Title

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Journal

Cancer Epidemiology, Biomarkers & Prevention, 32(10)

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Publication Date

2023-10-02

DOI

10.1158/1055-9965.EPI-23-0278

Peer reviewed

HHS Public Access

Author manuscript

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2024 October 02.

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2023 October 02; 32(10): 1356–1364.

doi:10.1158/1055-9965.EPI-23-0278.

New-Onset Diabetes after an Obesity-Related Cancer Diagnosis and Survival Outcomes in the Women's Health Initiative

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The publication costs of this article were defrayed in part by the payment of publication fees. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Authors' Disclosures

G.L. Anderson reports grants from NCI and NHLBI during the conduct of the study. B. Haaland reports other support from Pentara Corporation and personal fees from National Kidney Foundation outside the submitted work. R. Chlebowski reports personal fees from AstraZeneca, Novartis, and UptoDate outside the submitted work. S.A. Summers reports other support from Centaurus Therapeutics outside the submitted work. No disclosures were reported by the other authors.

Abstract

Background: Individuals diagnosed with an obesity-related cancer (ORC survivors) are at an elevated risk of incident diabetes compared with cancer-free individuals, but whether this confers survival disadvantage is unknown.

Methods: We assessed the rate of incident diabetes in ORC survivors and evaluated the association of incident diabetes with all-cause and cancer-specific mortality among females with ORC in the Women's Health Initiative cohort (N = 14,651). Cox proportional hazards regression models stratified by exposure-risk periods (0–1, >1–3, >3–5, >5–7, and >7–10 years) from ORC diagnosis and time-varying exposure (diabetes) analyses were performed.

Results: Among the ORC survivors, a total of 1.3% developed diabetes within ≤1 year of follow-up and 2.5%, 2.3%, 2.3%, and 3.6% at 1–3, 3–5, 5–7, and 7–10 years of follow-up, respectively, after an ORC diagnosis. The median survival for those diagnosed with diabetes within 1-year of cancer diagnosis and those with no diabetes diagnosis in that time frame was 8.8 [95% confidence interval (CI), 7.0–14.5) years and 16.6 (95% CI, 16.1–17.0) years, respectively. New-onset compared with no diabetes as a time-varying exposure was associated with higher risk of all-cause (HR, 1.27; 95% CI, 1.16–1.40) and cancer-specific (HR, 1.17; 95% CI, 0.99–1.38) mortality. When stratified by exposure-risk periods, incident diabetes in ≤1 year of follow-up was associated with higher all-cause (HR, 1.76; 95% CI, 1.40–2.20) and cancer-specific ($HR_{0–1}$, 1.82; 95% CI, 1.28–2.57) mortality, compared with no diabetes diagnosis.

Conclusions: Incident diabetes was associated with worse cancer-specific and all-cause survival, particularly in the year after cancer diagnosis.

Impact: These findings draw attention to the importance of diabetes prevention efforts among cancer survivors to improve survival outcomes.

Introduction

Diabetes and obesity-related cancers (ORC) share common risk factors (e.g., obesity), and underlying pathophysiological mechanisms. Common mechanisms in diabetes like hyperinsulinemia are purported to drive the development of many ORCs (1–3). Moreover, diabetes is an established risk factor for colorectal, hepatocellular, gallbladder, breast, endometrial, and pancreatic cancers (4). Patients with cancer with type 2 diabetes also remain at higher risk of cancer-specific mortality than non-diabetic patients (5). In addition, cancer treatments (chemotherapy, hormonal therapy, immunotherapy, and steroid use) and certain surgeries can induce glycemic dysfunction (6–10) and trigger secondary diabetes (11). Yet, data remain limited on the relationships among ORC, incident diabetes after cancer diagnosis, and mortality.

Few studies have examined the relationship between new-onset diabetes after ORC diagnosis and survival outcomes (12–15). These studies either had shorter follow-up durations (2–6 years), and/or the time to diabetes incidence after cancer diagnosis was not described. We characterized the incidence of diabetes after an ORC diagnosis and investigated the association of new-onset diabetes with cancer-specific and all-cause mortality among postmenopausal US women diagnosed with ORC (herein referred to as

ORC survivors) in the Women's Health Initiative (WHI). We hypothesized that a new diagnosis of diabetes among female ORC survivors, compared with no diabetes diagnosis, would be associated with a higher risk of all-cause and cancer-specific mortality.

Materials and Methods

Study design and population

The WHI is a large, prospective cohort of 161,808 postmenopausal females ages 50 to 79 years at enrollment between 1993 and 1998 (16, 17). The WHI comprises an observational study (OS) and randomized, controlled clinical trials (CT) where participants were assigned to a low-fat diet, and/or hormone therapy (HT), and/or calcium and vitamin D supplementation. Upon trial completion, follow-up of the WHI participants continued through two observational extension studies. Institutional Review Board approval and written informed consent were obtained from participants at all the WHI clinical centers in accordance with recognized ethical guidelines.

Information on medical outcomes, including diabetes and cancer, in the CTs was collected every 6-months during the CT intervention period with subsequent annual updates. Outcome ascertainment in the OS occurred annually. Reports of cancer were verified initially by medical record review by trained physician adjudicators at the local clinical centers. Final adjudication was performed at the WHI clinical coordinating center. Deaths were verified by medical record or death certificate review at the clinical coordinating center and, in some cases, by reports from relatives. Serial National Death Index (NDI) queries provided additional survival information, including cause of death, regardless of reconsent status.

The ORC analytic sample for the current analyses included the WHI OS and CT participants with no cancer diagnosis before enrollment but with incident ORC diagnosis during the study period. ORCs include cancers of the breast (postmenopausal), colon/rectum, uterus, ovary, pancreas, blood (multiple myeloma), thyroid, kidney (renal cell), gallbladder, liver, gastric cardia, esophagus (adenocarcinoma), and brain (meningioma; ref. 18). ORC survivors (N = 14,651 with first incident cancer after the WHI baseline assessment) with a mean (SD) follow-up time of 19.25 (5.41) years were included. Fig. 1 shows ORC analytic sample derivation.

Exposure classification

At the WHI study entry, participants responded to the question, "Did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant?" (this definition included those not receiving insulin or pills for diabetes). During ongoing follow-up, participants were asked by self-administered medical history questionnaires, "Since the date given on this form, has a doctor prescribed any of the following pills or treatments?" Choices included "pills for diabetes" and "insulin shots for diabetes." In previous validation studies, this method of diabetes ascertainment within the WHI had a positive predictive value of 78% to 82% (19, 20). We stratified analyses into exposure-risk periods because new-onset diabetes etiology could differ by duration since cancer diagnosis (i.e., 0–1, >1–3, >3–5, >5–7, and >7–10 years after an ORC diagnosis).

Outcome ascertainment

All-cause mortality was the primary outcome, and ORC-specific mortality was the secondary outcome, followed from 1, 3, 5, 7, and 10-years after ORC diagnosis date to the end of the extension 2 study period (2010–2020). Mortality was adjudicated from medical records through the WHI main and extension studies and via linkage to the NDI.

Covariate assessment

We adjusted models for potential confounders, including age, education (<high school, some college, and college graduate), race (white, other), ethnicity (Hispanic, non-Hispanic), marital status (married, not married), smoking status (never, past, current), alcohol use (≤ 1 vs. > 1 standard drink/d), physical activity (< vs. ≥30 minutes moderate activity/d), fiber (< or ≥25 g/d) and red-meat (< or ≥500 g/wk) intakes (21), body mass index (BMI <25, ≥25 to <30, ≥30 to <35, ≥35 Kg/m^2; ref. 22), prevalent cardiovascular disease (CVD; yes/no), hypertension (yes/no), cancer type, stage, and grade, early/multiparty, incidence of a secondary cancer, and HT use for hormone-driven cancers. Covariates measured closest to the date of ORC diagnosis were included in analyses. Education, race, ethnicity, hypertension, marital status, and smoking status were self-reported at baseline and during the WHI follow-up. We combined Black, Asian, American Indian/Alaska Native and Native Hawaiian/Other pacific islander in to one single category (other) for the purpose of this analysis, given the small percentage of participants identified for each group (the detailed classification by race is presented in Table 1). Dietary factors were measured via validated Food Frequency Questionnaire (FFQ; ref. 23). BMI was computed from objectively measured height and weight collected at the research clinic using study approved protocols. CVD was defined as coronary heart disease or stroke adjudicated from medical records through the WHI main and extension studies (24). Individuals with missing values for any of the covariates were excluded (N = 1,400; Supplementary Table S1).

Statistical analysis

Primary analysis—Characteristics of study participants are summarized as N(%) for categorical variables and mean standard deviation for continuous variables. Participants with and without incident diabetes were compared using a χ^2 test. To measure the association of new-onset diabetes with risk of all-cause and cancer-specific mortality among ORC survivors when compared with no diabetes diagnosis, we performed a time-varying analysis using Cox proportional hazards (PH) regression analysis where diabetes incidence was considered a time-varying exposure. To measure the association of incident diabetes between 0–1, >1–3, >3–5, >5–7, >7–10 years after the start of follow-up with all-cause mortality, we calculated hazard ratios (HR) and 95% confidence intervals (CI) using multivariable, stratified Cox PH regression analysis with time zero at 1, 3, 5, 7, and 10 years from a cancer diagnosis. We ran (i) age-adjusted (ii); age, BMI, and smoking-adjusted, and (iii) multivariable-adjusted models. For cancer-specific mortality, death due to other causes was considered a competing risk using multi-state Cox PH regression. Statistical significance was determined at $\alpha < 0.05$. Analyses were conducted using R (R Core Team, Vienna, Austria, URL: https://www.R-project.org/).

Secondary analysis—We performed tests for effect modification by BMI, smoking, HT use, and secondary cancer incidence among ORC survivors by including a variable by effect–modifier interaction term in the Cox models and testing its significance using likelihood ratio (LR) tests.

Sensitivity analysis—We performed a lag analysis allowing a lag period of 6-months during the first risk exposure period (0–1 years after ORC diagnosis) to account for potential existing but undiagnosed diabetes. We also performed a sensitivity analysis by excluding individuals diagnosed with distant-stage cancer.

To illustrate differences between cancer survivors and cancer-free females, we performed a comparative analysis in a parallel cohort of cancer-free individuals within the WHI (*N* = 29,302) who were matched on age at cancer diagnosis for the ORC analytic sample with a mean (SD) follow-up time of 17.96 (5.17) years (methods and results detailed in Supplementary Methods and Results and Supplementary Tables S2–S4).

Data availability—All the deidentified individual participant data collected during the trial will be available through the WHI online resource, https://www.whi.org/datasets whereas the WHI remains funded (currently through 2028) and indefinitely through BioLINCC, https://biolincc.nhlbi.nih.gov/studies/whi_ctos/. Eligible researchers (See https://www.whi.org/propose-a-paper for eligibility) with an approved specified purpose may download the data directly at the WHI online resource. Other researchers may download the publicly available data through BioLINCC, in accordance with NHLBI's BioLINCC guidelines.

Results

Participant characteristics are detailed in Table 1. Participants were predominantly white, and ages 72 ± 8 years at cancer diagnosis. Most participants had at least some college education, were married, non-smokers, non-drinkers, and about a third had a family history of diabetes. Breast cancer was the most diagnosed ORC (65%), followed by colorectal cancer (11%), and endometrial cancer (8%). Secondary cancer was diagnosed in 11% (*N* = 1,595) of participants.

The *N* (%) of new-onset diabetes diagnosed in each risk period were: 0–1 years, 168/13,139 (1.28%); >1–3 years, 284/11,434 (2.48%); >3–5 years, 223/9,878 (2.26%); >5–7 years, 194/8,511 (2.28%); and >7–10 years, 234/6,491 (3.60%; Table 1).

There were 2,022 ORC-specific deaths and 5,377 deaths from all causes during a median (IQR) 9.87 (10.10) years of follow-up.

New-onset diabetes and all-cause mortality among ORC survivors in the WHI

The median survival was 8.8 (95% CI, 7.0–14.5) years for those with new-onset diabetes diagnosed in the first year after cancer diagnosis, compared with 16.6 (95% CI, 16.1–17.0) years among those without a diagnosis of diabetes. Median survival was 13.3 (95% CI, 11.5–14.8) years for those diagnosed with diabetes >1–3 years after cancer diagnosis

compared with 15.8 (95% CI, 15.5–16.2) years for participants with no diabetes diagnosis (Fig. 2A and B).

In the time-varying exposure analysis, incident diabetes among ORC survivors compared with no diabetes was associated with 27% increased hazard of all-cause mortality (HR, 1.27; 95% CI, 1.16–1.40) and 17% increased hazard of cancer-specific mortality (HR, 1.17; 95% CI, 0.99–1.38).

When stratified by exposure-risk periods, new-onset diabetes diagnosed up to 5-years after ORC diagnosis was associated with higher risk of all-cause mortality (see Fig. 3; Supplementary Tables S2, S3, S5, and S6 for details).

In analyses stratified by cancer type, newly diagnosed diabetes was positively associated with all-cause mortality among breast cancer survivors across risk periods up to, but not after, 3 years [($HR_{0–1}$, 1.69; 95% CI, 1.26–2.27); ($HR_{>1–3}$, 1.51; 95% CI, 1.20–1.90)]. Increased risk of all-cause mortality was observed among colorectal cancer survivors ($HR_{0–1}$, 2.19; 95% CI, 1.09–4.39) and individuals with a history of pancreatic cancer ($HR_{0–1}$, 3.46; 95% CI, 1.56–7.69) when diabetes was diagnosed during the first year after cancer diagnosis. No associations of new-onset diabetes and all-cause mortality were observed among women with multiple myeloma, endometrial, ovarian, or thyroid cancers, but sample sizes were very small (e.g., 0–9 patients per risk period; Supplementary Tables S5 and S6). The results for (i) age adjusted, and (ii) age, BMI and smoking adjusted models are presented in Supplementary Tables S2 and S5.

When excluding participants diagnosed with diabetes in the first 6 months of the first risk period, 66 participants were removed and the estimates did not change materially (HR, 1.66; 95% CI, 1.22–2.24; Supplementary Table S7). Excluding individuals diagnosed with distant-stage cancer (N = 1,557) did not change the effect estimates materially (HR, 1.25; 95% CI, 1.13–1.38 compared with HR, 1.27; 95% CI, 1.16–1.40).

New-onset diabetes and cancer-specific mortality among ORC survivors in the WHI

Incident compared with no diabetes diagnoses early in the survivorship trajectory was associated with increased risk of cancer-specific mortality for all cancer types combined (see Fig. 4), pancreatic cancer–specific death in the first risk period that had adequate sample size to compute the HR, and multiple myeloma–specific death in the first three risk periods (see Supplementary Tables S5 and S6 for details).

The magnitude of association of new-onset diabetes after ORC diagnosis with cancer-specific mortality remained the same after accounting for a 6-month lag period ($HR_{0–1}$, 1.88; 95% CI, 1.16–3.04). When excluding participants with pancreatic cancer and multiple myeloma, the effect estimates were attenuated and became statistically insignificant ($HR_{0–1}$, 1.31; 95% CI, 0.78–2.18).

The association of diabetes incidence and all-cause mortality was not modified by BMI (P = 0.51), smoking status (P = 0.11), or secondary cancer (P = 0.06), but slightly modified by HT use (P = 0.04) when comparing models with/without a diabetes multiplied by effect modifier interaction term with the LR test.

Discussion

In a prospective cohort of postmenopausal women, incidence of new-onset diabetes was persistently higher across the time periods after an ORC diagnosis and was associated with increased risk of all-cause and cancer-specific mortality, with stronger magnitudes of association when diabetes was diagnosed in the first year after cancer diagnosis. New-onset diabetes was associated with cancer-specific mortality for all cancer types combined, but when stratified by cancer type only multiple myeloma and pancreatic cancer survivors experienced higher risk of cancer-specific mortality with diabetes diagnosed in the first 3-years after cancer diagnosis. Breast and colorectal cancer survivors with new-onset diabetes up to 5-years after ORC diagnosis had higher risk of all-cause mortality. Diabetes incidence in the later follow-up periods after ORC diagnosis was non-statistically significantly associated with mortality. It is possible that power was inadequate in the later follow-up periods owing to excluding individuals with diabetes incidence in the prior risk periods, loss to follow-up that increased over time, and competing death rates being higher. Another possibility is survivor bias, wherein individuals surviving longer tend to be healthier in general or have less aggressive cancers.

The biological mechanisms driving new-onset of diabetes among patients with ORC are not well understood, but may be a parallel comorbidity driven by shared genetics or risk factors like obesity (25), or a consequence of tumor metabolism, cancer treatment, or substantial changes to diet and physical activity that are influenced by cancer-related pain, discomfort, stress, and fatigue (26). In addition, a recent systematic review and meta-analysis showed that patients with cancer have high levels of insulin resistance, a precursor of type 2 diabetes (27). Anticancer agents such as mTOR or PI3K–Akt–mTOR pathway inhibitors, immune checkpoint inhibitors, and corticosteroids have been associated with metabolic toxicities like hyperglycemia (28), and they can trigger autoimmune diabetes (29). Pancreatectomy, radiotherapy to the pancreas (30, 31), and chemotherapy have each been associated with new-onset diabetes as well (32). According to a meta-analysis, breast cancer survivors receiving tamoxifen, but not aromatase, had elevated risk of secondary diabetes compared with patients not taking those medications (33). Cancer-induced cachexia, which is highly prevalent among patients with pancreatic and colorectal cancers and to some extent among breast cancer survivors (34), can also promote diabetes-relevant mechanisms like inflammation and insulin resistance (35). Additional obesity-related mechanisms common to both diabetes and cancer include inflammation, oxidative stress, and hormone metabolism (i.e., insulin-like growth factor-1, adiponectin and leptin; ref. 36). Alterations in mTOR signaling, as seen in diabetes (37), enable the hallmarks of cancer, including mTORC1-driven selective proliferative advantage, invasion, and metastasis (38). Tumor-induced inflammatory cytokines drive insulin resistance and hyperglycemia, which are hallmarks of diabetes (39). Furthermore, co-occurring diabetes at the time of cancer treatment (often during the first year after a cancer diagnosis) can complicate the choice of and response to cancer treatment, impacting overall survival (14).

Survivors of some cancer types are more likely to develop diabetes compared with cancer-free individuals, even when matched for level of adiposity (40–44). Yet, the prognostic consequences of new-onset diabetes in this population have rarely been investigated.

Diabetes is a major risk factor for cardiovascular disease, particularly among older adults, which is a leading cause of death among cancer survivors (45). Prevalent diabetes at cancer diagnosis, compared with no diabetes diagnosis, has been associated with a 40% higher risk of all-cause mortality among cancer survivors (46). Our findings suggest that risk of death may be higher (76%) if diabetes is diagnosed during the first year after cancer diagnosis (Fig. 3). A cohort of patients with cancer in Denmark similarly demonstrated a higher risk of all-cause mortality (HR, 1.21; 95% CI, 1.04–1.41) with new-onset compared with no diabetes after cancer diagnosis (12). However, median follow-up time was 2.34 years compared with 9.87 years in our study. In the National Health Interview Survey cohort, diabetes diagnosed after cancer with a median 13-years' follow-up was associated with increased risk of all-cause mortality among survivors of breast, prostate, and colorectal cancers combined (HR, 1.35; 95% CI, 1.12–1.63; ref. 14). In that study, the timing of diabetes exposure post-cancer diagnosis was not clearly defined or accounted for in the analysis, and the sample included males and females.

When stratified by cancer type, new-onset compared with no diabetes during the first 3 years after a cancer diagnosis among breast, colorectal, and pancreatic cancer survivors was associated with higher all-cause mortality. Similar results were reported by Shao and colleagues (15) among patients with breast cancer diagnosed with diabetes at or after cancer diagnosis (HR, 1.39; 95% CI, 1.16–1.66). In another study, new-onset diabetes among patients with pancreatic cancer was associated with greater risk of all-cause mortality compared with no diabetes (HR, 1.23; 95% CI, 1.09–1.40), but estimates were attenuated among patients with pancreatic resection (HR, 1.08; 95% CI, 0.82–1.43; ref. 13). However, the definition of new-onset diabetes included cases diagnosed within 3 years before pancreatic cancer diagnosis. In our study, data on pancreatic resection were unavailable.

We observed a higher risk of cancer-specific mortality (all cancers combined) among ORC survivors with incident diabetes compared with no diabetes diagnosis. However, a sensitivity analysis revealed that the higher cancer-specific death seen with new-onset diabetes was likely driven by the association among patients with pancreatic cancer and multiple myeloma, rather than other cancer types. Up to 80% of patients with pancreatic cancer present with new-onset diabetes or hyperglycemia, which often resolve upon pancreatic cancer resection, suggesting that pancreatic cancer is causal in the development of diabetes (47). Because long-term survival for patients with pancreatic cancer is <5%, estimates of cancer-specific mortality mirror those of all-cause mortality as nearly all patients die from the disease (48). We were unable to distinguish patients that received pancreatectomy, which may have resulted in misclassification of those at risk of diabetes. The 6-month lag analysis showed that a new-onset of diabetes among pancreatic cancer survivors remained associated with all-cause and cancer-specific mortality. Survivors of multiple myeloma, on the other hand, often receive high doses of glucocorticoids as part of their cancer treatment, which can induce hyperglycemia and diabetes (49). Furthermore, 20% of the patients newly diagnosed with multiple myeloma have renal failure, which is also associated with incident diabetes (50).

Diabetes and other metabolic complications are an important consideration in oncology clinical practice. A National Cancer Institute expert panel and various working groups

have published recommendations on managing metabolic dysregulation stemming from cancer treatment (51–53). Recommendations include close monitoring of blood glucose levels during treatment, at follow-up clinical visits, and at home between treatment cycles. Metformin use and lifestyle intervention are recommended for treating fasting glucose between 125 and 160 mg/dL, and insulin and oral medication are recommended when fasting glucose levels exceed 200 mg/dL. When fasting glucose levels are >500 mg/dL, it is recommended to postpone cancer treatment and receive endocrinology specialist treatment until blood glucose is <250 mg/dL (51–53).

Strengths of the current study include the prospective study design with extended follow-up of >20 years and adjudicated outcomes. Death because of other causes was considered a competing risk in cancer-specific analyses, which reduces risk of inflated estimates (54). We minimized the possibility of confounding by cancer treatment failure or peri-treatment mortality as time zero for the first exposure-risk period was 1-year post-cancer diagnosis. However, this could lead to survival bias. Cancer treatment data were unavailable and repeat assessment of diet, exercise, and other lifestyle behaviors after cancer diagnosis was not obtained, but our regression models were adjusted for cancer type, stage, and grade to account for disease severity, which is associated with cancer treatment type (55). Models were also adjusted for diet, physical activity, and smoking history measured closest to the date of ORC diagnosis. As our study evaluates incident diabetes among ORC survivors, it is less likely that patients with cancer received glucose lowering drugs that could influence selection or effect of cancer treatment. However, self-reported diabetes status could lead to exposure misclassification, and lack of information on cancer treatment type could contribute to residual confounding. Of note, prior analyses in the WHI suggest self-reported diabetes is accurately reported (20). The study population included postmenopausal, predominantly white females, limiting generalizability. Although powered to evaluate all-cause and cancer-specific mortality for all ORCs combined, power was weaker to investigate associations by cancer type, which will be important to replicate in future studies because cancers arising in different organs have vastly different etiology. Covariates were measured at different times close to, but not after, cancer diagnosis, which could result in residual confounding.

In conclusion, new-onset diabetes was associated with higher all-cause and cancer-specific mortality, most notably when diabetes was diagnosed early in the cancer survivorship trajectory. These findings draw attention to the importance of diabetes prevention efforts among cancer survivors to improve survival outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the WHI participants and staff for their many contributions. NIH/NCI, grant/award number: 1F99CA264400-01 and 4K00CA264400-02 (to P. Karra), University of Utah Health Driving Out Diabetes Seed grant, a Larry H. Miller Family Wellness Initiative and the Huntsman Cancer Institute Cancer Center (P30CA040214, to Mary C. Playdon), and NIH/NCI K07CA222060 (to S.Hardikar).

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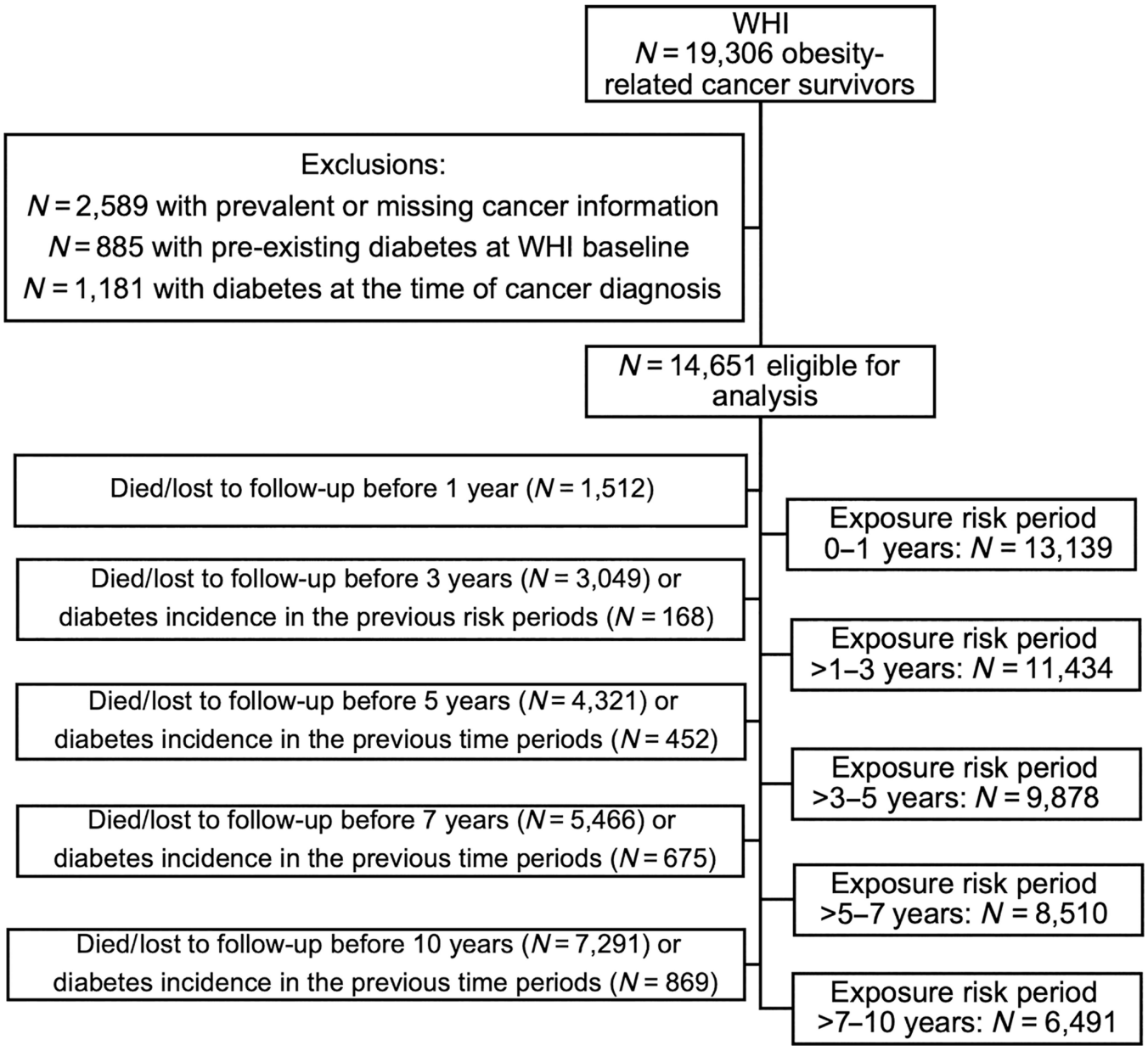

Figure 1.
Study schematic of participant selection for the obesity-related cancer analytic sample among postmenopausal US females in the WHI.

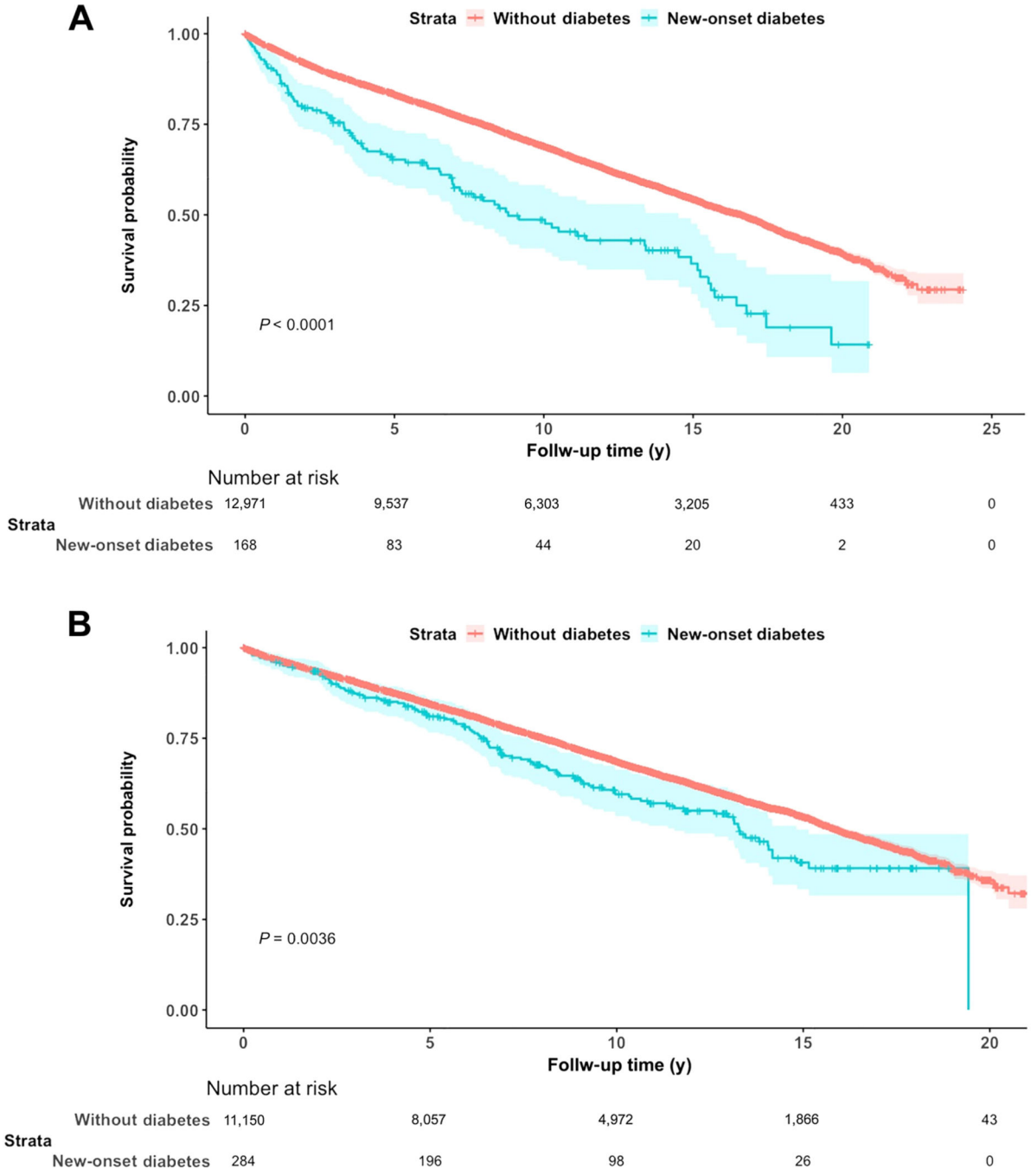

Figure 2.

Kaplan–Meier survival curveswith 95% confidence intervals for all-cause survival comparing new-onset diabetes diagnosed (*A*) 0–1 Years and (B) >1–3 years after ORC diagnosis with no diabetes diagnosis among postmenopausal females in the WHI.

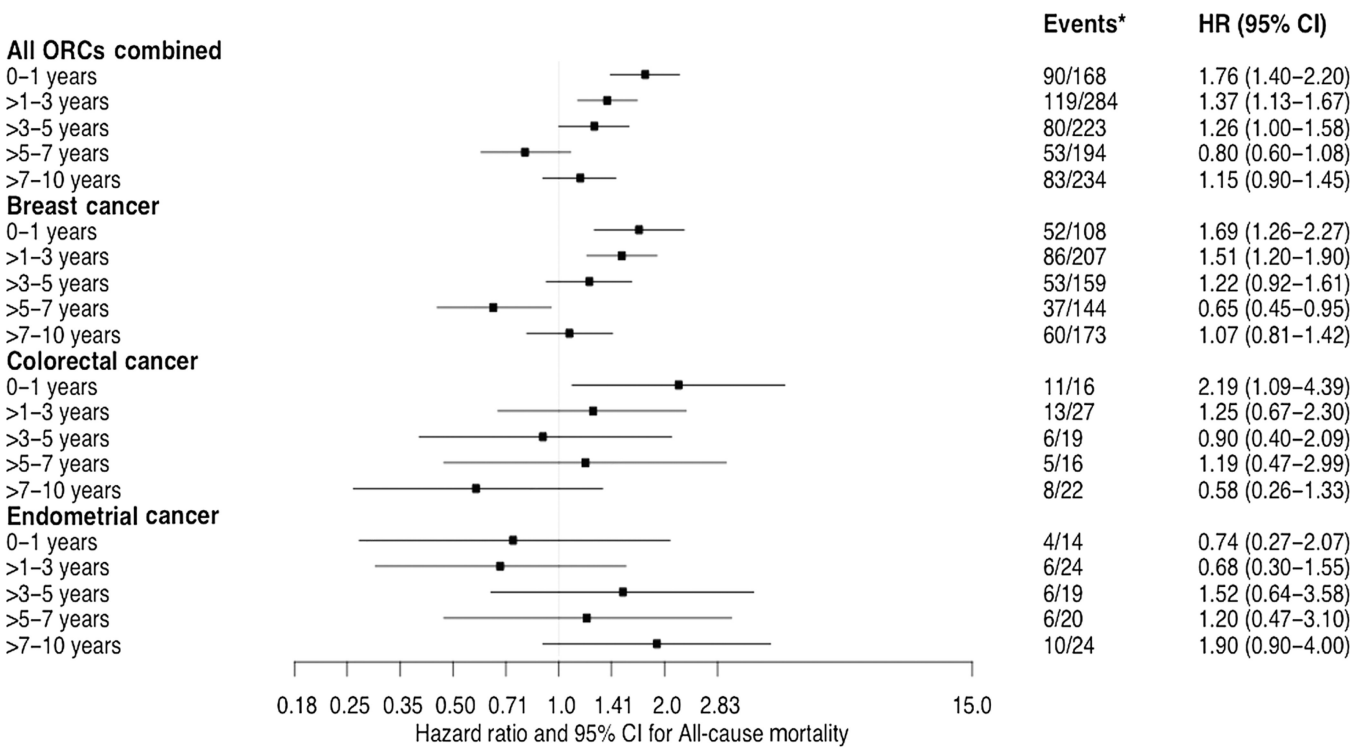

Figure 3.

Hazard ratios and 95% confidence intervals for the association of incident diabetes (0–1, >1–3, >3–5, >5–7, and >7–10 years after cancer diagnosis) with all-cause mortality among postmenopausal female ORC survivors in the WHI. **N*, deaths new-onset diabetes/*N*, new-onset diabetes. Model adjusted for demographics (age, education, race/ethnicity, and marital status), lifestyle (smoking status, physical activity, alcohol use, fruits and vegetable intake, fiber intake, red-meat intake, and BMI), comorbidities (hypertension and cardiovascular diseases), cancer characteristics (cancer type, stage, and grade), hormonal factors for female cancers (parity and hormone therapy use). Effect estimates for cancer-specific analyses with small sample sizes are not presented here.

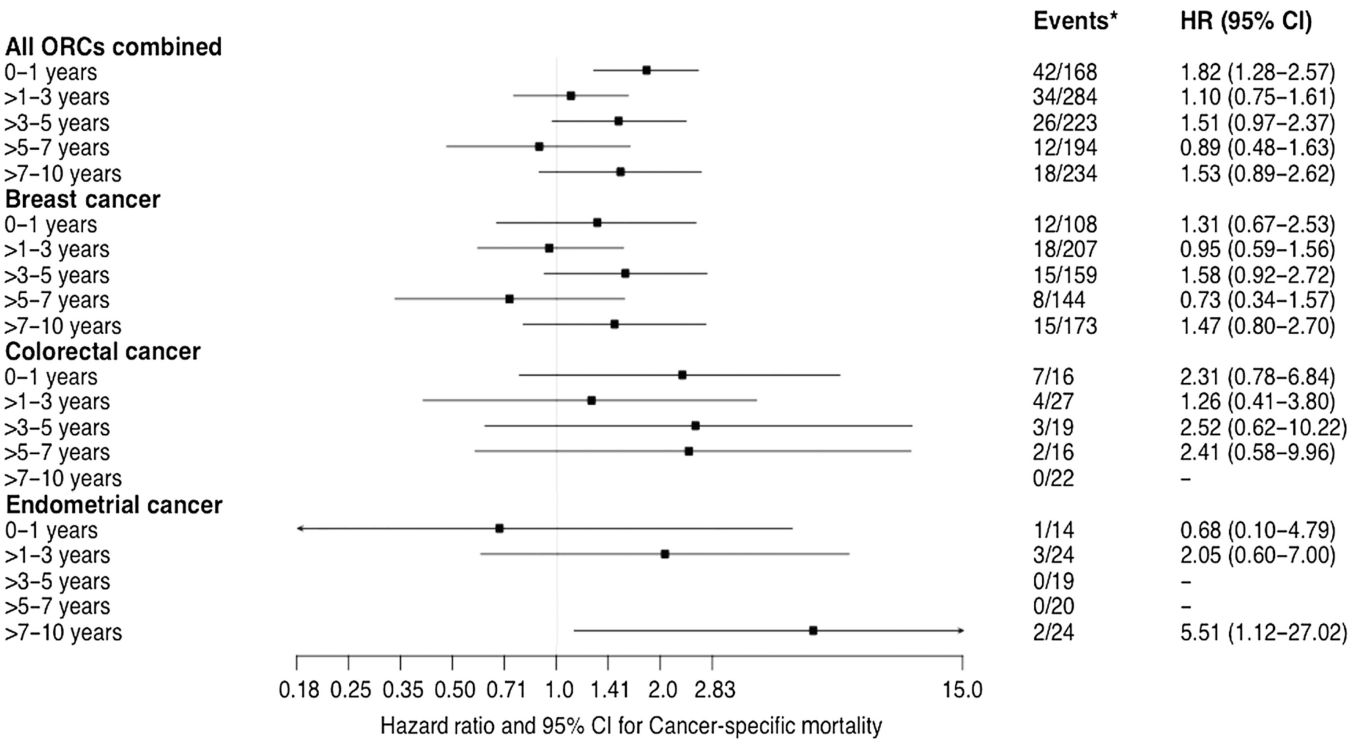

Figure 4.

Hazard ratios and 95% confidence intervals for the association of incident diabetes (0–1, >1–3, >3–5, >5–7, and >7–10 years after cancer diagnosis) with cancer-specific mortality among postmenopausal female ORC survivors in the WHI. **N*, deaths new-onset diabetes/*N* new-onset diabetes. Model adjusted for demographics (age, education, race/ethnicity, and marital status), lifestyle (smoking status, physical activity, alcohol use, fruits and vegetable intake, fiber intake, red-meat intake, and BMI), comorbidities (hypertension and cardiovascular diseases), cancer characteristics (cancer type, stage, and grade), hormonal factors for female cancers (parity and hormone therapy use). Effect estimates for cancer-specific analyses with small sample sizes are not presented here.

Table 1.

Demographic characteristics of postmenopausal US females with ORC in the WHI (N = 14,651).

Characteristic	All ORC analytic sample (N = 14,651)	ORC with diabetes incidence (N = 1,712)	ORC with diabetes incidence (N = 12,939)	P value (χ^2 test)
Age at cancer diagnosis (y; Mean ± SD)	72.03 ± 8.15	69.55 ± 7.37	72.47 ± 8.18	<0.001**
Education N(%)[a]				0.41
≤High school	3,944 (26.92%)	447 (26.11%)	3,497 (27.03%)	
Some college	3,886 (26.52%)	476 (27.80%)	3,410 (26.35%)	
College graduate	6,718 (45.85%)	777 (45.39%)	5,941 (45.92%)	
Race N(%)[a]				<0.001**
White	13,193 (90.05%)	1,454 (84.93%)	11,739 (90.73%)	
Black	856 (5.84%)	159 (9.29%)	697 (5.39%)	
Asian	278 (1.90%)	43 (2.51%)	235 (1.82%)	
American Indian/Alaska Native	28 (0.19%)	2 (0.11%)	26 (2.01%)	
Native Hawaiian/Other pacific islander	9 (0.06%)	2 (0.11%)	7 (0.05%)	
More than one race	147 (1.00%)	22 (1.29%)	125 (0.97%)	
Unknown/Not reported	140 (0.96%)	30 (1.75%)	110 (0.85%)	
Ethnicity N(%)[a]				0.02*
Not Hispanic/Latino	14,198 (96.91%)	1,645 (96.09%)	12,553 (97.02%)	
Hispanic/Latino	387 (2.64%)	60 (3.50%)	327 (2.53%)	
Marital status N(%)[a]				0.47
Married	8,960 (61.16%)	1,033 (60.34%)	7,927 (61.26%)	
Not Married	5,638 (38.48%)	672 (39.25%)	4,966 (38.38%)	
Smoking status N(%)[a]				
Never smoker	7,242 (49.43%)	827 (48.31%)	6,415 (49.58%)	0.68
Former smoker	6,374 (43.51%)	759 (44.33%)	5,615 (43.40%)	
Current smoker	866 (5.91%)	101 (5.90%)	765 (5.91%)	
Alcohol use N(%)[a]				<0.001**
≤1 standard drink/d	12,705 (86.72%)	1,533 (89.54%) 176	11,172 (86.34%)	
>1 standard drink/d	1,900 (12.97%)	(10.28%)	1,724 (13.32%)	0.21
Physical Activity N(%)[a]				

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2024 October 02.

Characteristic	All ORC analytic sample (*N* = 14,651)	ORC with diabetes incidence (*N* = 1,712)	ORC with diabetes incidence (*N* = 12,939)	*P* value (χ^2 test)
<30 min moderate activity/d	14,232 (97.14%)	1,668 (97.43%)	12,564 (97.10%)	
≥30 min moderate activity /d	318 (2.17%)	30 (1.75%)	288 (2.22%)	
BMI (Kg/m^2) *N*(%)[a]				<0.001**
<25	4,970 (33.92%)	2,747 (18.75%)	4,579 (35.39%)	
25 ≤ 30	5,101 (34.82%)	543 (31.72%)	4,558 (35.23%)	
30 ≤ 35	2,747 (18.75%)	423 (24.71%)	2,324 (17.96%)	
35+	1,704 (11.63%)	339 (18.80%)	1,365 (10.55%)	
CVD *N*(%)[a]				0.17
No	11,030 (75.28%)	1,265 (73.89%)	9,765 (75.47%)	
Yes	3,121 (21.30%)	386 (22.55%)	2,735 (21.14%)	
Hypertension *N*(%)[a]				<0.001*
No	4,485 (33.26%)	308 (17.99%)	4,177 (32.28%)	
Yes	9,993 (65.56%)	1,390 (81.19%)	8,603 (66.49%)	
Parity *N*(%)[a]				0.16
0	1,923 (13.13%)	211 (12.32%)	1,712 (13.23%)	
1–2	5,115 (34.91%)	631 (36.86%)	4,484 (34.65%)	
3+	7,552 (51.55%)	861 (50.29%)	6,691 (51.71%)	
HT use *N*(%)[a]				<0.001**
No	9,283 (63.36%)	1,023 (59.75%)	8,260 (63.84%)	
Yes	5,144 (35.11%)	671 (39.19%)	4,473 (34.57%)	
Cancer Type *N*(%)[a]				<0.001**
Breast: postmenopausal	9,558 (65.24%)	1,215 (70.97%)	8,343 (64.48%)	
Colorectal	1,553 (10.60%)	157 (9.17%)	1,396 (10.79%)	
Corpus uteri	1,235 (8.43%)	162 (9.46%)	1,073 (8.29%)	
Ovary	740 (5.10%)	39 (2.28%)	701 (5.42%)	
Pancreas	556 (3.79%)	43 (2.51%)	513 (3.96%)	
Multiple myeloma	357 (2.44%)	18 (1.05%)	339 (2.62%)	
Thyroid	318 (2.17%)	57 (3.33%)	261 (2.02%)	
Kidney: renal-cell	103 (0.70%)	13 (0.76%)	90 (0.70%)	
Gallbladder	80 (0.55%)	0 (0.00%)	80 (0.62%)	

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2024 October 02.

Characteristic	All ORC analytic sample (*N* = 14,651)	ORC with diabetes incidence (*N* = 1,712)	ORC with diabetes incidence (*N* = 12,939)	*P* value (χ^2 test)
Hepatocellular carcinoma	58 (0.40%)	3 (0.18%)	55 (4.25%)	
Gastric cardia	47 (0.32%)	4 (0.23%)	43 (0.33%)	
Esophagus: adenocarcinoma	46 (0.31%)	1 (0.06%)	45 (0.35%)	
Meningioma	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Cancer Stage *N*(%)[a]				<0.001**
In situ	1,864 (12.72%)	267 (15.60%)	1,597 (12.34%)	
Localized	8,016 (54.71%)	1,048 (61.21%)	6,968 (53.85%)	
Regional	2,990 (20.41%)	319 (18.63%)	2,671 (20.64%)	
Distant	1,557 (10.63%)	58 (3.38%)	1,499 (11.59%)	
Unknown	223 (1.52%)	20 (1.17%)	203 (1.57%)	
Cancer Grade *N*(%)[a]				0.04*
Well differentiated	2,639 (18.01%)	338 (19.74%)	2,301 (17.78%)	
Moderately differentiated	5,466 (37.30%)	663 (38.73%)	4,803 (37.12%)	
Poorly differentiated	3,116 (21.27%)	350 (20.44%)	2,766 (21.38%)	
Other	906 (6.18%)	101 (5.90%)	805 (6.22%)	
Unknown	2,524 (17.23%)	260 (15.19%)	2,264 (17.50%)	
Secondary cancer *N*(%)[a]				<0.001**
No	13,056 (89.11%)	1,451 (84.75%)	11,605 (89.69%)	
Yes	1,595 (10.89%)	261 (15.24%)	1,334 (10.31%)	
Proportion of diabetes incidence *N*(%)[a]				
0–1 years	168 (1.28%)	—	—	
>1–3 years	284 (2.48%)	—	—	
>3–5 years	223 (2.26%)	—	—	
>5–7 years	194 (2.28%)	—	—	
>7–10 years	234 (3.60%)	—	—	

[a]Values may not sum to 100% due to missing values.

*, <0.05

**, <0.001.

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