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Bethany B. Barone; Hsin-Chieh Yeh; Claire F. Snyder; et al.

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Long-term All-Cause Mortality in Cancer Patients With Preexisting Diabetes Mellitus

A Systematic Review and Meta-analysis

Bethany B. Barone, ScM

Hsin-Chieh Yeh, PhD

Claire F. Snyder, PhD

Kimberly S. Peairs, MD

Kelly B. Stein, MD

Rachel L. Derr, MD

Antonio C. Wolff, MD

Frederick L. Brancati, MD, MHS

ABOUT 20 MILLION AMERICANS have diabetes mellitus, corresponding to 7% of the US adult population.¹ Because some cancers—including cancers of the breast,² colorectum,³ endometrium,⁴ liver,⁵ and pancreas⁶—occur more commonly in individuals with diabetes, the prevalence of diabetes in newly diagnosed cancer patients is even higher, with estimates ranging from 8% to 18%.⁷ Adults with diabetes experienced increased cancer mortality in the American Cancer Society Cancer Prevention Study II,⁸ but not in the Second National Health and Nutrition Examination Survey Mortality Follow-Up.⁹

However, the association of preexisting diabetes in newly diagnosed cancer patients with long-term, all-cause mortality has not been systematically assessed. Cancer patients with diabetes may receive less aggressive cancer treatment or less aggressive diabetes care, both of which could compromise survival.¹⁰ Our objective was to

Context Diabetes mellitus appears to be a risk factor for some cancers, but the effect of preexisting diabetes on all-cause mortality in newly diagnosed cancer patients is less clear.

Objective To perform a systematic review and meta-analysis comparing overall survival in cancer patients with and without preexisting diabetes.

Data Sources We searched MEDLINE and EMBASE through May 15, 2008, including references of qualifying articles.

Study Selection English-language, original investigations in humans with at least 3 months of follow-up were included. Titles, abstracts, and articles were reviewed by at least 2 independent readers. Of 7858 titles identified in our original search, 48 articles met our criteria.

Data Extraction One reviewer performed a full abstraction and other reviewers verified accuracy. We contacted authors and obtained additional information for 3 articles with insufficient reported data.

Results Studies reporting cumulative survival rates were summarized qualitatively. Studies reporting Cox proportional hazard ratios (HRs) or Poisson relative risks were combined in a meta-analysis. A random-effects model meta-analysis of 23 articles showed that diabetes was associated with an increased mortality HR of 1.41 (95% confidence interval [CI], 1.28-1.55) compared with normoglycemic individuals across all cancer types. Subgroup analyses by type of cancer showed increased risk for cancers of the endometrium (HR, 1.76; 95% CI, 1.34-2.31), breast (HR, 1.61; 95% CI, 1.46-1.78), and colorectum (HR, 1.32; 95% CI, 1.24-1.41).

Conclusions Patients diagnosed with cancer who have preexisting diabetes are at increased risk for long-term, all-cause mortality compared with those without diabetes.

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systematically review and summarize data regarding the association of preexisting diabetes with long-term, all-cause mortality in cancer patients.

METHODS

Data Sources and Searches

We searched MEDLINE and EMBASE from inception to May 15, 2008, for articles evaluating the effect of diabetes

Author Affiliations: Departments of Epidemiology (Ms Barone and Drs Yeh and Brancati) and Health Policy and Management (Dr Snyder), Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; Division of General Internal Medicine (Drs Yeh, Snyder, Peairs, Stein, and Brancati), Division of Endocrinology and Metabolism (Dr Derr), and Division of Oncology (Drs Snyder and Wolff), Johns Hopkins Medical Institutes, Baltimore.

Corresponding Author: Frederick L. Brancati, MD, MHS, Division of General Internal Medicine, Johns Hopkins Bloomberg School of Public Health, 2024 E Monument St, Ste 2-619, Baltimore, MD 21205-2223 (fbrancat@jhmi.edu).

on any prognostic outcome in cancer patients. Our overall search strategy included terms for diabetes (eg, *diabetes*, *glucose intolerance*, *hyperglycemia*), cancer (eg, *cancer*, *malignant neoplasm*), and prognosis (eg, *mortality*, *survival*, *recurrence*) and was limited to English-language, human studies. We also searched references of included articles.

Study Selection

Our overall search targeted articles that met the 3 following criteria: they evaluated any prognostic outcome by glyce-mic status, they evaluated a cancer population, and they contained original data analysis. We included studies evaluating type 1 and type 2 diabetes but not hyperinsulinemia or metabolic abnormality such as impaired glucose tolerance. For inclusion in our systematic review, articles had to meet 2 additional criteria: they reported all-cause mortality or overall survival, and they had a follow-up period of 3 months or longer. To be included in our meta-analysis, articles had to meet both of the following 2 criteria: they reported a risk estimate (eg, hazard ratio [HR] or relative risk [RR] relating preexisting diabetes to subsequent death using survival analysis regression models), and they reported an estimate of precision, such as a standard error or 95% confidence interval (CI). We also included articles that failed to report precision directly but from which we could reconstruct an estimate of precision using *P* values and other study data.

To further explore the relationship between diabetes and mortality in cancer patients, we also systematically reviewed long-term, cancer-specific mortality or noncancer mortality.

Data Extraction and Quality Assessment

Titles, abstracts, and articles were reviewed independently. Disagreements were settled by consensus or a third review for adjudication. Abstracted data included study population characteristics and demographics, presence or absence of diabetes at baseline, duration of

follow-up, health outcomes (specifically all-cause and cause-specific mortality for this report), adjustment variables, and study quality. Quality was assessed using elements of the STROBE checklist for cohort studies considered important for quality in these studies.¹¹ To judge quality, we abstracted information on population source; method of diabetes and outcome ascertainment; whether diabetes was the primary exposure variable or 1 of a group of prognostic variables; and statistical methods, including the use of survival analysis and adjustment for confounders.

Data Synthesis and Statistical Analysis

To avoid overlapping patient populations, we compared data on recruitment years, data source, and geographic location. If a patient population was found to overlap, we included the article with the most comprehensive population or most adjusted estimate of risk associated with preexisting diabetes. This resulted in the exclusion of 12 articles from our systematic review.¹²⁻²³ If several estimates were reported in the same article, we chose the most fully adjusted estimate (ie, multivariate regression was selected over univariate regression, which was selected over unadjusted Kaplan-Meier analysis). If an article gave site-specific as well as overall estimates, the overall estimate was used in the primary meta-analysis and site-specific estimates were used in meta-analyses by cancer site. If an article only reported multiple estimates by subgroup, these estimates were entered separately into our meta-analysis.

Authors were contacted for clarification for the systematic review and for additional, unreported information for the meta-analysis. For the meta-analysis, in the case that a *P* value without a risk estimate was reported, authors were contacted to obtain the estimates. When diabetes was not included in the final adjusted model, authors were contacted and asked to provide an adjusted estimate of the risk of preexisting diabetes. Of the 12 au-

thors contacted, 3 were able to provide additional information, 4 were unable to furnish the necessary information, and 5 did not respond to our request. The 9 studies with insufficient reporting were still included in the systematic review as described here.

The results of the systematic review are summarized qualitatively. The null hypothesis of “no additional mortality risk in cancer patients with preexisting diabetes” for studies reporting direction of effect was tested with a non-parametric sign test.²⁴

For the meta-analysis, we calculated a pooled HR estimate across all studies. Heterogeneity between studies was assessed using Cochran Q statistics and *I*² statistics.²⁵ Publication bias was evaluated using the Begg funnel plot and Egger plot. Sensitivity analyses were conducted first by excluding unadjusted estimates and then by excluding estimates that did not adjust (or stratify) for age and stage at time of diagnosis. Second, to evaluate period effects, we calculated point estimates for studies where the midpoint of the case recruitment period fell on or before the median year of 1996 (range, 1981-1996) vs after 1996 (range, 1997-2005). Third, to explore the impact of study quality, we conducted sensitivity analyses by important quality components. Finally, we evaluated the influence of each study on the overall estimate by calculating a pooled HR, omitting each estimate 1 at a time.

Cancer sites with at least 3 estimates meeting our meta-analysis criteria (breast, colorectal, endometrial, gastric, hepatocellular, lung, pancreatic, and prostate cancer) are reported separately. We calculated all pooled HR estimates using the DerSimonian-Laird method²⁶ for a random-effects model since there was substantial between-study heterogeneity and to allow for variable effects across studies. Using the method described by Cohn and Becker,²⁷ post hoc power calculations based on the overall and site-specific pooled HRs revealed excellent power ($\geq 95\%$) for overall, endometrial, breast, and colorectal can-

cer estimates and low power (<50%) for prostate, gastric, hepatocellular, lung, and pancreatic cancer estimates. Type 1 error rate was set at $\alpha = .05$ and all tests were 2-sided. All analyses were conducted using Stata 10 (StataCorp, College Station, Texas).

RESULTS

Our literature search yielded 7858 articles, of which 94 met inclusion criteria for our overall systematic review of the effect of preexisting diabetes on cancer prognosis. Most excluded studies did not report the risk of preexisting diabetes on prognosis or lacked original data. Of the 94 articles, 48 were

eligible for inclusion in the present systematic review of the risk of preexisting diabetes on long-term, all-cause mortality. Of these, 23 studies met inclusion criteria for our meta-analysis (FIGURE 1). Descriptive data for studies included in our meta-analysis are listed in order of increasing risk ratios (TABLE 1). Descriptive data and main results for the remaining studies included only in the qualitative review are presented by cancer site (eTable 1; <http://www.jama.com>).

Description of Studies

The 48 articles included in our systematic review of long-term, all-cause mor-

tality were quite heterogeneous. Twenty-eight studies used traditional cohorts of newly diagnosed cancer patients, 18 studies used treatment or surgical cohorts, one was a case-control study, and another was a matched-cohort study. Four studies evaluated the effect of preexisting diabetes on a group of cancer patients with multiple types of cancer, but most studies ($n=44$) focused on a single cancer site. The studies had been conducted in the United States ($n=21$), Europe ($n=15$), Asia ($n=11$), and Australia ($n=1$). Sample sizes ranged from 42 to 58 498 with a median of 430. Across the 43 studies that reported the number of participants with diabetes, the overall prevalence of diabetes was 12% (range, 4%-60%). Across the 44 studies that reported participant sex, the total population was 49% male. Reporting of age and follow-up time varied widely across studies.

Survival analyses reported various outcomes, including cumulative 1-year, 2-year, 3-year, 5-year, 10-year, and overall survival or mortality rates. The studies employed a variety of analytic techniques, including life-table and Kaplan-Meier survival analysis, Cox proportional hazards regression, and Poisson regression. Time origin for survival analysis was generally the time of cancer diagnosis, except in the case of treatment or surgical cohorts where the time of origin was the beginning of treatment or the date of surgery.

Quality varied across studies (eTable 2). Ten studies used population-based cohorts and the other 38 used clinic-based cohorts. Although the majority of studies ascertained diabetes by either blood tests ($n=7$) or medical records ($n=34$), a few studies used self-report of diabetes ($n=3$) and 4 studies did not report method of diabetes ascertainment. Studies used death registries ($n=10$), medical records ($n=28$), or interviews ($n=8$) to ascertain vital status and 2 studies did not report method of outcome ascertainment. Fifteen studies investigated diabetes as the primary exposure of interest while the remaining 33 studies evaluated diabetes among other prognostic variables.

Figure 1. Study Selection

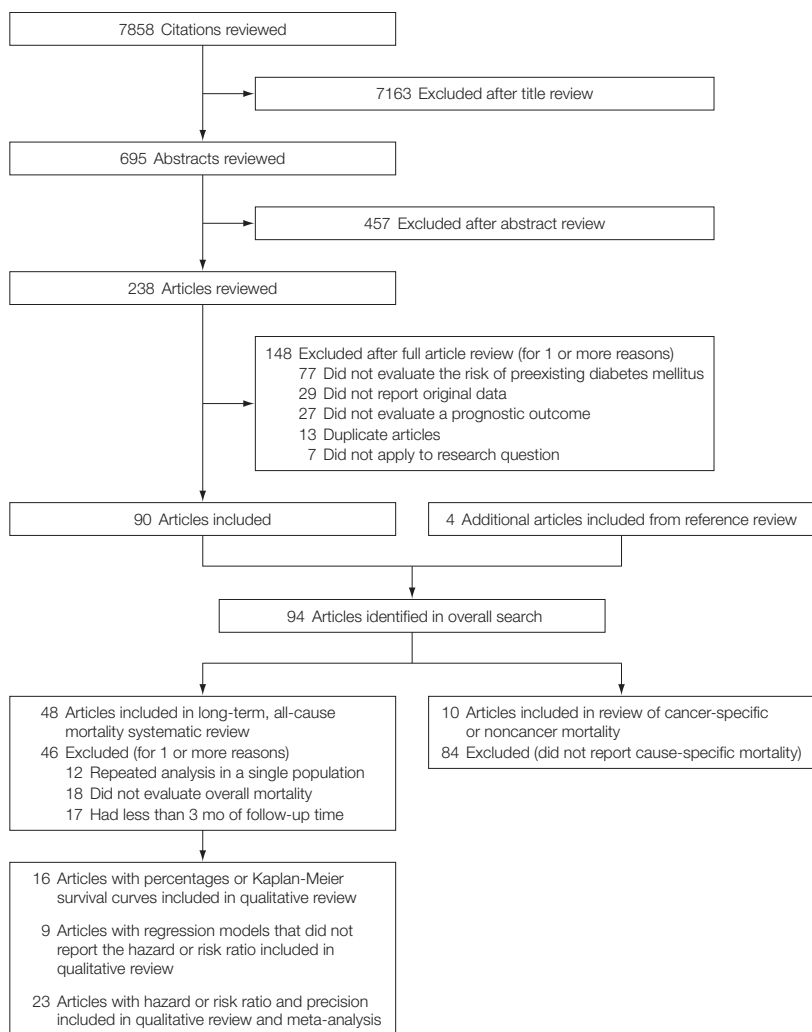


Table 1. Characteristics of 23 Studies Included in the Meta-analysis of the Effect of Preexisting Diabetes on All-Cause, Long-term Mortality

Source (Country of Study)	Study Type	Cancer Site	Years of Diagnosis	Exclusion Criteria	Patients With DM, No./Total No. (%)	Age, y	Men, No. (%)	Follow-up Time	Adjustment Variables
Sperti et al, ²⁸ 2003 (Italy)	TC	Pancreas	1996-2002	No PET scan with semiquantitative analysis of tracer uptake	20/60 (33)	Mean, 66.3 (range, 48-82)	34 (57)	Range, 1-35 mo	Age, tumor stage, standardized uptake value, tumor grade, treatment, CA 19-9, sex
Vasić, ²⁹ 2007 (Serbia)	TC	Lung (non-small cell)	2005-2006	Not stage III, IV; large cell cancer; operable or resectable cancer	11/87 (13)	Mean, 63.7 (range, 47-86)	75 (86)	6 mo	Age, sex, histology, Karnofsky score
Huo et al, ³⁰ 2004 (Taiwan)	C	Hepatocellular	1996-2001	Incomplete medical records	120/567 (21)	Resection: mean (SD), 61 (13) No resection: mean (SD), 67 (10)	473 (83)	Resection: mean (SD), 33 (18) mo No resection: mean (SD), 24 (15) mo	Three groups ^a
Valery et al, ³¹ 2006 (Australia)	MC	All ^b	1997-2002	Not state resident, private insurance only, no public hospital cancer visit, inaccessible medical record	192/1625 (12)	1-14 (4%), 15-39 (11%), 40-59 (40%), ≥60 (45%)	NA	Median, 42 mo (range, 12-84 mo)	Age, sex, diagnosis year, residence, cancer type, indigenous status, stage, treatment, comorbidities
Kouvaris et al, ³² 2001 (Greece)	C	Vulvar	1979-1997	Incomplete data and follow-up, cancer not invasive or squamous	30/50 (60)	Median, 73.5 (range, 38-84)	0	Median, 61 mo (range, 6-155 mo)	None
Shonka et al, ³³ 2006 (United States)	C	Colon	1986-2003	None	255/1853 (14)	DM median, 72 NG median, 71	891 (48)	NA	Age, stage, sex, diagnosis year, tobacco use, family history
Gross et al, ³⁴ 2006 (United States)	C	Colorectal	1993-1999	<67 y, not stage I-III, death same month as cancer diagnosis, data source autopsy or death certificate, ineligible for Medicare in 2 y prior to cancer diagnosis, missing demographic data	5283/29 733 (18)	Mean, 77.8 (range, 67-99)	13 380 (45)	Median, 4.1 y (range, 3-10 y)	Age, sociodemographic and cancer characteristics, comorbidities
Lin et al, ³⁵ 2007 (Taiwan)	C	Lymphoma (non-Hodgkin)	2000-2004	<30 y, AIDS, DM diagnosed <1 y prior to cancer diagnosis, prior malignancy	26/242 (11)	Median, 59	142 (59)	NA	None ^c
Polednak, ³⁶ 2006 (United States)	C	Colorectal	1994-1999	Data source death certificate or autopsy, unspecified race, additional reported cancer, unknown month of diagnosis or last contact	1014/9395 (11)	<60 (19%), 60-69 (22%), 70-79 (32%), ≥80 (27%)	4487 (48)	Range, 4-10 y	Age, extent of disease, lymph node status, sex, race, poverty rate
Park et al, ³⁷ 2006 (Korea)	C	All ^b	1996-2002	<20 y, not first cancer or multiple primary cancers, female	1223/14 578 (8)	Mean, 50.8	14 578 (100)	Mean, 3.03 y Maximum, 6.8 y	Age, alcohol use, BMI, cholesterol, physical activity, food preference, BP, comorbidities

(continued)

Table 1. Characteristics of 23 Studies Included in the Meta-analysis of the Effect of Preexisting Diabetes on All-Cause, Long-term Mortality (continued)

Source (Country of Study)	Study Type	Cancer Site	Years of Diagnosis	Exclusion Criteria	Patients With DM, No./Total No. (%)	Age, y	Men, No. (%)	Follow-up Time	Adjustment Variables
Tammemagi et al, ³⁸ 2003 (United States)	C	Lung	1995-1998	Not primary bronchogenic lung cancer, race not black or white, no principal care at Henry Ford Health System	NA/1155	NA	685 (59)	Median, 27 mo	Age, stage, sex, smoking, histology
Meyerhardt et al, ³⁹ 2003 (United States)	C	Colon	1988-1992	Not stage II, III; no en bloc resection, residual disease; ECOG >2; inadequate bone marrow, renal, or hepatic function; unavailable medical record; pregnant or lactating; other malignancy in the previous 3 y; previous chemotherapy, radiotherapy, fluorouracil	287/3549 (8)	DM mean, 66; NG mean, 62	1937 (55)	Median, 9.4 y	Age, stage, BMI, sex, race, baseline performance status, bowel obstruction, bowel perforation, presence of peritoneal implants, completion of chemotherapy
van de Poll-Franse et al, ⁴⁰ 2007 (the Netherlands)	C	All ^b	1995-2002	Not in the cancer registry	5555/58 498 (9)	DM mean, 71; NG mean, 64	30 782 (53)	Range, 3-10 y	Age, stage, sex, treatment, CVD
Du and Simon, ⁴¹ 2005 (United States)	C	Breast	1994-1997	Treatment at another institution, not stage I-III, race not black or white, <1 y follow-up	73/588 (12)	White: mean (SD), 58 (14.1) y; Black: mean (SD), 60 (13.6)	0	Mean, 3.68 y; Median, 3.72 y	Age, stage, nodal involvement, estrogen and progesterone receptor status, race, comorbidities
Chia et al, ⁴² 2007 (United States)	C	Endometrial	1991-1994	No telephone number, driver's license, or Medicare card; no physician or patient permission; contact not possible	93/739 (13)	Range, 40-79	0	Mean, 9.3 y (range, 1.1-12.9 y)	Age, stage, menopausal status, BMI, smoking, oral contraceptive use, parity, hormone therapy
Yancik et al, ⁴³ 2001 (United States)	C	Breast	1992	<55 y, missing data on death	NA/1800	≥55	0	30 mo	Age, stage, comorbidities
Ikeda et al, ⁴⁴ 1998 (Japan)	TC	Hepato-cellular	1985-1995	No curative hepatic resection	87/342 (25)	Mean (SD), 59.7 (8.3)	275 (80)	Median, 43 mo (range, 1-135 mo)	Microscopic intrahepatic metastasis
Tammemagi et al, ⁴⁵ 2005 (United States)	C	Breast	1985-1990	Not incident cancer, nonmember of Henry Ford Health System, race not black or white, incomplete data or follow-up	127/906 (14)	<50 (26%), 50-69 (43%), ≥70 (31%)	0	Median, 10.0 y (range, 0.04-17.8 y)	None
Steiner et al, ⁴⁶ 2007 (Germany, Japan)	C	Endometrial	Germany: 1985-2000; Japan: 1992-2003	Not histologically proven	64/313 (20)	Median, 64 (range, 32-91)	0	Mean, 45 mo; Median, 37 mo	Stage, depth of myometrial invasion

(continued)

Table 1. Characteristics of 23 Studies Included in the Meta-analysis of the Effect of Preexisting Diabetes on All-Cause, Long-term Mortality (continued)

Source (Country of Study)	Study Type	Cancer Site	Years of Diagnosis	Exclusion Criteria	Patients With DM, No./ Total No. (%)	Age, y	Men, No. (%)	Follow-up Time	Adjustment Variables
Merrick et al, ⁴⁷ 2007 (United States)	TC	Prostate	1995-2003	Not stage T1b-T3a and Gleason 7, not undergoing brachytherapy by single surgeon	64/530 (12)	Mean (SD), 66.1 (7.4)	530 (100)	Mean (SD), 6 (2.3) y	Age, stage, smoking, percentage positive biopsies, BMI
Folsom et al, ⁴⁸ 2004 (United States)	C	Endometrial	1986-2000	<55 y or >69 y in 1986, uterine sarcomas and mullerian mixed tumors	42/415 (10)	<68 (36%), 68-72 (33%), >72 (31%)	0	Median, 6.4 y	Age, extent of cancer
Sperti et al, ⁴⁹ 1996 (Italy)	TC	Pancreas	1970-1992	No surgical resection of ductal adenocarcinoma of the pancreas	62/113 (55)	Mean, 59.4 (range, 27-81)	66 (58)	NA	Age, stage, grade
Fujiwara et al, ⁵⁰ 2008 (Japan)	TC	Gastric	1998-2002	No gastrectomy with regional lymphadenectomy, distant metastasis	14/94 (15)	Mean (SD), 60 (11.5)	70 (74)	Minimum, 5 y	Age, lymph node metastasis

Abbreviations: BMI, body mass index; BP, blood pressure; C, cohort; CA 19-9, carbohydrate 19-9 antigen; CVD, cardiovascular disease; DM, diabetes mellitus; ECOG, Eastern Cooperative Oncology Group performance status; MC, matched cohort; NA, not available; NG, normoglycemic; PET, positron emission tomography; TC, treatment or surgical cohort.

^aSurgical resection: age, serum α -fetoprotein level >400 ng/mL; no resection, Childs Pugh A multifocal tumors, tumor size >5 cm; and no resection, Childs Pugh B tumor size >5 cm, number of tumors.

^bStudies that evaluated multiple cancer sites in single analysis.

^cStudy reported both an overall model and a model with a significant time \times diabetes interaction and further adjustment. The first model is reported for consistency and use in meta-analysis.

Most ($n=46$) of the studies used survival analysis, but only 30 used adjusted models and only 18 adjusted for age and cancer severity.

Systematic Review of Evidence

The best evidence from each study is summarized here. For example, if a study reported both a log-rank test from Kaplan-Meier survival curves and an adjusted Cox proportional HR, only the HR is included.

Of 5 studies reporting survival or mortality percentages comparing cancer populations with and without preexisting diabetes,⁵¹⁻⁵⁵ only 1 study reported a P value. Two studies observed higher risk in patients with diabetes and 3 studies observed higher risk in patients without diabetes.

Of 11 studies using Kaplan-Meier survival curves or life-table survival with either the log-rank or Wilcoxon tests,⁵⁶⁻⁶⁶ diabetes was associated with significantly decreased survival in 2 studies, nonsignificantly decreased survival in 5 studies, and nonsignificantly increased survival in 1 study; the remaining 3 studies reported a nonsignificant difference without a direction of effect.

Of the 4 studies with unadjusted Cox proportional HRs for the risk of preexisting diabetes,^{32,35,45,67} diabetes was associated with significantly increased risk in 2 studies and nonsignificantly increased risk in 1 study; 1 study did not have sufficient information to determine direction of effect.

Twenty-eight studies provided 30 adjusted Cox or Poisson models (HRs or RRs) of the risk of preexisting diabetes.* Of these 30 estimates, 17 reported that preexisting diabetes was associated with significantly increased risk of all-cause mortality in cancer patients, 3 that diabetes was associated with nonsignificantly increased mortality, 3 that diabetes was associated with nonsignificantly decreased mortality, and 1 that there was no effect; the remaining 6 estimates were not statistically significant, but sufficient information to determine directionality was unavailable.

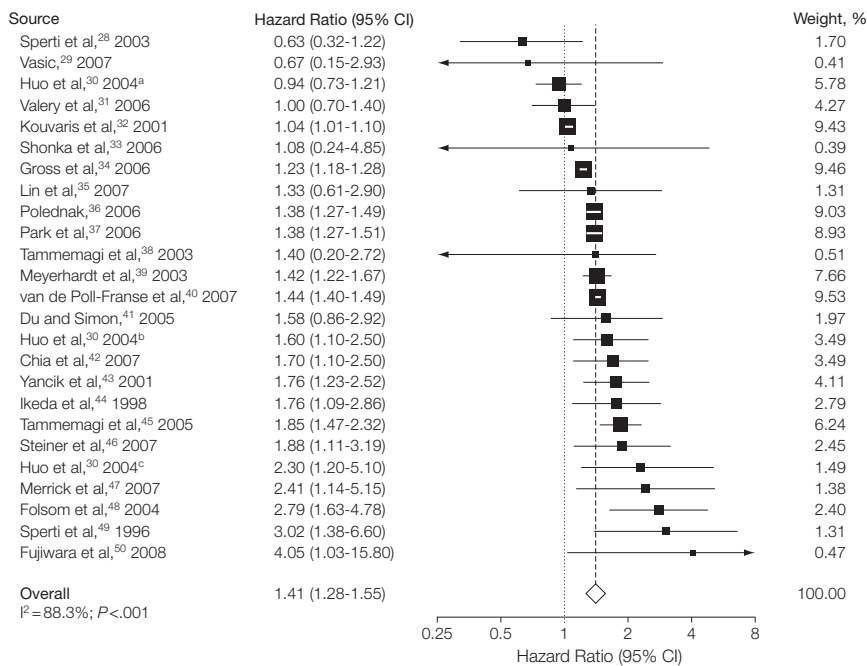
No study included in this systematic review reported that diabetes was associated with significantly better survival. For the nonparametric sign

test, we considered whether studies reported higher or lower mortality risk associated with preexisting diabetes, regardless of significance level or magnitude of effect. Overall, 32 study estimates found diabetes was associated with increased risk of mortality, 7 found diabetes was associated with decreased risk of mortality, 1 found a null effect, and 10 did not report a direction of effect. The sign test rejected the null hypothesis of equal mortality in patients with and without preexisting diabetes whether we excluded studies that did not report a direction of effect ($P=.001$) or assumed studies that did not report a direction of effect fell evenly in either category (5 each side, $P=.005$).

Meta-analysis

Of the 32 studies reporting unadjusted or adjusted regression models evaluating the risk of preexisting diabetes on long-term, all-cause mortality, 21 studies reported 22 estimates including both risk (HR or RR) and precision (standard error, P value, or 95% CI). The addition of 3 unreported estimates supplied by article

*References 28-31, 33, 34, 36-44, 46-50, 68-75.

Figure 2. Meta-analysis and Pooled Hazard Ratio of Long-term, All-Cause Mortality in 23 Studies Comparing Cancer Patients With and Without Preexisting Diabetes Mellitus

The 23 studies provided 25 estimates. Weights are from random-effects analysis. Data markers are proportional to study sample sizes. CI indicates confidence interval.

^aPatients who had no resection, Childs Pugh B.

^bPatients who had no resection, Childs Pugh A.

^cPatients undergoing surgical resection.

authors increased the size of our meta-analysis to 23 studies with 25 estimates.^{29,30,49} Characteristics and demographic information as well as adjustment or restriction variables for included articles are listed in Table 1.

Of the remaining 9 articles with regression models but insufficient reporting to include in our meta-analysis, 3 studies reported preexisting diabetes was associated with significantly increased risk of mortality ($P < .05$) while 6 found a nonsignificant relationship ($P > .05$) without indicating direction of effect.

FIGURE 2 displays the results of the meta-analysis of the 23 studies. Preexisting diabetes was associated with an increase in all-cause mortality following cancer diagnosis (HR=1.41; 95% CI, 1.28-1.55). No significant publication bias was observed according to the Begg test ($P = .92$) or Egger plot ($P = .34$)

(eFigure). Heterogeneity was significant by the Q statistic (205 on 24 *df*, $P < .001$) and by I^2 (88.3%, $P < .001$).

Sensitivity Analyses

Because the investigators' approaches to adjustment for confounding factors varied widely by study and type of cancer (Table 1), we conducted a sensitivity analysis to confirm robustness (TABLE 2). After excluding univariate estimates ($n = 3$),^{32,35,45} the HR remained 1.40 (95% CI, 1.29-1.52). Next, we excluded analyses that did not at least adjust or restrict age and disease severity at cancer diagnosis ($n = 7$),^{29-31,37,44,46} because we believe these are particularly important potential confounders. The estimated HR in this sensitivity analysis was 1.42 (95% CI, 1.28-1.56).

In a second sensitivity analysis to evaluate period effects, we calculated a pooled HR for studies with the mid-

point of case recruitment on or before 1996 ($n = 12$) and after 1996 ($n = 13$). The earlier group had an HR of 1.45 (95% CI, 1.26-1.67) and the more recent group had an HR of 1.37 (95% CI, 1.26-1.46).

A third sensitivity analysis evaluated the impact of additional quality components on the pooled HR (eTable 2A). First, we calculated separate estimates by source of study population and found that population-based studies (8 estimates) had a pooled HR of 1.39 (95% CI, 1.27-1.52) and clinic-based studies (17 estimates) had a pooled HR of 1.46 (95% CI, 1.21-1.78). Second, we excluded studies (4 estimates) that had either self-reported diabetes ascertainment or that did not report the method of diabetes or outcome ascertainment. The remaining studies had a pooled HR of 1.37 (95% CI, 1.24-1.51). We also calculated separate estimates for the 9 studies that considered diabetes as the primary exposure (HR, 1.42; 95% CI, 1.30-1.56) and the 14 studies that considered diabetes among prognostic factors (HR, 1.36; 95% CI, 1.20-1.55).

Finally, we excluded individual study estimates 1 at a time to examine the influence of each study on the overall HR. The omission of any one study did not appreciably change the pooled HR, and the estimates in each case were well within the confidence limits of the overall estimate.

Next, we investigated the risk associated with preexisting diabetes by cancer site for sites with at least 3 risk estimates qualifying for our meta-analysis. Park et al³⁷ as well as van de Poll-Franse et al⁴⁰ reported site-specific risk as well as the overall risk estimates, and these site-specific estimates were included in the meta-analyses by cancer type (TABLE 3). Preexisting diabetes was significantly associated with increased long-term, all-cause mortality for cancers of the endometrium (HR, 1.76; 95% CI, 1.34-2.31), breast (HR, 1.61; 95% CI, 1.46-1.78), and colorectum (HR, 1.32; 95% CI, 1.24-1.41). Diabetes was associ-

Table 2. Pooled Hazard Ratios of Long-term, All-Cause Mortality in Cancer Patients With and Without Preexisting Diabetes Mellitus

Type of Estimate	Studies (Estimates), No.	Total Patients, No.	Patients With Diabetes, No. ^a	Pooled HR (95% CI) ^b
All estimates	23 (25)	127 232	14 990	1.41 (1.28-1.55)
All adjusted estimates	20 (22)	126 034	14 806	1.40 (1.29-1.52)
Estimates adjusted for age and stage	15 (15)	110 489	13 400	1.42 (1.28-1.56)

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aNumber is extrapolated based on 21 of 23 studies that reported prevalence of diabetes.^bEstimates calculated using a random-effects model.

ated with a nonsignificant increase in risk in prostate (HR, 1.51; 95% CI, 0.94-2.43), gastric (HR, 1.36; 95% CI, 0.92-2.01), hepatocellular (HR, 1.30; 95% CI, 0.99-1.70), lung (HR, 1.15; 95% CI, 0.99-1.34), and pancreatic cancer (HR, 1.09; 95% CI, 0.70-1.69).

Cancer-Specific and Noncancer Mortality

To further describe the observed higher risk of mortality in cancer patients with preexisting diabetes, we searched the literature for articles reporting either cancer-specific mortality or noncancer mortality. From the 7858 citations and 94 articles included in the aforementioned systematic review, 10 articles reported the association of preexisting diabetes with cause-specific mortality (Figure 1). Seven articles reported the risk of diabetes associated with cancer-specific mortality,^{42,47,48,68,76-78} 1 article reported the risk of diabetes associated with both cancer-specific and noncancer mortality,³⁶ and 2 articles reported the risk of diabetes associated with noncancer mortality^{67,79} (eTable 1B). These articles evaluated patients with colorectal (n=3), endometrial (n=4), and prostate (n=3) cancer. Eight of 10 articles used Cox proportional hazards regression and 2 calculated Kaplan-Meier cumulative survival.

Of 9 estimates from 8 articles reporting the association of diabetes with cancer-specific mortality, 2 estimates found significantly higher risk,^{48,78} 2 estimates found a nonsignificantly higher risk,^{36,77} 2 estimates found a nonsignificantly lower risk,^{42,77} and 3 articles did not report a direction of effect.^{47,68,76} No study

Table 3. Pooled Hazard Ratios of Long-term, All-Cause Mortality in Cancer Patients With and Without Preexisting Diabetes Mellitus in Selected Cancer Sites

Cancer Site	Studies (Estimates), No.	Total Patients, No.	Patients With Diabetes, No.	Pooled HR (95% CI) ^a	I ² , %
Endometrial	4 (4) ^{40,42,46,48}	2900	429	1.76 (1.34-2.31)	44.3
Breast	4 (4) ^{40,41,43,45}	13 019	1107 ^b	1.61 (1.46-1.78)	0
Prostate	3 (3) ^{37,40,47}	6264	555 ^b	1.51 (0.94-2.43)	47.1
Gastric	3 (3) ^{37,40,50}	6200	687 ^b	1.36 (0.92-2.01)	83.6
Colorectal	6 (7) ^{33,34,36,37,39,40}	54 740	8028 ^b	1.32 (1.24-1.41)	52.4
Hepatocellular	3 (5) ^{30,37,44}	3724	848 ^b	1.30 (0.99-1.70)	68.9
Lung	4 (5) ^{29,37,38,40}	11 109	989 ^c	1.15 (0.99-1.34)	47.7
Pancreas	4 (4) ^{28,37,40,49}	1681	477 ^b	1.09 (0.70-1.69)	73.4

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aEstimates calculated using a random-effects model.^bNumber is extrapolated because 1 study did not report prevalence of diabetes.^cNumber is extrapolated because 2 studies did not report prevalence of diabetes.

reported that diabetes was associated with a significant decrease in cancer-specific mortality. We performed a nonparametric sign test and found no association between diabetes and increased cancer-specific mortality ($P=.69$).

Of the 3 studies evaluating noncancer mortality, 2 found a significant association with increased risk among patients with preexisting diabetes^{36,79} and 1 article reported a nonsignificant association with no direction of effect.⁶⁷

COMMENT

Preexisting diabetes in cancer patients at the time of diagnosis was associated with an HR of 1.41 for the risk of all-cause mortality compared with individuals without diabetes when pooled across 23 studies of various types of cancer. This estimate was robust across sensitivity analyses that accounted for population source, diabetes and mortality ascertainment, and statistical adjustment. While the association of diabetes and site-specific mortality risk reached statistical significance only for

cancers of the endometrium, breast, and colorectum, diabetes appeared to be associated with some additional mortality risk for all types of cancer.

Strengths of the study include a comprehensive, systematic review of the literature by a multidisciplinary team including specialists in cancer, diabetes, and epidemiologic methods. We used a broad search strategy to capture all relevant information. Even though we had to exclude about half of the apparently relevant articles from our meta-analysis for lack of regression models or insufficient reporting, the excluded articles were generally consistent with pooled, quantitative results. Moreover, there was no evidence of publication bias. The majority of the studies included in the review evaluated multiple prognostic variables, which likely decreased the risk of publication bias with respect to the relationship between diabetes and mortality in this patient population, and the pooled estimate was stable when restricted to these articles. Finally, a meta-analysis was performed on 23 articles that addressed the specific research ques-

tion, and influence and sensitivity analyses confirmed the robustness of the main results.

Several limitations of the literature as well as our systematic review and meta-analysis deserve comment. First, the studies showed great heterogeneity in terms of population demographics, ascertainment methods for diabetes, and measurement and adjustment for confounders. Despite the use of appropriate meta-analytic techniques with random-effect models, we are unable to account for these differences. However, multiple sensitivity analyses found the risk estimate was robust across various quality components. Second, studies included in the review span many decades (published between 1969 and 2008) during which great advances have been made in the treatment of cancer and diabetes. Despite this, point estimates for earlier and more recent studies were similar. Finally, differences in follow-up time, which was not always reported, may also limit interpretation of the results. However, the consistency of results across studies, cancer sites, follow-up time, and continents supports the main findings. The large I^2 value (88%) indicates that the range of plausible risk estimates is wide, but we found no evidence that preexisting diabetes might be protective.

There are several potential explanations for the observed association between increased all-cause mortality and preexisting diabetes in cancer patients. First, cancer patients with diabetes may have increased tumor cell proliferation and metastases in a physiologic environment of hyperinsulinemia and hyperglycemia.¹⁰ It is possible that high insulin or insulin-like growth factor levels may promote cancer cell and tumor growth.¹⁰ Another potential pathway is that acute exposure to hyperglycemia may increase endothelial cell permeability due to increased generation of reactive oxidative species and structural changes in the basement membrane, increasing the likelihood of metastasis.⁸⁰

Second, differences in cancer treatment between patients with and without diabetes may contribute to increased cancer-related mortality. Patients with diabetes often have other diabetes-related comorbid conditions, such as ischemic heart disease, chronic kidney disease, and neuropathy, that may influence clinical decisions.¹⁰ The study by van de Poll-Franse et al⁴⁰ found that patients with esophageal, colon, breast, and ovarian cancer and diabetes were treated less aggressively than those without diabetes after controlling for age, stage, and sex in the Eindhoven Cancer Registry of the Netherlands.

Third, patients with preexisting diabetes may have poorer response to cancer treatment, including increased infection risk and intraoperative mortality.^{39,81}

Fourth, patients with preexisting diabetes may present with later-stage disease because of suboptimal cancer screening practices.⁸² Fleming et al⁸³ found that women older than 67 years with preexisting diabetes had a 17% greater risk of being diagnosed with late vs early stage breast cancer in the SEER database compared with normoglycemic women. In our analysis, however, stage at diagnosis appeared not to be a major explanatory factor.

Fifth, the diagnosis and treatment of cancer may distract both the patient and the health care team from appropriate management of glycemia, blood pressure, and lipids, proven to reduce morbidity and mortality in diabetic adults. Although results are not consistent, a multidisciplinary approach that includes a diabetes-management team for the treatment of cancer patients with diabetes may be important for improving long-term outcomes and decreasing mortality.^{84,85}

Finally, it is possible that the excess mortality risk related to diabetes is completely independent of cancer and cancer treatment. Diabetes is a well-established risk factor for cardiovascular mortality in adults without cancer,⁸⁶ and the microvascular and macrovascular damage it causes likely accumulates to

some extent regardless of cancer status. If this were true, one might predict that the excess mortality risk would be confined to deaths attributed to causes other than cancer (eg, coronary heart disease). Our subsidiary analysis of studies that distinguished between cancer and noncancer mortality was inconclusive, so this possibility cannot be excluded. However, experts in cancer epidemiology recognize that attribution of cause of death is often problematic and that undue reliance on attributed cause can bias estimates of risk related to cancer treatment.⁸⁷⁻⁹⁰ Attention to all-cause mortality tends to reduce bias due to misattribution.

Future research should determine the relative importance of different pathways to diabetes-related mortality risk. If a clinical or biological interaction between diabetes and cancer care is confirmed, subsequent trials should test whether improvements in diabetes care for patients with newly diagnosed cancer might reduce long-term mortality.

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Study concept and design: Barone, Yeh, Wolff, Brancati.

Acquisition of data: Barone, Yeh, Peairs, Stein, Derr. **Analysis and interpretation of data:** Barone, Yeh, Snyder, Stein, Wolff, Brancati.

Drafting of the manuscript: Barone, Stein.

Critical revision of the manuscript for important intellectual content: Yeh, Snyder, Peairs, Stein, Derr, Wolff, Brancati.

Statistical analysis: Barone, Yeh, Peairs, Stein.

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Administrative, technical, or material support: Barone, Yeh, Stein, Wolff.

Study supervision: Yeh, Snyder, Peairs, Brancati.

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