Review: Diabetes, Obesity, and Cancer—Pathophysiology and Clinical Implications

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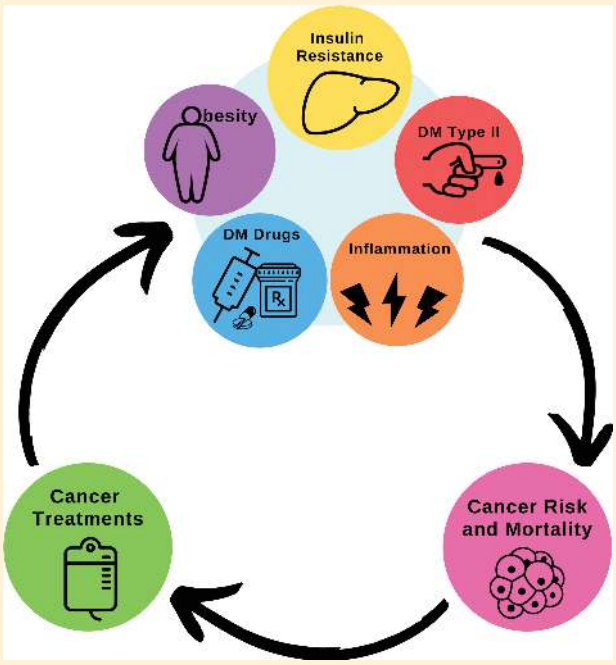
ABSTRACT Obesity and diabetes have both been associated with an increased risk of cancer. In the face of increasing obesity and diabetes rates worldwide, this is a worrying trend for cancer rates. Factors such as hyperinsulinemia, chronic inflammation, antihyperglycemic medications, and shared risk factors have all been identified as potential mechanisms underlying the relationship. The most common obesity- and diabetes-related cancers are endometrial, colorectal, and postmenopausal breast cancers. In this review, we summarize the existing evidence that describes the complex relationship between obesity, diabetes, and cancer, focusing on epidemiological and pathophysiological evidence, and also reviewing the role of antihyperglycemic agents, novel research approaches such as Mendelian Randomization, and the methodological limitations of existing research. In addition, we also describe the bidirectional relationship between diabetes and cancer with a review of the evidence summarizing the risk of diabetes following cancer treatment. We conclude this review by providing clinical implications that are relevant for caring for patients with obesity, diabetes, and cancer and provide recommendations for improving both clinical care and research for patients with these conditions. ***(Endocrine Reviews 41: 33 – 52, 2020)***

GRAPHICAL ABSTRACT



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ESSENTIAL POINTS

- Obesity and diabetes have both been associated with an increased risk of cancer
- The strongest and most robust associations are for postmenopausal breast, endometrial, and colorectal cancers, with diabetes and obesity primarily affecting the risk rather than survival of these cancers
- Hyperinsulinemia, chronic inflammation, antihyperglycemic medications, and shared risk factors have all been identified as potential mechanisms underlying the relationship
- The relationship between diabetes and cancer is bidirectional, as cancer survivors also appear to be more susceptible to subsequent diabetes
- With increasing rates of obesity and diabetes worldwide, a greater emphasis on cancer prevention strategies is needed
- Further research should focus on better elucidating the mechanisms underlying these relationships to inform potential targets for intervention

As early as 1932, scientists proposed a possible association between diabetes and cancer (1). It was not until much later, aided by large-scale registries and administrative health databases, that evidence emerged supporting a strong and consistent link between diabetes and higher risks of certain cancers. Cancers most commonly associated with diabetes are those of the pancreas, liver, endometrium, breast, colon, and bladder, while notably, prostate cancer has an inverse association with diabetes (2). The magnitude of risk between diabetes and cancer varies across cancer sites. For hepatocellular, pancreatic, and endometrial cancers, the increased risk associated with diabetes may be up to two-fold, whereas for other cancers, such as colon and breast, the relative risk increases are closer to 20% to 40%. Diabetes has also been associated with higher mortality after cancer, and survivors of some cancers have a higher incidence of developing subsequent diabetes. Finally, both cancer and diabetes treatments have been shown to influence associations between diabetes and cancer-associated outcomes.

The inflammatory and endocrine effects of obesity, a major risk factor for type 2 diabetes (DM2), have been proposed as central mechanisms explaining associations between diabetes and cancer. Indeed, epidemiological trends in diabetes closely follow those of obesity (3) and obesity has been independently associated with higher risks of gallbladder, esophageal, colorectal, endometrial, kidney, and postmenopausal breast cancers (4–6). Other factors specific to diabetes, such as hyperglycemia, insulin resistance, and hyperinsulinemia, have also been linked to cancer growth in vitro and in animal and human studies (7, 8).

Understanding this complex relationship and its clinical implications is of increasing importance as diabetes and concomitant obesity rates continue to rise globally. This review will summarize the epidemiological evidence for associations between diabetes, obesity, and cancer, describe potential pathophysiological mechanisms underlying these associations, and discuss the clinical implications for individuals with obesity, diabetes, and cancer.

A PubMed search was performed in March 2019, without restrictions, using the following keywords: "*Neoplasm or Cancer*" AND "*Obesity*", "*Diabetes*" and "*Insulin Resistance*." A manual review of references from eligible publications were also individually reviewed by the authors. We focused on recent publications (within 5 years), but relevant older articles were also selected at the authors' discretion.

Epidemiological Associations

Obesity and cancer risk

Overweight or obesity, defined as a body mass index (BMI) above 25 kg/m^2 (23 kg/m^2 in Asians) is associated with increased morbidity and mortality worldwide and is a major risk factor for many noncommunicable diseases, such as heart disease, stroke, and DM2 (9). The age-standardized prevalence of overweight and obesity is estimated at nearly 40% for both men and women, with over 2 billion adults affected globally (10). Overweight and obesity rates have risen dramatically in the last few decades, due to massive worldwide shifts in diet and physical activity patterns and are projected to continue rising over the next 2 decades (11).

Obesity has also been identified as an independent risk factor for many cancers. Some studies report that nearly 40% of all cancers can be attributed to overweight and obesity (12). In particular, endometrial, postmenopausal breast, and colorectal cancers account for over 60% of

cancers attributed to obesity (13, 14). In 2018 the World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) published a large systematic review showing that, in addition to those cancer sites, there is also strong evidence associating obesity with esophageal, liver, pancreatic, gallbladder, ovarian, thyroid, multiple myeloma, and renal cancers (15) (Table 1). Overweight and obesity may have different effects on risks of certain cancers according to sociodemographic factors. A large nationwide American study recently reported that the population attributable fraction of cancer was overall higher among women compared to men (9.6% vs 4.7%) (16). This sex-difference in obesity-related factors has been reported in other studies (14) and different populations (17, 18), and it is likely explained by a stronger association between obesity and female-related cancers. Obesity has also been associated with a higher risk of cancer among those in more developed countries and in populations of higher socioeconomic level (17). Furthermore ethnicity seems to moderate the risk of obesity, with stronger associations between BMI and cancer for non-Hispanic black and white populations (19).

Obesity as characterized by BMI is a measure of general adiposity and may not fully quantify the role of visceral adiposity in cancer risk. Visceral adipose tissue is increasingly recognized as an endocrine organ that synthesizes obesity-mediated hormones and cytokines, which have been directly implicated in cancer risk (20). Measures of waist circumference (WC) and waist-to-hip ratio (WHR) may be better surrogates for estimating visceral fat (21). Some studies have shown that WC and WHR are more strongly associated with cancer risk than BMI (22–24). In prostate cancer, a high BMI was associated with a reduced risk of prostate cancer, whereas an elevated WC was associated with an increased risk (25).

Weight gain over time may also modulate cancer risk, further supporting a direct relationship. For instance, a meta-analysis of observational studies reported that for each 5-kg increase in weight, the risk for endometrial, ovarian, postmenopausal breast cancer, colorectal (in men), and renal cancer increased. Interestingly, adult weight gain was not associated with an increased risk for premenopausal breast, colorectal (in women), pancreatic, and thyroid cancers (12). Another study using prospective data from 3850 adults in the United States, reported that weight gain of greater than 1 pound/year was associated with a 38% increase in overall cancer risk, with the highest risk among women (26).

For breast cancer, the relationship with obesity varies depending on menopausal status. There is consistent evidence of a positive linear relationship between high BMI and postmenopausal breast cancer incidence (27, 28), earlier onset of breast cancer, and reduced cancer-free survival (29). Moreover, multiple studies have confirmed that weight gain, as early as age 18, rather than sustained weight throughout adult life, may be a stronger risk factor for postmenopausal breast cancer (28, 30, 31). The association between obesity, weight gain, and premenopausal breast cancer is less linear. Interestingly, increased adiposity early in life has been associated with a lower risk of premenopausal breast cancer (30, 32, 33). Most recently, a large study of 758 952 premenopausal women found that women with the highest BMI category ($\geq$ 35 kg/m^2) had a 76% lower risk of premenopausal breast cancer compared with the lowest category (BMI < 17 kg/m^2) (34), and the negative association was even stronger for estrogen- and progesterone-positive cancers and for adiposity at an earlier age. The investigators also reported a dose-response relationship, with each 5-unit increase in BMI associated with a 12% to 23% reduction in breast cancer risk. A recent study using data from the Nurses' Health study reported that while changes in BMI starting at age 18 increases the risk of postmenopausal cancers, weight gain in early adulthood does not impact risk of premenopausal breast cancers (31).

Increasingly, there is a trend of cancers, in particular obesity-related cancers, being diagnosed at younger ages (35). Some suggest that the increasing rates of obesity early in life may in part explain these trends. For example, colon cancer previously had a peak incidence at 67 years, whereas it is now being diagnosed more commonly in adults younger than 50 years (36). Moreover, rates have been increasing among adults 20 to 40 years of age (37–39). The trends in increasing BMI in young adults closely parallel the increased rates of colon cancer, suggesting that obesity and associated risk factors (diet high in processed foods, low physical activity) (40) in part may explain these trends. Of concern, younger patients with colorectal cancer may be presenting with more advanced disease and have worse outcomes, partly because this age group is not routinely screened (41). Similarly, the incidence of colorectal adenomas, a premalignant precursor to colorectal cancer, has also been reported more commonly in younger obese individuals (42). A recent study from the United States confirmed this trend using 25 population-based state registries from 1995 to 2014, showing a

Table 1. Summary of the Associations Between Risk of Specific Cancers and Obesity and Diabetes

Cancer Site	Outcome	Obesity[a]		Diabetes[b]	
		Strength of Evidence[c]	Relative Risk Estimate[d]	Evidence of Bias[e]	Random (95% CI) Effects[f]
Bladder	Incidence	Inadequate	-	Yes	1.35 (1.17–1.56)
	Mortality	Inadequate	-	Yes	1.24 (0.95–1.62)
Breast (postmenopausal)	Incidence	Sufficient	1.1 (1.1–1.2)	No	1.20 (1.12–1.28)
	Mortality	-	-	-	1.24 (0.95–1.62)
Colorectal	Incidence	Sufficient	1.3 (1.3–1.4)	No	1.27 (1.21–1.34)
	Mortality			No	1.20 (1.03–1.40)
Endometrial	Incidence	Sufficient	7.1 (6.3–8.1)	No	1.97 (1.71–2.27)
	Mortality			Yes	1.23 (0.78–1.93)
Esophageal	Incidence	Sufficient	4.8 (3.0–7.7)	Yes	1.30 (1.12–1.50)
	Mortality				
Gallbladder	Incidence	Sufficient	1.3 (1.2–1.4)	No	1.52 (1.26–1.84)
	Mortality				
Gastric	Incidence	Sufficient	1.8 (1.3–2.5)	yes	1.09 (0.98–1.22)
	Mortality			Yes	1.29 (1.04–1.59)
Hepatocellular	Incidence	Sufficient	1.8 (1.6–2.1)	Yes	2.43 (1.67–3.55)
	Mortality			No	2.43 (1.67–3.55)
Kidney	Incidence	Sufficient	1.8 (1.7–1.9)	Yes	1.38 (1.10–1.72)
	Mortality			Yes	1.16 (1.01–1.33)
Non-Hodgkin Lymphoma	Incidence	Inadequate	-	Yes	1.27 (1.09–1.48)
	Mortality	-	-	-	-
Meningioma	Incidence	Sufficient	1.5 (1.3–1.8)	-	-
	Mortality	-		-	-
Multiple Myeloma	Incidence	Sufficient	1.5 (1.2–2.0)	Yes	1.27 (0.98–1.64)
	Mortality	-	-	-	-
Ovarian	Incidence	Sufficient	1.1 (1.1–1.2)	Yes	1.17 (1.02–1.34)
	Mortality	-	-	-	-
Pancreas	Incidence	Sufficient	1.5 (1.2–1.8)	No	1.95 (1.66–2.28)
	Mortality	-	-	-	-
Prostate	Incidence	-	-	No	0.91 (0.82–1.01)
	Mortality	-	-	-	-
Thyroid	Incidence	Sufficient	1.1 (1.0–1.1)	No	1.16 (0.97–1.39)
	Mortality	-	-	-	-

From Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JP. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. *BMJ.* 2015;350:g7607.

[a]Relative risk estimates for the risk of specific cancers with obesity taken from evidence compiled by the International Agency for Research on Cancer (IARC) Handbook Working Group, available at handbooks.iarc/fr/docs/Handbook16_Working-Procedures.PrimaryPrevention.pdf.

[b]Random effects estimates and 95% CI summarized from umbrella review of meta-analyses from Tsilidis et al., BMJ, 2015;350:g7607.

[c]Strength of evidence evaluated by authors of IARC working group be evaluating risk of bias and confounding in included studies.

[d]Where sufficient evidence was available, comprehensive meta-analyses or pooled analyses were calculated, using normal body mass index (BMI), defined as a BMI 18.5–24.9, as the comparator.

[e]Random effects synthesis from pooled risk ratios derived from meta-analyses of observational studies.

significant increase in incidence of obesity-related cancers among young adults (25-49 years of age) that rose more steeply in successively younger generations (43).

Impact of weight loss on cancer risk

There is increasing evidence that weight loss is associated with reduced risk of obesity-related cancers. In a prospective cohort of more than 20 000 women in the Iowa Women's Health Study, women who had an intentional 20-pound or more weight loss had a 14% lower risk of obesity-related cancers than women who did not lose weight (44). In a more recent study from the Women's Health Initiative, intentional weight loss among obese women was associated with a 54% lower risk of endometrial cancer compared with obese women with stable weight (45). Bariatric surgery has also been found to be associated with a reduction in cancer risk. A recent large retrospective cohort study including over 22 000 patients who underwent bariatric surgery evaluated the impact of surgery and weight loss on cancer risk (46). After 3.5 years of follow up, there was a 33% reduction in overall cancer risk and a 41% reduction in obesity-associated cancers (breast, colorectal, endometrial). An earlier study from the same group reported that the reduction in cancer incidence was independent of bariatric surgery and directly related to weight loss (47).

With regard to specific cancer sites, a study using Kaiser Permanente Integrated health data reported a reduction in both premenopausal (hazard ratio [HR] 0.72; 95% CI, 0.54–0.94) and postmenopausal (HR 0.55; 95% CI, 0.42–0.72) breast cancers with bariatric surgery (48). The association between bariatric surgery and risk of colorectal cancer is less clear. Surprisingly, a large Swedish study of 15 095 bariatric surgery patients found an increased risk of colorectal cancer after bariatric surgery (49), which was not confirmed in a more recent English study (50). It is important to note that the Swedish study did not differentiate between colon and rectal cancers, which have different associations with obesity. One study that separated the sites found a reduction in risk of colon cancer but no reduction in risk of rectal cancer with bariatric surgery (46). While findings from observational studies support a potential role of weight loss to reduce cancer risk, data from randomized control trials are currently lacking. Furthermore, studies that evaluate the degree and methods of weight loss that best optimize cancer prevention are necessary to guide clinical and population-based interventions.

Insulin resistance, prediabetes, and cancer risk

As a common consequence of obesity and precursor to DM2, insulin resistance has been proposed as a key factor underlying the obesity-related risk of cancer. Clinical manifestations of insulin resistance include centripetal or visceral adiposity, acanthosis nigricans, dyslipidemia, hypertension, polycystic ovary syndrome in women, and even mild hyperglycemia (51). Initially, insulin resistance is associated with compensatory hyperinsulinemia that can predate the onset of diabetes by up to 18 years (52).

Epidemiological studies have attempted to study clinical states of hyperinsulinemia and cancer risk by evaluating the risk of cancer prior to diabetes diagnosis, a time when insulin levels are known to be elevated (52). Two studies using US data by Onitilo et al found a 16% increased risk of breast cancer in the 10 years preceding a diagnosis of diabetes (53) and a 28% increased risk of colorectal cancer among men before diabetes onset (54), compared with persons who did not develop diabetes. Interestingly, neither study found an increased risk for breast or colorectal cancer following a diagnosis of diabetes. A population-based Canadian study conducted by our group evaluated the temporal relationship between diabetes and cancer by comparing the risk of cancer among diabetes-free individuals versus diabetic patients at 3 time points around a diagnosis of diabetes: 10 years prior to diabetes diagnosis, 3 months following diabetes diagnosis, and up to 10 years after diabetes diagnosis (55). Similar to Onitilo et al, we found that patients with diabetes were 23% more likely to have been diagnosed with any cancer in the 10 years prior to diabetes, with pancreatic and liver cancer being the most common cancers diagnosed in this time period. In addition, an elevated risk of cancer following a diabetes diagnosis was only seen in the first 3 months, with no ongoing increase in the subsequent 10 years (55). Other studies have also documented similar trends (56, 57). These findings have been attributed to possible detection or protopathic biases, to be discussed under *Methodological considerations in epidemiological studies*. The spike in cancer diagnoses shortly after diabetes diagnosis also supports a potential role for hyperinsulinemia in cancer development during the prediabetes phase, as the latency phase between risk factor exposure and clinically detectable cancers can be years (58).

Gestational diabetes (GDM) and cancer risk

Gestational diabetes mellitus (GDM) represents a unique prediabetes phase, as it is an early marker

of increased risk for subsequent diabetes and is often a hallmark of underlying insulin resistance (59). There have been numerous studies that have looked at the risk of cancer in women with a history of GDM, and results are inconsistent. An Israeli study of more than 100 000 women, at a mean follow-up of 12 years, reported a 70% increased risk of female malignancies (endometrial, ovarian, breast, cervix) compared with women who did not develop GDM in pregnancy (60). However, a Canadian study with a shorter mean follow-up period (8 years) reported an increased risk of thyroid cancer—and notably a decreased risk of breast cancer—for women who had GDM during pregnancy versus those with nondiabetic pregnancies (61). Similarly a follow-up study from the Nurses' Health Initiative also reported an inverse relationship between history of GDM and breast cancer after a mean follow up of 22 years (62). The inverse relationship between GDM and breast cancer reported in these latter 2 studies may be explained by the fact that they mostly captured premenopausal breast cancers, which are known to be less common in women with diabetes and obesity (63). Recently, a meta-analysis of 11 observational studies concluded that GDM is not associated with an increased risk of breast cancer overall; however, it may be associated with a decreased risk in certain settings (64). On the contrary, 1 study found that having 2 or more pregnancies with GDM was associated with a 68% increased risk of breast cancer (65). It is possible that repeat episodes of GDM and weight gain between pregnancies amplifies the risk of breast cancer through longer exposure to insulin resistance, and it may also be a marker of women at higher risk of abnormal glucose metabolism. Nevertheless, further research is needed to better understand the underlying mechanisms.

Diabetes and cancer risk

Type 2 diabetes (DM2)

There have been numerous epidemiological studies that have evaluated the risk of cancer associated with DM2. Earlier studies showed that diabetes was associated with a 35% increased risk of colorectal cancer (66), a 60% increased risk of cholangiocarcinoma (67), a 25% increased risk of breast cancer (68), and an 82% increased risk of pancreatic cancer (69). However, these older findings have been inconsistent and were limited by important methodological considerations that raised the possibility of bias or spurious observations (see discussion of *Methodological considerations in epidemiological studies* below). More recently, researchers have carefully tried to isolate associations that are causal from those that may reflect confounding or biases. In 2015, Tsilidis et al published an umbrella review of meta-analyses of observational studies of diabetes and cancer that carefully summarized the robustness of reported associations considering the quality and heterogeneity of studies (70). After excluding less robust associations, the authors were able to demonstrate consistent relationships between diabetes and an increased risk of cancers of the breast, colorectum, endometrium, and cholangiocarcinoma (70), with pooled risk estimates ranging from 1.20 to 1.97. The authors also note that positive associations between diabetes and other cancers that have been previously reported (ie, kidney, pancreatic, hepatocellular, gastric, and thyroid) remain more uncertain in light of concerns with methodological approaches in previous studies.

The relationship between prostate cancer and diabetes is unique, since it is the only cancer where diabetes appears to be protective. The most recent meta-analysis of 45 observational studies suggest that men with diabetes have a 14% lower risk of prostate cancer compared to men without diabetes (71). Biologically, this is supported by the fact that some men with diabetes may have lower circulating androgen levels potentially leading to reduced growth and stimulation of prostate cancer cells (72). There is also evidence that men with diabetes have lower circulating prostate-specific antigen (PSA) levels, a tumor marker that is controversially used to screen for prostate cancer, which would lead to a lower detection rate of prostate cancer in men (72).

Epidemiological studies have also evaluated the association between serum glucose and cancer risk. A large Korean population-based study evaluated the association between fasting glucose, diabetes status, and colon cancer risk (73). There was a significant direct relationship between fasting glucose and cancer risk even below the threshold for diabetes. However, glucose testing was done at 1 time point at baseline which may not be a reflection of persistent hyperglycemia.

Impact of obesity on cancer risk in DM2

As obesity is a major risk factor for DM2, studies that evaluate the risk of cancer in patients with diabetes must account for obesity as a potential mediator of risk. For endometrial cancer, obesity has been shown to be an effect modifier of the association between diabetes and cancer with a higher risk among women with both obesity and diabetes compared to those with diabetes alone (74). Studies

evaluating this association for other cancer sites are lacking. More recently a publication by Pearson-Stuttard et al sought to estimate the independent and combined contribution of diabetes and high BMI to cancer incidence (75). Using relative risks from published meta-analyses and WCRF and IARC publications for the association of diabetes, obesity, and site-specific cancers, they calculated population attributable fractions of incident cancers attributable to obesity and diabetes. They estimated that 5.7% of all incident cancers in 2012 were attributable to obesity and diabetes, and that obesity is responsible for nearly twice as many cancers as diabetes.

Interestingly, the relationship between BMI and cancer among patients with diabetes is not always linear. For example, a large Chinese population-based study evaluated the risk of cancer among a large cohort of women and men stratified by age (< or > 60 years) and sex. The authors reported a U-shaped curve for cancer risk among men with diabetes who were ≤ 60 years of age, with the highest risk among those within the lowest and highest BMI quartiles, whereas the relationship between BMI and cancer was linear among men > 60 years of age (76). For women, they reported a linear, dose-response relationship between BMI and cancer risk for those age > 60 years.

Type 1 diabetes (DM1)

There are fewer studies supporting an association between type 1 diabetes (DM1) and cancer. As the hallmark of DM1 is insulin deficiency rather than insulin resistance, epidemiological studies that evaluate the risk of cancer among patients with DM1 allow us to isolate the contribution of hyperglycemia from that of hyperinsulinemia. A systematic review and meta-analysis of epidemiological studies evaluating the risk of cancer among patients with DM1 that included 15 studies (13 cohort, 2 case-control) was published in 2018 (77). In a random effects model, the pooled odds ratio for increased cancer among persons with DM1 versus without DM1 was 1.29 (95% CI, 1.09–1.52) with an increased risk for thyroid, stomach, lung, pancreatic, liver, ovarian, and kidney cancers. There was a modestly lower risk of breast cancer associated with DM1 of borderline significance (relative risk 0.91; 95% CI, 0.86–0.95). Treatment with exogenous insulin therapy, increased insulin-like growth factor (IGF)-1 levels, changes in sex hormones and the presence of obesity and insulin resistance over the time have all been postulated as potential mechanisms for the modest increased risk of cancer among patients with DM1. Some studies have also suggested that the increased risk of cancer diagnosis is greatest within the first year following onset of DM1, indicating a possible detection bias (78). Overall, the age of patients with DM1 in these studies is younger than in studies of DM2 patients, and additional studies with longer-term follow-up are needed to confirm these findings.

Diabetes and mortality

Diabetes has also been associated with higher mortality after cancer, although associations are less robust than for risk of cancer (70). Earlier meta-analyses documented higher mortality and poorer outcomes in persons with diabetes who develop any cancer (79), breast cancer (80), and colorectal cancer (81). A more recent pooled analysis of 97 prospective studies from the Emerging Risk Factors Collaboration (ERFC) found that diabetes was associated with a significant 25% increase in mortality for most cancers (82) (Table 1). The majority of studies were limited to all-cause mortality outcomes and few accounted for prognostic factors such as cancer stage, which may be more advanced in people with diabetes, particularly women who develop breast cancer (83).

While some have reported an increased risk of cancer-specific mortality among patients with diabetes (84, 85), results are inconsistent (81, 86). In a recent study from our group, we report that patients with diabetes and breast cancer have similar cancer-specific survival as those without diabetes, but have a higher all-cause mortality (87). These findings suggest that diabetes may have a greater impact on noncancer mortality than on cancer-specific outcomes and survival.

Diabetes pharmacotherapy and cancer

Given the insulin- and glucose-modulating effects of antihyperglycemic medications, there have been numerous studies examining the potential impact of these drugs on the risk and prognosis of cancer. The first medication to be carefully studied was metformin, due to an early observational study in 2005 that reported a reduction in risk of cancer in patients with diabetes on metformin (88). Furthermore due to biological plausibility of metformin's antitumor effects through both indirect (insulin-mediated) and direct (increased AMPK activation, decreased mTOR signaling) pathways (89, 90), there was an explosion of studies looking at the impact of metformin on cancer risk, prognosis, and mortality. Initially, studies reported substantial reductions in cancer

risk and mortality with metformin; however, methodological concerns arose and it became apparent that numerous unaccounted-for biases led to inflated risk estimates (91). Biases included immortal time, healthy user, and other time-related biases that have been described extensively in the literature (92). Several subsequent studies that appropriately accounted for these biases reported null associations between metformin and cancer risk or mortality (93–95). Nevertheless, the biological evidence supporting metformin's antitumor effects is strong, and as a result, there are currently numerous ongoing clinical trials, including a large phase III randomized trial of metformin versus placebo in early-stage breast cancer (96), which continue to evaluate the potential for using metformin as an adjunct to cancer treatments.

The association between sulphonylureas and cancer risk remains uncertain. While no direct tumorigenic properties of sulphonylureas have been described, some studies have suggested an increased risk of cancer with sulphonlyureas (97, 98), while others have not (99), and some have even found sulphonylurea use to be protective (100). With regards to sulphonylureas, the main challenge remains finding appropriate comparator groups when designing studies and concerns with indication and healthy-user biases since these drugs are no longer used in clinical trials.

There was initially a concern that exogenous insulin was associated with an increased risk of cancer, when 4 studies documenting associations between insulin treatment and cancer risk were published simultaneously in *Diabetologia* in 2009 (101–104). However, after methodological concerns were carefully considered, more recent epidemiological studies have not consistently found an association between insulin, particularly insulin analogs, and cancer (105, 106). The Outcome Reduction With Initial Glargine Intervention (ORIGIN) randomized controlled trial of insulin glargine versus placebo on cardiovascular outcomes evaluated the risk of cancer as a secondary outcome. After a mean follow up of 6.3 years, the investigators did not find an increased risk of cancer associated with glargine use (107). Criticisms of this study include the fact that cancer was not a primary endpoint, and that the follow-up period was insufficient to evaluate cancer risk given the long latency period of cancer development (58). While in vitro studies have supported the hypothesis that exogenous insulin may have mitogenic effects, this has not been conclusively supported by epidemiological studies.

Similarly to metformin and insulin, the potential increased risk of cancer with thiazolidinediones (TZD) has been extensively debated. In particular, the Food and Drug Administration issued a warning in 2011 regarding pioglitazone (108), after early studies showed a signal for a higher risk of bladder cancer with pioglitazone, especially over more than 2 years of use (109). Since then, a multitude of studies have been conducted in this area, and a recent meta-analysis reported a small but statistically significant increased risk of bladder cancer with pioglitazone (110). Similarly, an increased risk of bladder cancer has been associated with rosiglitazone (111). However, TZDs are rarely used in clinical practice, and they have even been removed from the market in France due to concerns of higher risks of heart failure and myocardial infarction.

Incretin-based drugs, a new class of antihyperglycemic medications, include glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. While there were initial concerns about an increased risk of pancreatic cancer with incretin-based drugs and medullary thyroid cancer with GLP-1 receptor agonists, these effects have not been confirmed in recent studies (112–114). One recent meta-analysis did not find any association between DPP-4 inhibitors and any cancer type (115). However, another large observational study from the UK Clinical Practice Research Datalink (CPRD) reported a 77% increased risk of cholangiocarcinoma among DPP-4 inhibitor users (116). The absolute number of cancers was low (27 over 103 362 person-years of follow-up), but since there is biological plausibility to explain this association, additional studies are needed to investigate these findings. Specifically, elevated levels of GLP-1 (both endogenous and exogenous) have been associated with decreased apoptosis and increased proliferation of cholangiocytes (117, 118). More recently, preclinical data has also suggested that GLP-1 receptor agonist therapy may promote colonic tumor growth, although this has not been shown in any human studies (119).

Sodium glucose co-transporter 2 (SGLT2) inhibitors are the newest class of oral diabetes medications. In animal models, certain SLGT2 inhibitors have been associated with mammary (120), adrenal, testicular, and renal tumors (121). However, safety data from clinical trials and a recent meta-analysis do not suggest an association between SGLT2 inhibitors and overall cancer risk (122). An increased risk for bladder cancer has been reported with empagliflozin (122) and there

were concerns with an imbalance of bladder cancer occurrences in clinical trials with dapagliflozin (123). Given that SGLT2 inhibitors are still new to clinical practice, further studies evaluating their association with cancer are warranted.

Methodological considerations in epidemiological studies

To date, the majority of studies that evaluate the risk of cancer with diabetes are observational and therefore susceptible to certain biases. Specific biases present in studies that look at cancer risk in patients with diabetes have been extensively studied and identified (124, 125). This discussion will focus on issues surrounding reverse causality/protopathic bias, detection bias, and depletion of susceptibles. Reverse causality/protopathic bias refers to the situation where the symptoms of one condition are a sign of an underlying second condition that appears at a later date and the two are causally connected (126). Protopathic biases are present in particular when studying cancers that may present with hyperglycemia (ie, pancreatic, hepatocellular cancers). In this case, a patient may be diagnosed with new diabetes but may have developed hyperglycemia due to metabolic stress from an underlying malignancy that has yet to be detected (127). Similarly, detection bias refers to the increased likelihood for detecting a cancer in a patient who is newly diagnosed with diabetes, given increased medical surveillance leading to increased screening activities (eg, mammography, colonoscopy/fecal occult blood testing, etc.) (56, 57).

Multiple studies have illustrated evidence of reverse causality/protopathic bias and detection biases by looking at cancer risk at specific time points around the diagnosis of diabetes (eg, 3 months, 6 months, 1 year) (55–57, 128–130). All studies have found cancer risk to be the highest within the first 3 months after diagnosis, explained by either detection or protopathic bias. Interestingly, for pancreatic cancer, most studies report that the risk of pancreatic cancer declines after diagnosis of diabetes, but does not disappear. This suggests that while reverse causality/protopathic bias explains part of the association, there is likely also a causal relationship between diabetes and pancreatic cancer. Conversely, studies have shown that the risk for certain cancers disappears after the initial diabetes diagnostic period (ie, lung, bladder) (55, 127) suggesting that those observed associations are largely due to detection bias. As a result, researchers must be careful when designing these studies to minimize such biases by incorporating a time-lag period (125).

Another explanation for the decline in cancer risk with increasing duration of diabetes is the notion of depletion of susceptibles, or competing risks. This refers to a phenomenon whereby the highest-risk individuals exposed to risk factor will develop cancer early after exposure, leading to a reduction in the number of patients susceptible to developing cancer over time (131, 132). The association between diabetes and cancer may thus become attenuated over time, as has been reported in many studies (55, 130, 131). The competing risk of death that increases in diabetes patients over time also contributes to the consequent decline in their cancer risk relative to persons without diabetes (131, 132).

Potential Mechanisms of Obesity, Diabetes, and Cancer Risk

Adiposity

Adipose tissue, particularly visceral adiposity, is increasingly recognized as an important endocrine organ that secretes adipokines (133), inflammatory cytokines, and estrogen through peripheral aromatization of androgens (134). Excess visceral adiposity leads to increased lipid intermediates, increased leptin, and leptin resistance (135), impaired insulin signaling, insulin resistance (136, 137), and higher levels of circulating IGFs due to reduction in IGF-binding binding globulin levels (138) (Fig. 1). Increased adiposity also leads to reduced circulating adiponectin, an important adipokine that reduces levels of free fatty acids, improves lipid profiles, and decrease inflammatory cytokines (139). These metabolic disturbances have all been linked to oncogenic mechanisms, including cell proliferation and migration, angiogenesis, and reduced cellular apoptosis (13, 140, 141). There is also evidence of increased inflammatory markers, in particular tumor necrosis factor-alpha, interleukin-6, interleukin-1, and C-reactive protein, which may also promote carcinogenesis (142). In addition to these mechanisms, shared risk factors, such as sedentary lifestyle and excess caloric intake, may also contribute to increased mitogenesis through the production of reactive oxygen species (143).

In contrast to most cancers, there is an inverse relationship between obesity and premenopausal breast cancer which remains poorly understood. While childhood adiposity is associated with early pubertal onset, slower peak growth, and pubertal

tempo, some suggest this may also contribute to a lower breast cancer risk (34, 144). Other theories are that early adiposity leads to positive changes in breast cell differentiation, including expression of tumor suppressor genes (145) and that early adiposity affects long term levels of IGF-1 (146) and leptin (147), resulting in a protective effect on premenopausal breast cancer risk (146). What remains unclear is why this protective association is reversed for postmenopausal breast cancer, and why it is not seen for other cancers.

Hyperinsulinemia

DM2 develops when pancreatic beta cells fail to secrete sufficient insulin to maintain euglycemia, and it is most commonly preceded by an extended period of insulin resistance and compensatory hyperinsulinemia (148–150). Large prospective studies have shown that this compensatory hyperinsulinemia begins at least 6 years prior to onset of diabetes (although in some cases it may precede the diagnosis by 18 years) (52) and that peak levels of insulin production occur approximately 3 to 4 years prior to diabetes, followed by significant declines in the last 2 years before diagnosis (148).

Hyperinsulinemia has been hypothesized as a key mediator of cancer risk in patients with diabetes. There is strong evidence supporting an association between elevated insulin levels and risk of breast, colorectal, pancreatic, and endometrial cancers (151, 152). A large study from the National Health and Nutrition Examination Survey (NHANES) including more than 9 000 participants reported that hyperinsulinemia (defined as fasting insulin level > 10 μIU/mL) was associated with a 2-fold increased risk of cancer mortality, and this relative risk increase was seen even among individuals who were not obese (153). Insulin may promote carcinogenesis through direct and indirect mechanisms, via reduction in circulating levels of IGF-binding proteins, leading to excess IGF-1 and IGF-2 (146) (Fig. 1). Insulin and IGF signaling impact cell survival and proliferation through the RAS/RAF/MAPK kinase/ERK cascade (154). Tumors of the breast, colon, lung, ovary, and thyroid express insulin receptors in high levels (155, 156), particularly the insulin receptor-A variant that is thought to mediate the direct effects of excess insulin on carcinogenesis (156). It is noted that insulin receptors expressed in breast tumors are not downregulated in the setting of hyperinsulinemia (8, 157), as opposed to metabolic signaling through the insulin receptor pathway, therefore promoting direct

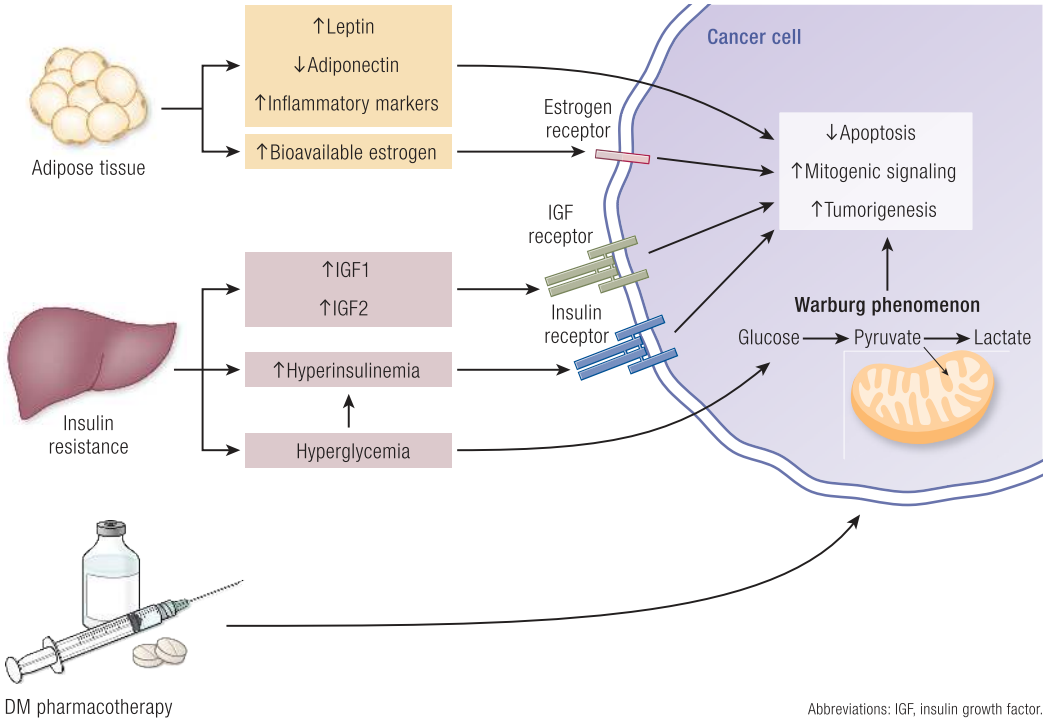

Figure 1. Main mechanisms and pathways between obesity, insulin resistance, and diabetes pharmacotherapy and cancer growth and progression.

hyperinsulinemia-induced signaling and tumor growth (158). Similarly in colorectal cancer, there is evidence that insulin activation through insulin receptor pathways leads to tumor growth (159), and IGF-based insulin receptor signaling and gut inflammatory processes through dysregulated insulin pathways have also been shown to be central to oncogenesis (160). Finally there is some evidence that insulin upregulates cellular metabolic activity, which can lead to oxidative stress and DNA damage, thereby promoting oncogenesis (161).

Hyperglycemia

Glucose is an important substrate for cellular metabolism in proliferating cells. Hyperglycemia has been postulated to have both a direct and indirect effect on cancer cells that can lead to cancer growth and proliferation (Fig. 1). The Warburg effect is the well-described process whereby cancer cells have increased glucose uptake and rely on aerobic glycolysis to generate energy, instead of more efficient oxidative phosphorylation (162). It is postulated that cancer cells have adapted to this method of energy production due to damaged mitochondria in cancer cells, and as an adaptive strategy for maximizing available energy sources to support rapid proliferation (163). Studies have shown that cancer cells have a high concentration of glucose uptake (164) as a result of this means of energy production. There is also evidence that supports a direct role of glucose on cancer cell proliferation (165–167), cancer cell anti-apoptosis (168) and cancer cell invasiveness (167, 169). Indirectly, hyperglycemia leads to counter-regulatory increases in insulin and IGF levels, which, as discussed above, have a direct impact on cancer cell proliferation and metastases. There is much controversy as to the independent contribution of hyperglycemia on cancer growth, and whether the impact of hyperglycemia on tumor growth is mostly dependent on hyperinsulinemia and other inflammatory markers (134, 170). A meta-analysis from 2016 evaluated the association of fasting glucose, insulin, and insulin resistance (using the homeostasis model of risk assessment- insulin resistance [HOMA-IR]) with the risk of colorectal cancer (171). After reviewing 35 studies the authors found that all these markers of glucose metabolism were significantly associated with an increased risk of colon cancer, with the HOMA-IR having the strongest impact on cancer risk. While this study does not fully clarify the direct role of hyperglycemia in the risk of colon cancer, it does highlight the complexity deciphering the independent contribution of markers of glucose metabolism, including hyperglycemia, on cancer risk.

Prostate cancer is unique in that men with diabetes appear to have a reduced risk of prostate cancer (71). A recent meta-analysis of 15 observational studies reported that hyperglycemia among men with diabetes is associated with a lower risk of prostate cancer (172), further supporting the inverse relationship between diabetes and prostate cancer. Explanations for the reverse association between diabetes and cancer include reduced circulating androgen levels (173) and PSA levels (174) among patients with diabetes. While diabetes medication, specifically metformin, was initially thought to contribute to the reverse association between diabetes and prostate cancer, most recent studies and meta-analyses do not support this association (175). Interestingly, despite the reverse association between diabetes and prostate cancer, obesity is associated with an increased risk of prostate cancer and increased aggressivity (176).

New Research Approaches—Mendelian Randomization

Mendelian randomization is an analytic method to address the role of biases and residual confounding in observational studies, to strengthen evidence for a causal relationship between an exposure and an outcome. Mendelian randomization studies use germline variants, which are determined at birth and remain constant through life, as instruments (proxies) for exposure to certain risk factors. Since these variants are randomly allocated at conception and their association with exposures is generally independent of other factors, they support causal inferences about the effect of modifiable risk factors on health outcomes by minimizing effects of unmeasured biases (177–179). As common genetic polymorphisms have been characterized through whole genome-wide association studies (GWAS), Mendelian randomization studies use very large databases and provide results that are precise (180).

There has been much interest in using Mendelian randomization methods in the area of diabetes and cancer, to better elucidate the relationship between the various clinical components of abnormal glucose metabolism (ie, obesity, insulin resistance, diabetes) and cancer risk. Gao et al (181) used GWAS data from 32 studies to identify genetic variants for birthweight, childhood

and adulthood BMI, and adult waist-hip ratio. Mendelian randomization analyses were then used to determine the association between each of these adiposity-related variants and the risk for breast, ovarian, lung, prostate, and colorectal cancers. They reported an inverse association between breast cancer and BMI (both childhood and adulthood), a direct association between BMI and the risk of lung, ovarian, and colorectal cancers, and no association between BMI and prostate cancer (181). Other variants of adiposity studied by this group were not associated with cancer risk. The findings of inverse relationship between adulthood BMI and breast cancer contrast previous epidemiological findings (27, 28, 30, 31). The authors suggest that the variant for BMI more closely reflects BMI early in life and does not account for environmental factors that contribute to increasing weight later in life (182). Adult weight gain has been strongly associated with breast cancer risk, and therefore this study highlights some limitations of interpreting Mendelian randomization studies. Other Mendelian randomization studies on breast cancer have shown similar findings including the inverse association between breast cancer risk and increasing BMI (183). However, in a study where obesity was further broken down into metabolic components, a positive association was found with risk of breast cancer and both increasing 2-hour glucose and fasting insulin levels (184). These data support a causative role for both hyperinsulinemia and glucose tolerance on the development of breast cancer. These studies also underscore the complexity of the relationship between obesity and breast cancer and the need for further studies to determine the role of weight gain later in adult life on breast cancer risk (28).

With regard to other cancer sites, a recent study using Mendelian randomization methods reported positive associations between the risk of renal cell carcinoma and high BMI, elevated fasting insulin, and insulin resistance (185). Interestingly, the variants for diabetes, beta-cell dysfunction, and fasting glucose were not associated with an increased risk of renal cell carcinoma. Studies on pancreatic cancer have also reported a strong causal relationship between increasing BMI and fasting insulin, with again, no increase in risk associated with diabetes and fasting glucose (186). In contrast to data on breast cancer, these studies support a primary causal role of hyperinsulinemia on the risk of renal and pancreatic cancer while de-emphasizing the role of hyperglycemia and diabetes.

Mendelian randomization studies provide us with unique information on causal relationships between components of obesity, glucose metabolism and cancer risk. However findings are limited by the robustness of the methods used, and results should be interpreted in the context of results from other epidemiological studies. Most importantly, these studies cannot isolate "critical period effects" for exposures and are only suitable for studying exposure that have a heritable component (178).

Reverse Association: Risk of Diabetes Following Cancer

There is emerging evidence of a bidirectional relationship between diabetes and cancer, in that cancer survivors may also have an increased subsequent risk of developing diabetes. This relationship has been attributed to shared risk factors between the two conditions, as well as cancer treatment effects, and it has been shown for both pediatric and adult cancer survivors.

Pediatric cancers

Long term survival of childhood cancer approaches 85%; therefore, adult survivors of childhood cancer represent a steadily growing population. Long-term cohort studies such as the Childhood Cancer Survivor Study (CCSS) (187) and the British Childhood Cancer Survivor Study (BCCSS) (188) have been instrumental in identifying the long-term health consequences following treatment for childhood cancer. Diabetes has emerged as a late effect following treatment for childhood cancer (187, 189–191). The first study came from the CCSS group where an 80% increased risk of diabetes was reported among childhood cancer survivors compared to sibling controls (189). Of note, the risk of diabetes was independent of BMI and level of physical activity, suggesting cancer-related and potentially treatment-related risk factors for developing diabetes. The risk of diabetes was highest among those who received total body irradiation (odds ration [OR] 12.6), abdominal radiation (OR 3.4) and cranial radiation (OR 1.6). Two large population based studies have also been conducted, one in Scandinavia and the most recent by our group in Canada, and both have demonstrated a 60% increased risk of diabetes in adult survivors of childhood cancer compared to age- and sex-matched controls in the general population (190, 191). Childhood cancers with the

highest risk of diabetes are Wilms tumors, leukemia, central nervous system neoplasms, germ cell neoplasms, and Hodkgin lymphoma (190, 191).

The most common cancers in childhood are treated with a combination of systemic chemotherapy and either total body, thoracic/abdominal, or brain radiation. While cranial irradiation may lead to insulin resistance due to hypothalamic obesity-mediated pathways and growth hormone deficiency (192), abdominal and total body irradiation and alkylating chemotherapy agents (189, 193) have been associated with beta cell dysfunction as a result of direct pancreatic injury (187, 189, 194, 195). Insulin resistance due to changes in adiponectin, leptin, and resistin levels have also been associated with abdominal radiation (196, 197). Once cured, survivors of childhood cancer have significant physical and psychosocial morbidity, and there is evidence of less-healthy behaviors (smoking, alcohol use, unhealthy diets, and decreased physical activity) (198), which may also contribute to their increased risk of diabetes.

Adolescent and young adult (AYA) cancers

There also appears to be an increased risk of diabetes in survivors of adolescent and young adult (AYA) cancers, a relatively understudied cancer survivor group (199). Subset analyses from larger childhood cancer studies have often been used to extrapolate knowledge with regard to late effects in AYA survivors. A recent Danish population-based study explored the risk of endocrine late effects in a cohort of 32 548 survivors of AYA cancer using hospital contacts to evaluate the outcomes (200). The investigators reported a 29% increased risk of diabetes compared to the general population and found that diabetes was one of the leading reasons for hospital contacts in this population. Studies on diabetes risk after specific AYA cancers have also reported an increased risk of diabetes among patients treated for Hodgkin lymphoma (201) and among men receiving para-aortic radiation for testicular cancer (202). No studies have evaluated the risk of diabetes following breast or thyroid cancer, two common cancers in this age group, specifically among survivors of AYA cancers.

Adult cancers

There is also an increased risk of diabetes following cancers treated in adulthood. As there are often shared risk factors between diabetes and many obesity-related adult cancers, isolating specific risk factors for diabetes in cancer survivors has been challenging. A large Korean study evaluated the risk of diabetes after cancer treatment for any solid cancer, and found an overall 35% increased risk for diabetes in cancer survivors compared to noncancer controls (203). While the risk was highest in the first 2 years, it remained elevated until 10 years following cancer (HR 1.19; 95% CI, 1.00–1.43). The risk was highest for survivors of pancreatic, kidney, and liver cancers, although gallbladder, lung, blood, breast, stomach, and thyroid cancers were also significantly associated with an increased risk for diabetes.

With regards to specific cancer sites, an increased risk of diabetes has been reported following colorectal and breast cancers. A large Canadian population-based study of colorectal cancer survivors found a 53% increased risk of diabetes within the first year after cancer compared to noncancer controls, and the risk remained elevated for up to 5 years (204). Also in a Canadian study, our group reported a 7% increased relative risk of diabetes 2 years after breast cancer diagnosis compared with women without cancer; this relative risk rose to 21% after 10 years (205). Interestingly, the relative risk of diabetes varied significantly over time according to receipt of adjuvant chemotherapy (205). While women who received chemotherapy had the highest risk (HR 1.24; 95% CI, 1.12–1.38) within the first 2 years of treatment, diabetes incidence only began increasing 3 years after diagnosis in women who did not receive chemotherapy and continued to rise over the 10-year follow-up. These findings suggest that chemotherapy may bring out diabetes earlier in susceptible women, possibly through increased health contact, weight gain or use of corticosteroids for nausea. Treatment-induced estrogen deficiency may also promote diabetes risk through apoptosis of pancreatic beta cells (206). Indeed, we showed that women with breast cancer who received therapy with the selective estrogen receptor modulator tamoxifen had a significantly higher risk of diabetes than untreated women (207). Shared risk factors between diabetes and obesity-related cancers, such as obesity, physical inactivity, and poor diet may contribute to this bidirectional relationship. These findings also provide further support for a central role of hyperinsulinemia in the diabetes-cancer association. In the setting of insulin resistance, the risk of cancer would be expected to rise early, when insulin levels are elevated, with diabetes developing only after insulin levels decline.

Clinical Implications and Future Directions

For persons with obesity and insulin resistance

While individuals with obesity have a higher risk of 13 obesity-related cancers as outlined by the IARC, the most common obesity-related cancers are endometrial, colorectal, and postmenopausal breast cancers (15). Risk of obesity-related cancers has been shown to be particularly elevated in individuals with insulin resistance and prediabetes (53, 54, 153), likely due to prolonged exposure to excessive circulating insulin. Despite the strong association between obesity and these cancers, there are currently no specific guidelines that recommend earlier or more aggressive cancer screening protocols in the setting of a high BMI (Table 2). Even in colorectal cancer, where there is a worrying trend towards an increased rate among young adults with obesity, no specific screening guidelines exist beyond the normal recommendations.

Regarding preventing obesity-related cancer, there is mounting evidence from observational studies that weight loss, either through surgical procedures or lifestyle modification can reduce cancer risk, especially among women who have the highest burden of obesity-related cancers (44–46, 48). However many unanswered questions exist as to the degree of weight loss that is required to reduce cancer risk, how regaining weight affects risk, and the optimal weight loss strategy for maximal benefit in cancer prevention. Randomized trials that evaluate the impact of weight loss on cancer risk will be instrumental in providing practical clinical guidance for how best to advise obese patients with regard to cancer prevention. For the time being, we must continue counseling obese patients on the benefits of weight loss and the potential benefit on cancer risk reduction.

For persons with diabetes

Individuals with diabetes are more likely to be diagnosed with cancer shortly after diabetes diagnosis (55, 57). While this finding has been attributed to a detection bias, prolonged exposure

Table 2. Obesity, Diabetes, and Cancer: Clinical Implications

Patient Population	Implications	Potential Interventions
Persons with high BMI, obesity	• ↑ risk of cancer with rising BMI • ↑ risk of cancer with centripetal adiposity, GDM, prediabetes	• Weight loss programs • Bariatric surgery • Insulin sensitizing medications • Modified cancer screening guidelines
Persons with diabetes		
Type 1	• Possible ↑risk of certain cancers	• Optimize cancer screening adherence • Further research needed
Type 2	• ↑ risk of certain cancers • Strongest risk at diabetes diagnosis • ↑ BMI adds to cancer risk • Antihyperglycemic agents may modulate cancer risk	• Clinical screening for cancer at diabetes diagnosis • Optimize cancer screening adherence • Weight loss • Further research on drug effects needed
Cancer survivors		
Pediatric/adolescent	• ↑risk of future diabetes • Strongest diabetes risk with total body or abdominal irradiation • Insulinopenia more common	• Earlier, more frequent diabetes screening • Diabetes prevention programs
Adult	• ↑risk of future diabetes for most cancers • Certain cancer therapies may promote diabetes risk	• Earlier, more frequent diabetes screening • Diabetes prevention programs • Further research on cancer therapy effects needed
Cancer survivors with diabetes	• ↑ all-cause mortality • ↑risk of avoidable diabetic complications after cancer diagnosis	• Better diabetes management resources during cancer treatment • Optimize long-term diabetes care • Further research needed

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus

to hyperinsulinemia prior to diabetes development may also be a factor. A greater awareness of this risk by providers and patients newly with diabetes is important to ensure that patients are clinically screened for cancer at diabetes diagnosis. There is some evidence that individuals with diabetes are less adherent to recommended cancer screening programs than those without diabetes (208–211), possibly due to competing demands of diabetes care. While there are no additional cancer screening recommendations for patients with diabetes, clinicians should endeavor to optimize general cancer screening adherence for both patients with DM1 and DM2. Among patients with obesity and diabetes, weight loss should be encouraged and lifestyle modifications that optimize healthy behaviors should be reinforced regularly. With regards to choice of antihyperglycemic agents, further research is warranted to identify possible risks and benefits, especially among newer agents, on cancer risk (see table 2).

For persons with cancer

Though survivors of many childhood, adolescent, and even adult cancers are at increased risk of diabetes, there are currently no specific guidelines or recommendations for diabetes screening among cancer survivors with the exception of childhood cancer survivors. The Children's Oncology Group have an extensive set of treatment-based recommendations for follow-up of children treated for cancer (212). Regarding diabetes, they recommend screening individuals who received abdominal radiation, total body radiation, or alkylating chemotherapy with a fasting glucose and HbA1c every 2 years. This recommendation differs from the general screening recommendations in Canada and the United States, where screening is recommended either by glycated hemoglobin (HbA1c) assay, a fasting glucose test or a 75-g oral glucose tolerance test (OGTT) (213) yearly after age 50 years. In light of evidence that radiation directly damages pancreatic beta cells, leading to impaired insulin secretion in adult survivors of childhood and AYA cancer exposed to abdominal radiation, OGTT screening may be more sensitive for diagnosing diabetes in this population. This was recently highlighted in a small study of childhood cancer survivors treated with bone marrow transplantation where performing only a fasting glucose or HbA1c level missed one-third of patients who met criteria for diabetes based on results from OGTT (214). In addition, OGTT can diagnosis impaired glucose tolerance, therefore providing an opportunity for interventions for diabetes prevention. Future studies are needed to explore optimal diabetes screening strategies as well as the benefits of routine OGTT screening in this population. While no diabetes screening guidelines exist for survivors of AYA cancer, the International Guidelines Harmonization Group for Late Effects of Childhood Cancer is currently working on guidelines with regards to screening for diabetes and metabolic disease in this population of survivors (215) (Table 2).

There are no specific guidelines that recommend additional or a specialized diabetes screening approach for adult survivors of cancer. A greater awareness and modification of shared risk factors is warranted particularly for patients with obesity-related cancers. Furthermore, as cancer survivorship continues to improve, evidence indicates that comorbid conditions such as diabetes have a greater impact on life expectancy and quality of life than the initial cancer (216). For instance, patients with diabetes have an elevated risk of avoidable diabetic complications in the first year after a cancer diagnosis, suggesting a need for better diabetes care in cancer patients (217). Further studies regarding the reasons for this association and the most effective healthcare interventions are needed.

Conclusion

In summary, we have shown that the relationship between obesity, diabetes, and cancer is complex and multifactorial. The strongest and most robust associations are for postmenopausal breast, endometrial, and colorectal cancers, with diabetes and obesity primarily affecting the risk rather than survival of these cancers. Mounting evidence has indicated a primary role of hyperinsulinemia and associated changes in inflammatory markers and adipokines on tumorigenesis and tumor growth in the setting of obesity and diabetes. With increasing rates of obesity and diabetes worldwide, a greater emphasis on cancer prevention strategies is needed. Since cancer survivors also appear to be more susceptible to subsequent diabetes, diabetes screening and prevention need to be optimized for this growing population. Further research is needed to better elucidate the mechanisms underlying these relationships, including the impact of diabetes and cancer treatments, to inform potential targets for intervention.

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