DIABETES AND CANCER—AN AACE/ACE CONSENSUS STATEMENT

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EXECUTIVE SUMMARY

Epidemiologic data have demonstrated significant increases of various cancers in people with obesity and diabetes. Recently, concern has emerged that antihyperglycemic medications may also be associated with an increased prevalence of multiple cancers; however, available data are limited and conflicting. The American Association of Clinical Endocrinologists (AACE) convened a conference to review factors associated with cancer development in people with obesity and diabetes and to discuss the possible cancer risk of antihyperglycemic medications. Increased body mass index is associated with an increased risk of multiple cancers based on observational epidemiological data, and is closely associated with increased levels of endogenous insulin, insulin-like growth factors, inflammatory cytokines, and other factors that can have downstream pro-cancer growth effects.

The role of hyperglycemia in cancer development is less clear, but an association cannot be ruled out, as current observational data additionally suggest an increased cancer risk in people with diabetes. There is currently insufficient evidence that antihyperglycemic medications may be definitively associated with an increased cancer risk owing to a lack of data from large-scale randomized study designs. Similarly, there is also insufficient evidence showing a positive impact of these medications on cancer development. Clinicians can continue to confidently prescribe all FDA-approved antihyperglycemic medications for the management of hyperglycemia according to established practice guidelines. In patients who have an elevated cancer risk or positive family history of cancer, the cautious selection of antihyperglycemic medications is both prudent and warranted. The AACE additionally advocates for the improved treatment and management of obesity, early cancer screening in patients at increased risk, increased research collaboration, and improved study designs to address outstanding concerns surrounding the diabetes-cancer relationship.

Abbreviations:
AACE = American Association of Clinical Endocrinologists; **BMI** = body mass index; **CI** = confidence interval; **DPP-4** = dipeptidyl peptidase-4; **EMA** = European Medicines Agency; **FDA** = U.S. Food and Drug Administration; **GLP-1** = glucagon-like peptide-1; **HR** = hazard ratio; **IGF** = insulin-like growth factor; **IGFBP** = insulin-like growth factor binding protein; **IR** = insulin receptor; **RR** = relative risk; **T2D** = type 2 diabetes; **TZD** = thiazolidinedione

INTRODUCTION

A conference and writing task force was commissioned by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology to determine the possible roles of obesity, hyperinsulinism, glucose, and diabetes and its therapies in the pathogenesis of cancer. The purpose of this document is to review the available evidence, provide recommendations to practicing clinicians, and highlight research needs.

Contributions of Different Types of Evidence

Basic research provides mechanisms to explain why an agent may increase the risk of cancer. Epidemiological studies can be hypothesis formulating or testing. Observational analytic epidemiological studies are hypothesis testing for moderate to large effects, but hypothesis formulating for small effects which require large-scale randomized evidence. All types of research contribute to a totality of evidence upon which rational clinical decisions for individual patients and policy for the health of the general public can be safely based.

OBESITY AND CANCER

Basic Research

Many proposed biological mechanisms link obesity to cancer development (Fig. 1) through the direct or indirect effects of obesity on insulin and insulin-like growth factor-1 (IGF-1), sex hormones, adipokines, and inflammation (1,2). The collective activation of these individual mechanisms promotes an environment of increased proliferation, inhibited apoptosis, and increased genomic instability (1).

Recent tissue-based breast cancer studies have provided support for hypothetical obesity-related cancer mechanisms in humans (3,4). Breast tissue samples obtained from women undergoing surgery for breast cancer have shown a significant direct correlation between body mass index (BMI) and inflammation ($P<.001$), adipocyte size ($P<.001$), and aromatase expression and activity ($P = .02$) (3). Visceral fat and mammary tissues from obese ovariectomized mice were found to have significantly greater numbers of inflammatory foci ($P<.001$), pro-inflammatory mediators ($P\leq.003$), and aromatase activity ($P<.001$) than samples from other low-fat and high-fat comparator groups (4).

Epidemiologic Studies

Obesity is emerging as a leading avoidable cause of mortality, including cancer mortality. In an analysis of data from 57 prospective cohort studies with approximately 900,000 total participants, BMI was a strong predictor of death above and below the apparent optimum of 22.5 to 25 kg/m^2 (5). The progressive excess mortality for BMI above this range is mainly due to vascular diseases. Median survival (average age at death) is reduced by 2 to 4 years at ages 30 to 45 and 8 to 10 years at ages 40 to 45, which is comparable to the hazard of cigarettes.

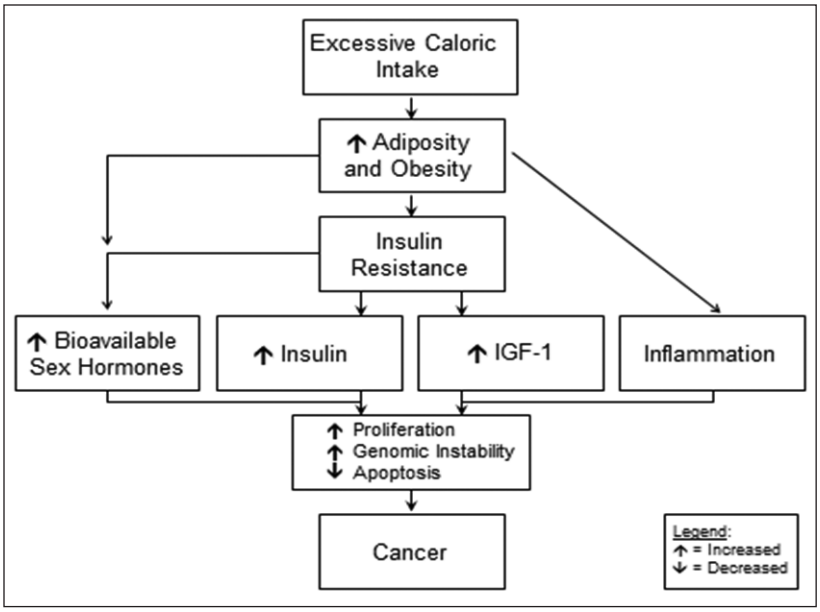

Fig. 1. Biological mechanisms that link obesity with cancer development. *IGF-1* = insulin-like growth factor-1. Adapted from (1).

When compared with overweight or nonobese people, obese individuals or those with a 5-point increase in BMI have a significantly increased risk of many different cancer types (Table 1) (6-10). The strongest associations appear to be for endometrial, gall bladder, esophageal (adenocarcinoma), renal, thyroid, ovarian, breast, and colorectal cancer. Weaker but still statistically significant associations were also observed for leukemia, malignant and multiple melanoma, pancreatic cancer, and non-Hodgkin lymphoma (7,9). Paradoxically, there is some evidence that increased BMI may be protective for lung, esophageal (squamous) (9), and prostate cancer (11) in men, though obesity seems to impart an increased incidence of more aggressive prostate cancers (12). In women, increased BMI may be protective for premenopausal breast and lung cancer (9). In the Swedish Obese Subjects (SOS) prospective controlled intervention trial, obese women undergoing bariatric surgery were observed to have a decreased incidence of cancer compared with controls (hazard ratio [HR], 0.58; 95% confidence interval [CI], 0.44-0.77; $P = .0001$) (13). The same effect was not observed in men (HR, 0.97; 95% CI, 0.62-1.52; $P = .90$).

The observed relationship of elevated cancer risk with increased BMI supports the need to advocate for improved diet, greater physical activity, and early cancer screening in obese patients. Opportunities for educating patients on the obesity–cancer relationship and appropriate lifestyle changes may be possible at the cancer screening visit or following the clinical identification of cancer, when patient health awareness and openness to change are likely to be at higher levels (14-16).

Evidence for the link between obesity and cancer outcomes after diagnosis is less clear. In one cohort of the prospective Cancer Prevention Study II, BMI in the obese range (≥30 kg/m^2) was associated with increased overall cancer mortality compared to normal weight (18.5 to 24.9 kg/m^2) in both men (relative risk [RR], 1.09; 95% CI, 1.05-1.14) and women (RR, 1.23; 95% CI, 1.18-1.29) (17). Increased BMI is associated with worsened outcomes for breast (18-20), colon (21), and aggressive prostate cancer (12), but improved outcomes for renal cell carcinoma (22) and endometrial cancer (23). Furthermore, Adams et al observed decreased mortality (HR, 0.54; 95% CI, 0.37-0.78; $P = .001$) for obesity-related cancers with bariatric surgery in women with a BMI ≥35 kg/m^2 (24).

ROLE OF ENDOGENOUS INSULIN IN CANCER

Insulin, IGF-1 and Cancer Development

Obesity-related hyperinsulinemia may affect cancer development through ligand binding with the insulin receptor and/or by increasing circulating IGF-1 levels (Fig. 2) (2). Circulating IGFs are normally bound by insulin-like growth factor binding proteins (IGFBPs). IGFBP-3 binds almost 90% of circulating IGF-1 and -2. In conditions of prolonged hyperinsulinemia, the activities of IGFBP-1 and -2 are diminished, potentially resulting in increased "free" IGF-1 and -2. Direct relationships among increased obesity (or percentage body fat), increased insulin, and "free" IGF-1 levels have been demonstrated (2,25).

Table 1
Meta-analyses Linking Increased BMI (≥25 kg/m^2) With Cancer Risk

Study group	Cancer evaluated	Risk	95% CI
Druesne-Pecollo et al 2012 (7)	Endometrial (second primary)	RR 1.46[a]	1.17-1.83
	Breast (second primary)	RR 1.14[a]	1.07-1.21
	Breast (contralateral)	RR 1.12[a]	1.06-1.20
Crosbie et al 2010 (6)	Endometrial	RR 1.60[a]	1.52-1.68
Renehan et al 2008 (men) (9)	Esophageal (adenocarcinoma)	RR 1.52[a]	1.33-1.74
	Thyroid	RR 1.33[a]	1.04-1.70
	Colon	RR 1.24[a]	1.20-1.28
	Renal	RR 1.24[a]	1.15-1.34
	Malignant melanoma	RR 1.17 [a]	1.05-1.30
	Multiple myeloma	RR 1.11[a]	1.05-1.18
	Rectal	RR 1.09[a]	1.06-1.12
	Leukemia	RR 1.08[a]	1.02-1.14
	Non-Hodgkin lymphoma	RR 1.06[a]	1.03-1.09
	Lung	RR 0.76[a]	0.70-0.83
	Esophageal (squamous)	RR 0.71[a]	0.60-0.85
Renehan et al 2008 (women) (9)	Endometrial	RR 1.59[a]	1.50-1.68
	Gallbladder	RR 1.59[a]	1.02-2.47
	Esophageal (adenocarcinoma)	RR 1.51[a]	1.31-1.74
	Renal	RR 1.34[a]	1.25-1.43
	Leukemia	RR 1.17[a]	1.04-1.32
	Thyroid	RR 1.14[a]	1.06-1.23
	Breast (postmenopausal)	RR 1.12[a]	1.08-1.16
	Pancreatic	RR 1.12[a]	1.02-1.22
	Multiple myeloma	RR 1.11[a]	1.07-1.15
	Colon	RR 1.09[a]	1.05-1.13
	Breast (premenopausal)	RR 0.92[a]	0.88-0.97
	Lung	RR 0.80[a]	0.66-0.97
Schouten et al 2008 (10)	Ovarian (premenopausal)	RR 1.72[b]	1.02-2.89
	Ovarian (Postmenopausal)	RR 1.07[b]	0.87-1.33
Olsen et al 2007 (8)	Ovarian	RR 1.30[c]	1.12-1.50

Abbreviations: BMI = body mass index; CI = confidence interval; RR = relative risk.
[a] Risk values per 5-kg/m^2 increase in BMI.
[b] Multivariate risk, obese (BMI≥30 kg/m^2) versus nonobese (BMI 18.5-23 kg/m^2) patients.
[c] Pooled risk, obese (BMI≥30 kg/m^2) versus nonobese (BMI 18.5-24.9 kg/m^2) patients.

Insulin has multiple effects, depending on its interaction with insulin receptors (IRs), which exist in two major isoforms (IR-A and -B) (26,27). Pro-growth mitogenic effects are elicited through the actions of insulin and IGF-1 binding with the IR-A and IGF-1 receptors, respectively (28,29). The independent role of the IR was confirmed by Zhang et al (30), when downregulation of IRs in LCC6 cells reduced xenograft tumor growth in athymic mice and inhibited lung metastasis. Blockade of the IGF-1 receptor has been associated with decreased growth of breast cancer cells (31,32), while enhanced IGF-1 activity has been associated with decreased susceptibility to chemotherapy (33). Both IR-A and IGF-1 receptors are predominantly located in fetal tissue and in adult cancer cells (34). IRs and IGF-1 receptors are overexpressed in human breast cancers (35-38).

Insulin, Insulin-related Markers, and Cancer Risk

Several study groups have investigated the predictive value of plasma insulin levels for pre- and postmenopausal breast cancer (Table 2), with some conflicting observations (39-42). In a case-control study of 99 premenopausal women with recently diagnosed breast cancer, those in the highest quintile of fasting insulin concentration had a nearly 3-fold increased risk of breast cancer

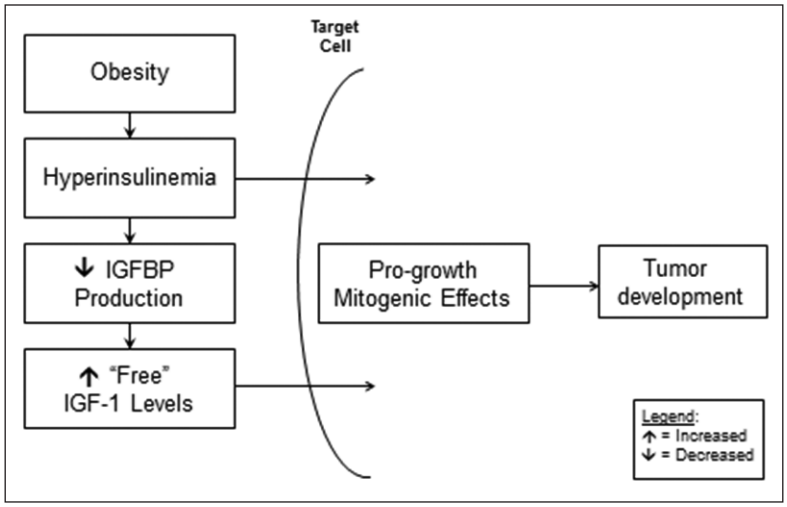

Fig. 2. Obesity and the insulin-IGF-1 hypothesis of cancer development. *IGFBP* = insulin-like growth factor binding protein; *IGF-1* = insulin-like growth factor-1. Adapted from (2).

Table 2
Summary of the Association of Elevated[a] Plasma Insulin, C-Peptide, and IGF-1 Levels With Cancer Risk

Study group	Cancer evaluated	Risk	95% CI
Insulin			
Hirose et al 2003 (41)	Postmenopausal breast cancer	OR 4.48[b]	1.07-18.7
Goodwin et al 2002 (40)	Breast cancer (distant recurrence)	HR 2.0	1.20-3.30
	Breast cancer death	HR 3.1	1.70-5.70
Mink et al 2002 (42)	Breast cancer	RR 1.01[c]	0.55-1.86
Del Giudice et al 1998 (39)	Premenopausal breast cancer	OR 2.83[d]	1.22-6.58
C-Peptide			
Wolpin et al 2009 (47)	Nonmetastatic colorectal death	HR 1.87[e]	1.04-3.36
Pisani et al 2008 (46)	Colorectal	RR 1.35	1.13-1.61
	Breast	RR 1.26	1.06-1.48
	Pancreatic	RR 1.70	1.10-2.63
	Bladder	RR 1.22	1.01-1.47
Ma et al 2004 (44)	Colorectal	RR 2.7[f]	1.20-6.20
IGF-1			
Duggan et al 2013 (43)	Breast cancer (all-cause mortality)	HR 3.10[g]	1.21-7.93
Ma et al 1999 (45)	Colorectal	RR 2.51	1.15-5.46

Abbreviations: CI = confidence interval; HR = hazard ratio; IGF-1 = insulin-like growth factor 1; OR = odds ratio; RR = relative risk.
[a] Defined as values at the highest tertile, quartile, etc.
[b] BMI >23.07, multivariable-adjusted for age, family history, and age at menarche, parity, and at first delivery.
[c] Multivariable-adjusted for age, race, study center, BMI, age at menarche, menopause, and at parity, family history, number of sisters, alcohol intake, and pack-years of smoking.
[d] Multivariable-adjusted for age and weight.
[e] Age-adjusted.
[f] Multivariable-adjusted for BMI, alcohol consumption, vigorous exercise, and aspirin treatment.
[g] Adjusted for BMI, ethnicity, tamoxifen use at time of blood draw, treatment received at diagnosis, and IGFBP-3 levels.

after adjustment compared with those in the lowest quintile (39). Likewise, Hirose et al showed a >4-fold adjusted increased risk of breast cancer in postmenopausal Japanese women with BMI >23.1 kg/m^2 and in the highest tertile of insulin levels compared with the lowest tertile, though not all blood samples were fasting profiles (41). At least one study showed no association of insulin levels with breast cancer risk (42), albeit in a smaller cohort. With respect to distant recurrence and death, Goodwin et al observed that fasting insulin levels in the highest quartile were found to be significantly positively associated in patients with early breast cancer (40).

C-peptide levels and IGF-1 levels have also been linked to cancer risk (43-47). A meta-analysis of 12 epidemiological studies observed that prior to diagnosis, C-peptide or insulin levels at the highest subgrouping were significantly predictive of pancreatic, colorectal, breast, and bladder cancer when compared with lower levels prior to diagnosis (46). Wolpin et al, in a prospective observational study of 373 patients with diagnosed nonmetastatic colorectal cancer, observed a nearly 2-fold higher age-adjusted mortality risk in patients in the top quartile of plasma C-peptide levels compared with those in the lowest quartile (47). Men from the Physician's Health Study in the highest quintile for IGF-1 concentration prior to cancer diagnosis had an increased risk of colorectal cancer compared with those in the lowest quintile (RR, 2.51; 95% CI, 1.15-5.46) (45). Finally, IGF-1 levels and an IGF-1/IGFBP-3 ratio at the highest quintile in women with breast cancer has been observed to confer an approximate 3-fold increased risk of adjusted all-cause mortality compared with patients in the lowest quintiles of these measures (43). Interestingly, clinical trials using humanized monoclonal IGF-1 receptor antagonists to affect cancer outcomes have generally been very disappointing. Besides the suggestive evidence that hyperinsulinemia and obesity are involved in the increased incidence of cancer, other factors, such as leptin, inflammatory cytokines, and reduced sex hormone-binding globulin resulting in more free sex hormones have also been invoked (48).

DIABETES AND CANCER

Animal Models of Diabetes

The independent role of diabetes on cancer development has been difficult to discern, given the fact that obesity is closely associated with inflammation and hyperinsulinemia. Animal studies in transgenic diabetic mice may shed some light on the relative contributions of each of these factors. Models of both skin and mammary carcinogenesis in fatless diabetic (A-ZIP/F-1) mice were found to demonstrate a higher tumor incidence and greater tumor volume than controls in the presence of significantly elevated levels of insulin, IGF-1, growth hormone, and inflammatory cytokines ($P \leq .05$) (49). In a model of murine breast cancer, lean female MKR mice with pronounced diabetes and inactivated IRs and IGF-1 receptors in skeletal muscle were found to have significantly increased insulin/IGF-1 receptor activation in prepubertal mammary gland tissue and increased mammary tumor volume and weight compared with wild-type controls ($P < .05$) (50). Reduced insulin/IGF-1 receptor activation in MKR mice with mammary tumors blocked tumor progression (51). Taken collectively, there appears to be strong support for the interconnected roles of hyperinsulinemia and diabetes in cancer development.

Glucose and Tumor Metabolism

The independent role of hyperglycemia in cancer development is less clear. To achieve growth and proliferation, tumor cells must replicate at higher rates than normal cells, necessitating the need for increased intake of nutrients from the surrounding microenvironment. Glucose is one source of energy for tumor cells to support growth and proliferation. Tumor cells may also rely on the intake of amino acids such as glutamine (52). Glucose uptake is closely regulated by growth factor signaling in normal nonproliferating cells (53); but through genetic mutations, tumor cells can bypass these limitations (52). Activation of growth factor receptors stimulates changes in intracellular signaling, which in turn modify metabolic pathways in support of proliferative growth. Pyruvate kinase isoform M2 (PK-M2) is an example of an enzyme whose activity state is modified to support proliferation in response to changes in intracellular signaling (54). Thus, hyperglycemia is often wrongly implicated as the sole source of cancer nutrition in patients with diabetes, when cancer cells can thrive using other energy sources promoted by genetic mutations and aberrant intracellular signaling.

Diabetes and Cancer Risk

Multiple meta-analyses of case-control and cohort studies have shown that diabetes is associated with a significantly increased risk of breast (55), colorectal (56), endometrial (57), pancreatic (58), and hepatic cancer (59), and non-Hodgkin lymphoma (Table 3) (60). Bladder cancer has also been shown to be positively correlated with diabetes (61), although a recent prospective cohort study of over 170,000 patients indicates that this positive association may be limited to patients with long-standing diabetes (>15 years) or insulin users (62). Prostate cancer risk appears to be decreased in patients with diabetes (63); one possible explanation is that testosterone levels have been shown to be reduced in men with diabetes (64). The conversion of testosterone to dihydrotestosterone promotes prostate cell growth.

Diabetes is also associated with an increase in cancer mortality (Table 4) (65). In the Cancer Prevention II Study, men with diabetes were found to have an increased risk of mortality from hepatic, oropharyngeal, pancreatic,

bladder, colon, and breast cancer and a decreased risk of mortality from prostate cancer (65). In women, diabetes was associated with an increased risk of mortality from breast, hepatic, pancreatic, endometrial, and colon cancer. The findings of the Cancer Prevention II Study are supported by a smaller retrospective cohort study in the United Kingdom of over 8,000 patients with type 2 diabetes (T2D) (66). Two notable discrepant results in the Currie study were the findings of increased prostate cancer mortality and decreased mortality for lung cancer in patients with T2D.

WHAT IS NEEDED FOR CANCER DEVELOPMENT?

After examining the relative contributions of obesity, insulin, IGFs, and diabetes to cancer development, it would appear that the most compelling scenario for cancer development may include a combination of prolonged obesity due to excess caloric intake plus the resulting increase of circulating insulin, IGFs, cytokines, and inflammatory molecules (67). Compelling research in animals has shown that caloric restriction (>10 to 40% of daily intake) can

Table 3
Summary of the Association of Diabetes and Cancer Risk

Study group	Cancer evaluated	Risk	95% CI
Mitri et al 2008 (60)	Non-Hodgkin lymphoma	RR 1.19	1.04-1.35
Friberg et al 2007 (57)	Endometrial	RR 2.10	1.75-2.53
Larsson et al 2007 (55)	Breast	RR 1.20	1.12-1.28
El-Seraq et al 2006 (59)	Hepatic (case-control studies)	OR 2.54	1.82-3.54
	Hepatic (cohort studies)	Risk ratio 2.50	1.93-3.24
Kasper et al 2006 (63)	Prostate	RR 0.84	0.76-0.93
Larsson et al 2006 (61)	Bladder	RR 1.24	1.08-1.42
Huxley et al 2005 (58)	Pancreatic	OR 1.82	1.66-1.89
Larsson et al 2005 (56)	Colorectal	RR 1.30	1.20-1.40

Abbreviations: CI = confidence interval; OR = odds ratio; RR = relative risk.

Table 4
Summary of the Association of Diabetes and Cancer Mortality

Study group	Cancer evaluated	Risk	95% CI
Campbell et al 2012 (men) (65)	Breast	RR 4.20[a]	2.20-8.04
	Hepatic	RR 2.26[a]	1.89-2.70
	Oropharyngeal	RR 1.44[a]	1.07-1.94
	Pancreatic	RR 1.40[a]	1.23-1.59
	Bladder	RR 1.22[a]	1.01-1.47
	Colon	RR 1.15[a]	1.03-1.29
	Prostate	RR 0.88[a]	0.79-0.97
Campbell et al 2012 (women) (65)	Hepatic	RR 1.40[a]	1.05-1.86
	Endometrial	RR 1.33[a]	1.08-1.65
	Pancreatic	RR 1.31[a]	1.14-1.51
	Colon	RR 1.18[a]	1.04-1.33
	Breast	RR 1.16[a]	1.03-1.29
Currie et al 2012 (66)	All cancers	HR 1.09[b]	1.06-1.13
	Breast	HR 1.32[b]	1.17-1.49
	Prostate	HR 1.19[b]	1.08-1.31
	Bladder	HR 1.16[b]	1.02-1.32
	Lung	HR 0.84[b]	0.77-0.92

Abbreviations: CI = confidence interval; HR = hazard ratio; RR = relative risk.
[a] Adjusted for age, education, BMI, smoking, alcohol, vegetable, and red meat intake, physical activity, and aspirin use.
[b] Adjusted for age, sex, smoking status, year of cancer diagnosis, Charlson comorbidity index, Townsend index of deprivation, hemoglobin A_{1C}, and number of general practice contacts.

prevent cancer development (68), with diminished levels of IGF-1 believed to play a central role in mediating this effect (69-71). With tumor cells deriving energy from a variety of sources (glucose and amino acids such as glutamine) and adjusting metabolic pathways to meet homeostatic needs, hyperglycemia may not be an essential component for cancer development in patients with diabetes.

Time from Exposure to Cancer Development

In animal models, the first exposure to a carcinogen causes an "initiating event," whereas genetic damage and consequent DNA repair mechanisms result in fixed genetic mutations (72). Continued exposure to the carcinogen promotes growth of the damaged cell line, resulting in eventual progression to clinical cancer and malignancy. In mice, the time from carcinogen exposure to cancer development is approximately 20 to 50 weeks (73). In humans, this lag time can be as long as 20 to 50 years (74). This is an essential point to consider when weighing the totality of evidence linking disease-state relationships with cancer or the role that pharmacotherapy may play in cancer development.

ANTIHYPERGLYCEMIC DRUGS AND CANCER

Metformin

Metformin use appears to be associated with a neutral-to-decreased effect on cancer incidence and mortality, based on available epidemiological data (Table 5) (66,75-78). A meta-analysis of 13 randomized controlled trials (RCTs) by Stevens et al (78) showed a clinically insignificant 2% increase in the RR of cancer mortality with metformin use in patients with or at risk for diabetes, relative to comparator therapy. The RCTs included in the analysis were not designed a priori to look at cancer incidence but merely reported cancer incidence. Only 9 RCTs looked at metformin monotherapy against a comparator. Other retrospective data point to decreased cancer incidence and mortality in metformin-treated patients (66,75-77). When looking at individual cancer types, metformin use is associated with a significantly lower risk of colorectal, hepatocellular, and lung cancer (77). Nonsignificant lower risks have also been observed for prostate, breast, pancreatic, gastric, and bladder cancer. Overall, metformin has been safely used for the treatment of hyperglycemia for decades. In light of encouraging in vivo and in vitro studies indicating anticancer properties, the use of metformin to improve cancer-related outcomes is actively being investigated in prospective clinical trials (79).

Thiazolidinediones (TZDs)

Evidence from a recent meta-analysis and several observational analytic studies point to a potential concern for increased bladder cancer risk with the use of pioglitazone, particularly with long-term use and large cumulative doses. In a meta-analysis by Colmers et al (80), overall bladder cancer incidence with TZD treatment was 53.1 cases per 100,000 patient-years of treatment. A statistically significant increase in bladder cancer risk was observed when looking at only cohort studies, while a numerically greater but statistically non-significant increase in risk was observed with TZD treatment in RCTs (Table 6). In a similar study, also by Colmers et al (81), TZD use was associated with a decreased risk of colorectal, lung, and

Table 5
Summary of the Association Between Metformin and Cancer Incidence and Mortality

Study group	Outcome	Risk	95% CI
Currie et al 2012 (66)	Cancer mortality	HR 0.85[a]	0.78-0.93
Noto et al 2012 (77)	Cancer incidence	Risk ratio 0.67	0.53-0.85
	Colorectal	Risk ratio 0.68	0.53-0.88
	Hepatocellular	Risk ratio 0.20	0.07-0.59
	Lung	Risk ratio 0.67	0.45-0.99
	Cancer mortality	Risk ratio 0.66	0.49-0.88
Stevens et al 2012 (78)	Cancer mortality	RR 1.02	0.82-1.26
DeCensi et al 2010 (75)	Cancer incidence	RR 0.68	0.52-0.88
	Cancer mortality	RR 0.70	0.51-0.96
Landman et al 2010 (76)	Cancer mortality	HR 0.43[b]	0.23-0.80

Abbreviations: CI, confidence interval; HR, hazard ratio; RR, relative risk.
[a] Adjusted for age, sex, smoking status, cancer diagnosis year, and Charlson comorbidity index.
[b] Adjusted for smoking status, age, sex, diabetes duration, hemoglobin A_{1C}, serum creatinine, BMI, blood pressure, total cholesterol-to-high-density lipoprotein (HDL) ratio, albuminuria, insulin use, sulfonylurea use, and presence of macrovascular complications.

breast cancer. Pioglitazone, but not rosiglitazone, was significantly associated with increased bladder cancer risk (80). These findings are supported by retrospective data indicating that pioglitazone exposure for >24 months or at cumulative doses >28,000 mg is also associated with significantly increased bladder cancer risk (82,83).

When looking at overall cancer incidence in RCTs, there is less concern with TZD use. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study, there were a total of 97 cases (3.7%) of malignancy reported in the pioglitazone treatment group and 99 cases (3.8%) in the placebo group (84). Of these, 14 cases (0.5%) of bladder cancer were reported with pioglitazone versus 6 cases with placebo (0.2%). After 6 years of observational follow-up of participants in the PROactive study, rates of bladder cancer evened out between the treatment groups (23 cases [0.9%] for pioglitazone versus 22 cases [0.8%] for placebo) (85).

In the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) trial, rosiglitazone treatment was associated with lower rates of malignancy compared with metformin (0.94 cases per 100 patient-years versus 1.15 cases per 100 patient-years; HR, 1.22; 95% CI, 0.86-1.74) in patients on background sulfonylurea treatment and lower rates of malignancy compared with sulfonylurea (0.93 cases per 100 patient-years versus 1.23 cases per 100 patient-years; HR, 1.33; 95% CI, 0.94-1.88) in patients on background metformin (86). The occurrence of overall malignancy for rosiglitazone, metformin, and glibenclamide in the A Diabetes Outcome Progression Trial (ADOPT) was 1.12, 1.03, and 1.31 cases per 100 patient-years, respectively (86). A meta-analysis of 80 RCTs found no increase in cancer risk with rosiglitazone use relative to comparator groups (odds ratio, 0.91; 95% CI, 0.71-1.16) (87). There is some evidence that TZD use may improve survival in patients with T2D and breast or prostate cancer (88,89).

In summary, TZD-based therapy has been associated with potential cancer risk, primarily pioglitazone with bladder cancer, as well as a protective role (e.g., in colorectal, lung, and breast cancer). Recent data on pioglitazone and bladder cancer essentially removes statistical significance or points to a very small risk leading to bladder cancer. Therefore, clinicians should be confident and continue to use TZDs. However, until more definitive data are available, clinicians should observe and monitor their patients on pioglitazone and follow the U.S. Food and Drug Administration's (FDA) recommendation to not prescribe the drug to people with a history or high risk of bladder cancer.

Incretins

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists and Thyroid Carcinoma

Prescribing information for GLP-1 agonists includes a cautionary message about preclinical carcinogenicity studies which have shown an increase in thyroid C-cell

Table 6
Summary of TZDs and Cancer Risk

Study group	Analysis groups	Risk	95% CI
Azoulay et al 2012 (82)	Pioglitazone	Rate ratio 1.83[a]	1.10-3.05
	Rosiglitazone	Rate ratio 1.14[a]	0.78-1.68
	Pioglitazone >24 months exposure	Rate ratio 1.99[a]	1.14-3.45
	Pioglitazone >28,000 mg cumulative dosage	Rate ratio 2.54[a]	1.05-6.14
Colmers et al 2012 (80)	TZDs (RCTs)	Risk ratio 1.45	0.75-2.83
	TZDs (cohort studies)	Risk ratio 1.15	1.04-1.26
	Pioglitazone	Risk ratio 1.22	1.07-1.39
	Rosiglitazone	Risk ratio 0.87	0.34-2.23
Colmers et al 2012 (81)	TZDs (colorectal)	Risk ratio 0.93	0.87-1.00
	TZDs (lung)	Risk ratio 0.91	0.84-0.98
	TZDs (breast)	Risk ratio 0.89	0.81-0.98
Lewis et al 2011 (83)	Pioglitazone	HR 1.20[b]	0.90-1.50
	Pioglitazone >24 months exposure	HR 1.40[b]	1.03-2.00

Abbreviations: CI = confidence interval; HR = hazard ratio; RCTs = randomized controlled trials; TZDs = thiazolidinediones.

[a] Adjusted for excess alcohol use, obesity, smoking status, hemoglobin A_{1C}, previous bladder conditions, previous cancer (other than nonmelanoma skin cancer), Charlson comorbidity score, and use of antidiabetic agents at any time.

[b] Adjusted for age, sex, race/ethnicity, smoking status, renal function, bladder conditions, congestive heart failure, income, baseline hemoglobin A_{1C}, diabetes diagnosis at follow-up, duration of diabetes, other cancer prior to baseline, use of antidiabetic medications, and pioglitazone use.

carcinomas in rats (90,91). There are approximately 22- to 45-fold more total C-cells in rodents than in humans, and only rat C-cell lines have been shown to express functional GLP-1 receptors (92). In phase 3 clinical trials, plasma calcitonin, a measure of C-cell hyperplasia and medullary thyroid carcinoma (MTC), did not increase in liraglutide-treated patients and remained below the upper normal ranges for men and women for the duration of the study (92-94). This is in contrast to dose-dependent increases in calcitonin that have been observed in rodents given liraglutide (92). A total of 6 cases of thyroid C-cell hyperplasia have been reported in clinical trials with liraglutide treatment, compared with 2 cases for controls (1.3 cases per 1,000 patient-years versus 1.0 cases per 1,000 patient-years) (90).

A pooled analysis of 19 RCTs by MacConell et al (95) which investigated exenatide BID showed an exposure-adjusted incidence rate of thyroid neoplasms of 0.3 per 100 patient-years compared with zero cases per 100 patient-years for comparators. In an integrated analysis of 10 studies evaluating once-weekly exenatide conducted by the European Medicines Agency (EMA), no cases of MTC were reported (96). While the EMA has currently identified no association between once-weekly exenatide and any malignant neoplasms, future data from ongoing trials and analyses of databases will be monitored.

GLP-1 Receptor Agonists, Dipeptidyl Peptidase-4 (DPP-4) Inhibitors, and Pancreatic Cancer

Based on data gathered from the FDA adverse event databases, GLP-1 receptor agonists and DPP-4 inhibitors may be associated with significantly elevated risks of acute pancreatitis. This has led to speculations about the theoretical possibility of increased incidence of pancreatic cancer (97). However, it is believed that pancreatic tissue requires long-term chronic inflammation to invoke cancer development rather than episodic inflammation due to acute episodes (98,99). In fact, Yachida (100) states that the average time for the development of a pancreatic intraepithelial neoplasia from initiation to the first tumor cell is approximately 12 years, with another 10 years until metastatic pancreatic cancer occurs. Because it has been less than 8 years since the introduction of the first drug in the incretin class (exenatide in 2005), there would not have been enough time for a definitive exposure–cancer development relationship to be established. On the other hand, one cannot exclude the possibility that exposure to these pharmacological classes could theoretically serve as an initiating event or even act to promote an established mutated cell line. From epidemiological data, it is known that the median age of diagnosis of pancreatic cancer is 59 to 64 years, depending on BMI (101). It is possible that patients may have pancreatic cancer without symptoms prior to drug exposure. At this time, no randomized controlled prospective human study of GLP-1 receptor agonists or DPP-4 inhibitors has conclusively shown that these drug classes play a role in the genesis of pancreatic cancer.

Regarding the pancreatitis risk for exenatide, results from two retrospective cohort studies indicate no risk of pancreatitis (102,103), while one study indicates an increased risk for past users but not for recent or current users (Table 7) (104). For sitagliptin, a pooled analysis by

Table 7
GLP-1 Agonists, DPP-4 Inhibitors, and the Risks of Pancreatitis and Pancreatic Cancer

Study group	Risk	95% CI
Acute Pancreatitis: Exenatide		
Dore et al 2011 (104)	Rate ratio (current use) 0.5[a]	0.2-0.9
	Rate ratio (recent use) 1.1[a]	0.4-3.2
	Rate ratio (past use) 2.8[a]	1.6-4.7
Elashoff et al 2011 (97)	OR 10.68	Not given, $P = 2 \times 10^{-16}$
Garg et al 2010 (103)	HR 0.9[b]	0.6-1.5
Dore et al 2009 (102)	RR 1.0	0.6-1.7
Acute Pancreatitis: Sitagliptin		
Garg et al 2010 (103)	HR 0.9[b]	0.7-1.3
Dore et al 2009 (102)	RR 1.0	0.5-2.0
Pancreatic Cancer: Exenatide		
Elashoff et al 2011 (97)	OR 2.95	Not given; $P = 9 \times 10^{-5}$

Abbreviations: CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HR = hazard ratio; OR = odds ratio; RR = relative risk.
[a] Propensity score-adjusted.
[b] Adjusted for age, sex, hypertriglyceridemia, alcohol abuse, biliary stone disease, cholestatic liver disease, and drug therapy.

Engel et al (105) of 19 RCTs reported the rate of pancreatitis to be 0.08 events per 100 patient-years versus 0.10 events per 100 patient-years for patients not treated with sitagliptin (difference versus nonexposed, –0.02; 95% CI, –0.20-0.14). Two retrospective cohort studies indicate that sitagliptin has a risk of pancreatitis similar to that of sulfonylureas and metformin (102). Patients taking sitagliptin have the same pancreatitis incidence as control patients with diabetes, at 5.6 cases per 1,000 patient-years (103). There have been postmarketing reports of acute pancreatitis and necrotizing pancreatitis associated with both exenatide and sitagliptin (106,107); however, these events appear to be rare. The use of both DPP-4 inhibitors and GLP-1 receptor agonists is currently discouraged in patients with a history of acute pancreatitis (90,91,108-112).

In March 2013, the FDA released a safety communication stating that the agency was evaluating a new study (113) that suggested an increased risk for precancerous cellular changes in patients with T2D treated with incretin mimetics (114). We added this information for the sake of completeness, although the quality, relevance, and importance of the study are not clear.

In summary, although incretin-based therapies have been associated with a few reports of acute pancreatitis, causal mechanisms have not been established. Moreover, the link to pancreatic cancer is unclear; pathophysiology suggests that a long history of chronic pancreatitis is most likely to be associated with the development of pancreatic neoplasia rather than acute pancreatitis.

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

Within the SGLT2 inhibitor drug class, dapagliflozin, which is not approved in the United States but is approved in Europe, was implicated with an increased incidence of breast and bladder cancer (115). The increased incidence was not statistically significant (116), nor has it been further substantiated. The other members of the class, in particular the now approved canagliflozin, have not shown any cancer signal and are not presently implicated in cancer development (115).

Insulin

Due to the proposed mechanistic association of endogenous hyperinsulinemia with cancer growth and promotion, there is a concern that exogenously administered insulin may amplify the cancer development process. There is evidence from RCTs demonstrating the relative safety of insulin in patients with diabetes with respect to malignancies. The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) study was a RCT that investigated the impact of insulin glargine compared with standard of care for the reduction of cardiovascular outcomes over approximately 6 years of treatment. The rate of cancer incidence was comparable at about 7.6% in both the insulin glargine and standard-care treatment groups (117). Long-term insulin glargine use was not associated with an increased risk of any cancer (HR, 1.0; 95% CI, 0.88-1.13) or cancer death (HR, 0.94; 95% CI, 0.77-1.15) (117), confirming earlier findings by Home et al (118).

Retrospective database analyses provide additional, albeit conflicting, information about the insulin–cancer risk. Insulin treatment alone has been associated with a slightly increased risk of cancer incidence (adjusted HR, 1.44; 95% CI, 1.23-1.67) (119) and cancer mortality (HR, 1.13; 95% CI, 1.01-1.27) (66). However, when looking at patients taking insulin and metformin together, the increased cancer incidence and mortality risks are reduced and are no longer statistically significant (66,120). Cancer risk with insulin therapy has also been observed to rise with an increasing number of yearly prescriptions compared to metformin (120). For insulin glargine, daily doses of 10, 30, and 50 units have been associated with cancer HRs of 1.09 (95% CI, 1.00-1.19), 1.19 (95% CI, 1.10-1.30), and 1.31 (95% CI, 1.20-1.42), respectively, compared with other insulins (121).

There has been recent concern that insulin glargine use may be associated specifically with increased breast cancer risk (122), particularly for patients with T2D and more than 5 years of insulin use (123). More recent studies of large-scale patient databases by the University of North Carolina, Kaiser Permanente of Northern California, and an EMA-commissioned study of Northern European data (124-127), and especially the prospective ORIGIN trial (117), ultimately showed no increased risk of cancer with insulin glargine use, despite previous observational reports of potential increased breast cancer risk. An updated meta-analysis conducted from data in the EMA-commissioned study indicated a summary RR of 0.9 (95% CI, 0.82-0.99) for all cancer and 1.11 (95% CI, 1.0-1.22) for breast cancer (128).

Medications Summary

The contribution of diabetes therapy to cancer development, if at all, appears to be relatively small or nonexistent (Table 8). Prospective clinical studies are not long enough to adequately capture the timeframe of cancer development; thus, it is appropriate for clinicians to remain vigilant based on available evidence. For medications found to be significantly associated with cancer risk, the observed risks or hazards were generally 2-fold or less. Various confounders or poor methodology and study designs may have impacted the observed results. For context, observed risks of 5-fold or higher would represent a signal for safety concerns. For most people with diabetes, the benefits of treatment should take precedence over concerns for potential low-grade cancer risk until more definitive evidence becomes available. The recommendation to consider cancer risk in making medication choices for patients at very high risk of first cancer occurrence or cancer recurrence

Table 8
Summary of Diabetes Medications and Cancer Risk

Medication class	Summary of cancer risk
Metformin	No discernible cancer risk Possible protective benefits on cancer outcomes
TZDs	
Rosiglitazone	No evidence of cancer risk
Pioglitazone	Possible risk of bladder cancer at chronic high doses (>24 months and >28,000-mg cumulative dose)
SGLT2 Inhibitors	No evidence of cancer risk
Incretins	
GLP-1 agonists	No evidence of MTC or pancreatic cancer in humans
DPP-4 Inhibitors	No evidence of MTC or pancreatic cancer in humans
Insulins	Concern of cancer risk at very high doses

Abbreviations: DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MTC = medullary thyroid carcinoma; SGLT2 = sodium-glucose cotransporter 2; TZDs = thiazolidinediones.

(129) is prudent. The evidence suggesting a protective effect of metformin and other antihyperglycemic medications against cancer is interesting, but data are limited at this time. Multiple planned and currently ongoing clinical trials may help to shed some light on the protective effects of metformin (79).

IMPLICATIONS FOR PRACTICE

Based on the evidence reviewed, we recommend that healthcare professionals consider the following points for clinical practice:

- Obesity and diabetes are associated with statistically significant and clinically important increased risks of multiple malignancies. This suggests that cancer screening and counseling on lifestyle changes should be a part of regular preventive care in people with obesity and/or diabetes.
- Conversely, individuals who develop "typical" obesity-related cancers, especially at a younger age, should be screened for metabolic abnormalities like insulin resistance, metabolic syndrome, diabetes, and cardiovascular disease.
- Cancer screening tests of proven benefit for malignancies (breast cancer, colon cancer, skin cancer, etc.) in at-risk individuals should begin relatively early. For example, if regular screening for colon cancer starts at age 50, the clinician may consider starting to screen at age 40, as is customary for people with a high risk or family history of colon cancer. Future screenings should be based on current existing recommendations.
- Based on currently understood mechanisms for the development of cancer in obesity and diabetes, proper nutrition management, weight loss, and exercise are equally important to the management of people with cancer as it is to people with obesity and diabetes.
- Several antihyperglycemic medications have been suggested to play a role in the development of certain cancers. The evidence implicating these medications is primarily based on basic research and descriptive epidemiologic studies useful to formulate, not test, hypotheses. To detect reliably the most plausible small to moderate effects requires large-scale randomized evidence. The current totality of evidence should not change clinical practice, though clinicians should be alert to the potential risk and should monitor patients more closely.
- It generally takes many years for cancer to occur clinically, following a complex process of initiation and promotion. Short exposure to any new medication may—but is less likely to—result in clinical cancer development. It is also plausible that the growth of a previously initiated cancer could be promoted by medications.
- At present, the totality of available evidence supports the need for astute clinical judgment in which remote yet plausible cancer risks are weighed against suboptimal glycemic control and higher likelihoods of diabetes complications, especially microvascular, but also macrovascular complications. When prescribing antihyperglycemic medications, a comprehensive risk-benefit analysis must be performed to include an assessment of the baseline personal and familial risk of malignancies in specific organ systems.
- Patients with diabetes undergoing treatment for malignancies should have rigorous and multifactorial approaches to the control of their diabetes. For inpatients, aggressive glycemic management has been associated with improved outcomes.

- There is emerging evidence indicating that metformin and possibly TZDs are associated with lower risks of certain cancers and even may aid as adjunctive therapy in cancer management. Nonetheless, it is premature to prescribe metformin and TZDs solely for these as yet unproven indications.
- The sum of evidence implicating antihyperglycemic medications in the development or promotion of certain cancers is less persuasive. Healthcare professionals should have greater confidence in prescribing all FDA-approved antihyperglycemic medications according to current clinical practice recommendations. Clinicians should exercise caution when choosing medications implicated in the etiology of cancer for patients with the specific organ-related risk.

FUTURE STEPS AND RESEARCH

Given the long duration between exposure to a carcinogen and the development of clinically apparent cancer, large-scale randomized evidence is necessary to detect the most plausible small to moderate effects. A RCT designed to detect a change in risk for overall cancer or a specific cancer, assuming historical rates of occurrence of 1.0 and 0.1%, respectively, would require a total of approximately 25,000 and 250,000 patients, respectively (130). While such trials may be less feasible and too costly, even well-designed observational analytic studies are hypothesis-generating for small to moderate effects.

Multiple questions about the relative contributions of obesity and diabetes to cancer development remain. For instance, what role, if any, does various levels of hyperglycemia play? Do patients with diabetes and controlled glucose levels have a decreased risk of cancer compared with those with uncontrolled glucose levels? It is clear that the basic research in the development of cancers in obesity and diabetes is in its very early stages. Indeed, there is a need for worldwide collaboration, and we call on researchers and academic centers to develop appropriate and needed prospective basic and clinical research.

In light of concerns about diabetes-related medications, future studies should be designed a priori to detect cancer-related outcomes in addition to standard measures of efficacy and safety. Phase 3 randomized trials with longer follow-up times would also be helpful. Greater care and attention to detail are required when communicating scientific data to the community at large and the media. The media should be aware of the implications and potential harms of communicating outcomes without relevant caveats or perspectives.

Obesity is becoming the leading avoidable cause of premature mortality in the world and a leading cause of a variety of health risks, including diabetes and certain cancers; therefore this major risk factor requires preventive and therapeutic interventions. In particular, a focus on children is critical to prevent the further growth of obesity, diabetes, and cancer. Multidisciplinary programs which include basic researchers, epidemiologists, oncologists, endocrinologists, primary care clinicians, and others are critical to understanding and advancing the science.

CONCLUSION

Epidemiology demonstrates a significant increase of cancer in obesity, insulin-resistant states (i.e., metabolic syndrome and polycystic ovary syndrome), and ultimately diabetes. Basic science has suggested plausible mechanisms linking these conditions to the development of cancer. Although medications to treat the hyperglycemia of diabetes have been implicated in increasing the risk of cancer, the totality of evidence is less persuasive, and there is a need for current vigilance and future research. At present, it is necessary to effectively treat hyperglycemia and ensure that the risks of adverse diabetes-related outcomes are minimized in patients. There is currently insufficient evidence to warrant withholding of the use of certain glucose-lowering medications on the basis of cancer concerns. The majority of data linking diabetes medications to cancer arise from meta-analyses of trials not designed to test the hypothesis and observational analytic studies that are subject to bias and confounding. At present, caution and proper monitoring are essential pending the results of RCTs of sufficient size and duration, which are required to minimize the roles of bias, confounding, and chance. It is important to keep in mind that the chronology of cancer development is generally far longer than the time period in which most clinical trials are conducted. The entirety of evidence concerning the interrelationships of obesity, as well as diabetes and its therapies, is incomplete. Further collaborative research between clinicians, including endocrinologists and oncologists, as well as basic, clinical, and epidemiologic researchers, is necessary to complete the evidence on these complex issues.

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