CHAPTER 29

CANCER AND DIABETES

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SUMMARY

Diabetes and cancer are both common diseases and share several behavioral risk factors, including obesity, smoking, dietary factors, and physical inactivity, and disease pathways, such as hyperglycemia and hyperinsulinemia. According to data from the National Health Interview Surveys 2009–2010, after standardizing for age, 11.5% of U.S. adults with diabetes had a history of any cancer (excluding skin cancer), which was significantly greater than the estimate of 8.9% in adults without diabetes. This chapter discusses knowledge of the relationship between diabetes and various cancer outcomes, with emphases on epidemiologic and clinical evidence.

Data from large observational studies and meta-analyses have shown that diabetes is significantly and positively associated with increased overall cancer risk and specific risk of pancreas (pooled relative risk [RR] 1.94, 95% confidence interval [CI] 1.66–2.27), colon (pooled RR 1.38, 95% CI 1.26–1.51), rectum (pooled RR 1.20, 95% CI 1.09–1.31), liver (pooled RR 2.20, 95% CI 1.7–3.0), kidney (pooled RR 1.42, 95% CI 1.06–1.91), bladder (pooled RR 1.29, 95% CI 1.08–1.54), breast (pooled RR 1.27, 95% CI 1.16–1.39), and endometrium (pooled RR 2.10, 95% CI 1.75–2.53) cancers, while negatively associated with the risk of prostate cancer (pooled RR 0.84, 95% CI 0.76–0.93). However, some of the meta-analyses included heterogeneous populations or study designs, resulting in problems of concluding the combining effects.

Large cohort studies have found that diabetes increases cancer mortality. The American Cancer Society Cancer Prevention Study II reported that diabetes increased cancer mortality for colon (RR 1.20, 95% CI 0.77–1.27 in men; RR 1.24, 95% CI 1.07–1.43 in women), liver (RR 2.19, 95% CI 1.76–2.75 in men; RR 1.37, 95% CI 0.94–2.00 in women), pancreas (RR 1.48, 95% CI 1.27–1.73 in men; RR 1.44, 95% CI 1.21–1.72 in women), bladder (RR 1.43, 95% CI 1.14–1.80 in men; RR 1.30, 95% CI 0.85–2.00 in women), and breast (RR 1.27, 95% CI 1.11–1.45 in women) cancers.

Certain diabetes medications are suggested to be associated with decreased or increased risk of cancer. However, various biases and confounding due to observational design or data analysis pitfalls may lead to biased conclusions. In the other direction, certain cancer treatments, such as chemotherapy for breast cancer, androgen deprivation therapy for prostate cancer, surgical resection of the pancreas, and steroid therapy, could increase the risk of diabetes through weight gain, insulin resistance, insulin intolerance, or hyperglycemia.

Meta-analyses indicate diabetes is associated with increased mortality in patients with any cancer (hazard ratio [HR] 1.41, 95% CI 1.28–1.55), as well as cancers of the endometrium (pooled HR 1.76, 95% CI 1.34–2.31), breast (pooled HR 1.49, 95% CI 1.35–1.65), colorectum (pooled HR 1.32, 95% CI 1.24–1.41), prostate (pooled HR 1.57, 95% CI 1.12–2.20), and liver (pooled HR 1.34, 95% CI 1.18–1.51). Furthermore, diabetes is associated with an increased odds of postoperative mortality across all cancer types (pooled odds ratio 1.51, 95% CI 1.13–2.02).

The American Diabetes Association and American Cancer Society Consensus Panel has recommended several strategies for primary and secondary preventions. The panel recommended that healthy diet, physical activity, and weight management should be advised for all. In addition, doctors should screen diabetic patients for cancer as recommended for all people in their age and sex groups. Finally, for most diabetic patients, cancer risk should not be a major factor in choosing diabetes treatment.

INTRODUCTION

Diabetes and cancer are both common diseases and share several behavioral risk factors, including obesity, smoking, dietary factors, and physical inactivity, and disease pathways, such as hyperglycemia and hyperinsulinemia. Findings from major large cohort studies and meta-analyses have shown that obesity and diabetes increase the risk of multiple cancers. Other studies have examined the influence of diabetes on other aspects of cancer outcomes, including mortality, cancer screening, and cancer treatment. This chapter discusses data on the relationship between

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diabetes and various cancer outcomes, with emphases on epidemiologic and clinical evidence: (1) diabetes and cancer incidence and mortality, focusing on common cancers and obesity or diabetes-related cancers: lung, pancreas, colorectum, liver, kidney, bladder, female breast, endometrium, and prostate; (2) diabetes medications and cancer risks; (3) weight gain, hyperglycemia, and diabetes induced by cancer treatment; and (4) diabetes in cancer patients. The majority of the understanding of associations between diabetes and cancer incidence and mortality arises from observational data—while there are many examples of consistent associations, there are also several methodologic pitfalls and potential misinterpretations, which are discussed in this chapter.

CANCER IN ADULTS WITH AND WITHOUT DIABETES

According to a new analysis of age-standardized data from the National Health Interview Surveys 2009–2010 conducted for *Diabetes in America, 3rd edition*, 11.5% of U.S. adults with type 2 diabetes had a history of any cancer (excluding skin cancer), which was significantly greater than the estimate of 8.9% in adults without diabetes (Table 29.1). In adults with type 2 diabetes, 5.6% of women had a history of breast cancer and 5.1% of men had a history of prostate cancer compared to 4.2% of women without diabetes and 4.9% of men without diabetes. Among adults with type 2 diabetes, the age-standardized cancer prevalence (excluding skin cancer) was 17.3% in those age ≥65 years versus 7.6% in those age 30–64 years; in adults without diabetes, the age-standardized cancer prevalence was lower—16.4% in those age ≥65 years versus 5.3% in those age 30–64 years (Table 29.2).

TABLE 29.1. Age-Standardized Prevalence of Cancer History in Adults Age ≥30 Years With and Without Type 2 Diabetes, by Sex and Race/Ethnicity, U.S., 2009–2010

	PERCENT (STANDARD ERROR)					
CHARACTERISTICS	Any Cancer	Any Cancer, Excluding Skin Cancer	Breast	Prostate	Colorectum	Lung
Diabetes						
Total	15.7 (0.59)	11.5 (0.55)	2.8 (0.26)		1.1 (0.16)	0.4 (0.10)
Sex						
Men	16.1 (0.86)	10.8 (0.79)	[3]	5.1 (0.56)	1.1 (0.24)	0.3 (0.13)[1]
Women	15.4 (0.77)	12.3 (0.74)	5.6 (0.52)		1.1 (0.21)	0.4 (0.14)[1]
Race/ethnicity, sex						
Non-Hispanic white	19.0 (0.81)	13.0 (0.76)	3.0 (0.34)		1.3 (0.22)	0.5 (0.14)
Men	19.4 (1.17)	12.2 (1.08)	[3]	5.1 (0.70)	1.3 (0.31)	0.5 (0.19)[2]
Women	18.6 (1.10)	13.9 (1.05)	6.1 (0.71)		1.3 (0.30)	0.5 (0.18)[1]
Non-Hispanic black	10.1 (1.02)	9.9 (1.00)	3.3 (0.64)		0.7 (0.27)[1]	[3]
Men	11.4 (1.84)	11.2 (1.82)	[3]	7.3 (1.40)	[3]	[3]
Women	9.4 (1.35)	9.2 (1.34)	5.8 (1.11)		0.6 (0.30)[2]	[3]
Hispanic	8.3 (1.16)	7.8 (1.10)	1.7 (0.44)		0.4 (0.17)[2]	[3]
Men	6.3 (1.66)	5.3 (1.48)	[3]	3.8 (1.59)[2]	[3]	[3]
Women	10.4 (1.66)	10.2 (1.66)	3.2 (0.85)		[3]	[3]
Mexican American	6.4 (1.15)	6.1 (1.12)	1.4 (0.50)[1]		[3]	[3]
Men	4.7 (1.16)	4.2 (1.09)	[3]	[3]	[3]	[3]
Women	8.0 (1.89)	7.9 (1.89)	2.7 (0.95)[1]		[3]	[3]
Other Hispanic	11.5 (2.26)	10.4 (2.01)	2.1 (0.73)[1]		[3]	[3]
Men	8.7 (3.65)[2]	6.6 (2.85)[2]	[3]	7.6 (3.64)[2]	[3]	[3]
Women	14.2 (2.85)	13.9 (2.87)	4.0 (1.44)[1]		[3]	[3]
Non-Hispanic Asian	4.9 (1.24)	4.9 (1.24)	[3]		[3]	[3]
Men	6.3 (2.01)[1]	6.3 (2.01)[1]	[3]	3.6 (1.71)[2]	[3]	[3]
Women	3.6 (1.29)[1]	3.6 (1.29)[1]	[3]		[3]	[3]
No diabetes						
Total	13.4 (0.24)	8.9 (0.19)	2.4 (0.12)		1.0 (0.08)	0.5 (0.05)
Sex						
Men	14.1 (0.41)	8.9 (0.34)	0.1 (0.02)[2]	4.9 (0.28)	1.2 (0.13)	0.5 (0.08)
Women	13.1 (0.32)	9.3 (0.26)	4.2 (0.20)		1.0 (0.10)	0.5 (0.08)
Race/ethnicity, sex						
Non-Hispanic white	15.3 (0.29)	9.8 (0.23)	2.6 (0.14)		1.1 (0.09)	0.5 (0.07)
Men	16.0 (0.48)	9.7 (0.39)	0.1 (0.03)[2]	5.2 (0.31)	1.2 (0.15)	0.5 (0.10)
Women	15.1 (0.38)	10.2 (0.32)	4.5 (0.24)		1.0 (0.12)	0.5 (0.09)
Non-Hispanic black	7.7 (0.54)	7.4 (0.53)	1.9 (0.29)		1.3 (0.22)	0.5 (0.15)
Men	7.9 (0.93)	7.7 (0.91)	[3]	5.2 (0.76)	1.4 (0.37)	[3]
Women	7.8 (0.72)	7.4 (0.71)	3.2 (0.48)		1.3 (0.29)	0.6 (0.19)[1]

Table 29.1 continues on the next page.

TABLE 29.1. (continued)

CHARACTERISTICS	PERCENT (STANDARD ERROR)					
	Any Cancer	Any Cancer, Excluding Skin Cancer	Breast	Prostate	Colorectum	Lung
Hispanic	5.4 (0.47)	4.7 (0.45)	1.4 (0.26)		0.5 (0.15)[1]	0.3 (0.13)[2]
Men	5.9 (0.85)	4.7 (0.82)	[3]	2.7 (0.67)	0.6 (0.26)[2]	[3]
Women	5.4 (0.59)	5.0 (0.58)	2.5 (0.47)		0.4 (0.16)[2]	[3]
Mexican American	5.1 (0.72)	4.9 (0.73)	1.7 (0.47)		0.3 (0.13)[2]	[3]
Men	4.0 (1.06)	3.7 (1.05)	[3]	2.7 (0.96)[1]	[3]	[3]
Women	6.3 (1.09)	6.2 (1.09)	3.5 (0.95)		[3]	[3]
Other Hispanic	5.9 (0.69)	4.6 (0.63)	1.0 (0.23)		0.7 (0.28)[2]	[3]
Men	8.6 (1.47)	6.2 (1.41)	[3]	2.8 (0.88)[1]	[3]	[3]
Women	4.9 (0.65)	4.1 (0.61)	1.7 (0.38)		[3]	[3]
Non-Hispanic Asian	5.7 (0.76)	5.1 (0.71)	2.0 (0.48)		1.1 (0.20)	[3]
Men	6.1 (1.39)	5.0 (1.27)	[3]	2.4 (0.98)[2]	1.2 (0.29)	[3]
Women	5.6 (0.89)	5.2 (0.87)	3.4 (0.81)		1.1 (0.38)[1]	[3]

Data are self-reported for history of cancer and diabetes. Individuals with probable type 1 diabetes were excluded based on age of diabetes diagnosis <25 years and current insulin use. Data are standardized to the National Health Interview Surveys 2009–2010 diabetic population using age categories 30–64, 65–74, and ≥75 years.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health Interview Surveys 2009–2010

TABLE 29.2. Crude and Age-Standardized Prevalence of Cancer History in Adults Age ≥30 Years With and Without Type 2 Diabetes, by Age and Sex, U.S., 2009–2010

AGE (YEARS), SEX	PERCENT (STANDARD ERROR)					
	Any Cancer	Any Cancer, Excluding Skin Cancer	Breast	Prostate	Colorectum	Lung
Diabetes						
Crude						
30–64	10.2 (0.67)	7.6 (0.60)	1.7 (0.26)		0.6 (0.14)	0.3 (0.12)[1]
Men	8.9 (0.99)	6.2 (0.81)	[3]	2.1 (0.49)	0.6 (0.19)[1]	[3]
Women	11.6 (0.97)	9.2 (0.93)	3.5 (0.53)		0.5 (0.21)[1]	[3]
≥65	24.1 (1.07)	17.3 (1.02)	4.6 (0.52)		1.9 (0.32)	0.5 (0.17)[1]
Men	26.9 (1.63)	17.6 (1.59)	[3]	9.7 (1.13)	1.9 (0.52)	[3]
Women	21.3 (1.31)	17.1 (1.24)	8.8 (1.01)		1.9 (0.43)	0.7 (0.28)[1]
Age-standardized						
30–64	10.2 (0.66)	7.6 (0.59)	1.7 (0.26)		0.6 (0.14)	0.3 (0.12)[1]
Men	8.9 (0.98)	6.3 (0.81)	[3]	2.1 (0.50)	0.6 (0.19)[1]	[3]
Women	11.6 (0.96)	9.2 (0.92)	3.5 (0.53)		0.5 (0.21)[1]	[3]
≥65	24.1 (1.07)	17.3 (1.01)	4.6 (0.52)		1.9 (0.32)	0.5 (0.17)[1]
Men	27.0 (1.64)	17.7 (1.60)	[3]	9.8 (1.13)	1.9 (0.51)	[3]
Women	21.1 (1.28)	17.0 (1.22)	8.8 (1.01)		1.8 (0.43)	0.7 (0.28)[1]
No diabetes						
Crude						
30–64	6.3 (0.18)	4.0 (0.14)	1.0 (0.07)		0.3 (0.04)	0.1 (0.02)
Men	4.8 (0.24)	2.5 (0.16)	[3]	0.7 (0.09)	0.3 (0.06)	0.1 (0.03)[1]
Women	7.8 (0.26)	5.5 (0.21)	2.0 (0.14)		0.3 (0.05)	0.2 (0.04)
≥65	24.1 (0.52)	16.4 (0.45)	4.5 (0.29)		2.2 (0.19)	1.0 (0.13)
Men	28.0 (0.95)	18.3 (0.82)	[3]	11.0 (0.68)	2.3 (0.31)	1.1 (0.20)
Women	21.3 (0.67)	15.0 (0.58)	7.6 (0.47)		2.0 (0.25)	0.9 (0.17)
Age-standardized						
30–64	8.3 (0.26)	5.3 (0.20)	1.5 (0.10)		0.5 (0.06)	0.2 (0.04)
Men	6.7 (0.34)	3.5 (0.23)	[3]	1.3 (0.15)	0.5 (0.10)	0.2 (0.06)[2]
Women	9.8 (0.37)	6.9 (0.30)	2.8 (0.20)		0.4 (0.09)	0.2 (0.05)
≥65	24.1 (0.52)	16.4 (0.45)	4.4 (0.29)		2.2 (0.19)	1.0 (0.13)
Men	28.3 (0.95)	18.6 (0.83)	[3]	11.2 (0.69)	2.4 (0.31)	1.0 (0.20)
Women	21.2 (0.68)	15.0 (0.58)	7.5 (0.47)		2.0 (0.24)	0.9 (0.18)

Data are self-reported for history of cancer and diabetes. Individuals with probable type 1 diabetes were excluded based on age of diabetes diagnosis <25 years and current insulin use. Data are standardized to the National Health Interview Surveys 2009–2010 diabetic population using age categories 30–49 and 50–64 years for persons age 30–64 years and 65–74 and ≥75 years for persons age ≥65 years.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health Interview Surveys 2009–2010

DIABETES AND CANCER INCIDENCE

Large observational studies have reported that diabetes is significantly associated with increased overall cancer risks and risk of certain cancer sites. The Atherosclerosis Risk in Communities (ARIC) Study included 12,792 cancer-free participants in four U.S. communities, who were followed for up to 16 years. Nondiabetic women with glycosylated hemoglobin (A1c) ≥5.7% (≥39 mmol/mol) had an increased risk of cancer incidence (hazard ratio [HR] 1.24, 95% confidence interval [CI] 1.07–1.44), as did diabetic women (HR 1.30, 95% CI 1.06–1.60), compared with nondiabetic women with normal A1c levels; A1c values in nondiabetic and diabetic men were not statistically significantly associated with total cancer risk (1). In a cohort of 1.3 million Koreans with an average body mass index (BMI) of 23.2 kg/m², self-reported diabetes in men was significantly associated with overall cancer incidence (HR 1.24, 95% CI 1.20–1.28) and risk of stomach (HR 1.11, 95% CI 1.04–1.20), liver (HR 1.66, 95% CI 1.53–1.79), pancreas (HR 1.78, 95% CI 1.50–2.11), bladder (HR 1.32, 95% CI 1.10–1.57), and leukemia (HR 1.62, 95% CI 1.23–2.13) cancers; self-reported diabetes in women was associated with overall cancer incidence (HR 1.33, 95% CI 1.25–1.41) and risk of pancreas (HR 1.56, 95% CI 1.14–2.14), breast (HR 1.51, 95% CI 1.26–1.80), and cervix (HR 2.20, 95% CI 1.90–2.54) cancers (2).

The associations between diabetes and cancer risk have also been documented in many meta-analyses. Diabetes is associated with increased risk of pancreas (3), colorectal (4), liver (5), kidney (6), bladder (7), breast (8), and endometrial (9) cancers, while negatively associated with the risk of prostate cancer (10) (Table 29.3).

TABLE 29.3. Summary of Meta-Analyses: Diabetes as a Risk Factor for Cancer

REF.	TUMOR TYPE	NUMBER OF STUDIES	RISK (95% CI)
3	Pancreas	35 cohort	RR 1.94 (1.66–2.27)
4	Colon and rectum	14 (6 case-control; 8 cohort)	Colon: RR 1.38 (1.26–1.51) Rectum: RR 1.20 (1.09–1.31)
5	Liver	49	RR 2.2 (1.7–3.0)
6	Kidney	9 cohort	RR 1.42 (1.06–1.91)
7	Bladder	29 cohort	RR 1.29 (1.08–1.54)
8	Breast	39	RR 1.27 (1.16–1.39)
9	Endometrium	16 (13 case-control; 3 cohort)	RR 2.10 (1.75–2.53)
10	Prostate	19	RR 0.84 (0.76–0.93)

The summary risk estimates are not standardized, and there should no attempt by the reader to rank the diabetes-cancer associations based on the data presented. CI, confidence interval; RR, relative risk.

SOURCE: References are listed within the table.

Several methodologic issues arise when examining the diabetes-cancer incidence associations. First, compared to individuals without diabetes, a bias associated with the detection time may occur—that is, people with diabetes who are under regular medical surveillance might be diagnosed when their cancer is at an earlier stage compared with people without diabetes who may access routine medical care less frequently. Second, it takes many years for cancer to develop and additional years for cancer to be diagnosed. In the analysis of diabetes and cancer incidence, understanding the temporal relationship between diabetes diagnosis and cancer diagnosis is important, including the order in which the two diagnoses occur and the possible length of time between diabetes diagnosis and cancer development. Finally, some meta-analyses of diabetes and cancer included heterogeneous study designs, resulting in problems with combining the studies. In an umbrella review of meta-analyses of observational studies, Tsilidis *et al.* pointed out that only a minority of these associations had strongly significant results with no suggestion of bias, as evidenced by substantial heterogeneity in methods between the studies, small study effects, and excess significances (11).

DIABETES AND CANCER MORTALITY

Large cohort studies have found that diabetes increases cancer mortality (defined as total number of deaths from cancer causes divided by the number of persons at risk in the population). The American Cancer Society Cancer Prevention Study II (12) reported that diabetes increased mortality from colon, liver, pancreas, bladder, and breast cancers (summarized in Table 29.4). Similar findings were reported in large cohorts in other countries. In the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study, including 17 cohorts from seven European countries (13), compared with people in the normal glucose category, multivariable adjusted hazard ratios for cancer mortality were 1.13 (95% CI 1.00–1.28), 1.27 (95% CI 1.02–1.57), and 1.71 (95% CI 1.35–2.17) in men with prediabetes, previously undiagnosed diabetes, and known diabetes, respectively; in women, they were 1.11 (95% CI 0.94–1.30), 1.31 (95% CI 1.00–1.70), and 1.43 (95% CI 1.01–2.02), respectively. Significant increases in deaths from cancers of the stomach, colon-rectum, and liver in men with prediabetes and diabetes, as well as deaths from cancers of the liver and pancreas in women with diabetes, were also observed. In the Asia-Pacific Cohort Studies Collaboration, including nine countries in Asia (14), participants with diabetes had a 23% greater risk

TABLE 29.4. Relation Between Diabetes and Fatal Cancer in Men and Women, American Cancer Society Prevention Study II, 1982–1998

	MEN			WOMEN		
	Rate*			Rate*		
TYPE OF CANCER	Diabetes	No Diabetes	RR (95% CI)†	Diabetes	No Diabetes	RR (95% CI)†
Esophageal	18.1	15.5	1.20 (0.94–1.53)			
Stomach	18.7	17.1	0.99 (0.77–1.27)	10.0	6.8	1.25 (0.90–1.73)
Colon	67.3	53.1	1.20 (0.77–1.27)	50.2	36.7	1.24 (1.07–1.43)
Rectal	9.4	8.6	1.07 (0.75–1.51)	5.0	5.1	0.90 (0.57–1.42)
Liver‡	28.1	10.5	2.19 (1.76–2.75)	8.0	4.7	1.37 (0.94–2.00)
Gallbladder	5.3	3.4	1.45 (0.92–2.30)	5.4	3.9	1.19 (0.77–1.83)
Pancreas	68.3	45.1	1.48 (1.27–1.73)	46.7	31.0	1.44 (1.21–1.72)
Lung	179.5	171.5	1.05 (0.97–1.14)	70.6	71.1	1.11 (0.98–1.25)
Female breast§				61.5	48.8	1.27 (1.11–1.45)
Endometrial‖				12.8	7.8	1.33 (0.92–1.90)
Melanoma	7.9	9.7	0.93 (0.64–1.36)			
Ovarian¶				29.9	29.1	1.02 (0.80–1.29)
Prostate	66.0	72.9	0.90 (0.80–1.02)			
Bladder	21.4	15.0	1.43 (1.14–1.80)	5.2	4.2	1.30 (0.85–2.00)
Kidney#	14.1	15.3	0.82 (0.61–1.10)	9.6	6.3	1.12 (0.80–1.58)
Brain	14.1	15.3	0.96 (0.72–1.29)	10.6	10.1	1.03 (0.74–1.43)
Non-Hodgkin lymphoma	26.9	23.7	1.21 (0.99–1.48)	14.2	14.7	0.93 (0.71–1.21)
Multiple myeloma	16.0	12.2	1.27 (0.98–1.66)	8.2	8.6	0.87 (0.62–1.24)
Leukemia	22.9	24.8	0.88 (0.71–1.10)	15.1	13.2	1.10 (0.85–1.44)

* Mortality rate per 100,000, age-standardized to the Cancer Prevention Study II population.
† Multivariable adjusted relative risk (RR) (and 95% confidence interval [CI]). All analyses were adjusted for a core group of covariates (age, race, years of education, body mass index, cigarette smoking history, alcohol consumption, total red meat consumption, consumption of citrus fruits and juices, consumption of vegetables, physical activity). Except for melanoma, non-Hodgkin lymphoma, and multiple myeloma, analyses for each type of cancer were also adjusted for a family history of that cancer in a first-degree relative.
‡ Also adjusted for hepatitis and cirrhosis.
§ Also adjusted for parity, age at menarche, age at first live birth, and menopausal status.
‖ Excludes women who have had a hysterectomy. Also adjusted for parity, age at menarche, age at first live birth, menopausal status, and oral contraceptive use.
¶ Excludes women who have had a hysterectomy or oophorectomy. Also adjusted for parity, age at menarche, age at first livebirth, menopausal status, and oral contraceptive use.
# Also adjusted for hypertension.

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of mortality from all-cause cancer compared with those without diabetes (HR 1.23, 95% CI 1.12–1.35). Diabetes was associated with mortality due to cancers of the liver (HR 1.51, 95% CI 1.19–1.91), pancreas (HR 1.78, 95% CI 1.20–2.65), and colorectum (HR 1.32, 95% CI 0.98–1.78).

Mortality is clearly an index of the severity of a disease from both clinical and public health standpoints. Epidemiologic studies often use cancer mortality as a surrogate for cancer incidence, because mortality data are easier to collect in large populations. However, mortality is influenced by factors other than incidence alone. For instance, cancer progression and cancer treatment contribute substantially to cancer mortality. When a disease is not fatal, mortality is not a good index of incidence. Furthermore, the cause of death may be incorrect on some death certificates (15). These factors should be considered when evaluating evidence based on mortality data.

SHARED RISK FACTORS BETWEEN DIABETES AND CANCER

Shared risk factors represent one likely explanation for the higher prevalence of cancer in diabetic adults. Many of these factors are strong, well-established, and common.

Non-Modifiable Risk Factors

Non-modifiable risk factors common to both cancer and diabetes include age, sex, and race/ethnicity. Similar to diabetes, cancer incidence and mortality increase with age (Table 29.2). While certain cancers are sex-specific, cancer occurs more frequently in men than in women overall. Blacks, particularly black men, are more likely to develop and die from cancer than other race/sex groups (Appendix 29.1), while cancer rates are lower in Asian Americans, Hispanics, and Native Americans (16). Similarly, in the United States, type 2 diabetes and its complications disproportionately affect African Americans. However, other minority populations, including Native Americans, Hispanics, and Asian Americans/Pacific Islanders, also have higher incidence of diabetes than non-Hispanic whites (17,18).

Modifiable Risk Factors

Modifiable risk factors common to both cancer and diabetes include obesity, smoking, diet, physical activity, and alcohol consumption (19).

Obesity. A study by the International Agency for Research on Cancer (IARC) showed that nearly one-half million new cancer cases per year could be attributed to high BMI; overweight and obesity were responsible for an estimated 3.6% of all new cancer cases in 2012 (20). Overweight or obese individuals had a higher risk for many types of cancer compared with individuals with normal BMI (21,22). The cancers most consistently associated with overweight and obesity include breast in postmenopausal women, colon/rectum, endometrium, pancreas, esophagus, kidney, gallbladder, and liver. However, the association between weight loss and subsequent cancer risk is unclear. In the Nurses' Health Study, a statistically significant inverse association between adult weight loss and postmenopausal breast cancer was found when the weight loss had been maintained for 4 years (23). Generally, observational studies of weight loss and cancer risk require extremely large sample sizes with long-term follow-up on weight change; weight loss may be a sign of undiagnosed cancer. Still, randomized clinical trials to study the effect of weight loss on cancer risk would require very large sample sizes, significant amounts of weight loss, and weight loss maintenance over time. Hence, data from bariatric surgery may be a more feasible resource regarding evidence on weight loss and cancer risk.

The Swedish Obese Subjects (SOS) study involved 2,010 obese patients (BMI ≥34 kg/m^2 in men and ≥38 kg/m^2 in women) who underwent bariatric surgery and 2,037 well-matched obese controls (24). Over 10 years, bariatric surgery resulted in a sustained mean weight reduction of 19.9 kg (standard deviation 15.6 kg), whereas the mean weight change in controls was a gain of 1.3 kg (standard deviation 13.7 kg). Compared to the control group, the rate of first cancer was lower in the surgery group (HR 0.67, 95% CI 0.53–0.85). In the sex-specific analysis, the decreased risk of cancer was significant in women (HR 0.58, 95% CI 0.44–0.77), but not in men (HR 0.97, 95% CI 0.62–1.52). However, the study did not have sufficient statistical power to study site-specific cancer risks (24). A meta-analysis of four studies reported that bariatric surgery was associated with a reduction in the risk of cancer (odds ratio [OR] 0.42, 95% CI 0.24–0.73, I^2 93.3%, p for heterogeneity <0.001) (25).

Smoking. The 2014 Surgeon General's Report concluded a causal relationship between cigarette smoking and the risks of lung, liver, and colorectal cancers (26). Smoking also increased the risk for cancers of the oral cavity, nasal cavity, nasopharynx, larynx, esophagus, pancreas, stomach, cervix, kidney, bladder, leukemia (27,28,29), and the more aggressive prostate cancers (30). Several large cohort studies suggested that smoking is an independent risk factor for the development of diabetes. Meta-analysis suggested a 40% increased risk of diabetes in people who smoked versus those who did not (pooled adjusted relative risk [RR] 1.44, 95% CI 1.31–1.58) (31). While smoking cessation may result in weight gain and increase the risk of developing diabetes (32), smoking cessation reduces the risk of cardiovascular disease (33), other tobacco-related diseases, and all-cause mortality. The health benefits of quitting can be seen at all ages and can be measured almost immediately after cessation (34).

Diet. Observational studies have suggested that diets low in red and processed meats and higher in vegetables, fruits, and whole grains are associated with a lower risk of diabetes and many types of cancer (35). Low-carbohydrate diets have also been associated with weight loss and improvements in insulin sensitivity and glycemic control. Several studies suggested that diets with a high glycemic load are associated with an increased risk of type 2 diabetes (36). However, evidence of an association between a low-carbohydrate diet or low glycemic load diet with cancer risk is uncertain (37,38).

Physical Activity. Observational epidemiologic studies have shown that higher levels of physical activity are associated with a lower risk of colon, postmenopausal breast, and endometrial cancer (39) and may prevent other cancers, including lung and aggressive prostate cancer, but a clear link has not been established. Benefits from increased physical activity on glucose, blood pressure, cholesterols, and cardiovascular diseases have been demonstrated. The Diabetes Prevention Program suggested that those who did not reach weight loss goals still significantly reduced their risk of diabetes if they reached the exercise goals (40).

Alcohol Consumption. Alcohol use has been associated with increased risk for multiple cancers, including oral cavity, pharynx, larynx, esophagus, liver, colon/rectum, and female breast (41). A meta-analysis of 18 cohort studies found a J-shaped relationship between all cancer mortality and alcohol intake in men, although not in women (42). The pooled relative risks for cancer mortality for light, moderate, and heavy drinkers versus abstainers in this meta-analysis were 0.91 (95% CI 0.89–0.94), 1.02 (95% CI 0.99–1.06), and 1.31 (95% CI 1.23–1.39), respectively. On the other hand, moderate alcohol consumption has been associated with reduced diabetes incidence in both men and women (43).

HYPOTHESIZED CAUSAL PATHWAYS

Hyperinsulinemia and Insulin-Like Growth Factors

Elevated levels of insulin are linked to greater tumor growth and recurrence. In a systematic review, Renehan *et al.* (44) reported that high concentrations of insulin-like growth factor-1 (IGF-1) were associated with an increased risks of prostate cancer (OR comparing 75th and 25th percentiles 1.49, 95% CI 1.14–1.95) and premenopausal breast cancer (OR 1.65, 95% CI 1.26–2.08); high concentrations of IGF-binding protein-3 (IGFBP-3) were associated with increased risk of premenopausal breast cancer (OR 1.51, 95% CI 1.01–2.27). In a prospective study of 14,916 men, those with IGF-1 in the highest quintile were more likely

to develop colorectal cancer compared to those with values in the lowest quintile (RR 2.51, 95% CI 1.15–5.46) after controlling for IGFBP-3, age, smoking, BMI, and alcohol intake; in contrast, increased plasma concentrations of IGFBP-3 were associated with reduced risk of colorectal cancer (RR 0.28, 95% CI 0.12–0.66) in an adjusted model (45).

Hyperglycemia

Chronic hyperglycemia is one potential mediator of the association between diabetes and cancer. Hyperglycemia may have an independent influence on cancer risk, or it may be a surrogate for obesity and/or the metabolic perturbations associated with obesity and diabetes, such as hyperinsulinemia (46). Observational studies have found increased fasting blood glucose, independent of adiposity, is associated with an increased risk of cancer incidence and cancer mortality (2,47,48). However, large randomized controlled trials of intensified glycemic control did not find that cancer risk was reduced by improving glycemic control in type 2 diabetes (49). Nonetheless, the duration of clinical trials could be too short for cancer outcomes.

DIABETES AND SELECTED CANCERS

The following sections describe the epidemiology of selected cancers and their associations with diabetes in white and black men and women. The age-adjusted cancer incidence and mortality in the United States based on data from the Surveillance, Epidemiology, and End Results Program (SEER) 2007–2011 are shown in Appendix 29.1 (16). The SEER Program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the United States. SEER collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 30% of the U.S. population (16).

Colon and Rectum

Colorectal cancer is the third most common cancer in the United States among both men and women. Based on data from the SEER 2007–2011, the age-adjusted incidence rate and mortality rate of colorectal cancer are higher in men than in women and higher in blacks than in whites (Appendix 29.1) (16). The established risk factors for colorectal cancer include colorectal polyps, family history of colorectal cancer, genetic factors, obesity, personal history of cancer, ulcerative colitis or Crohn's disease, high fat diet, and smoking (50).

Increasing evidence suggests that diabetes is associated with an elevated risk of colorectal cancer. A meta-analysis of 14 studies (six case-control and eight cohort) estimated that the risk of colon cancer among adults with diabetes was 38% higher than those without diabetes (RR 1.38, 95% CI 1.26–1.51); for rectal cancer, the risk was 20% higher (RR 1.20, 95% CI 1.09–1.31) (Table 29.3) (4). The associations remained when the analysis was limited to studies that controlled for smoking, obesity, and physical activity.

Some literature has suggested that obesity may be associated with lower rates of colon cancer screening. In a meta-analysis of 23 studies, BMI was not associated with colon cancer screening overall. However, the subgroup of obese white women reported lower rates of colon cancer screening compared with those with a normal BMI with odds ratios of 0.87 (95% CI 0.82–0.93), 0.80 (95% CI 0.65–0.99), and 0.73 (95% CI 0.58–0.94) for obesity class I (BMI 30–34.9 kg/m^2), class II (BMI 35–39.9 kg/m^2), and class III (BMI ≥40 kg/m^2), respectively (51). Lower rates of screening may lead to advanced stages at cancer diagnosis and increased cancer mortality in individuals with obesity or diabetes.

Liver

In the United States, liver cancer is among the top 10 leading causes of cancer death (52). Based on data from the SEER 2007–2011, the age-adjusted incidence and mortality rates of liver and intrahepatic bile duct cancer were higher in men than in women (Appendix 29.1) (16). Major risk factors for liver cancer include infection with hepatitis B or hepatitis C virus, heavy alcohol use, exposure to aflatoxin, iron storage disease, and cirrhosis (50). The incidence of liver cancer has increased steadily over time since 1975 in both men and women, as well as in whites and blacks. Studies suggest that diabetes prevention, as well as avoidance of heavy alcohol use and hepatitis B and C virus infections, could make an important contribution to hepatocellular carcinoma prevention in the United States (53).

Epidemiologic studies have suggested a possible link between diabetes and liver cancer (54,55), and systematic reviews and meta-analyses have also found an association. A systematic review of 49 case-control and cohort studies estimated that the risk was increased by approximately two-fold (RR 2.2, 95% CI 1.7–3.0) in patients with diabetes (Table 29.3), although few studies adjusted for diet and obesity (5). A meta-analysis of 14 prospective epidemiologic studies also found an increased risk of liver cancer among patients with diabetes (RR 1.9, 95% CI 1.2–2.3) (56).

Associations between diabetes and liver cancer should be interpreted with caution. Cirrhosis results in glucose intolerance. Thus, diabetes may be a surrogate for cirrhosis, which increases the risk of liver cancer. Many patients with diabetes also have nonalcoholic fatty liver disease, which has been associated with an increased risk of liver cancer. More information about nonalcoholic fatty liver disease and cirrhosis in persons with diabetes is provided in Chapter 26 *Liver and Gallbladder Disease in Diabetes*.

Pancreas

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States among both men and women. In addition to diabetes, the established risk factors for pancreatic cancer include smoking, obesity, pancreatitis, and genetic factors (50).

Numerous epidemiologic studies have described an association between diabetes and pancreatic cancer.

In a meta-analysis of 35 cohort studies, the pooled relative risk for pancreatic cancer in individuals with diabetes compared to people without diabetes was 1.94 (95% CI 1.66–2.27) with significant evidence of heterogeneity among these studies (I^2 for heterogeneity 93.6%, p<0.001) (Table 29.3) (3). The temporal sequence between diabetes and pancreatic cancer has not always been clear. The same meta-analysis reported the relative risk of pancreatic cancer was negatively associated with the duration of diabetes. The relative risks were 5.38 (95% CI 3.49–8.30), 1.95 (95% CI 1.65–2.31), and 1.47 (95% CI 1.05–2.12) in individuals who had diabetes <1 year, 1–4 years, and >10 years, respectively. It is possible that detection bias occurred if adults with diabetes had more frequent contact with their physicians and, therefore, were more likely to be detected with cancer earlier.

In a case-cohort study within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study, a primary prevention trial that enrolled 29,133 male Finnish smokers age 50–69 years, abnormal glucose metabolism and insulin resistance were associated with pancreatic cancer (57). The study included 169 incident cases of pancreatic cancer that were diagnosed after 5 years of follow-up and 400 randomly selected controls. After multiple adjustments for covariates, higher glucose, higher insulin, and insulin resistance were significantly associated with the risk of pancreatic cancer. The positive associations were stronger among the cases that occurred >10 years after baseline (highest vs. lowest quartile: glucose >107 vs. 93 mg/dL [>5.94 vs. 5.16 mmol/L], HR 2.16, 95% CI 1.05–4.42; insulin >6.1 vs. <2.75 microIU/mL [>36.6 vs. <16.5 pmol/L], HR 2.90, 95% CI 1.22–6.92; and insulin resistance, HR 2.71, 95% CI 1.19–6.18). Although the prospective study design and a minimum 5-year follow-up prior to the pancreatic cancer diagnosis decreased the possibility of reverse causation, it is possible that asymptomatic pancreatic cancer had developed even earlier than insulin and glucose abnormalities were detected.

Lung

Lung cancer is one of the most common cancers in the United States. In the SEER 2007–2011, the age-adjusted incidence and mortality rates were higher in men than in women (Appendix 29.1) with a significant racial difference: black men had the highest incidence, while white women had slightly higher incidence than black women (16). Similarly, mortality rates were higher in black men and white women. The primary risk factor for lung cancer is cigarette smoking, which is estimated to account for approximately 90% of all lung cancers. Other important risk factors include radiation therapy to other cancers (e.g., breast, Hodgkin lymphoma) and environmental toxins (e.g., second-hand smoke, asbestos, radon, metals such as arsenic, chromium, and nickel, ionizing radiation, and polycyclic aromatic hydrocarbons) (58).

Previous studies did not provide consistent findings on the association between diabetes and lung cancer incidence. In studies based on the U.K. General Practice Research Database (59) and Kaiser Permanente Northern California database (60), diabetes was not associated with the risk of lung cancer. However, in the Danish National Diabetes Register and Cancer Registry (61) study, diabetes was associated with 10%–20% increased risk of lung cancer in both men and women with rate ratios of 1.1–1.2. In a study using the Taiwan National Health Insurance Database, diabetes was associated with a significantly higher risk of lung cancer. However, the associations attenuated with longer diabetes duration with odds ratios for diabetes duration <1, 1–3, 3–5, and ≥5 years versus no diabetes of 2.2 (95% CI 1.5–3.2), 1.42 (95% CI 1.01–1.99), 1.55 (95% CI 1.13–2.11), and 1.33 (95% CI 1.06–1.66), respectively (62). The underlying reason for this trend was not clear. There was a possibility of detection bias if adults with newly diagnosed diabetes had more frequent contact with their physicians and, therefore, were more likely to be detected with cancer earlier. In addition, smoking status often was not sufficiently adjusted in studies using administrative databases. The possibility of residual confounding cannot be ruled out.

Breast

In the United States in 2007–2011, the age-adjusted incidence rate of female breast cancer was slightly higher in white women than in black women, but breast cancer mortality was higher in blacks than in whites (Appendix 29.1) (16). Several factors increase the risk of breast cancer in women, including the use of combination hormonal therapy, exposure to radiation, alcohol, family history of breast cancer, and obesity. A higher BMI and/or weight gain have been consistently associated with a higher risk of breast cancer among postmenopausal women. In the Nurses' Health Study, women who gained ≥10 kg since menopause had a higher risk of breast cancer compared with women who maintained their weight (400 vs. 339 per 100,000 person-years; RR 1.18, 95% CI 1.03–1.35) (23).

The potential for an increased risk of breast cancer in women with diabetes has been the subject of a great deal of research, but the results are not consistent. In a meta-analysis of 39 studies, the pooled relative risk for breast cancer in women with diabetes was 1.27 (95% CI 1.16–1.39) (Table 29.3) (8). The same study reported type 1 diabetes (RR 1.00, 95% CI 0.74–1.35) and diabetes in premenopausal women (RR 0.86, 95% CI 0.66–1.12) were not associated with risk of breast cancer. Studies adjusting for BMI showed lower estimates (RR 1.16, 95% CI 1.08–1.24) compared with studies that were not adjusted for BMI (RR 1.33, 95% CI 1.18–1.51) (8).

Endometrium (Uterine Corpus)

In the United States, uterine cancer is the most common gynecologic malignancy. Based on SEER 2007–2011 data, the age-adjusted incidence of uterine cancer was higher in white than in black (Appendix 29.1) (16), Hispanic, or Asian/Pacific Islander women (63). However, mortality was almost twofold higher in blacks than in whites (Appendix 29.1), possibly due to a higher incidence of aggressive cancer subtypes, as well as issues of access to and quality of health care services. The main risk factors for uterine cancer are endometrial

hyperplasia, parity, and having more menstrual cycles during a woman's lifetime, history of taking estrogen alone, history of taking tamoxifen, radiation therapy to the pelvis, family history of endometrial cancer, and obesity (50).

A meta-analysis of diabetes and endometrial cancer risk based on three cohort and 13 case-control studies (9) showed that diabetes was significantly associated with an increased risk of endometrial cancer (RR 2.10, 95% CI 1.75–2.53) (Table 29.3). The risk estimates were stronger among case-control (RR 2.22, 95% CI 1.80–2.74) than among cohort studies (RR 1.62, 95% CI 1.21–2.16) and slightly lower in studies conducted in the United States than in Europe. In studies adjusted for multiple risk factors, the association remained significant (RR 1.92, 95% CI 1.58–2.33). This meta-analysis also reported a statistically significant positive association with type 1 diabetes (RR 3.15, 95% CI 1.07–9.29) based on three studies. Still, it is noteworthy that obesity plays an important role in the diabetes-endometrial cancer association. A meta-analysis reported significantly increased risk in endometrial cancer with increasing BMI (RR 1.59, 95% CI 1.50–1.67 per 5 kg/m^2 increase) (21).

Prostate

Prostate cancer is the most common cancer in men in the United States. The established risk factors for prostate cancer are older age, African American race, and family history of prostate cancer (50).

Multiple prospective cohort and case-control studies have investigated the associations among obesity, diabetes, and prostate cancer risk. A meta-analysis of 19 studies found an inverse association between diabetes and prostate cancer (RR 0.84, 95% CI 0.76–0.93) (Table 29.3) (10). In a Japanese study including nonobese men age 40–79 years, the serum prostate-specific antigen (PSA) levels were lower in diabetic men compared with those in healthy men after adjustments for age and BMI (64). This finding was in line with the results from a meta-analysis showing decreased risk of prostate cancer in patients with type 2 diabetes. On the other hand, some large cohort studies (15,65) reported type 2 diabetes was associated with an increased risk of prostate cancer mortality and all-cause mortality. These observations were consistent with the evidence from studies that demonstrated the positive relationship between obesity and advanced stage prostate cancer (66,67,68). While the biologic basis of the contrasting associations of type 2 diabetes on prostate cancer incidence and prognosis remain unclear, it is possible that the incidence effect is driven dominantly by the relatively low androgen levels in men with diabetes compared with men without diabetes, while the prognosis effect may be driven by the proposed stimulatory effects of hyperinsulinemia on prostate cancer behavior (65,69).

Bladder

For bladder cancer, the age-adjusted incidence and mortality rates in the SEER 2007–2011 were higher in men than in women (Appendix 29.1) with a significant racial difference: white men had the highest incidence and mortality compared to women and black men (16). The main risk factors for bladder cancer include smoking, environmental exposures such as arsenic, and family history of bladder cancer (50).

A meta-analysis of 29 cohort studies showed that diabetes was associated with an increased incidence of bladder cancer (RR 1.29, 95% CI 1.08–1.54) (Table 29.3) (7). In stratified analysis, the relative risks of bladder cancer were 1.36 (95% CI 1.05–1.77) for men and 1.28 (95% CI 0.75–2.19) for women. When the meta-analysis was restricted to those studies controlled for smoking, the significance remained (RR 1.33, 95% CI 1.19–1.47). Similarly, in studies adjusted for BMI, the association was still significant (RR 1.30, 95% CI 0.95–1.77). Furthermore, diabetes was positively associated with bladder cancer mortality (RR 1.33, 95% CI 1.14–1.55), and the positive association was observed for both men (RR 1.54, 95% CI 1.30–1.82) and women (RR 1.50, 95% CI 1.05–2.14) (7).

Kidney

In the United States in 2007–2011, the age-adjusted incidence and mortality rates of kidney and renal pelvis cancer were higher in men than in women (Appendix 29.1) (16). The incidence of kidney cancer increased steadily over time since 1975 in both men and women, as well as in whites and blacks, but the trends show signs of plateauing in later years. Although the reason for this increase is not clear, it may be due to earlier detection (70). The major risk factors for kidney cancer are smoking, obesity, high blood pressure, and family history of kidney cancer (50).

A history of diabetes has been associated with a modest increase in the risk of kidney cancer in some studies (71,72), but not in others (15,73). The association may be mediated through an increase in the incidence of hypertension (74) or obesity. The NIH-AARP Diet and Health Study, including more than 300,000 participants age 50–71 years at baseline, showed the risk of kidney cancer increased progressively with baseline BMI (75). Multivariate relative risks were significantly elevated at a BMI of 25–<27.5 kg/m^2 (RR 1.43, 95% CI 1.07–1.92 for men; RR 1.57, 95% CI 1.07–2.29 for women) relative to a BMI of 18.5–<22.5 kg/m^2 (referent group). Among participants whose BMI was ≥35 kg/m^2, relative risks were 2.47 (95% CI 1.72–3.53) for men and 2.59 (95% CI 1.70–3.96) for women.

A meta-analysis of nine cohort studies showed that compared with individuals without diabetes, patients with diabetes had a statistically significant increased risk of kidney cancer (RR 1.42, 95% CI 1.06–1.91) (Table 29.3) (6). The association was stronger in women (RR 1.70, 95% CI 1.47–1.97) than in men (RR 1.26, 95% CI 1.06–1.49). When restricting the analysis to studies that had adjusted for BMI or cigarette smoking, the relative risks attenuated to 1.12 (95% CI 0.99–1.27) and 1.29 (95% CI 1.05–1.58), respectively (6). Only two studies adjusted for both BMI and smoking (76,77). Neither study showed significant associations in women. One study reported significant association between diabetes and kidney cancer in men (77).

Thyroid

Thyroid cancer occurred more frequently in women than in men and more in whites than in blacks, according to the SEER 2007–2011 data (Appendix 29.1) (16). The mortality rate of thyroid cancer was very low, about 0.5 per 100,000. The most well-known factor for thyroid cancer is radiation exposure (78); other known risk factors include family history of thyroid cancer and history of thyroid nodules (79).

The literature on diabetes and thyroid cancer is limited. A study reported an increased risk of thyroid cancer among the users of glucagon-like peptide-1 (GLP-1) agonists or dipeptidylpeptidase-4 (DPP-4) inhibitors (80), but the study design had significant limitations (see the *Diabetes Medications and Cancer Risks: Methodologic Considerations* section). Most studies examined the association between obesity and risk of thyroid cancer. A pooled analysis of three case-control studies showed an increased risk of thyroid cancer was associated with greater weight, BMI, percent body fat, and body surface area in both men and women. Compared with normal-weight adults (BMI 18.5–24.9 kg/m^2), the odds ratios for thyroid cancer for overweight (BMI 25–29.9 kg/m^2) and obese (BMI ≥30 kg/m^2) individuals were 1.72 (95% CI 1.48–2.00) and 4.17 (95% CI 3.41–5.10), respectively. Compared with the lowest quartile of percent body fat, the odds ratios for thyroid cancer for the highest quartile were 3.83 (95% CI 2.85–5.15) in women and 4.05 (95% CI 2.67–6.15) in men (81).

Hematologic Cancers

Hematologic malignancies are a heterogeneous group of diseases characterized by the malignant uncontrolled growth of hematopoietic cells. According to the SEER 2007–2011, age-adjusted incidence and mortality rates were higher in men than women and higher in whites than in blacks (Appendix 29.1) (16). The development of hematologic malignancies has been associated with different causes, such as infectious processes, autoimmune disorders, or a positive family history, but the etiology of these hematologic cancers remains largely unexplained. Type 2 diabetes is a condition associated with immunosuppression, chronic inflammation, and B and T cell dysfunction (82), all of which have been associated with the development of lymphoproliferative disorders.

A systematic review identified 26 studies (13 case-control and 13 cohort studies) and reported that the odds ratio for non-Hodgkin lymphoma overall was 1.22 (95% CI 1.07–1.39), but the increased odds ratio was seen for the peripheral T cell lymphoma subtype only. The odds ratio of leukemia was increased overall (OR 1.22, 95% CI 1.03–1.44), but no significant associations were observed with myeloid or lymphoid leukemia, specifically. The association between diabetes and myeloma was not statistically significant (OR 1.22, 95% CI 0.98–1.53) (83).

SUMMARY OF DIABETES AND CANCER INCIDENCE AND MORTALITY

Diabetes is associated with increased incidence and mortality with some, but not all, cancers. Positive associations are generally found for cancers of the colorectum, pancreas, breast, endometrium, bladder, and kidney. An inverse association between diabetes and prostate cancer has been reported by many studies. Nonetheless, the possibility of residual confounding from obesity, smoking, or other unadjusted variables cannot be ruled out. Furthermore, potential reverse causation between cancer development and diabetes diagnosis is an important consideration in evaluating the prospective associations.

DIABETES MEDICATIONS AND CANCER RISKS

Studies have suggested that certain diabetes medications are associated with decreased or increased risk of cancer. This section reviews evidence for the associations of metformin, thiazolidinediones (TZD), insulin, and incretin-based therapies with cancer risk. In addition, the methodologic challenges of examining these associations are described.

METFORMIN

Metformin has multiple potential mechanisms by which it inhibits cancer development and growth. For example, metformin inhibits hepatic gluconeogenesis, and, as a result, leads to a reduction in circulating glucose levels; it also increases insulin sensitivity, thus reducing circulating insulin levels. Within cells, metformin activates adenosine monophosphate kinase (AMPK), which decreases protein synthesis and cell proliferation (84).

In 2005, Evans *et al.* reported a 23% reduction in cancer risk associated with metformin use (85). This observation triggered a huge interest in the scientific community. Several large-scale observational studies, systematic reviews, and meta-analysis have been conducted ever since, most of them alluding to a potential protective role for metformin in cancer risk. At the same time, several *in vitro* and *in vivo* studies also suggested antineoplastic properties for metformin (86,87,88) and, thus, generated greater momentum for recognizing metformin as a new chemopreventive agent.

A 2012 meta-analysis of 10 studies reported that the risk of cancer among metformin users was significantly lower than that among non-metformin users: the pooled relative risks were 0.66 (95% CI 0.49–0.88) for all cancer mortality, 0.67 (95% CI 0.53–0.85) for all cancer incidence, 0.68 (95% CI 0.53–0.88) for colorectal cancer (n=6), 0.20 (95% CI 0.07–0.59) for hepatocellular cancer (n=4), and 0.67 (95% CI 0.45–0.99) for lung cancer (n=3) (89). However, many observational studies of metformin use that reported decreased cancer risk suffered from several biases, particularly time-related biases (immortal time bias in cohort studies and time-window bias in case-control studies) and confounding by indication (see additional discussion in

the *Methodologic Considerations* section). In studies properly accounting for these biases, many large cohorts and nested case-controls did not observe a decreased incidence of cancer associated with metformin use (90,91,92,93,94,95,96).

Multiple clinical trials, including large, multi-country trials (97), are evaluating the effect of metformin on cancer progression among individuals with and without diabetes. Results from well-conducted clinical trials will provide direct evidence whether metformin reduces cancer risk.

THIAZOLIDINEDIONE

The peroxisome proliferator-activated receptor-gamma (PPAR-γ)-activating TZD medications, including pioglitazone and rosiglitazone, are a class of drugs used to improve lipid and glucose metabolism in type 2 diabetes (98). In preclinical studies, exposure of male rats to pioglitazone was associated with an increased risk of bladder cancer (99). The ProActive trial, a large randomized controlled trial evaluating the effects of pioglitazones on cardiovascular outcomes, found a nonsignificant increase in the incidence of bladder cancer in the pioglitazone-treated group: 14 (0.5%) cases compared with 6 (0.2%) in controls (100). Still, the study and trial durations may have been too short (average follow-up 34.5 months) to observe meaningful difference in cancer outcomes. A similar increase in risk was also observed in a French cohort (101), which led to the withdrawal of pioglitazone in France and Germany. In 2010, the U.S. Food and Drug Administration (FDA) issued a recommendation that pioglitazone should be avoided in patients with bladder cancer and prescribed with caution in patients with previous bladder cancer (102).

A meta-analysis of observational cohort studies of any TZD use (pooled RR 1.15, 95% CI 1.04–1.26) and of pioglitazone specifically (pooled RR 1.22, 95% CI 1.07–1.39) showed significantly increased associations with bladder cancer (103). The majority of studies on TZDs suffer from small sample size and confounding by indication. To address these limitations, a pooled analysis of data from six countries (104) with better accounting for confounding by indication was performed. This study found no evidence for any association between cumulative exposure to pioglitazone and bladder cancer in men (RR per 100 days of cumulative exposure 1.01, 95% CI 0.97–1.06) or women (RR 1.04, 95% CI 0.97–1.11) after adjustment for age, calendar year, diabetes duration, smoking, and ever use of pioglitazone. No association was observed between rosiglitazone and bladder cancer in men (RR 1.01, 95% CI 0.98–1.03) or women (RR 1.00, 95% CI 0.94–1.07).

INSULIN

There are many forms of insulin; several observational cohort studies (105,106) reported that use of certain insulins increased cancer risk in type 2 diabetes patients. Insulin glargine, one type of long-acting insulin, has been studied extensively. An increased risk of cancer attributed to insulin glargine use among patients with diabetes attracted attention in 2009 (106,107,108,109). This was further substantiated by the observation that glargine is more mutagenic *in vitro* compared to the human insulin (110). Results of observational studies on the association between glargine and cancer risk have been heterogeneous (111,112). The discrepancies in the findings have been attributed to the methodologic differences in the design and analysis of these observational studies, including confounding by indication (113). While studies from Sweden did not detect a significant association between insulin glargine (alone or in combination with another insulin) and cancer incidence compared with treatment with non-glargine insulin (108), a German cohort study suggested a dose-response relation after a mean follow-up time of 1.63 years: those taking higher doses of insulin glargine had an increased risk for cancer incidence compared with those prescribed human insulin and those taking lower doses of glargine (107). Data from Kaiser Permanente Northern and Southern California compared cancer risk in users of insulin glargine (n=27,418) with users of Neutral Protamine Hagedorn (NPH) insulin (n=100,757) after a median follow-up of 3.3 years (114). Among users of NPH at baseline, there was no clear increase in risk of breast, prostate, colorectal, or all cancers combined associated with switching to glargine. Among those initiating insulin, ever use or ≥2 years of glargine was not associated with increased risk of prostate or colorectal cancer or all cancers combined. Among initiators, the hazard ratio for breast cancer associated with ever use of glargine was 1.3 (95% CI 1.0–1.8); the hazard ratio for breast cancer associated with use of glargine for ≥2 years was 1.6 or 1.7, depending on whether glargine users had also used NPH. Results of this study should be viewed cautiously, given the relatively short duration of glargine use to date and the potential multiple comparisons in the study. On the other hand, the Medical Outcomes Research for Effectiveness and Economics Registry (MORE² Registry) that included 50,000 patients with an average 1.2 years of follow-up reported that patients initiating insulin glargine rather than NPH were not at an increased risk for cancer (115). This is the largest study so far to assess the association between glargine insulin and cancer risk. Using real-world data, the overall hazard ratio for glargine insulin compared to NPH insulin was 1.12 (95% CI 0.95–1.32).

The Outcome Reduction With Initial Glargine Intervention (ORIGIN) Trial reported no link between insulin glargine use and incidence of any cancer (HR 1.00, 95% CI 0.88–1.13, p=0.97), death from any cancer (HR 0.94, 95% CI 0.77–1.15, p=0.52), or cancer at specific sites after a median 6 years of follow-up (116). Although the ORIGIN data may be the best data available because of its randomized trial design and longer study duration than other typical drug trials, there are caveats to the interpretation of the ORIGIN trial and cancer risk. First, although median follow-up was 6.2 years, there was a rapid drop-off thereafter, such that only 14% of those recruited were followed to the seventh year. The follow-up period may have been too short to assess associations between an exposure and cancer incidence. Second, there was considerable contamination across the arms—16.7%

of patients in the glargine arm had discontinued glargine, while 11.5% of patients in the standard treatment arm had commenced some insulin by the end of the study follow-up. Finally, the number of cancer cases was not sufficient to study associations with specific cancer types.

INCRETIN-BASED THERAPIES

Incretin-based therapies, including GLP-1 agonists and DPP-4 inhibitors, are newer medications for glucose lowering in patients with type 2 diabetes. In an analysis using the FDA adverse events reporting system during 2004–2009, a significantly higher risk of pancreatic cancer (OR 2.95) and pancreatitis (OR 10.68) was observed for the GLP-1 agonist exenatide and the DPP-4 inhibitor sitagliptin; a significantly higher risk of thyroid cancer (OR 4.73) was observed for GLP-1 agonists compared to other medications (80). Nonetheless, major limitations exist due to selection bias in using the adverse events reporting system. However, in an administrative database study of U.S. adults with type 2 diabetes, treatment with the GLP-1-based therapies, sitagliptin and exenatide, was associated with increased odds of hospitalization for acute pancreatitis (117). Current use of GLP-1-based therapies within 30 days (adjusted OR 2.24, 95% CI 1.36–3.68) and recent use from the past 30 days to less than 2 years (OR 2.01, 95% CI 1.37–3.18) were associated with significantly increased odds of acute pancreatitis relative to the odds in nonusers. However, a meta-analysis of 55 randomized trials did not suggest an increased risk of pancreatitis with incretins versus controls (OR 1.11, 95% CI 0.57–2.17) (118). Based on current evidence, continuous monitoring of the cancer issues related to incretin-based therapies is required.

METHODOLOGIC CONSIDERATIONS

In general, data from randomized clinical trials on diabetes medication and cancer outcomes are very scant due to relatively short follow-up times in trial settings. Several methodologic issues must be considered when evaluating the pharmacoepidemiology of diabetes medications on cancer risks. (1) Studies have often had limited power to detect modest associations, particularly for site-specific cancers. Several studies have pulled data from multiple cancer sites to increase the sample size. This practice might conceal the true effect of medication on a specific cancer site (119). (2) Most diabetic patients were treated with one or more medications, making it difficult to assess independent associations of individual medications. (3) In the majority of the studies of diabetes medication and cancer, the definition of medication exposure is based on a simple binary categorization of ever and never users. This method of exposure definition, although simple to quantify, cannot provide an in-depth measure of exposure to medications over time. Incorporating information on duration, cumulative dose, and continuity of drug use where available could give a more in-depth understanding of the true nature of the medication effect. (4) Observational studies of diabetes medication on cancer outcomes are subject to several methodologic flaws in their design and analysis, which affect the validity of the findings. The most common methodologic flaws include time-related biases (immortal-time bias, time-window bias), confounding by indication, and prevalent user bias. More details on these biases are discussed later in this section. (5) Cohort studies using pharmacy or administrative databases are often confounded by unmeasured or incompletely measured risk factors, such as A1c and obesity. Unmeasured confounding may be less of an issue with an active comparison group that is a clinical alternative for the drug of interest at a similar stage of disease progression. (6) Studies of new agents, such as insulin analogs and incretins, assessed only risks associated with short-term use. Future studies should minimize the potential for these biases and examine drug interactions and competing risks from other causes.

Immortal Time Bias

Immortal time bias is a special case of exposure misclassification. It refers to an initial follow-up time during which the outcome could have not occurred due to the definition of the exposure. The exposure definition and time of study initiation are key in determining immortal time bias. For example, consider a cohort of diabetes patients followed since they were diagnosed. In this case, the time between cohort entry and the first prescription is considered immortal time, since by the virtue of the study design, drug users could not have had cancer during that period. By misallocating unexposed time as exposed, the event-free person-time will be overestimated among drug users, and the incidence rate of the event will be consequently diluted. The "immortal time biases" are known to exaggerate downward the effect of a drug, thus making a drug seem to be protective, when in fact it may have no effect (120). Methods to overcome immortal time bias include new user design (121), discrete time survival model, and including terms for time-dependent ever exposure and time-dependent cumulative exposure in the analyses of evaluating diabetes medication and cancer risks (104). It is important to note that using time-dependent exposure in the analysis without appropriate adjustment for confounders (i.e., time-dependent covariate adjustment) leads to biased results (122,123).

Confounding by Indication

The choice of medication is determined by patient-specific factors, including complications, disease stage, and comorbid conditions. These factors are also associated with outcomes whose risk is increased among patients with diabetes, such as cardiovascular disease and cancer. The unbalanced distribution of risk factors between users of different diabetes medications leads to a biased association between drugs and outcomes (e.g., cancer), namely, confounding by indication. Thus, when comparing patients with diabetes treated with first-line agents to those treated with second- or third-line agents, the reported association gives an indication of the effect of disease durations and severity of cancer and not medication. Identifying an appropriate comparator group at the design and/or analysis stage can control confounding by indication. Some of the proposed strategies to control for confounding by indication in the analysis include propensity score methodology and instrumental variable analysis (124).

WEIGHT GAIN, HYPERGLYCEMIA, AND DIABETES INDUCED BY CANCER TREATMENTS

Certain cancer treatments may increase weight, change metabolic profiles, and potentially increase the risk of diabetes.

WEIGHT GAIN AND DIABETES AFTER BREAST CANCER CHEMOTHERAPY

The risk of sustained weight gain increases after treatment for breast cancer. An average weight gain of 2.5–6.2 kg occurs in 50%–80% of women receiving adjuvant chemotherapy (125). Data from the Women's Healthy Eating and Living (WHEL) Study found that only 10% of women returned to their pre-cancer weight after 6 years of follow-up; of women receiving chemotherapy, African American women had an increased risk of weight gain compared to Caucasian and Asian women, but this study was limited by small numbers of African American women enrolled (~4% of the cohort) (126).

Weight gain can increase the risk of developing diabetes. A Canadian study reported a modest increase in the incidence of diabetes among postmenopausal breast cancer survivors. The study showed, in most women, the risk began to increase 2 years after cancer diagnosis, but the highest risk was in the first 2 years in those who received adjuvant therapy (127). Another study in the same population reported that current tamoxifen therapy was associated with an increased incidence of diabetes in older breast cancer survivors compared to those who had no tamoxifen therapy (adjusted OR 1.24, 95% CI 1.08–1.42) (128).

ANDROGEN DEPRIVATION THERAPY-INDUCED INSULIN RESISTANCE AND DIABETES

Androgen deprivation therapy (ADT) for treatment of prostate cancer is likely to cause changes in body composition, alterations in lipid profiles, and decreased insulin sensitivity (129). Consequently, ADT may increase the risk of diabetes (130).

Short-term prospective studies consistently reported that ADT significantly increased insulin levels after a few months (131). Smith *et al.* reported that ADT significantly increased fasting plasma insulin by 26% and decreased insulin sensitivity by 13% (132). Another short-term study showed that ADT for 3 months resulted in a 63% increase in fasting insulin levels without any changes in fasting blood glucose (133).

Men on long-term ADT (≥12 months) were not only insulin resistant but also had developed hyperglycemia (134). Using data from the Medicare population, Keating *et al.* reported in a population-based cohort of 73,196 men that gonadotropin-releasing hormone agonist use was associated with increased risk of incident diabetes with a hazard ratio of 1.44 (95% CI 1.34–1.55) (135).

PANCREATIC RESECTIONS AND DIABETES

Endocrine pancreatic insufficiency occurring after surgical resection of the pancreas may lead to development of new-onset diabetes, exacerbation of preexisting diabetes, or progression of preexisting glucose intolerance to overt diabetes (136). After total and distal pancreatectomy, patients are at increased risk for rapid development of hypoglycemia due to deficiency of glucagon-secreting alpha cells. Patients with a partial pancreatectomy show wide variability in postoperative insulin requirements. A small study reported that a higher, preoperative A1c (>6% [>42 mmol/mol]) was predictive of patients who will require postoperative insulin therapy, with 90% sensitivity, 88% specificity, 82% positive predictive value, and 94% negative predictive value (137).

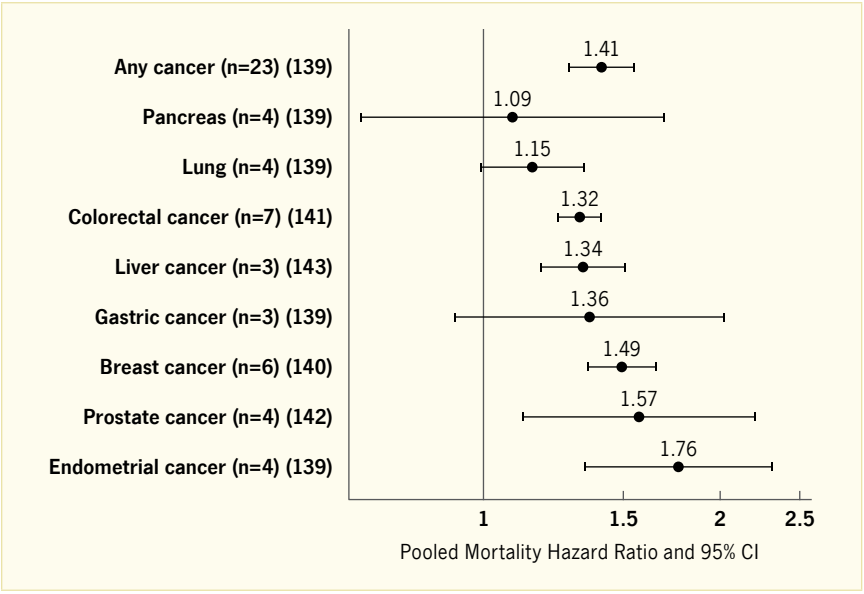
STEROID THERAPY AND HYPERGLYCEMIA

Patients with glioblastoma multiforme are at particular risk for hyperglycemia, because their peritumoral edema is routinely treated with high-dose glucocorticoids, which are known to increase plasma glucose by impairing glucose transport. Derr *et al.* reported an association between higher mean glucose and shorter survival in patients with glioblastoma multiforme after adjustment for mean daily glucocorticoid dose, age, and baseline Karnofsky performance score. Compared with patients in the lowest mean glucose quartile, those in quartile two (adjusted HR 1.29, 95% CI 0.85–1.96), quartile three (adjusted HR 1.35, 95% CI 0.89–2.06), and quartile four (adjusted HR 1.57, 95% CI 1.02–2.40) were at higher risk of mortality (p=0.041 for trend) (138).

DIABETES IN CANCER PATIENTS

Large cohort studies have shown higher mortality rates and higher cancer case-fatality rates (defined as number of individuals dying during a specific period of time after cancer diagnosis divided by the number of individuals with the specific cancer) in cancer patients with diabetes than those without diabetes. In a community-based cohort of 2,481 adults who developed cancer during the study period, adults with diabetes had a higher risk of cancer case fatality (HR 1.34, 95% CI 1.002–1.79) and all-cause mortality (HR 1.61, 95% CI 1.29–2.01). Diabetes also conferred a higher risk of death in adults who developed cancers of the colorectum (HR 2.14, 95% CI 1.19–3.83), breast (HR 2.48, 95% CI 1.23–4.98), and prostate (HR 2.32, 95% CI 1.29–4.19) (15). Similar findings were reported in meta-analyses (Figure 29.1): diabetes was associated with increased mortality in patients with any cancer (HR 1.41, 95% CI 1.28–1.55) (139), as well as cancers of the endometrium (HR 1.76, 95% CI 1.34–2.31) (139), breast (HR 1.49, 95% CI 1.35–1.65) (140), colorectum (HR 1.32, 95% CI 1.24–1.41) (141), prostate (HR 1.57, 95% CI 1.12–2.20) (142), and liver (HR 1.34, 95% CI 1.18–1.51) (143). Moreover, a meta-analysis showed diabetes was associated with an increased odds of postoperative mortality across all cancer types (OR 1.51, 95% CI 1.13–2.02) (144).

FIGURE 29.1. Summary of Meta-Analyses of Diabetes and Mortality in Patients Diagnosed With Cancer



CI, confidence interval.

SOURCE: References 139, 140, 141, 142, and 143, as listed in parentheses within the figure.

Diabetes might influence the risk of mortality in cancer patients through a variety of pathways. First, cancer is more advanced at diagnosis in diabetic patients. Second, obese/diabetic cancer patients may be treated less aggressively. Third, patients with diabetes are more likely to have cancer recurrence. Fourth, cancer diagnosis interferes with diabetes and chronic disease care. Fifth, diabetes increases risk of cancer complications, such as infections.

DIABETES AND STAGE AT CANCER DIAGNOSIS

Previous studies and meta-analyses noted that obese and diabetic women were less likely to receive mammography and colorectal cancer screening (145,146,147), which may lead to advanced stages at cancer diagnosis. Fleming *et al.* found that older women with preexisting diabetes had a 19% ($p<0.01$) greater risk of being diagnosed with late versus early stage breast cancer compared to normoglycemic women (148), while studies of colorectal cancer did not observe differences between patients with and without diabetes concerning stage or tumor differentiation (149,150). In addition, cancer patients with diabetes may have increased tumor cell proliferation and metastases in a physiologic environment of hyperinsulinemia and hyperglycemia (151).

DIABETES AND CANCER TREATMENT

Patients with diabetes often have other diabetes-related comorbid conditions, e.g., ischemic heart disease, chronic kidney disease, and neuropathy, that may influence clinical decision-making (152). Van de Poll-Franse *et al.* found that Dutch 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 (153). Few other studies have investigated this potential influence.

DIABETES AND CANCER RECURRENCE AND SECOND CANCER

Diabetes might negatively influence the effect of cancer therapies, and cancer cells of patients with diabetes may be less sensitive to systemic therapy or radiotherapy (153). These adverse effects may increase the likelihood of cancer recurrence or a second cancer in diabetic patients. Clinical studies have observed patients with diabetes had increased risks of recurrence of acute lymphocytic leukemia (154), colon cancer (149), and of a second cancer after endometrial cancer (155). However, many studies did not fully consider tumor characteristics, comorbid conditions, and number of screening visits after the diagnosis of a first cancer. Furthermore, it is possible that detection bias occurred if adults with diabetes had more frequent contact with their physicians and, therefore, were more likely to be detected with cancer. Future studies should try to rule out the biases associated with access to care or treatment selection.

DIABETES CARE AFTER CANCER DIAGNOSIS

When cancer occurs in an adult with diabetes, it can divert attention and resources, leading to inadequate diabetes care and increased risk of diabetic complications. Based on SEER-Medicare data from the early 1990s, Earle *et al.* found that colorectal carcinoma survivors with and without diabetes tend to be less likely than those not having had colorectal cancer to receive necessary care across a broad range of chronic medical conditions (156). On the other hand, Keating *et al.* reported cancer patients with diabetes received generally similar or sometimes better quality of care relative to those without cancer among Kaiser Northern California members (157). Future studies should investigate whether the "cancer effect" on diabetes care has changed over time.

DIABETIC COMPLICATIONS IN CANCER PATIENTS

Diabetes is a well-established risk factor for sepsis and infection-related mortality in the general population (158). In a population of bone marrow transplantation recipients, Derr *et al.* reported positive associations between pre-neutropenia glycemia and the subsequent risk of infection after transplantation (159). In patients who did not receive glucocorticoids during neutropenia, each 10 mg/dL (0.56 mmol/L) increase in mean pre-neutropenia glucose was associated with an odds ratio of 1.15 (95% CI 1.03–1.28) for bloodstream infections; in those who received glucocorticoids during neutropenia, the adjusted odds ratios associated

with a 10 mg/dL increase in mean glucose was 1.24 (95% CI 1.11–1.38) for bloodstream infections. Diabetes is also 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 (160). Many cancer treatments increase the risk of cardiovascular complications, such as heart failure, myocardial ischemia/infarction, hypertension, thromboembolism, and arrhythmias (161). Certain chemotherapy (e.g., oxaliplatin) has side effects on peripheral neuropathy, which limits its uses in patients with preexisting neuropathy or at increased risk for neuropathy (e.g., diabetic patients). Despite ample evidence of increased mortality related to diabetes, no studies have determined the joint effects of diabetes and cancer with regard to specific complications.

CONCLUSION

Diabetes is associated with cancer outcomes across the full spectrum—from cancer development and progression to death from cancer. A multidisciplinary collaboration among basic scientists, endocrinologists, oncologists, surgeons, primary care physicians, and clinical researchers is needed to elucidate the biologic mechanisms mediating diabetes-cancer associations and to improve clinical outcomes. The American Diabetes Association and American Cancer Society Consensus Panel recommended several strategies for primary and secondary preventions. The panel recommended that healthy diet, physical activity, and weight management should be advised for all. In addition, doctors should screen diabetic patients for cancer as recommended for all people in their age and sex groups. Finally, for most diabetic patients, cancer risk should not be a major factor in choosing diabetes treatment (46).

LIST OF ABBREVIATIONS

A1c. . . . . glycosylated hemoglobin
ADT . . . . . androgen deprivation therapy
BMI . . . . . body mass index
CI. . . . . confidence interval
DPP-4 . . . . . dipeptidylpeptidase-4
FDA . . . . . U.S. Food and Drug Administration
GLP-1. . . . . glucagon-like peptide-1
HR . . . . . hazard ratio
IGF-1 . . . . . insulin-like growth factor-1
IGFBP-3 . . . . . insulin-like growth factor binding protein-3
NPH insulin . . . Neutral Protamine Hagedorn insulin
OR . . . . . odds ratio
ORIGIN . . . . . Outcome Reduction With Initial Glargine Intervention Trial
RR . . . . . relative risk
SEER . . . . . Surveillance, Epidemiology, and End Results Program
TZD . . . . . thiazolidinedione
WHEL. . . . . Women's Healthy Eating and Living Study

CONVERSIONS

Conversions for A1c, glucose, and insulin values are provided in *Diabetes in America Appendix 1 Conversions*.

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DUALITY OF INTEREST

Drs. Yeh, Golozar, and Brancati reported no conflicts of interest.

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APPENDIX

APPENDIX 29.1. Age-Adjusted Incidence and Mortality of Selected Cancers, by Sex and Race, U.S., 2007–2011

	RATE (PER 100,000 PERSON-YEARS)			
	White		Black	
	Men	Women	Men	Women
Incidence				
Any cancer	532.1	424.4	600.9	398.8
Colon and rectum	49.6	37.3	62.3	47.5
Liver and intrahepatic bile duct	10.8	3.6	15.6	4.6
Pancreas	14.0	10.7	7.0	4.7
Lung and bronchus	72.4	53.8	93.0	51.2
Female breast		128.0		122.8
Endometrium		25.4		23.2
Prostate	139.9		223.9	
Bladder	39.4	9.5	21.3	6.9
Kidney and renal pelvis cancer	21.7	11.0	24.7	12.7
Thyroid	6.9	20.4	3.3	11.3
Non-Hodgkin lymphoma	24.9	17.2	17.4	11.9
Myeloma	7.2	4.3	14.8	10.5
Leukemia	17.5	10.7	12.9	8.0
Mortality				
Any cancer	209.8	147.5	269.3	169.0
Colon and rectum	18.5	13.0	27.7	18.5
Liver and intrahepatic bile duct	7.8	3.2	12.1	4.2
Pancreas	12.5	9.4	15.3	12.4
Lung and bronchus	61.4	39.8	75.7	36.5
Female breast		21.7		30.6
Endometrium		4.0		7.5
Prostate	20.6		48.9	
Bladder	8.1	2.2	5.4	2.6
Kidney and renal pelvis cancer	5.9	2.6	5.6	2.6
Thyroid	0.5	0.5	0.4	0.6
Non-Hodgkin lymphoma	8.4	5.2	5.8	3.5
Myeloma	4.0	2.5	7.7	5.3
Leukemia	9.7	5.4	8.0	4.8

Data are from the National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) on cancer incidence and death rates in 2007–2011 and are age-adjusted to the 2000 U.S. standard population.

SOURCE: Reference 16