some cancer sites, particularly among women. The greatest increases in death risks were observed in black females with diabetes. However, the differing death risks by cancer site for white males and females compared to black males and females, suggest the need for further research to examine how prevalent diabetes can affect cancer deaths differently by race.

Several studies have investigated the association between preexisting diabetes and cancer mortality and were summarized in a recent meta-analysis. This report included different types of studies involving small or selected patient populations, studies limited to one cancer site, or studies conducted outside the US. The study reported a 41% increased risk of mortality among cancer patients who had diabetes compared to those without diabetes across all cancer types. Their investigation also noted significant associations between the prevalence of diabetes and increased long-term, all-cause mortality and cancers of the endometrium, breast, and colon/rectum along with nonsignificant but elevated mortality risks for prostate, gastric, hepatocellular, lung, and pancreatic cancers. While limited to using Medicare patients older than 66 years, we extend this prior research by examining differences in the risks or cancer-specific death by cancer and race for the top 14 cancer sites contributing to cancer mortality in the US through using a single large and more representative cohorts of cancer patients. Our cancer death risk estimates for specific cancers were similar to the meta-analysis findings.

In general, our findings were consistent with other previous studies showing increased cancer death risks among black men across most cancer sites. These associations remained after controlling for the presence of diabetes, suggesting racial disparities between whites and blacks regardless of the presence of diabetes. The one exception was for Hodgkin lymphoma in which death risks were not different between white and black males, perhaps due to the limited number of cases. One prior study found higher rates of deaths in black patients with Hodgkin lymphoma primarily attributed to lower socioeconomic status among black cancer patients in the population-based California Cancer Registry.

With regard to cancer-specific death risks among women, our findings supported previously reported associations between prevalent diabetes by race and cancer mortality risks with 2 notable exceptions. In our study, black females with and without prevalent diabetes had higher death risks compared to white women except for cervical cancer and myeloma in which white women with diabetes were at higher risk of mortality. One prior study has examined whether differences in mortality risk may be explained by the additional burden of comorbidities among black women with cervical cancer. The authors suggested that the lower cervical cancer mortality observed among black women with cervical cancer was due to competing morbidities. We should also note that although black women had a higher prevalence of diabetes and the difference in prevalence between whites and blacks was greater than for male cancer patients, they did not experience markedly worse 5-year survival rates as observed among colon/rectum, Hodgkin lymphoma, pancreas and stomach cancer patients.

Previous studies have suggested several explanations for the increased cancer-specific deaths reported among cancer
patients with diabetes. The association between diabetes and cancer may be direct as some evidence suggests that high levels of insulin or blood sugar in some diabetic patients may promote cancer cell growth due to increased tumor cell proliferation and metastases.\textsuperscript{48-51} Hyperglycemia may increase endothelial cell permeability, effectively changing the structure of the cell and membrane making it more susceptible to metastases.\textsuperscript{52-55} The relationship between diabetes and cancer may also be indirect, because diabetes and cancer share common risk factors such as age, sex, obesity, weight gain, poor diet, alcohol use, smoking, and physical inactivity,\textsuperscript{46} and some of these exposures may be more prevalent among blacks. Despite demographic and lifestyle risk factors having a higher impact on death risks for blacks, these risk factors may only partially explain the general pattern of increased cancer death risks for black populations,\textsuperscript{19,56} and further research is needed to identify other unknown modifiable or biologic risk factors.

Interpretation of how diverse factors may underlie the association between diabetes and cancer deaths is further complicated by treatments used to manage these conditions. Prior research has examined whether differences in cancer treatment between patients with and without diabetes may explain the differences in mortality risks. Patients with diabetes may have other diabetes-related comorbid conditions which may influence treatment plans,\textsuperscript{51} more limited response to cancer treatment, or be given less aggressive cancer treatments.\textsuperscript{57-61} It is possible that the diagnosis and treatment of cancer in diabetic patients may influence the management of their diabetes,\textsuperscript{55,51,62,63} particularly with regard to medication intensity and adherence for black populations.\textsuperscript{64,65} Existing racial disparities may be additionally worsened by difficulties in diagnosis, access to care, or access to follow-up especially for blacks.\textsuperscript{56} While we were not able to investigate specific treatment-related risk factors, there may be differences in how treatments are offered as well as differences in response to chemotherapy. It is possible that death risks may differ with regard to biological mechanisms and reactions to treatment by race. However, it was beyond the scope of our descriptive study to examine in detail the different effects by treatment. Future research including more detailed treatment data specific to each type of cancer is needed to explore that issue. Societal factors including education and socioeconomic status may also play a role in the observed health disparities regarding treatment, particularly among black women.\textsuperscript{67} Additionally, the increased risk of cancer deaths among diabetics has also been attributed to lower or suboptimal cancer screening rates.\textsuperscript{57,68,69} However, detailed data to examine those issues were not available in this study.

The main limitations in our study were the lack of biologic data, specific cancer-related and diabetes-related treatment, and lifestyle-related health behaviors that may influence diabetes and cancer outcomes. We were able to adjust for stage and initial cancer treatment according to SEER data, although some components of cancer treatment, such as chemotherapy, hormonal therapy and some forms of radiation therapy, are underreported in these data.\textsuperscript{70} Therefore, we were not able to completely control for the effect of treatment. We were also not able to assess deaths due to competing risks, particularly death due to diabetes; therefore, our estimates may not accurately reflect the risks due to cancer-specific deaths. However, this study provides a unique contribution in terms of the high-quality surveillance data including deaths from SEER linked to the Medicare data to provide population-based risk estimates of cancer-specific deaths among diabetics and nondiabetics by race. Because the Medicare data are limited to adults 65 and older, our study may not be generalizable to younger cancer populations. However, this study provides for the first time, risk estimates on the independent and joint effects of diabetes and race on cancer deaths for several cohorts of cancer patients that is more representative of this age group of cancer patients in the US than has been provided in prior studies. We also show that while the differences in diabetes rates contribute to the differences in cancer death risks between whites and blacks, those differences do not fully explain why whites have different survival than blacks.

This study is the first descriptive study to investigate how the prevalence of diabetes affects population-based cancer-specific death risks for US cancer patients across several cancer sites by race and sex. Our study provides insight for new directions for future research to address racial disparities and to better understand how prevalent diabetes may affect cancer deaths differentially by race and sex. Diabetes prevalence is increasing, and these findings can provide important information to facilitate prevention efforts to reduce the burden of diabetes among cancer populations.

**CONFLICT OF INTEREST**

There are no conflict of interest disclosures from any authors.

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**REFERENCES**

1. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. JAMA. 2015;314:1021-1029.
2. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2014.
3. Centers for Disease Control and Prevention. Diabetes Public Health Resource website. http://www.cdc.gov/diabetes/statistics/prev/national/figracesthsex.htm. Accessed May 9, 2016.

4. Beckles GL, Chou C. Disparities in the prevalence of diagnosed diabetes – United States, 1999-2002 and 2011-2014. MMWR Morb Mortal Wkly Rep. 2016;65:1265-1269.

5. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2012 Incidence and Mortality Web-based Report. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2015. www.cdc.gov/uscs.

6. Ryerson AB, Ehenman CR, Altekruse SF, et al. Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. Cancer. 2016;122:1312-1337.

7. DeSantis CE, Siegel RL, Sauer AG, et al. Cancer statistics for the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. Cancer. 2016;122:1312-1337.

8. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer. 2007;121:856-862.

9. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst. 2005;97:1679-1687.

10. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia. 2007;50:1365-1374.

11. El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol. 2006;4:369-380.

12. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer. 2005;92:2076-2083.

13. Dankner R, Boffetta P, Balicer RD, et al. Time-dependent risk of cancer after a diabetes diagnosis in a cohort of 2.3 million adults. Am J Epidemiol. 2016;183:1088-1106.

14. Connor AE, Viswanathan K, Baumgartner KB, et al. Ethnic differences in the relationships between diabetes, early age adiposity and mortality among breast cancer survivors: the Breast Cancer Health Disparities Study. Breast Cancer Res Treat. 2016;157:167-178.

15. Barone BB, Yeh H-C, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus, a systematic review and meta-analysis. JAMA. 2008;300:2754-2764.

16. Olson SH, Aatoria CL, Cote ML, et al. The impact of race and comorbidity on survival in endometrial cancer. Cancer Epidemiol Biomarkers Prev. 2012;21:753-760.

17. Waheed S, Azad N, Waheed S, Yeh HC. Racial disparities and colorectal cancer survival in older adults with and without diabetes mellitus. J Gastroenterol Hepatol. 2014;29:1963-1968.

18. Ma Y, Hebert JR, Balasubramanian R, et al. All-cause, cardiovascular, and cancer mortality rates in postmenopausal white, black, Hispanic, and Asian women with and without diabetes in the United States: the Women’s Health Initiative, 1993-2009. Am J Epidemiol. 2013;178:1533-1541.

19. Tammemagi CM, Nerenz D, Neslund-Dudas C, Feldkamp C, Nathanson D. Comorbidity and survival disparities among black and white patients with breast cancer. JAMA. 2005;294:1765-1772.

20. Charlot M, Castro-Webb N, Bethea TN, et al. Diabetes and breast cancer mortality in black women. Cancer Causes Control. 2017;28:61-67.

21. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2013. National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2013/; based on November 2015 SEER data submission, posted to the SEER web site, April 2016.

22. Warren JL, Klabunde CN, Schrage D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care. 2002;40(8 suppl):IV3-IV18.

23. Surveillance, Epidemiology, and End Results Program (SEER), National Cancer Institute. SEER*Stat software, version 8.2.1 [software program]. www.seer.cancer.gov/seerstat. Accessed November 16, 2015.

24. Engels EA, Pfeiffer RM, Ricker W, Wheeler W, Parsons R, Warren JL. Use of surveillance, epidemiology, and end results – medicare data to conduct case-control studies of cancer among the US elderly. Am J Epidemiol. 2011;174:860-870.

25. Klabunde CN, Legler JM, Warren JL, Baldwin LM, Schrag D. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. Ann Epidemiol. 2007;17:584-590.

26. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. J Clin Epidemiol. 2000;53:1258-1267.

27. Comorbidity SAS Macro (2014 version); Healthcare Delivery Research Program; National Cancer Institute. www.healthcare-delivery.care.gov/seermedicare/considerations/macro-2014.html. Accessed November 16, 2015.

28. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. Incidence of congestive heart failure in type 2 diabetes. Diabetes Care. 2004;27:1879-1884.

29. Benjamin EJ, Levy D, Vaziri SM, D’Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA. 1994;271:840-844.

30. McClellan WM, Flanders WD. Risk factors for progressive chronic kidney disease. J Am Soc Nephrol. 2003;14:S65-S70.

31. Li W, Huang E, Gao S. Type 1 diabetes mellitus and cognitive impairments: a systematic review. J Alzheimer Dis. 2017;57:29-36.

32. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1994;339:229-234.

33. Schramm TK, Gislason GH, Kober L, et al. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. Circulation. 2008;117:1945-1954.

34. Andersson C, van Gaal L, Caterson ID, et al. Relationship between HbA1c levels and risk of cardiovascular adverse outcomes and all-cause mortality in overweight and obese cardiovascular high-risk women and men with type 2 diabetes. Diabetologia. 2012;55:2348-2355.

35. Norgaard ML, Andersen SS, Schramm TK, et al. Changes in short- and long-term cardiovascular risk of incident diabetes and incident myocardial infarction – a nationwide study. Diabetesologia. 2010;53:1612-1619.

36. Mohammadi K, Woodward M, Hirakawa Y, et al. Microvascular and macrovascular disease and risk for major peripheral
arterial disease in patients with type 2 diabetes. *Diabetes Care*. 2016;39:1796-1803.

37. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560-2572.

38. Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. *Diabetes Care*. 2001;24:1433-1437.

39. Megherbi S-E, Milan C, Minier D, et al. Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke, data from the European BIOMED Stroke Project. *Stroke*, 2003;34:688-694.

40. Mantovksy B, Metzger B, Molitch M, Biller J. Cerebrovascular disorders in patients with diabetes mellitus. *J Diabetes Complications*. 1996;10:228-242.

41. Abbott RD, Donahue RO, MacMahon SW, Reed DM, Yano K. Howlader N, Ries LA, Mariotto AB, Reichman ME, Ruhl J, Cronin KA. Improved estimates of cancer-specific survival rates from population-based data. *J Natl Cancr Inst*. 2010;102:1584-1598.

42. Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. SEER cause-specific death classification. http://seer.cancer.gov/causespecific/. Accessed November 16, 2015.

43. Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. Cancer Survival Statistics: Cohort Definition Using Diagnosis Year, https://surveillance.cancer.gov/survival/cohort.html. Accessed November 16, 2015.

44. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes Care*. 2010;33:1674-1685.

45. National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2007 [article online], 2008. Atlanta, Georgia: Center for Disease Control and Prevention. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf.

46. Keegan TH, Clarke CA, Chang ET, Shema SJ, Glaser SL. Disparities in survival after Hodgkin lymphoma: a population-based study. *Cancer Causes Control*. 2009;20:1881-1892.

47. Onitilo AA, Engel JM, Glurich I, et al. Diabetes and cancer II: role of diabetes medications and influence of shared risk factors. *Cancer Causes Control*. 2012;23:991-1008.

48. Pollak M. Insulin-like growth factor-related signaling and cancer development. *Recent Results Cancer Res*. 2007;174:49-53.

49. Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. *Nat Rev Cancer*. 2004;4:505-518.

50. Richardson LE, Pollack LA. Therapy insight: influence of type 2 diabetes on the development, treatment and outcomes of cancer. *Nat Clin Pract Oncol*. 2005;2:48-53.

51. Dowling RJ, Niraula S, Stambolic V, Goodwin PJ. Metformin in cancer: translational challenges. *J Mol Endocrinol*. 2012;48:R31-R43.

52. Goodwin PJ, Ennis M, Pritchard KI, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J Clin Oncol*. 2002;20:42-51.

53. Pollak M. Insulin and insulin-like growth factor signaling in neoplasia. *Nat Rev Cancer*. 2008;8:915-928.

54. Morris AS, Edel ER. Glucose modulates basement membrane fibroblast growth factor-2 via alterations in endothelial cell permeability. *J Biol Chem*. 2007;282:14635-14644.

55. Arnold LD, Patel AV, Yan Y, et al. Are racial disparities in pancreatic cancer explained by smoking and overweight/obesity? *Cancer Epidemiol Biomarkers Prev*. 2009;18:2397-2405.

56. Lipscombe LL, Hux JE, Booth GL. Reduced screening mammography among women with diabetes. *Arch Intern Med*. 2005;165:2090-2095.

57. Pears KS, Barone BB, Snyder CF, et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. *J Clin Oncol*. 2011;29:40-46.

58. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coeberg JW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. *Int J Cancer*. 2007;129:1986-1992.

59. Meyerhardt JA, Catalano PJ, Haller DG, et al. Impact of diabetes mellitus on outcomes in patients with colon cancer. *J Clin Oncol*. 2003;21:433-440.

60. Weiser MA, Cabanillas ME, Konopleva M, et al. Relation between the duration of remission and hyperglycemia during induction chemotherapy for acute lymphocytic leukemia with a hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone/methotrexate/cytarabine regimen. *Cancer*. 2004;100:1179-1185.

61. Lefetan CS, Salas JR, Wilks IF, Zumoff B. Impact of endocrine and diabetes team consultation on hospital length of stay for patients with diabetes. *Am J Med*. 1995;99:22-28.

62. Keating NL, Zaslavsky AM, Herrinton LJ, Selby JV, Wolf RE, Ayanian JZ. Quality of diabetes care among cancer survivors with diabetes. *Med Care*. 2007;45:869-875.

63. Ferdinand KC, Nasser SA. Racial/ethnic disparities in prevalence and care of patients with type 2 diabetes mellitus. *Curr Med Res Opin*. 2015;31:913-923.

64. Rael MA, Ellis JL, Schroeder EB, et al. Intensification of antihyperglycemic therapy among patients with incident diabetes: a Surveillance Prevention and Management of Diabetes Mellitus (SUPREME-DM) study. *Pharmacoepidemiol Drug Saf*. 2014;23:699-710.

65. Heisler M, Smith DM, Hayward RA, Krein SL, Kerr EA. Racial disparities in diabetes care processes, outcomes, and treatment intensity. *Med Care*. 2003;41:1221-1232.

66. Ward E, Jemal A, Cokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. *CA Cancer J Clin*. 2004;54:78-93.

67. Beckman TJ, Cuddihy RM, Scheitel SM, Naessens JM, Killian JM, Pankratz VS. Screening mammogram utilization in women with diabetes. *Diabetes Care*. 2001;24:2049-2053.

68. Fleming ST, Pursley HG, Newman B, Pavlov D, Chen K. Comorbidity as a predictor of stage of illness for patients with breast cancer. *Med Care*. 2005;43:132-140.

69. Noone AM, Lund JL, Mariotto A, et al. Comparison of SEER treatment data with Medicare claims. *Med Care*. 2016;54:e55-e64.