

# Postoperative Mortality in Cancer Patients With Preexisting Diabetes

## Systematic review and meta-analysis

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**OBJECTIVE** — Diabetes appears to increase risk for some cancers, but the association between preexisting diabetes and postoperative mortality in cancer patients is less clear. Our objective was to systematically review postoperative mortality in cancer patients with and without preexisting diabetes and summarize results using meta-analysis.

**RESEARCH DESIGN AND METHODS** — We searched the Medical Literature Analysis and Retrieval System Online (MEDLINE) and Excerpta Medica Database (EMBASE) for articles published on or before 1 July 2009, including references of qualifying articles. We included English language investigations of short-term postoperative mortality after initial cancer treatment. Titles, abstracts, and articles were reviewed by at least two independent readers. Study population and design, results, and quality components were abstracted with standard protocols by one reviewer and checked for accuracy by additional reviewers.

**RESULTS** — Of 8,828 titles identified in our original search, 20 articles met inclusion criteria for qualitative systematic review. Of these, 15 reported sufficient information to be combined in meta-analysis. Preexisting diabetes was associated with increased odds of postoperative mortality across all cancer types (OR = 1.85 [95% CI 1.40–2.45]). The risk associated with preexisting diabetes was attenuated but remained significant when we restricted the meta-analysis to models that controlled for confounders (1.51 [1.13–2.02]) or when we accounted for publication bias using the trim and fill method (1.52 [1.13–2.04]).

**CONCLUSIONS** — Compared with their nondiabetic counterparts, cancer patients with preexisting diabetes are ~50% more likely to die after surgery. Future research should investigate physiologic pathways to mortality risk and determine whether improvements in perioperative diabetes care can reduce postoperative mortality.

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In established market economies, the prevalence of diabetes in adults  $\geq 20$  years of age has reached almost 7% (1). Because some cancers—including cancers of the breast, colorectum, endometrium, liver, and pancreas—occur more commonly in individuals with diabetes, the prevalence of diabetes in newly diagnosed cancer patients is even higher, with estimates ranging 8–18% (2,3).

Among cancer patients, preexisting diabetes is associated with a higher risk of all-cause long-term mortality (4). Because diabetes can lead to infections, metabolic derangements, and acute cardiovascular events, cancer patients with diabetes may also be at greater risk of short-term mortality, especially in the peri- and postoperative interval (2,5). However, this risk has not been systematically studied. We

therefore sought to review and summarize data evaluating the risk of short-term postoperative mortality related to preexisting diabetes in newly diagnosed cancer patients.

## RESEARCH DESIGN AND METHODS

### Data sources and searches

We searched Medical Literature Analysis and Retrieval System Online (MEDLINE) and Excerpta Medica Database (EMBASE) from inception to 1 July 2009 for articles evaluating the effect of diabetes on any prognostic outcome in cancer patients. Our overall search strategy included terms for diabetes (e.g., diabetes, glucose intolerance, hyperglycemia), cancer (e.g., cancer, malignant neoplasm), and prognosis (e.g., 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 following three criteria: 1) evaluated any prognostic outcome by glycemic status, 2) evaluated a cancer population, and 3) contained original data. The current review further required articles to evaluate short-term postoperative mortality after initial cancer surgery, including 30-day and hospital mortality. To be included in our meta-analysis, articles had to meet either of the following two criteria: 1) report a risk estimate (e.g., hazard ratio [HR], relative risk [RR], or odds ratio [OR]) relating preexisting diabetes to subsequent death and an estimate of precision such as a standard error or 95% CI or 2) report rates of short-term mortality in patients with and without diabetes as well as the prevalence of diabetes in the study population.

### Data extraction and quality assessment

Titles, abstracts, and articles were reviewed independently by two authors. Disagreements were settled by consensus or a third review for adjudication. Ab-

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stracted data included study population characteristics, health outcomes (specifically short-term postoperative mortality for this report), adjustment variables, and study quality. Quality was assessed using elements of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist for cohort studies that we considered important for quality in these studies (6). To judge quality, we abstracted information on population source; method of diabetes and outcome ascertainment; whether diabetes was the primary exposure variable or one of a group of prognostic variables; and adjustment for confounders.

### Data synthesis and analyses

Articles reporting unadjusted or adjusted risk estimates (OR, RR, or HR) and confidence intervals (CIs) or standard errors (SEs) were included in the meta-analysis. An unadjusted OR was calculated for manuscripts reporting rates of mortality, study sample size, and prevalence of diabetes. SE of the OR was calculated using the delta method. If an article only reported multiple risk estimates by subgroup, these estimates were input separately into our meta-analysis. We attempted to contact four authors for additional unreported information necessary for inclusion in the meta-analysis, but none were able to furnish the required information. These four articles were only included in the systematic review.

The results of the overall systematic review are summarized qualitatively. Additionally, cancer sites with at least three studies meeting inclusion criteria are discussed in more detail. For the meta-analysis, potential sources of heterogeneity between studies were assessed using Cochran's  $Q$  and  $I^2$  statistics (7). Due to substantial between-study heterogeneity, we calculated a pooled OR including all estimates using the DerSimonian-Laird method for a random-effects model, which weights individual studies by the inverse of the variance (8). Publication bias was evaluated using Begg's funnel plot and the Egger plot. Several sensitivity analyses were conducted. First, we excluded unadjusted risk estimates. We also calculated separate pooled estimates for population-based and clinic-based cohorts, as well as studies evaluating diabetes as the primary exposure or among prognostic factors. Next, we performed the Duval and Tweedie nonparametric trim and fill procedure to further assess the potential effect of publication

bias. This method considers the possibility of hypothetical missing studies, imputes their ORs, and recalculates a pooled estimate (9). Finally, we evaluated the influence of each study on the overall estimate by calculating a random-effects pooled OR, omitting each estimate one at a time. We repeated the analysis of influence among studies with adjusted estimates. All analyses were conducted using STATA 10 (College Station, TX).

## RESULTS

### Search results

Our literature search yielded 8,828 articles, of which 20 were eligible for inclusion in the present systematic review of the risk of preexisting diabetes on short-term postoperative mortality in cancer patients after initial surgical treatment. Descriptive data and main results from these studies are presented according to cancer site (Table 1). Of these, 15 met additional inclusion criteria for our meta-analysis (Fig. 1).

Nineteen articles included in our systematic review evaluated postoperative, 30-day, or hospital mortality in cohorts of patients who had undergone cancer surgery; one article evaluated a composite outcome of hospital mortality or morbidity. Publication year ranged from 1983 to 2009. Studies evaluated the effect of preexisting diabetes in patients with colon or colorectal ( $n = 5$ ) (10–14), esophageal and/or gastroesophageal junction ( $n = 5$ ) (15–19), liver ( $n = 2$ ) (20,21), lung ( $n = 4$ ) (22–25), pancreatic ( $n = 2$ ) (26,27), stomach ( $n = 1$ ) (28), and prostate cancer ( $n = 1$ ) (29). The studies were conducted in Europe ( $n = 8$ ), the U.S. ( $n = 7$ ), and Asia ( $n = 5$ ). Sample sizes ranged from 70 to 32,621 with a median of 427. The prevalence of diabetes, where reported, ranged from 1 to 42% with a median of 10%. Crude postoperative mortality rates ranged from 0.73 to 53.5% with a median of 6.5%.

Quality varied across studies (see supplemental Table, available in an online appendix at <http://care.diabetesjournals.org/cgi/content/full/dc09-1721/DC1>). Five studies used population-based cohorts, and the other 15 used clinic-based cohorts. Two studies ascertained diabetes by a blood test, and the remainder used medical records ( $n = 18$ ). A few studies used death registries ( $n = 3$ ) to ascertain vital status, but most studies used medical records or study follow-up ( $n = 17$ ). Only three studies focused specifically on diabetes; the re-

maining 17 studies investigated diabetes as one potential prognostic variable among many. Twelve studies reported unadjusted percentages or risk estimates of preexisting diabetes on short-term mortality, whereas the other eight reported adjusted estimates.

### Systematic review

Of the 10 studies that reported simple percentages comparing cancer patients with and without preexisting diabetes, four reported that diabetes was associated with significantly higher short-term mortality, four reported nonsignificant differences, and two did not report a statistical comparison. Neither of the two studies reporting unadjusted estimates from regression models found a significant difference. Of the 10 adjusted estimates (eight studies) from regression models, five indicated significantly increased risk of postoperative mortality, one reported significantly increased risk of postoperative mortality or morbidity, and four found nonsignificant associations. No studies reported that diabetes was associated with significantly decreased short-term postoperative mortality.

Our search yielded at least three studies of colon/colorectal cancer, esophageal/gastrointestinal junction cancer, and lung cancer. Results from these studies are summarized below. We did not perform meta-analysis by cancer site because of insufficient number of studies with adjustment and the high degree of heterogeneity.

Five studies evaluated the risk of diabetes on postoperative mortality in colon (10,12) or colorectal (11,13,14) cancer. Koperna et al. (10) and Tsugawa et al. (12) both evaluated small clinical populations ( $n = 99$  and  $n = 71$ , respectively) of patients >70 years of age undergoing emergency surgery for colon cancer. Both studies reported high rates of postoperative mortality (50.5 and 53.5%, respectively) and found a significant survival advantage for patients without diabetes in a simple comparison of postoperative mortality rates. Little et al. (11) and Julumstrø et al. (14) evaluated larger clinical cohorts ( $n = 727$  and  $n = 1,194$ , respectively) of colorectal cancer patients and reported unadjusted rates of 30-day mortality in patients with and without diabetes. Little et al. (11) found that patients with diabetes had a significantly increased risk of 30-day mortality (8.2 vs. 2.4%,  $P = 0.02$ ) in a cohort of patients with colorectal cancer that was metastatic to the liver and who underwent hepatic re-

Table 1—Study characteristics and main results

Author, year, country	Cancer site	Exclusion criteria	n with DM/n total (%)	Age (years)	Outcome (mortality rate)	Results	Adjustment variables
Kopera et al., 1997, Austria (10)	Colon	No emergency surgery for colon cancer, aged ≤70 years, not treated between 1986 and 1995	11/99 (11%)	Mean ± SD 81.5 ± 5.9	Postoperative mortality (50.5%)	DM: 91%; NG: 47% (P = 0.005)	None
Little et al., 2002, U.S. (11)	Colorectal	No hepatic resection, colorectal cancer not metastatic to the liver, not treated at Memorial Sloan-Kettering Cancer Hospital between 1990 and 1997	61/727 (8%)	Median (range) 62 (23–85)	30-day mortality (2.9%)	DM: 8.0%; NG: 2.4% (P = 0.02)	None
Tsugawa et al., 2002, Japan (12)	Colon	No emergency surgery for colon cancer, aged ≤70 years, not treated between 1988 and 1997	10/71 (14%)	Mean ± SD 75.4 ± 5.1	Postoperative mortality (53.5%)	DM: 80%; NG: 49% (P = 0.006)	None
Davila et al., 2005, U.S. (13)	Colorectal	No surgical resection of colorectal cancer within 6 months of diagnosis, previous colon cancer, ulcerative colitis, Crohn's disease, not in Veteran's Affairs database, not diagnosed between 1987 and 2000	NA/32,621	Mean ± SD 68 ± 9	30-day mortality (4.5%)	HR = 1.19 (1.04–1.36)*	Age, sex, race, marital status, metastatic disease, site, surgical volume, time of surgery
Jullumstrø et al., 2009, Norway (14)	Colorectal	Not histologically confirmed, not treated between 1980 and 2004	97/1,194 (8.1%)	DM: median 76.2; NG: median 71.7	30-day mortality (5.1%)	DM: 6%; NG: 5% (P = 0.61)	None
Zhang et al., 1994, Japan (15)	Esophagus	No esophagectomy (subtotal through right thoracotomy) between 1986 and 1989	42/100 (42%)	Mean (range) 60.7 (42–82)	Hospital complication mortality (7.0%)	OR = 1.19 (P = 0.024)§	Age, ECG, operation, vital capacity, T-factor, creatinine clearance, 15' indocyanine green test
Bartels et al., 1998, Germany (16)	Esophagus	No curative esophagectomy between 1982 and 1991	NA/432	Mean 56.7	30-day mortality (10.0%)	OR = NA (P > 0.05)	Karnofsky index, mental cooperation, vital capacity, arterial partial pressure of oxygen, aminopyrine breath test, cirrhosis, cardiac risk

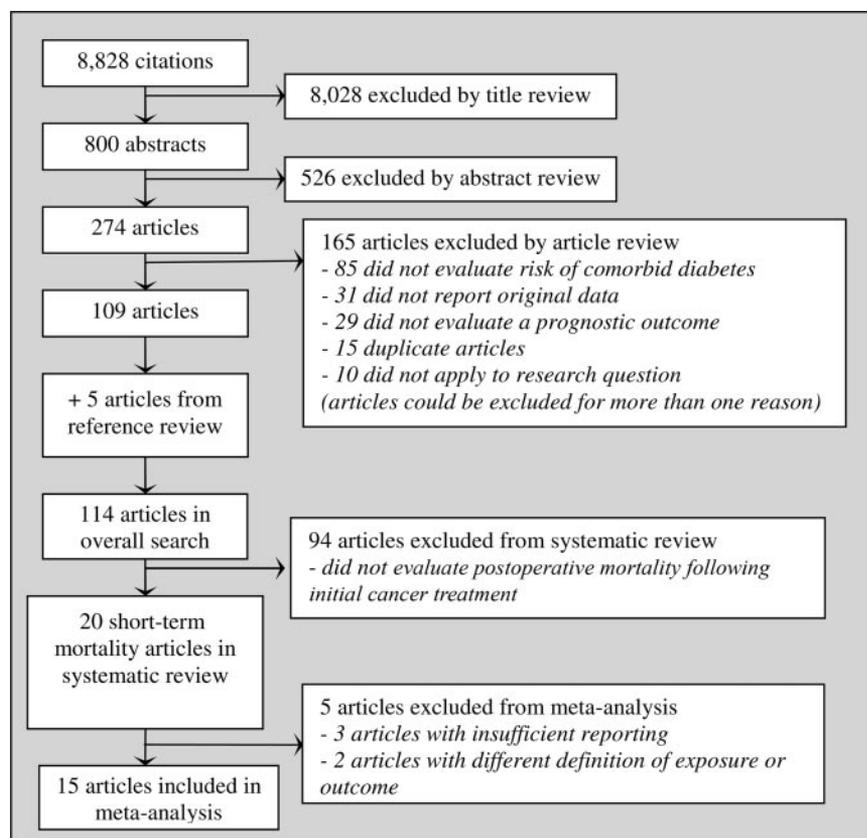
Table 1—Continued

Author, year, country	Cancer site	Exclusion criteria	n with DM/n total (%)	Age (years)	Outcome (mortality rate)	Results	Adjustment variables
Karl et al., 2000, U.S. (17)	Gastroesophageal junction	No esophagectomy between 1989 and 1999	15/143 (10%)	Mean (range) 63.7 (33–83)	30-day mortality (2.1%)	DM: 13%; NG: 1% (P value NA)	None
Abunasa et al., 2005, U.K. (18)	Esophagus or gastroesophageal junction	No esophagectomy, neoadjuvant chemotherapy, not treated between 1990 and 2003	47/773 (6%)	Median 67.8	30-day mortality (3.5%)	DM: 11%; NG: 4% (P = 0.030)	None†
Wright et al., 2009, U.S. (19)	Esophagus	No esophagectomy, emergency operations, sites with inconsistent reporting, aged <30 years, missing data for age or discharge mortality, not treated between 2002 and 2007	373/2,315 (16%)	<60: 35%; 60–69: 35%; 70–80: 25%; 80+: 5%	Hospital mortality and morbidity (23.9%)	OR = 1.19† (P = 0.009)	Age, sex, race, comorbidities, Zubrod score, ASA class, steroids, induction therapy, smoking, BMI, time trend
Nagasue et al., 1993, Japan (20)	Liver	No radical hepatic resection between 1980 and 1986	66/229 (29%)	Mean (range) 60.8 (32–79)	Hospital mortality (10.5%)	DM: 15.2%; NG: 11.7% (P > 0.05)	None
Poon et al., 2002, Hong Kong (21)	Liver	No hepatic resection between 1989 and 1999	62/525 (12%)	Mean ± SD DM: 60.5 ± 9.7; NG: 52.4 ± 13.4	30-day mortality (3.0%)	DM: 3.2%; NG: 3.0% (P = 0.583)	None
Romano and Mark, 1992, U.S. (22)	Lung	No pneumonectomy, lobectomy, wedge or segmental resection; not adults; not discharged from non-federal acute care hospital; not principal or secondary diagnosis; not treated between 1983 and 1986	577/12,439 (5%)	Mean 64	30-day mortality (5.0%)	Lesser resections OR = 1.5 (1.1–2.2); Pneumonectomies OR = 1.4 (0.7–2.9)	Age, sex, primary diagnosis, resection type, comorbidities, type of hospital, hospital volume
Au et al., 1994, Scotland (23)	Lung	No pneumonectomy, aged <70 years, classified as medically unfit, not treated between 1980 and 1987	5/70 (7%)	Mean (range) 72.3 (70–82)	30-day mortality (21.4%)	NA: Fisher's exact test (P > 0.05)	None
Duque et al., 1997, Spain (24)	Lung	No thoracotomy between 1993 and 1994	46/605 (8%)	≤70: 75% >70: 25%	30-day mortality (6.6%)	OR = 1.83 (0.68–4.91)	None†

Table 1—Continued

Author, year, country	Cancer site	Exclusion criteria	n with DM/n total (%)	Age (years)	Outcome (mortality rate)	Results	Adjustment variables
Dominguez-Ventura et al., 2006, U.S. (25)	Lung	No pulmonary resection, aged <80 years, not non-small cell, not treated between 1985 and 2004	28/379 (7%)	Median (range) 82 (80–95)	30-day mortality (6.3%)	OR = 0.71 (0.09–5.49)	None
Wu et al., 1995, Taiwan (26)	Stomach	No radical gastrectomy between 1987 and 1993	7/474 (1%)	NA	Hospital mortality (3.0%)	OR = NA† (P > 0.05)	Age, extent of gastric resection, combined organ resection, respiratory system disease
Andrén-Sandberg and Ihse, 1983, Sweden (27)	Pancreas	No total pancreatectomy, incomplete data, not treated between 1959 and 1982	12/86 (14%)	Mean 61.2	Hospital mortality (29.1%)	DM: 58%; NG: 24% (P value NA)	None
Bakkevoold and Kambestad, 1993, Norway (28)	Pancreas	No radical or palliative surgery for pancreatic cancer, unconfirmed adenocarcinoma of the exocrine pancreas or the papilla of Vater, not treated between 1984 and 1987	NA/360	Mean 67	30-day mortality (13.1%)	Radical pancreatectomy OR = NA (P > 0.05); Palliative surgery OR = 0.20 (0.06–0.64)‡	Radical pancreatectomy: Karnofsky's index—palliative surgery: liver metastasis, Karnofsky's index
Wilt et al., 1999, U.S. (29)	Prostate	No radical prostatectomy at a Veterans Affairs Medical Center, not aged 45–84 years, not treated between 1986 and 1996	1,352/13,398 (10%)	Mean ± SD 65.0 ± 5.4	30-day mortality (0.73%)	OR = 1.87 (1.11–3.15)	Age, race, alcohol abuse, comorbidities, region

ASA, American Society of Anesthesiology; DM, diabetes; NA, not available; NG, normoglycemic. \*95% CI. †Study included multivariate model in which diabetes was not included. ‡Used hospital mortality plus morbidity as outcome. §Used four-level definition of diabetes based on oral glucose tolerance test results. ¶Diabetes population as reference.



**Figure 1**—Flowchart of study selection.

section. Jullumstrø et al. (14) found no significant difference in 30-day mortality between patients with and without diabetes (6 vs. 5%,  $P = 0.61$ ) in a cohort of colorectal cancer patients. Finally, Davila et al. (13) evaluated the risk of 30-day mortality in 32,621 colorectal cancer patients with and without diabetes from the Veteran's Affairs Database. After adjustment for confounders, they observed a significant increase in risk for patients with diabetes (HR 1.19 [95% CI 1.04–1.36]).

Five studies reported the risk of diabetes on postoperative mortality in patients undergoing treatment for cancer of the esophagus or gastroesophageal junction (15–19). Karl et al. (17) and Abu-nasra et al. (18) reported rates of 30-day mortality in clinical populations with cancer of the gastrointestinal junction or gastrointestinal junction/esophagus, respectively. Both reported higher rates of 30-day mortality among patients with diabetes (13 vs. 1%,  $P$  not reported; and 11 vs. 4%,  $P = 0.030$ , respectively). Bartels et al. (16) reported that, after adjustment for confounders, diabetes was not associated with 30-day mortality in a clinical cohort of 432 patients undergoing cura-

tive esophagectomy (OR not reported;  $P < 0.05$ ). Zhang et al. (15) found that a four-level ordinal definition of diabetes based on an oral glucose tolerance test significantly predicted hospital complication mortality (OR 1.19 per level;  $P = 0.024$ ) in an adjusted prediction model in a clinical cohort of 100 esophageal cancer patients. Finally, Wright et al. (19) found that concomitant diabetes in 2,315 cancer patients undergoing esophagectomy from the Society of Thoracic Surgeons' Database was associated with an adjusted OR of 1.19 ( $P = 0.009$ ) for the composite outcome of hospital morbidity or mortality.

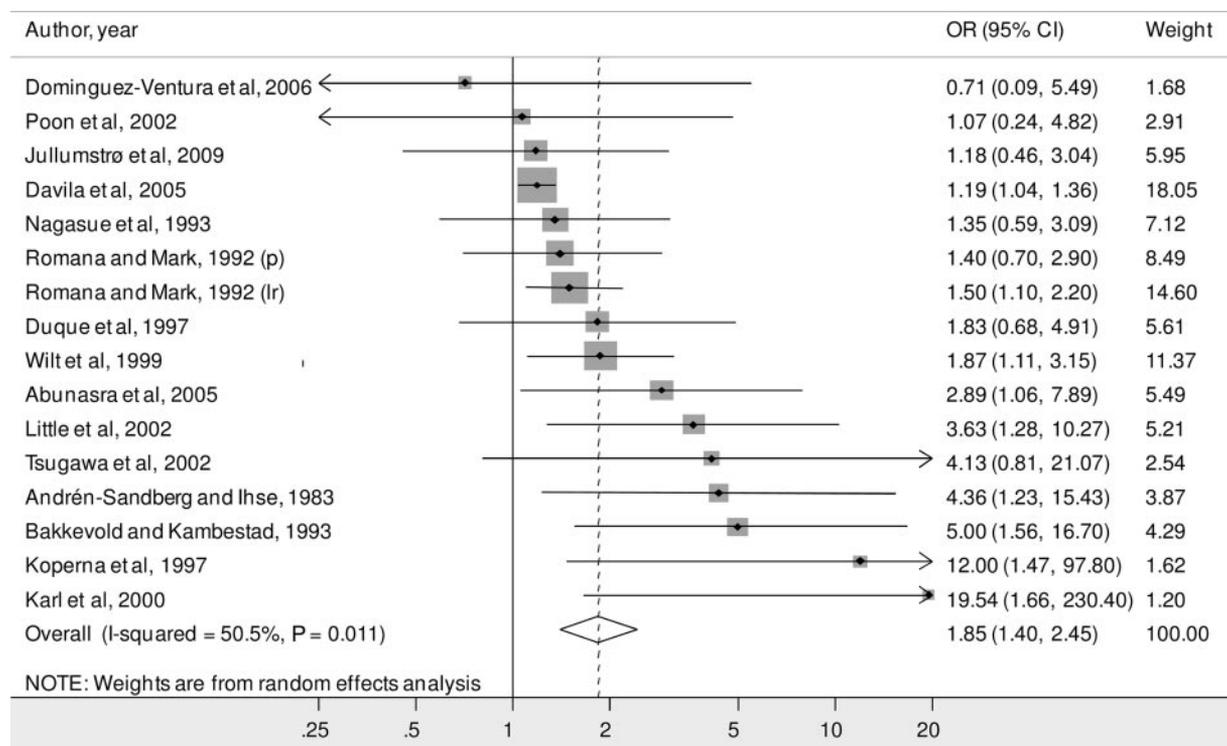
Four studies investigated the effect of diabetes on postoperative mortality in patients with lung cancer (22–25). In a cohort of 12,439 patients from California hospitals, Romano and Mark (22) found that diabetes was associated with an increased risk of 30-day mortality in lung cancer patients undergoing lesser resections (OR 1.5 [95% CI 1.1–2.2]) but not in patients undergoing complete pneumonectomy (1.4 [0.7–2.9]). Duque et al. (24) found a nonsignificant association between diabetes and 30-day mortality (1.83 [0.68–4.91]) in 605 lung cancer

patients from 16 hospitals in Spain. Au et al. (23) and Dominguez-Ventura et al. (25) studied older clinical populations, and each found nonsignificant associations between diabetes and 30-day mortality.

### Meta-analysis

Of the 20 studies with 22 risk estimates included in our systematic review, we excluded six estimates for the purpose of meta-analysis: four estimates for lack of sufficient information (16,23,26,28) and two for use of different exposure or outcome definitions from other included studies (15,19). Thus, we included in the meta-analysis 15 studies reporting 16 risk estimates.

Figure 2 displays the results of the meta-analysis of the 16 estimates in order of magnitude. Compared with their non-diabetic counterparts, cancer patients with preexisting diabetes had greater odds of mortality after surgery (OR 1.85 [1.40–2.45]). Although the studies included in the meta-analysis spanned different continents and cancer sites, the risk estimate was above the null in 15 of 16 estimates and significantly above the null in 9 of 16 estimates. This relationship was attenuated, but still statistically significant, after excluding unadjusted estimates (1.51 [1.13–2.02]; Table 2). Age ( $n = 4$ ), sex ( $n = 4$ ), and other comorbidities ( $n = 4$ ) were adjustment variables in the majority of these studies (see Table 1 for a complete list in each study). The pooled risk estimates were lower in population-based cohorts (1.51 [1.13–2.02]) than clinic-based cohorts (2.28 [1.46–3.58]), likely because the former reported adjusted risk estimates and the latter did not. Estimates were similar in the three studies where diabetes was the primary exposure variable (1.69 [0.73–3.88]) and the 12 studies where diabetes was one among several prognostic variables (1.88 [1.38–2.55]). We observed evidence of publication bias according to the Begg test ( $P = 0.096$ ) and the Egger plot ( $P = 0.001$ ) (supplemental Fig. A). There was also significant evidence of heterogeneity ( $Q = 30.31$  on 15 d.f.,  $P = 0.011$ ; and  $I^2 = 50.5\%$ ,  $P = 0.011$ ). To reduce the influence of publication bias, we used the trim and fill method for both adjusted and unadjusted estimates. This method added five estimates to balance the funnel plot (supplemental Fig. B), and the adjusted risk estimate was attenuated but remained significant (OR 1.52 [1.13–2.04]).



**Figure 2**—Meta-analysis and pooled ORs of postoperative mortality in 15 studies comparing cancer patients with and without preexisting diabetes. *p*, pneumonectomies; *lr*, lesser resections.

Analysis of influence for the overall pooled estimate revealed that the risk of postoperative mortality among patients with diabetes remained significant with the omission of each study in turn (data not shown). When the analysis of influence was repeated in the five studies that reported adjusted estimates, the pooled risk estimate ranged from OR 1.32 (95% CI 1.10–1.59) to 1.73 (1.23–2.43) and remained statistically significant with the omission of each study.

**CONCLUSIONS**— We found that preexisting diabetes conferred a 50% increased risk of mortality in newly diagnosed cancer patients after surgery. This additional risk was present across a range of cancers and a range of surgical cancer treatments. It was not explained by confounding factors, publication bias, or undue influence by a single study. Strengths

of our 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.

Limitations of the literature and of our systematic review and meta-analysis deserve comment. First, the published literature showed great heterogeneity in population demographics and in assessment of confounders. Despite the use of appropriate meta-analytic techniques with random-effect models, we were unable to account fully for these differences. However, we continued to observe a significant association when limiting our pooled estimate to adjusted models, most of which were high-quality studies performed in large cohorts. Second, we found no studies evaluating the effect of diabetes on postoperative mortality in

women with breast or endometrial cancer. Thus, we are uncertain whether our findings apply to women with these cancers.

All articles included in the present systematic review were based on surgical cohorts. A notable gap in the literature is data regarding diabetes' effect on short-term survival in cancer patients who do not undergo surgery. This gap may be especially important because diabetes is known to influence treatment decisions and might steer some patients toward nonsurgical treatment (2).

Previous studies of preexisting diabetes and the risk of postoperative or in-hospital mortality related to noncancer surgery have shown mixed results (30,31). However, there are two main pathways through which preexisting diabetes might specifically influence postoperative mortality risk after cancer surgery. The first pathway is via sepsis and other serious infection. Diabetes is a well-established risk factor for infection and for infection-related mortality in the general population. Diabetes complications like peripheral arterial disease and bladder dysfunction represent chronic predisposing factors. In addition to these factors is perioperative hyperglycemia, which predicts in-hospital infection likely re-

**Table 2**—Pooled ORs of postoperative mortality in cancer patients with and without preexisting diabetes

Type of estimate	Number of estimates	Pooled OR (95% CI)
All estimates	16	1.85 (1.40–2.45)
Only adjusted estimates	5	1.51 (1.13–2.02)
Adjustment for publication bias by trim and fill	21	1.52 (1.13–2.04)

lated to acute effects on leukocyte function (32). In a population of bone marrow transplantation recipients, who are highly susceptible to infection, Derr et al. (33) reported positive associations between preneutropenia glycemia and risks of any infection and bloodstream infection.

The second pathway to postoperative mortality risk is via myocardial infarction. Diabetes is a chronic risk factor for atherosclerosis in multiple vascular beds, including the coronary arteries, and is a strong predictor of myocardial infarction and cardiovascular disease death in the general population (34). Superimposed on long-standing atherosclerosis are short-term effects of hyperglycemia on platelet function and thrombotic tendency (35). Perioperative renal failure (e.g., diabetes-related contrast nephropathy), in addition to diabetes-related chronic kidney disease (36), may also aggravate cardiovascular risk.

These observations raise a therapeutic question: might improvements in perioperative diabetes care reduce the risk of postoperative mortality after cancer surgery? There are no clinical trials that address this question directly. Trials and quasi-experimental studies of improved glycemic control in the setting of noncancer surgery have been generally favorable (37,38). However, randomized controlled trials of intensive insulin therapy to achieve glycemic control in surgical intensive care units have yielded mixed results (39,40).

The main implication of our study is that oncologists, surgeons, and cancer patients should be aware of the excess postoperative mortality risk related to diabetes when considering treatment options. Whether improvements in perioperative diabetes care can reduce this excess risk is uncertain. Future research should investigate physiologic pathways to mortality risk and determine whether improvements in perioperative diabetes care can reduce postoperative mortality.

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