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REVIEW

Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer

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Abstract In this paper we address methodological aspects of aetiological importance in the link between diabetes and mortality in patients with cancer. We identified nine key points on the cancer pathway at which confounding may arise—cancer screening use, stage at diagnosis, cancer treatment selection, cancer treatment complications and failures, peri-treatment mortality, competing risks for long-term mortality, effects of type 2 diabetes on anti-cancer therapies, effects of glucose-lowering treatments on cancer outcome and differences in tumour biology. Two types of mortality studies were identified: (1) inception cohort studies that evaluate the effect of baseline diabetes on cancer-related mortality in general populations, and (2) cohorts of patients with a cancer diagnosis and pre-existing type 2 diabetes. We demonstrate, with multiple examples from the literature, that pre-existing diabetes affects presentation, cancer treatment, and outcome of several common cancer types, often to varying extents. Diabetes is associated with increased all-cause mortality in cancer patients, but the evidence that it influences cancer-specific mortality is inconsistent. In the absence of data that address the potential biases and confounders outlined in the above framework, we caution against the reporting of cancer-related mortality as a main endpoint in analyses determining the impact of diabetes and glucose-lowering medications on risk of cancer.

Keywords Bias · Cancer · Confounding · Diabetes · Epidemiology · Review · Type 2 diabetes

Abbreviations

BRFSS	Behavioural Risk Factor Surveillance System
CaPSURE	Cancer of the Prostate Strategic Urologic Research Endeavour
FOBT	Faecal occult blood screening
NHL	Non-Hodgkin lymphoma
pCR	Pathologic complete response
PSA	Prostate-specific antigen
RCT	Randomised controlled trial
SEER	Surveillance, Epidemiology, and End Results
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
VA	Veterans Administration

Introduction

This is the second of two papers developing frameworks to evaluate methodological issues in studies linking diabetes and

Members of the Diabetes and Cancer Research Consortium are shown in Appendix 1.

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cancer. The first paper summarises associations between type 2 diabetes mellitus and increased incidence of several common cancer types [1]. In addition, studies report that glucose-lowering treatments may modulate cancer risk but many of these pharmaco-epidemiological studies have methodological limitations. For this paper, we note that some studies on the relationship between treatments for diabetes and cancer risk report cancer incidence as the primary endpoint [2–8], while others report cancer mortality [9–14]—but are these two endpoints interchangeable? Here, we develop a conceptual framework within which to evaluate this question. We identified nine key steps in the cancer pathway at which differences may arise—uptake of cancer screening, cancer stage at diagnosis, cancer treatment selection bias, cancer treatment complications and failures, peri-treatment mortality, competing risks for long-term mortality, effects of type 2 diabetes on anti-cancer therapies, effects of glucose-lowering treatments on cancer outcome and differences in tumour biology (Table 1). We used a comprehensive literature review to explore differences in these steps between patients with and without type 2 diabetes, which might be considered as either potential confounders or effect modifiers using definitions detailed by the STROBE reporting group (see Appendix 2) [15]. The motivation to this paper is to improve the interpretation of studies evaluating aetiological associations between diabetes, its treatment and mortality in cancer patients. A similar concept paper has recently been presented regarding the observed differences in cancer mortality between countries [16].

Table 1 A framework to evaluate the impact of diabetes on mortality in patients with cancer

	Potential confounders and modifiers	Suggested approaches to minimise confounding
1.	Differential use of cancer screening	Record screen-detected cancers; perform a priori subgroup analyses
2.	Advanced stage at diagnosis	Capture tumour stage; where possible, compare diabetic and non-diabetic populations
3.	Selection bias for initial and adjuvant cancer treatment	Randomised treatment setting is ideal; alternative is to use matching techniques
4.	Complications of initial cancer treatment/treatment failures	Capture details on treatment, complications and treatment-related mortality; where possible, compare diabetic and non-diabetic populations
5.	Peri-treatment mortality (short-term mortality)	
6.	Competing risks for death (long-term mortality)	Capture non-cancer deaths; perform competing risk survival analyses
7.	Interactions with anti-cancer therapies	Collect anti-cancer therapy data and treatment responses; perform test for interactions—for example in 2×2 designs: potential treatment predictor with and without anti-cancer therapy
8.	Effects of glucose-lowering treatments on cancer treatments	
9.	Differences in tumour biology	Ongoing tissue banking and molecular profiling

Diabetes and cancer incidence: the evidence

Several systematic reviews have evaluated the associations between diabetes and risk of incident cancers, and are discussed in greater detail in the first review paper [1]. In brief, the meta-analyses indicate modestly increased risks for colon and rectal cancer, postmenopausal (but not premenopausal) breast cancer, endometrial cancer, kidney cancer, bladder cancer, pancreatic cancer, hepatocellular carcinomas and non-Hodgkin lymphoma (NHL) among people with diabetes (most of whom are assumed to have type 2 diabetes) as compared with the general population.

Diabetes and cancer mortality: the evidence

Population cohorts We identified two groups of mortality studies: (1) inception cohort studies that evaluate the effect of baseline type 2 diabetes, and (2) cohorts of patients with a cancer diagnosis and pre-existing diabetes. The former are prospective cohorts in which diabetes is determined at baseline and subsequent cancer-related mortality is reported. Findings from four major analyses (five papers) [17–21] are summarised in Table 2. As expected, there are some findings consistent with those noted for cancer incidence. Thus, there are positive associations between baseline diabetes and mortality from cancer of the colorectum (or colon), liver, pancreas and bladder. However, associations for diabetes and mortality from prostate, breast and endometrial cancers are inconsistent, and there appear to be no associations between diabetes and mortality from kidney cancer. For lung cancer (where there does not appear to be a link between diabetes and cancer incidence), one large pooled analysis of 97 prospective cohorts [21] reported a significant positive association (HR 1.27, 95% CI 1.13, 1.43), although this was not replicated in the other analyses (even after adjustment for smoking and body mass index [BMI]) [18, 19].

The message from these studies seems consistent—baseline diabetes is associated with increased mortality from cancers of some types. These data support the cancer incidence data, and, at a public health level, they are helpful as an index of disease burden. However, there are limitations to their interpretation:

- As mortality from cancer is itself conditional on the occurrence of cancer, these studies fail to disentangle the impact of diabetes on incidence versus treatment outcome, and

Table 2 Associations between diabetes (mainly type 2) and cancer mortality in inception cohorts

Authors, year [ref.], study	No. of participants (FU)	Risk estimates (95% CI) by main cancer types							
		Breast and endometrial	Colorectal	Lung	Liver	Pancreas	Bladder	Prostate	Other cancers
Coughlin et al. 2004 [18], Cancer Prevention Study II	M: 467,922 W: 588,321 16-year FU	B: 1.27 (1.11, 1.45) E: 1.33 (0.92, 1.90)	Colon, M: 1.20 (1.06, 1.37) Colon, W: 1.24 (1.07, 1.43)	M: 0.93 (0.64, 1.36) W: 1.11 (0.98, 1.25)	M: 1.05 (0.97, 1.14) W: 1.37 (0.94, 2.00)	M: 1.48 (1.27, 1.73) W: 1.44 (1.21, 1.72)	M: 1.43 (1.14, 1.80) W: 1.30 (0.85, 2.00)	0.90 (0.80, 1.02)	No associations with kidney; NHL: 1.21; MM: 1.27 in men
Lam et al. 2010 [19], pooled analysis 36 mainly Asian cohorts	367,361 Median FU: 4 years	B: 0.75 (0.39, 1.47) E: not stated	M and W: 1.32 (0.98, 1.78)	M and W: 0.88 (0.69, 1.13)	M and W: 1.51 (1.19, 1.91)	M and W: 1.78 (1.20, 2.65)	M and W: 1.42 (0.72, 2.86)	1.27 (0.84, 1.93)	No associations with kidney MM: 1.89
Whitehall I study 2009 and 2011 [20]	19,019 men only FU: 38 and 40 years					M: 2.47 (0.79, 7.75)			
Emerging Risk Factor Collaboration 2011, 97 cohorts [21]	820,900 FU: 12 M person-years	B: 1.25 (1.02, 1.52) E: not stated	M and W: 1.40 (1.01, 1.96)	M and W: 1.27 (1.13, 1.43)	M and W: 2.16 (1.62, 2.88)	M and W: 1.51 (1.24, 1.83)	M and W: 1.40 (1.01, 1.96)	0.89 (0.71, 1.10)	No associations with kidney Ovary: 1.45

B, breast cancer; E, endometrial cancer; FU, follow-up; M, men; MM, multiple myeloma; W, women

- As most cohorts used baseline diabetes in a fixed cohort design, it is not possible to take account of the influence on diabetes development after the baseline date (i.e. a time-varying approach).

Furthermore, the observation that there were differences for some cancer sites between mortality and incidence suggests that some residual confounding may be present, and the most likely place to look for these is in the second group of studies—patient cohorts (referred to by some epidemiologists as cancer case fatality studies).

Mortality in cancer patients with diabetes The influence of pre-existing diabetes on mortality in cancer patients (compared with patients with cancer and no diabetes) was addressed in a meta-analysis reported by Barone and colleagues published in 2008 [22]. From 23 articles, they showed that diabetes is associated with an increased all-cause mortality among people with cancer with an HR of 1.41 (95% CI 1.28, 1.55) compared with normoglycaemic individuals, across all cancer types. Updated meta-analyses of these data have since been published [23–25]. Together with data from the Eindhoven Cancer Registry (including cancer types not covered in the Barone meta-analysis) [26], they show the emergence of four patterns of associations with pre-existing diabetes (Table 3): (1) cancers with increased incidence and increased mortality (for example: colorectal, breast, endometrial and kidney cancers and NHL); (2) increased incidence but no effect on mortality (for example: pancreatic and hepatocellular cancers); (3) decreased incidence but increased mortality (for example: prostate cancer) and (4) no apparent effect on either incidence or mortality (for example: lung and ovarian cancers).

Importantly, this grouping relates to all-cause mortality following a diagnosis of cancer, as opposed to cancer-specific mortality, which further complicates epidemiological assessments. The remainder of this review will dissect out the various steps on the cancer pathway at which pre-existing diabetes may influence mortality from any cause.

Cancer screening

We reviewed the impact of diabetes on the use of screening in four cancer types with five modalities—breast (mammography) cervical (Papanicolaou 'Pap' smearing), colorectal (faecal occult blood testing [FOBT]; flexible sigmoidoscopy) and prostate (serum prostate-specific antigen [PSA]) (Table 4).

Breast cancer screening Two early case–control studies [27, 28] showed that the rates for mammographic screening were significantly lower among women with diabetes than among those without diabetes. A further study using Surveillance, Epidemiology, and End Results (SEER)-Medicare linkage (women ≥67 years old) showed similar findings [29]. A Canadian study [30] of women aged 50–67 years additionally showed a lower rate of attending mammographic screening among those with diabetes than those without. In contrast, the Behavioural Risk Factor Surveillance System (BRFSS) database (USA) study [31] reported that women aged 40 years or more with diabetes had a similar screening rate for breast cancer to those without diabetes. At first glance, these findings seem inconsistent, but on

Table 3 All-cause mortality in patients by different cancer types

Cancer type	All-cause mortality		
	Ref. type	No. of studies (diabetes/no diabetes)[a]	Risk estimates (95% CI)
Increased incidence and mortality			
Colorectal	MA [24]	6 (8,028/46,712)	1.32 (1.24, 1.41)
Breast	MA [25]	4 (1,107/12,912)	1.49 (1.35, 1.65)
Endometrial	MA [22]	4 (429/2,471)	1.76 (1.34, 2.31)
Kidney	ECR [26]	1 (174/1,223)	33 vs 48% at 5 years
NHL	ECR [26]	1 (123/1,607)	32 vs 51% at 5 years
Increased incidence, no effect on mortality			
Pancreas	MA [22]	4 (477/1,204)	1.09 (0.70, 1.69)
Hepatocellular	MA [22]	3 (848/2,876)	1.30 (0.99, 1.70)
Decreased incidence/increased mortality			
Prostate	MA [23]	4 (555/5,709)	1.57 (1.12, 2.20)
No effect on incidence and mortality			
Lung	MA [22]	4 (989/10,120)	1.15 (0.99, 1.34)
Gastric	MA [22]	3 (687/5,513)	1.36 (0.92, 2.01)

ECR, Eindhoven Cancer Registry; MA, meta-analysis

[a]Number of patients with cancers with and without diabetes

Table 4 Diabetes and cancer screening: study characteristics and findings

Author, year [ref.] (country)	Study name	Study design	Diabetes/ non-diabetes	Main results (95% CI)	Comments and adjustments
Breast cancer screening					
Fontana et al. 1997 [28] (USA)	Primary Care Prevention Project	Case–control	173/1,986	OR 0.53 (0.29, 0.97)	Evidence of outcome reporting bias
Beckman et al. 2001 [27] (USA)	Midwestern multispecialty group	Case–control, 50 to 75 years	424/845	78 vs 85%; OR 0.63, p=0.002	Adjusted for insurance status and race
McBean et al. 2007 [29] (USA)	SEER-Medicare, ≥67 years	Population based		OR 0.83 (0.78, 0.88)	
Lipscombe et al. 2005 [30] (Canada)	Ontario Diabetes database and Ontario Health Insurance Plan	Case–control (1999–2002)	69,168/663,519 (aged 50 to 67 years)	OR 0.68 (0.67, 0.70)	Lower 2-year mammogram rates despite higher physician contacts
Zhao et al. 2009 [31] (USA)	BRFSS, women only	Population based	16,256/124,680	OR 0.96 (0.87, 1.05)	Adjusted for age, BMI, race, smoking, health insurance, check-up visit
Jimemez-Garcia et al. 2009 [32] (Spain)	Spanish National Health Survey	Case–control	1,222/11,207	58 vs 62%, p<0.05	Adjusted for age, education, income, smoking
Marshall et al. 2010 [35] (USA)	BRFSS	Screening programme	Total population: 9 million	66 vs 68%, no difference	Adjusted using PRECEDE
Cervical cancer screening					
Fontana et al. 1997 [28] (USA)	Primary Care Prevention Project	Case–control	173/1,986	OR 0.64 (0.399, 1.07)	Evidence of outcome reporting bias
Zhao et al. 2009 [31] (USA)	BRFSS women only	Population based	16,256/124,680	OR 0.83 (0.66, 0.81)	Adjusted for age, BMI, race, smoking, health insurance, check-up visit
Jimemez-Garcia et al. 2009 [32] (Spain)	Spanish National Health Survey	Case–control	614/13,124	62 vs 66%, p<0.05	Adjusted for age, education, income, smoking
Marshall et al. 2010 [35] (USA)	BRFSS	Screening programme	Total population: 13 million	78 vs 86%, p<0.01	Adjusted using PRECEDE
Colorectal cancer screening					
Fontana et al. 1997 [28] (USA)	Primary Care Prevention Project	Case–control	173/1,986	OR 0.54 (0.32, 0.89) for FS in women OR 0.54 (0.27, 1.05) for FOBT in men	
Bell et al. 2001 [36] (USA)	North Carolina BRFSS	Case–control	116/887	FS: 30 vs 29% FOBT: 35 vs 26%	Dropped in multivariate analysis as not significant
McBean et al. 2007 [29] (USA)	SEER-Medicare, women ≥67 years	Population based		OR 0.79 (0.70, 0.88)	
Zhao et al. 2009 [31] (USA)	BRFSS, women only	Population based	16,256/124,680	OR 1.05 (0.97, 1.14) for FS OR 1.24 (1.12, 1.36) for FOBT	Adjusted for age, BMI, race, smoking, health insurance, check-up visit

FS, flexible sigmoidoscopy; PRECEDE, Predisposing, Reinforcing, and Enabling Constructs in Educational Diagnosis and Evaluation model

stratified analysis among women aged ≥70 years, the screening rates for breast cancer tended to be lower among those with diabetes than among those without (76 vs 79% in 2006, p=0.069). Thus, the apparent differences may partially result from the different age compositions of study populations. In addition, the BRFSS is a self-reported, telephone base survey with a high non-respondent rate, and may not be representative.

Outside North American populations, there are few reported studies of cancer screening uptake among people with diabetes. However, one Spanish study reported underuse of breast cancer screening among patients with diabetes [32]. One small UK study reported that, among women undergoing breast cancer screening, the percentages with diabetes were similar to those for the general population [33]. Finally, diabetes per se does not appear to significantly influence mammographic breast density [34].

Cervical cancer screening Cervical cancer screening reported in the BRFSS [31] also suggests that women with diabetes (aged 18 to 70 years) are considerably less likely to undergo Pap screening than women without diabetes (OR 0.73, 95% CI 0.66, 0.81). Despite adjustments, these findings may be confounded by age, BMI, smoking, educational levels and health insurance. Furthermore, the cervical cancer screening prevalence rates in patients with diabetes declined from 2000 to 2006 (end of study). Nonetheless, further analyses of a subset of the BRFSS [35] and other studies [28, 32] have consistently reported that diabetes is associated with lower Pap testing rates than in the non-diabetic population.

Colorectal cancer screening Early small case–control studies [28, 36] of the impact of diabetes on colorectal cancer screening reported mixed results. Using the SEER-Medicare linkage dataset, McBean and Yu [29] reported that women (≥67 years old) with diabetes were less likely to be screened for colorectal cancer than those without diabetes, though the type of screening modality was not analysed separately. In contrast, the recent BRFSS analysis [31] demonstrated that women (≥50 years old) with diabetes were more likely than those without diabetes to be screened for colorectal cancer by FOBT (adjusted OR 1.24, 95% CI 1.12, 1.36) and were marginally more likely to receive screening by sigmoidoscopy or colonoscopy (adjusted OR 1.05, 95% CI 0.97, 1.14).

We found no direct comparisons for type of colorectal screening by men and women with diabetes, but noted that, where BMI was the exposure of interest, compared with normal weight, men in the overweight and obesity class I categories were more likely to have obtained a screening flexible sigmoidoscopy than men with normal weight, while women in the obesity class I and II categories were less likely to have obtained a screening flexible sigmoidoscopy compared with normal weight women [37].

Prostate cancer screening and PSA measurements We found no studies where the use of prostate cancer screening (i.e. serum PSA measurement) was separately reported in people with and without diabetes, although we noted that at least one US study observed that prostate cancer screening was used more frequently among obese than non-obese men [38]. Nonetheless, the relationships between serum PSA, obesity and diabetes are worthy of brief discussion. Several studies have shown that, in general, there is an inverse relationship between mean serum PSA levels and BMI (levels are 0.15 to 0.30 ng/ml lower in overweight individuals compared with normal weight men) (reviewed by Beebe-Dimmer et al. [39]). Lower PSA values may in part be explained by haemodilution with increasing weight [40], but this is not routinely adjusted for in clinical practice. These findings are consistent with the heterogeneity of risk associations seen between increasing BMI and prostate cancer in cohort studies [41]. PSA levels are also lower in people with diabetes compared with non-diabetic individuals. Controlling for age, Werny and colleagues [42] reported that men with self-reported diabetes had a 21.6% lower geometric mean PSA level than men without diabetes, and this appears to be independent of BMI. This observation may partly be explained by diabetes-associated hypogonadism [43] or the renal impairment associated with diabetes [44].

For patients with diabetes compared with non-diabetic populations, there is evidence that breast and cervical cancer screening uptake is lower in most populations, but results are inconsistent for colorectal cancer screening use

It is speculated that the provision of diabetes-related services during a healthcare visit competes for resources and time availability with preventive services in patients with diabetes in some healthcare systems [45].

Advanced stage at diagnosis

The hypothesis that diabetes is associated with more advanced stage at cancer diagnosis is best demonstrated by the example of breast cancer. In a recent meta-analysis, Peairs and colleagues [25] identified four studies that examined the influence of pre-existing diabetes on stage of breast cancer—three found a positive association. Fleming et al. [46] evaluated women older than 67 years with breast cancer using SEER-Medicare data and found an increased risk of late-stage disease with diabetes (OR 1.17, 95% CI 1.08, 1.27 vs early stage disease). Srokowski et al. [47] demonstrated that a higher

percentage of women with diabetes presented with a more advanced stage than their non-diabetic counterparts (47 vs 42% stage II or III, $p<0.0001$). In the Eindhoven Cancer Registry study, van de Poll-Franse et al. [26] reported that a larger proportion of women with diabetes and breast cancer had stage III or IV disease at diagnosis than women without diabetes (19 vs 12%). In contrast, Yancik et al. [48] found no association between diabetes and breast cancer stage; however, a large number of patients in this study did not have a cancer stage assignment, which limits the conclusions one can draw.

The Eindhoven Cancer Registry study (5,555 cancers in patients with diabetes and 52,943 cancers in patients without diabetes) [26] reported staging by diabetes status for a number of other cancers. More advanced stage at diagnosis was noted for ovarian (70 vs 57% stage III or IV, $p<0.05$) and for colon cancers, although the latter was based on the observation that a larger proportion of colon cancer patients with diabetes were diagnosed with stage II disease, and that a smaller proportion had stage I disease at diagnosis than in individuals without diabetes. There were no apparent differences in stage at diagnosis between people with and without diabetes for cancers of the oesophagus, stomach, rectum, pancreas, lung, uterus and kidney, and NHL, although the power of the study was limited to detect statistically significant effects for less common cancers.

Increasingly, an association between increasing BMI and more aggressive prostate cancer is recognised [49, 50] but there are few data on the association with diabetes. D'Amico and colleagues [51] recently reported data from the Chicago Prostate Cancer Center, and found that pre-existing diabetes was associated with high-grade disease (defined as Gleeson score 8 to 10) after adjustment for other known risk factors (OR 1.85, 95% CI 1.25, 2.74).

There is evidence, particularly for breast cancer, that diabetes is associated with more advanced stage disease at diagnosis. In turn, this is consistent with the evidence of lower uptake of cancer screening in people with diabetes

Selection for initial and adjuvant cancer treatment

We hypothesised that people with diabetes and its complications, as for other chronic diseases, will receive less aggressive cancer treatment and altered radiotherapy and chemotherapy dose scheduling compared with people without co-morbidities. We found that cancer treatment selection in patients with diabetes was best studied for women with breast cancer [25]. In the Eindhoven Cancer Registry study [26], younger (age 35 to 65 years) patients with diabetes and breast cancer were more likely than those without diabetes to receive surgery (OR 2.32, 95% CI 1.01, 5.38; $p<0.05$), whereas older patients (>65 years) with breast cancer and diabetes were less often treated with breast-conserving therapy than women without diabetes (39 vs 46%; $p<0.01$). Likewise, women with insulin-treated diabetes were less likely to undergo axillary lymph node dissection than their non-diabetic counterparts [48].

The Eindhoven Cancer Registry study [26] also reported rates of definitive surgery as first treatment in several cancer types—among these, patients with diabetes and cancer of the ovary were treated less aggressively (OR for aggressive treatment 0.59, 95% CI 0.34, 1.01 after adjusting for age and stage) but patients with diabetes and cancer of the colon were treated more aggressively (OR 1.62, 95% CI 1.10, 2.39) compared with those without diabetes. Young men with prostate cancer and diabetes were more likely to receive radiotherapy than young men with prostate cancer and no diabetes. Chan et al. [52] found in the Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE) study that, compared with surgery, men with diabetes were more likely to undergo external beam radiation (OR 1.54, 95% CI 1.12, 2.13) for prostate cancer treatment, but they found no difference in the use of brachytherapy or watchful waiting compared with men without diabetes.

Much of the information describing use of adjuvant treatments in diabetic patients with cancer again comes from the Eindhoven Cancer Registry study [26]. This study showed the following: young breast cancer patients with diabetes were (1) less likely to receive adjuvant chemotherapy (OR 0.52, 95% CI 0.36, 0.75) after adjusting for age, stage and oestrogen receptor status; but (2) more likely to receive hormonal therapy (OR 1.66, 95% CI 1.18, 2.31) after similar adjustments; (3) older breast cancer patients with diabetes were less likely to receive radiotherapy; (4) older men with NHL were less likely to receive radiotherapy if they have diabetes. The CaPSURE study found that men with prostate cancer and diabetes were more likely to receive hormonal therapy (OR 1.63, 95% CI 1.17, 2.27) than surgery [52].

In the SEER-Medicare study [47], among breast cancer patients receiving adjuvant chemotherapy, women with diabetes were less likely to receive anthracyclines and taxanes compared with women without diabetes.

There is considerable evidence that cancer clinicians modify anti-cancer treatments in patients with cancer and diabetes i.e. treatment selection bias

Cancer treatment-related complication and chemotherapy toxicity

A number of studies have addressed treatment-related complications and toxicity in patients with cancer and diabetes (Table 5). In relation to breast cancer, Srokowski et al. [47] analysed data on 11,826 women who received adjuvant chemotherapy, and found that diabetes was associated with an increased risk of being hospitalised for any chemotherapy toxicity, for infection or fever, for neutropoenia, for anaemia, and for any cause toxicity.

Analyses from patients with colorectal cancer and diabetes come from various settings (Table 5). A cancer centre study [53] of patients with hepatic metastases of colorectal origin (262 non-diabetes to 24 diabetes patients) found no statistically significant difference in the incidence of infectious complications or cardiovascular complications in persons with diabetes compared with those without diabetes. Patients with diabetes, however, were at much higher risk of postoperative hepatic decompensation compared with individuals without diabetes (21.2 vs 2.5%). A second study of 3,759 patients with stage II and stage III colon cancer, treated within a randomised controlled trial (RCT) of 5-fluorouracil adjuvant chemotherapy, reported a higher incidence of severe treatment-related diarrhoea in patients with diabetes compared with patients without diabetes (29 vs 20%, $p<0.001$) [54]. However, there were no significant differences in other major toxicities, including severe nausea, vomiting, stomatitis, leucopoenia, fever or infection, or grade 3 or greater toxicity for people with and without diabetes (56 vs 57%). A third study of Veterans Administration (VA) patients with colorectal cancer undergoing surgical resection found a higher risk of acute myocardial infarction ($p=0.01$) and anastomotic complications ($p=0.02$) in persons with diabetes post-operatively [55]. Finally, a study of 5,330 stage III colon cancer patients from the SEER-Medicare database found that patients with

Table 5 Adverse effects and treatment complications in cancer patients with pre-existing diabetes

Author, year [ref.] (country)	Study name, design (size)	Treatment	Surgical complications	Radiotherapy toxicity	Chemotherapy toxicity (95% CI)
Breast cancer					
Srokowski et al. 2009 [49] (USA)	SEER-Medicare, ≥67 years, population based (11,826)	Adjuvant chemotherapy			Any toxicity: OR 1.38 (1.23,1.56) Infection/fever: OR 1.43 (1.20, 1.70) Neutropenia: OR 1.22 (1.03, 1.45) Anaemia: OR 1.24 (1.05, 1.47)
Colorectal cancer					
Little et al. 2002 [53] (USA)	SKMCC; case series (727 patients: complications reported for 286 patients)	Undergoing liver resections	Infections: 29 vs 15%, $p=0.09$ Cardiovascular: 6 vs 10%, $p=1.00$ Hepatic decompensation: 21 vs 2.5%, $p=0.001$		
Meyerhardt et al. 2003 [54] (USA)	RCT (3,759 stage II and III)	Adjuvant chemotherapy			Diarrhoea: 29 vs 20%, $p<0.001$ Grade 3 and 4: 56 vs 57%, no difference
Davila et al. 2005 [56] (USA)	VA patients Administrative database	Undergoing surgery	Higher MI rate ($p=0.01$) Higher anastomotic complications ($p=0.02$)		
Gross et al. 2007 [55] (USA)	SEER-Medicare, population based (5,330 stage III)	Adjuvant chemotherapy			No difference in hospitalisation rates ($p=0.85$)
Prostate cancer					
Herold et al. 1999 [57] (USA)	Fox Chase Cancer Center, hospital based (944 men)	Radical RT (72 Gy)		Early effects: no difference Late effects: 34 vs 23%, $p=0.013$	

MI, myocardial infarction; RT, radiotherapy; SKMCC, Sloan-Kettering Memorial Cancer Center

diabetes receiving adjuvant chemotherapy had the same rate of hospitalisations as their non-diabetic counterparts and no difference in treatment completion rates [56].

For prostate cancer, Herold et al. [57] found no difference in acute morbidities between men with and without diabetes receiving radiotherapy, but they did find differences in late complications—combined grades 2–4 gastrointestinal and genitourinary late complications for men with vs without diabetes (34 vs 23%, p=0.013).

Among patients with cancer and diabetes, there are reported increased rates of treatment-related adverse effects and complications but the patterns vary across different settings

Peri-treatment mortality (short-term mortality)

Peri-treatment mortality has typically been reported in the context of 30-day postoperative deaths. Barone and colleagues [58] reported a meta-analysis of 15 studies of postoperative death rates in diabetic vs non-diabetic patients with cancers of several types, and reported an overall summary risk estimate of 1.85 (95% CI 1.40, 2.45) disadvantaging people with diabetes. The authors did, however, identify considerable heterogeneity (statistical and clinical), risk of publication biases and outcome reporting biases. Recently updated systematic reviews from the same investigators have focused on colorectal and prostate cancers. For colorectal cancer, the systematic review [24] included four studies that reported short-term mortality, but two of these were in the emergency setting. The other two studies [53, 56] evaluated postoperative mortality after elective surgery for colorectal cancer, and both showed significantly increased risk of death among patients with pre-existing diabetes compared with people without diabetes (Table 6).

For prostate cancer, the updated systematic review [23] identified only one study addressing short-term mortality—Wilt et al. [59], which examined the 30-day mortality in 13,398 men from the VA database who underwent radical prostatectomy and found that pre-existing diabetes was associated with increased odds of 30-day mortality after adjusting for a number of factors (p=0.02).

Evidence supports the hypothesis that diabetes is associated with increased short-term mortality in patients with cancer, particularly following major surgical procedures

Cancer-specific mortality and competing risks for death

A key question is the cause of death in patients with cancer—whether from the cancer or other causes, i.e. competing risk for death. In an updated systematic review in patients with breast cancer [25], six studies reported a risk estimate of pre-existing diabetes with respect to all-cause mortality, and after pooling reported that diabetes was associated with a 49% increased risk for all-cause mortality. However, two studies on cancer-specific mortality provided mixed results. Srokowski et al. [47] observed elevated breast cancer-specific mortality in women with diabetes who received chemotherapy compared with their non-diabetic counterparts (follow-up, 2 to 12 years; OR 1.20, 95% CI 1.07, 1.35) but no diabetes-related increase in breast cancer-specific mortality risk in women who had not received chemotherapy. Fleming et al. [46] found no increased risk for breast cancer-specific mortality at 1-year follow-up in patients with diabetes.

For the updated systematic review on colorectal cancer [24], six studies were included in the meta-analysis for the outcome of all-cause mortality. The pooled summary reported a 32% increased risk for long-term all-cause mortality among people with diabetes compared with people without diabetes. Four studies evaluated long-term colorectal cancer-specific mortality, but only one found an association between poorly

Table 6 Short-term mortality among patients with cancers and pre-existing diabetes

Author, year [ref.] (country)	Study name, design (size)	Setting, treatment	30 day mortality	Outcome (95% CI)
Colorectal cancer				
Little et al. 2002 [53] (USA)	SKMCC, case series (727 patients)	Undergoing liver resections	DM: 8.4% Non-DM: 2.4%	HR 3.63, p=0.02
Davila et al. 2005 [56] (USA)	VA patients, administrative database (32,621)	Undergoing surgery	3.9%	OR 1.19 (1.04, 1.36)
Prostate cancer				
Wilt et al. 1999 [59] (USA)	VA patients, administrative database (13,398)	Undergoing radical prostatectomy 1986–1996		OR 1.87 (1.11, 3.15)

DM, diabetes mellitus; SKMCC, Sloan-Kettering Memorial Cancer Center

controlled, pre-existing diabetes mellitus and the risk of death attributed to colorectal cancer. This study evaluated 269 individuals with colorectal cancer at the VA North Texas Health Care System and found an unadjusted 64% cancer-specific survival among persons without diabetes compared with 74 and 52% cancer-specific survival rates among persons with well-controlled type 2 diabetes (HbA_{1c} <7.5%) and poorly controlled type 2 diabetes (HbA_{1c} >7.5%), respectively ($p<0.05$) [60]. A second study utilised a state cancer registry of 9,395 individuals diagnosed with colorectal cancer and found an HR of only 1.06 (95% CI 0.94, 1.20) for colorectal cancer mortality among people with colorectal cancer and diabetes compared with colorectal cancer patients without diabetes. The presence of diabetes, however, was associated with increased mortality from non-cancer causes (HR 1.84, 95% CI 1.65, 2.06) [61]. A third study of 207 colorectal cancer patients operated on at a single institution reported a median survival, excluding colorectal cancer deaths, of 160 months in patients without diabetes and 68 months in patients with diabetes ($p=0.014$) [62]. A further study evaluated 7,224 individuals with colorectal cancer in the Cancer Prevention Study, and reported no association between diabetes and subsequent death from colorectal cancer. This study did not evaluate non-colorectal cancer death [63].

Of the 11 studies in the updated prostate cancer review [23], four reported a risk estimate of pre-existing diabetes with respect to all-cause mortality, and after pooling reported that diabetes was associated with a 57% increased risk for all-cause mortality. Four studies reported cancer-specific mortality, but only one found an elevated risk of prostate cancer-specific mortality among men with type 2 diabetes (estimate not reported; $p=0.035$) [64]. Three other studies that evaluated prostate cancer-specific mortality did not find statistically significant relationships. Merrick et al. [65] investigated prostate cancer-specific mortality among 530 men who had undergone brachytherapy at least 3 years previously but did not find a significant relationship in univariate analyses ($p=0.712$); therefore, diabetes was not included in the multivariate analyses. Smith et al. [66] evaluated 1,551 men with prostate cancer participating in an RCT of radiation therapy with short- vs long-term adjuvant goserelin for locally advanced prostate cancer. In their evaluation of prostate cancer-specific mortality, they found an HR of 0.80 (95% CI 0.51, 1.25). Froehner et al. [67] reported only that diabetes was not significantly associated with prostate cancer mortality.

There is evidence that diabetes in cancer patients, for example, breast, colorectal and prostate, is associated with increased risk of all-cause mortality, but the evidence on cancer-specific mortality is inconsistent

Effects of diabetes on anti-cancer therapies

This question can be best addressed within the context of secondary analyses of randomised trials, where treatment selection biases and confounding by indication are minimised. Surprisingly few trial groups have reported secondary analyses, partly as cancer trials often exclude patients with chronic illnesses, such as diabetes, in their recruitment criteria. One clear exception is that of the Intergroup 0089 trial [54]. This analysis was within a large randomised adjuvant chemotherapy trial (four arm design of combinations of 5-fluorouracil, leucovorin and levamisole; 1988–1992) of 3,759 patients with high-risk stage II and stage III colon cancer. All patients were allocated to receive chemotherapy, and the main study reported no difference in overall survival (OS). At 5 years, patients with diabetes ($n=287$), compared with patients without diabetes, experienced significantly worse disease-free survival (48% diabetics vs 59% non-diabetics; $p<0.0001$), OS (57 vs 66%; $p<0.0001$), and recurrence-free survival (56 vs 64%, $p=0.012$).

It is worth noting that studies have evaluated diabetes in survivors of cancer using quality indicator assessment tools, and found no differences compared with patients with diabetes but without cancer, for all cancer types [68], colorectal [69] and breast [70] cancer groups.

Based on data from the setting of a large trial, diabetes in patients with cancer may be associated with poorer response to anti-cancer treatment

Effects of glucose-lowering treatments on cancer treatments

Glucose-lowering treatments may impact upon cancer treatments, which in turn may influence cancer-specific mortality. This clearly does not apply in the analysis of the relationship between glucose-lowering treatment and cancer incidence. Here again, a randomised trial would offer the optimal setting in which to test this hypothesis, but we did not find such a study. Nonetheless, one clinical paper is worthy of mention. A retrospective study from the MD Anderson Cancer Centre determined whether metformin use was associated with a change in pathologic complete response (pCR) rates in women with breast cancer and diabetes receiving neoadjuvant chemotherapy [71]. The rate of pCR was 24% in the metformin group, 8.0% in the non-metformin group and 16% in the non-diabetic group (Fig. 1), illustrating two important points: (1) many patients with diabetes have a poorer response rate to chemotherapy

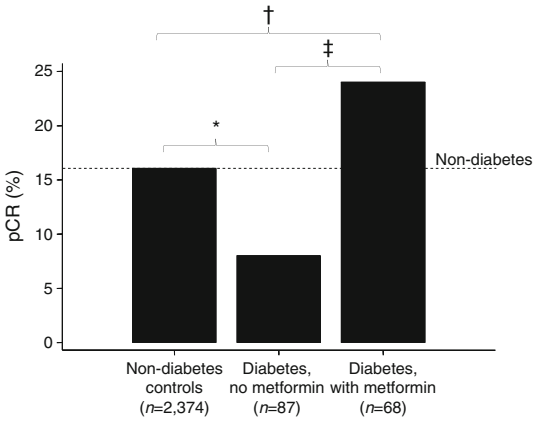

Fig. 1 Response to neoadjuvant chemotherapy in early stage breast cancer, MD Anderson 1990–2007; proportions of pathologic complete response (pCR) between study groups. Pairwise statistical comparisons of pCR rates between the study groups; *p=0.04 for non-diabetic controls vs diabetic patients with no metformin treatment; ‡p=0.007 for diabetic patients with or without metformin; †p=0.1 for non-diabetic controls and diabetic patients taking metformin (constructed based on data from Jiralerspong et al. [71])

than non-diabetic patients (as discussed in the preceding section), and (2) accepting the non-randomised nature of the study, metformin may not only confer a degree of beneficial response in diabetes patients, but may confer an advantage that is even greater than that for non-diabetic patients. This is an example of an effect modification (although in this example the authors did not formally test for an interaction). Furthermore, two recently published studies have found similar beneficial effects of metformin among patients with colorectal cancer and diabetes [72], and among patients with advanced non-small-cell lung cancer undergoing first-line chemotherapy [73].

Differences in tumour biology

We have long appreciated that, for example, the link between increasing BMI and endometrial cancer is best described for the endometrioid subtype of uterine carcinoma [74]. Increasingly, risk exposure is linked with specific molecular signatures—for example, BMI is associated with increased risk of postmenopausal breast cancer [41], but we now appreciate that this is in the main limited to oestrogen receptor/progesterone receptor positive breast tumours [75, 76]. Similarly, BMI is associated with increased risk of colon cancer [41], but this is mainly linked to microsatellite stable tumours [77]. These molecular types in turn have distinct natural histories. We found no similar analogies described for diabetes and tumour biology, but it seems likely that patterns will be similar to those for BMI.

Recommendation

The aim of this paper has been to highlight the complexity of the relationship between diabetes, cancer occurrence and mortality, and to form the framework to improve the interpretation of studies evaluating aetiological associations between diabetes, its treatment and mortality in cancer patients. We have demonstrated many examples of confounding of the association between diabetes and mortality in cancer patients, including presentation and stage at diagnosis, treatment selection biases, differential adverse effects and peri-treatment mortality, and modification of treatment effects. Furthermore, there appears to be considerable heterogeneity in the impact of these factors on the relationship between diabetes and mortality for different cancer subtypes. We conclude that cancer incidence (based on the framework set out in Johnson et al. [1]) and cancer-related mortality are not interchangeable in the setting of diabetes. This conclusion has direct implications for the study of glucose-lowering treatment and cancer mortality. Where cancer-related mortality is pursued as the primary outcome measure, we recommend that researchers take into account the nine factors listed in our framework. In the absence of data that address these potential biases, we caution against the reporting of cancer-related mortality as a main endpoint in analyses determining the impact of glucose-lowering treatment on cancer risk.

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Contribution statement All authors mentioned at the top of this manuscript contributed to the writing of this paper and gave final approval of the version to be published.

Appendix 1

Members of the Diabetes and Cancer Research Consortium

The Diabetes and Cancer Research Consortium is a non-commercial group of international investigators interested in the links between diabetes, diabetes treatment and cancer, partially funded by the EASD. The views expressed in this manuscript are not necessarily those of the EASD. The members of the group include:

Sweden: U. Smith (University of Goteborg); S. Gudbjornsdottir (Nordic School for Population Health);

J. Jonasson (University of Goteborg); R. Ljung (National Board of Health)

Denmark: B. Carstensen, D. Witte, M. Linnemann Jensen (Steno Diabetes Center, Copenhagen); S. Friis, J. Olson (Danish Cancer Society)

Canada: J. Johnson, S. Bowker (University of Alberta); C. Marra (University of British Columbia); L. Lipscombe (University of Toronto); M. Pollak (McGill University)

UK: E. A. M. Gale (University of Bristol); A. Renehan, I. Buchan (University of Manchester); H. Møller (King's College London); H. Colhoun (University of Dundee); C. Currie, C. Poole (University of Cardiff); S. Wild (University of Edinburgh)

Finland: R. Sund, I. Keskimäki (National Institute for Health and Welfare); E. Pukkala, T. Hakulinen (Finnish Cancer Registry); S. Hartikainen (University of Eastern Finland); S. Koski (Finnish Diabetes Association); J. Tuomilehto (National Institute for Health and Welfare; University of Helsinki)

USA: L. Habel, A. Ferrara (Kaiser Permanente); H.T. Zhang (FDA).

Appendix 2

Glossary (direct from STROBE)

Bias is a systematic deviation of a study's result from a true value. Typically, it is introduced during the design or implementation of a study and cannot be remedied later. Bias and confounding are not synonymous. Bias arises from flawed information or subject selection so that a wrong association is found.

Confounding produces relations that are factually correct, but that cannot be interpreted causally because some underlying, unaccounted for factor is associated with both exposure and outcome.

Interaction (*or effect modification*) exists when the association of an exposure with the risk of disease differs in the presence of another exposure.

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