

# Diabetes and Cancer

## A consensus report

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Epidemiologic evidence suggests that cancer incidence is associated with diabetes as well as certain diabetes risk factors and diabetes treatments. This consensus statement of experts assembled jointly by the American Diabetes Association and the American Cancer Society reviews the state of science concerning 1) the association between diabetes and cancer incidence or prognosis, 2) risk factors common to both diabetes and cancer, 3) possible biologic links between diabetes and cancer risk, and 4) whether diabetes treatments influence risk of cancer or cancer prognosis. In addition, key unanswered questions for future research are posed.

*Diabetes Care* 33:1–12, 2010

**D**iabetes and cancer are common diseases with tremendous impact on health worldwide. Epidemiologic evidence suggests that people with diabetes are at significantly higher risk for many forms of cancer. Type 2 diabetes and cancer share many risk factors, but potential biologic links between the two diseases are incompletely understood. Moreover, evidence from observational studies suggests that some medications used to treat hyperglycemia are associated with either increased or reduced risk of cancer. Against this backdrop, the American Diabetes Association and the American Cancer Society convened a consensus development conference in December 2009. Following a series of scientific presentations by experts in the field, the writing group independently developed this consensus report to address the following questions:

1. Is there a meaningful association between diabetes and cancer incidence or prognosis?

2. What risk factors are common to both diabetes and cancer?
3. What are possible biologic links between diabetes and cancer risk?
4. Do diabetes treatments influence risk of cancer or cancer prognosis?

For each area, the authors were asked to address the current gaps in evidence and potential research and epidemiologic strategies for developing more definitive evidence in the future. Table 1 includes a summary of findings and recommendations. Recommendations in this report are solely the opinions of the authors and do not represent official position of the American Diabetes Association or the American Cancer Society.

### 1. Is there a meaningful association between diabetes and cancer incidence or prognosis?

Both diabetes and cancer are prevalent diseases whose incidence is increasing globally. Worldwide, the prevalence of

cancer has been difficult to establish because many areas do not have cancer registries, but in 2008 there were an estimated 12.4 million new cancer cases diagnosed. The most commonly diagnosed cancers are lung/bronchus, breast, and colorectal, whereas the most common causes of cancer deaths are lung, stomach, and liver cancer (1). In the U.S., the most commonly diagnosed cancers are prostate, lung/bronchus, and colon/rectum in men and breast, lung/bronchus, and colon/rectum in women. Of the world population between the ages of 20 and 79 years, an estimated 285 million people, or 6.6%, have diabetes (2). In 2007, diabetes prevalence in the U.S. was 10.7% of persons aged 20 years and older (23.6 million individuals), with an estimated 1.6 million new cases per year. Type 2 diabetes is the most common form, accounting for ~95% of prevalent cases (3). Worldwide, cancer is the 2nd and diabetes is the 12th leading cause of death (4). In the U.S., cancer is the 2nd and diabetes is the 7th leading cause of death; the latter is likely an underestimate, since diabetes is underreported on death certificates as both a cause and comorbid condition (3).

Cancer and diabetes are diagnosed within the same individual more frequently than would be expected by chance, even after adjusting for age. Both diseases are complex with multiple subtypes. Diabetes is typically divided into two major subtypes, type 1 and type 2 diabetes, along with less common types, while cancer is typically classified by its anatomic origin (of which there are over 50, e.g., lymphoma, leukemia, lung, and breast cancer) and within which there may be multiple subtypes (e.g., leukemia). Further, the pathophysiologies underlying both cancer and diabetes are (with rare exceptions) incompletely understood.

For more than 50 years, clinicians have reported the occurrence of patients with concurrent diabetes and cancer. However, as early as 1959, Joslin et al. (5) stated, "Studies of the association of diabetes and cancer have been conducted over a period of years, but evidence of a positive association remains inconclu-

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This article is jointly published by the American Diabetes Association and the American Cancer Society.

DOI: 10.2337/dc10-0666

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sive.” Subsequently, an association between the two diseases was identified in the 1960s in population-based studies. More recently, the results of several studies have been combined for meta-analytic study (6), indicating that some cancers develop more commonly in patients with diabetes (predominantly type 2), while prostate cancer occurs less often in men with diabetes. The relative risks imparted by diabetes are greatest (about twofold or higher) for cancers of the liver, pancreas, and endometrium, and lesser (about 1.2–1.5 fold) for cancers of the colon and rectum, breast, and bladder. Other cancers (e.g., lung) do not appear to be associated with an increased risk in diabetes, and the evidence for others (e.g., kidney, non-Hodgkin lymphoma) is inconclusive. Few studies have explored links with type 1 diabetes.

Since insulin is produced by pancreatic  $\beta$ -cells and then transported via the portal vein to the liver, both the liver and the pancreas are exposed to high concentrations of endogenously produced insulin. Diabetes-related factors including steatosis, nonalcoholic fatty liver disease, and cirrhosis may also enhance susceptibility to liver cancer. With regard to pancreatic cancer, interpretation of the causal nature of the association is complicated by the fact that abnormal glucose metabolism may be a consequence of pancreatic cancer (so-called “reverse causality”). However, a positive association between diabetes and pancreatic cancer risk has been found when restricted to diabetes that precedes the diagnosis of pancreatic cancer by at least 5 years, so reverse causation does not likely account for the entirety of the association.

Only for prostate cancer is diabetes associated with a lower risk. This association has been observed both before and after the advent of screening with prostate-specific antigen (PSA), so detection bias due to differential PSA utilization does not account for this finding. Some metabolic factors associated with diabetes, such as reduced testosterone levels, may be involved (although circulating testosterone levels have not been consistently associated with prostate cancer incidence). While obesity has not been associated, and in some studies is even inversely associated, with prostate cancer incidence, obese men with prostate cancer have higher cancer mortality rates than those of normal weight (7). In addition to metabolic factors such as hyperinsulinemia, obesity may be associated with

clinical factors (such as delayed diagnosis, poorer treatment) that may underlie the worsened prostate cancer prognosis.

Results of some, but not all, epidemiological studies suggest that diabetes may significantly increase mortality in patients with cancer (8). For example, in one study, 5-year mortality rates were significantly higher (hazard ratio 1.39) in patients diagnosed with both breast cancer and diabetes than in comparable breast cancer patients without diabetes (9). Since diabetes is associated with excess age-adjusted mortality, whether the apparent excess mortality associated with diabetes in cancer patients is any greater than the excess mortality observed among diabetic patients without cancer is unclear. Of note, higher pre-diagnosis C-peptide levels (an indirect marker of insulin resistance) have been associated with a poorer disease-specific survival for prostate cancer (7) and colorectal cancer (10).

### **Unanswered questions**

Diabetes has been consistently associated with increased risk of several of the more common cancers, but for many, especially the less common cancers, data are limited or absent (6) and more research is needed. Uncertainty is even greater for the issue of diabetes and cancer prognosis or cancer-specific mortality. It remains unclear whether the association between diabetes and cancer is direct (e.g., due to hyperglycemia), whether diabetes is a marker of underlying biologic factors that alter cancer risk (e.g., insulin resistance and hyperinsulinemia), or whether the cancer-diabetes association is indirect and due to common risk factors such as obesity. Whether cancer risk is influenced by duration of diabetes is a critical and complex issue and may be further complicated by the multidrug therapy often necessary for diabetes treatment (as discussed in question 4). What is also required is a better understanding of whether diabetes influences cancer prognosis above and beyond the prognosis conferred by each disease state independently.

To adequately address these questions, prospective population-based studies with high-quality databases are needed to compare incidence of specific cancers between individuals with high circulating insulin levels with or without diabetes and nondiabetic individuals with normal insulin sensitivity (and therefore low insulin levels). Examining other dia-

betes-related biomarkers (e.g., adiponectin, hyperglycemia) is also critical. Importantly, common confounders (such as body weight and physical activity) must also be more readily available and assessed. Better characterization of aspects of diabetes (diabetes duration, therapy, degree of glycemic control) in relation to cancer risk is needed. In view of the variable associations between diabetes and cancer risk at specific sites, the authors discourage studies exploring links between diabetes and risk of all cancers combined. For example, since lung cancer does not appear to be meaningfully linked with diabetes, including this common cancer in studies will dilute observed associations, should they exist.

### **2. What risk factors are common to both cancer and diabetes?**

Potential risk factors (modifiable and nonmodifiable) common to both cancer and diabetes include aging, sex, obesity, physical activity, diet, alcohol, and smoking.

#### **Nonmodifiable risk factors**

**Age.** Although the incidence of some cancers peaks in childhood or in young adults, the incidence of most cancers increases with age. In economically developed countries, 78% of all newly diagnosed cancer occurs among individuals aged 55 years and older (11). Diabetes also becomes increasingly common with age: Prevalence is 2.6% in U.S. adults 20–39 years of age, 10.8% in those 40–59 years of age, and increases to 23.8% in those 60 years of age or older (3). In parallel with the obesity epidemic, type 2 diabetes is becoming more frequent among adolescents and young adults (12,13), potentially adding years of additional risk from diabetes to the population.

**Sex.** While certain cancers are sex-specific (e.g., cervix, uterine, testicular, prostate), or nearly so (breast), overall cancer occurs more frequently in men. Men have slightly higher age-adjusted risk of diabetes than women (3).

**Race/ethnicity.** The age-standardized incidence of cancer and diabetes varies significantly among different populations. Factors that may contribute to this variability include differences in the prevalence of major risk factors, genetic factors, medical practices such as screening, and completeness of reporting. In the U.S., African Americans are more likely to develop and die from cancer than other

race or ethnic groups. Following African Americans are non-Hispanic whites, with Hispanics, Native Americans, and Asian Americans/Pacific Islanders having lower cancer incidence and mortality (14). As with the worldwide situation, the U.S. race/ethnic variability in cancer incidence is attributed, at least in part, to socioeconomic and other disparities, but biological factors, such as levels of hormones that vary by race (15), may also play a role.

In the U.S., type 2 diabetes and its complications disproportionately affect a number of specific populations, including African Americans, Native Americans, Hispanics, and Asian Americans/Pacific Islanders compared with non-Hispanic whites (3). While incompletely understood, genetic, socioeconomic, lifestyle, and other environmental factors are thought to contribute to these disparities.

### Modifiable risk factors

**Overweight, obesity, and weight change.** Overweight (BMI  $\geq 25$  and  $< 30$  kg/m<sup>2</sup>) or obese (BMI  $\geq 30$  kg/m<sup>2</sup>) individuals have a higher risk for many types of cancer compared with individuals whose BMI is considered within the normal range (18.5 to  $< 25$  kg/m<sup>2</sup>) (16,17). The cancers most consistently associated with overweight and obesity are breast (in postmenopausal women), colon/rectum, endometrium, pancreas, adenocarcinoma of the esophagus, kidney, gallbladder, and liver. Obesity may also increase risk of mortality from some cancers, such as prostate (7). A growing body of evidence suggests that weight gain is associated with an increased risk of some cancers, breast cancer in particular (17). Increases in body weight during adulthood largely reflect increases in adipose tissue rather than lean mass, so total body fat may be a better measure of the risk for cancer than BMI.

Studies over decades have consistently shown a strong association between obesity and both insulin resistance and type 2 diabetes incidence (18), with risk of diabetes and earlier age at onset directly linked to obesity severity (19). For type 2 diabetes (20) as well as certain cancers (e.g., colon) (21), some studies suggest that waist circumference, waist-to-hip ratio, or direct measures of visceral adiposity are associated with risk independently of BMI.

The case for a causal relationship between obesity and disease is strengthened by evidence that weight loss lowers disease risk. In the case of diabetes, numer-

ous studies have shown that weight loss decreases diabetes incidence and restores euglycemia in a significant fraction of individuals with type 2 diabetes. In the randomized, prospective, multicenter Diabetes Prevention Program trial, an intensive lifestyle intervention of diet (targeting 5–7% weight loss) and physical activity was associated with a 58% reduction in diabetes incidence in high-risk individuals (22), and weight loss accounted for most of the effect (23). In addition, weight loss may also limit the risk of developing gestational diabetes (24).

The association between weight loss and subsequent cancer risk is less clear. Most evidence has been derived from breast cancer studies, where weak or null associations were observed. Since the weight loss definition and the referent groups differed across studies, these studies are difficult to compare. Weight loss categories tend to have small numbers, and many women who do lose weight do not maintain their weight loss beyond 1 year. In the Nurses' Health Study, a statistically significant inverse association between adult weight loss and postmenopausal breast cancer was found only when the weight loss had been maintained for two survey cycles, or 4 years (25). Observational studies of weight loss and cancer risk require extremely large sample sizes with long-term follow-up and careful monitoring of weight change. One concern of all observational studies of weight loss and subsequent cancer risk is that weight loss may be a sign of undiagnosed cancer. As a practical matter, a randomized clinical trial to study the effect of weight loss on cancer risk is unlikely to be feasible; such a study would have to be very large and would likely be stopped early due to a protective effect on diabetes and heart disease before enough cancer end points would accumulate.

The significant amount of weight lost with bariatric surgery may also provide clarity to this issue. However, a recent summary (26) noted the limited evidence of the effects of bariatric surgery on cancer incidence. Among the studies published to date, three found that obese women who underwent bariatric surgery were at lower risk of cancer (relative risks ranging from 0.58 to 0.62) compared with untreated obese women. The inverse associations appeared to be due in large part to a protective effect on breast and endometrial cancer. In the two studies that included men, no association between

bariatric surgery and cancer risk was observed.

Bariatric surgery is a very effective treatment for type 2 diabetes, with a meta-analysis showing that type 2 diabetes resolved in 78% and resolved or improved in 87% of patients after bariatric surgery (27). In contrast to the known effects of bariatric surgery on treating diabetes, the therapy's role in preventing diabetes would seem likely but has not been established through prospective trials.

**Diet.** A majority of studies (despite different study designs and differing study populations) suggest that diets low in red and processed meats and higher in vegetables, fruits, and whole grains are associated with a lower risk of many types of cancer (17,28,29). Diets that are low in red and processed meat but high in monounsaturated fatty acids, fruits, vegetables, whole grain cereals, and dietary fiber may protect against type 2 diabetes, possibly through improving insulin sensitivity (30,31). Low-carbohydrate diets (which often include greater consumption of red meats and fat) have also been associated with weight loss and improvements in insulin sensitivity and glycemic control. However, randomized controlled trial evidence of dietary interventions and diabetes prevention only exists for low-fat, low-calorie, plus/minus high-fiber diets (22,32).

Several studies suggest that diets high in foods with a high glycemic index or load are associated with an increased risk of type 2 diabetes (28,33). However, evidence of their associations with cancer risk is mixed (28,34,35). Regardless, to the extent that energy-dense and sugary foods contribute to overweight and obesity, the American Cancer Society, the World Cancer Research Fund, and the American Institute for Cancer Research recommend limiting consumption of these foods (17,29).

**Physical activity.** Evidence from observational epidemiologic studies consistently shows that higher levels of physical activity are associated with a lower risk of colon, postmenopausal breast, and endometrial cancer (17,36,37). Physical activity may also help prevent other cancers, including lung and aggressive prostate cancer, but a clear link has not been established. Some evidence also suggests that physical activity postdiagnosis may improve cancer survival for some cancers, including breast (38) and colorectal (39).

A protective role for increased physical activity in diabetes metabolism and

outcomes has been demonstrated. Data from observational and randomized trials suggest that ~30 min of moderate-intensity exercise, such as walking, at least 5 days per week substantially reduces (25–36%) the risk of developing type 2 diabetes (40). Analyses of the effects of different components of the intensive lifestyle intervention in the Diabetes Prevention Program suggested that those who did not reach weight loss goals still significantly reduced their risk of diabetes if they reached the exercise goals, although weight loss was the only component independently associated with diabetes prevention in multivariate analyses (23).

**Tobacco smoking.** It is estimated that worldwide, tobacco smoking accounts for 71% of all trachea, bronchus, and lung cancer deaths (41). Other cancers strongly associated with smoking are larynx, upper digestive, bladder, kidney, pancreas, leukemia, liver, stomach, and uterine cervix. Studies suggest that smoking is also an independent risk factor for the development of diabetes (42,43). In addition, because of the effect of smoking on increasing risk of cardiovascular disease, retinopathy, and other complications of diabetes, smoking has an adverse effect on diabetes-related health outcomes (44).

**Alcohol.** Alcoholic beverage consumption, even in moderate amounts, increases the risk of many types of cancer including those of the oral cavity, pharynx, larynx, esophagus, liver, colon/rectum, and female breast (45). While excess alcohol consumption is also a risk factor for diabetes, moderate alcohol consumption has been associated with reduced diabetes incidence in both men and women (46,47).

### Unanswered questions

A critical question is whether the associations between diabetes and risk of certain cancers is largely due to shared risk factors (obesity, poor diet, physical inactivity, and aging), or whether diabetes itself, and the specific metabolic derangements typical of diabetes (e.g., hyperglycemia, insulin resistance, hyperinsulinemia), increase the risk for some types of cancer. While it is clear that lower levels of adiposity, healthy diets, and regular physical activity are associated with reduced risk for type 2 diabetes and for several common types of cancer, these factors are generally interrelated, making the contribution of each factor difficult to assess. More research is needed to under-

stand the role of specific components of healthy lifestyles independent of others (e.g., diet quality independent of body weight). In addition, further study of those who are of normal body weight but have hyperinsulinemia or are sedentary, and of those who are obese but have normal metabolic parameters, is necessary to better understand the relationship between diabetes and cancer risk. Little is known about how modifiable lifestyle factors influence prognosis in cancer patients. How genetic variants that influence diverse aspects of diabetes (e.g., insulin resistance,  $\beta$ -cell depletion) influence cancer risk may provide insights into the nature of the diabetes-cancer relationship. Addressing these questions will require large, long-term observational studies, with their inherent limitations. Although not powered for cancer outcomes, long-term trials such as the Look AHEAD trial of the effects of weight loss on cardiovascular outcomes in patients with diabetes (48), and follow-up of cohorts in lifestyle studies such as the Diabetes Prevention Program, may provide further evidence for the impact of lifestyle improvements on cancer incidence.

### 3. What are possible biologic links between diabetes and cancer risk?

Carcinogenesis is a complex process. Normal cells must undergo multiple genetic “hits” before the full neoplastic phenotype of growth, invasion, and metastasis occurs. This process of malignant transformation can be divided into multiple steps: initiation (irreversible first step toward cancer), promotion (stimulation of the growth of initiated cells), and progression (development of a more aggressive phenotype of promoted cells). Factors that affect one or more steps of this pathway could be associated with cancer incidence or mortality. Diabetes may influence the neoplastic process by several mechanisms, including hyperinsulinemia (either endogenous due to insulin resistance or exogenous due to administered insulin or insulin secretagogues), hyperglycemia, or chronic inflammation.

#### The insulin/IGF axis

Insulin and insulin-like growth factor (IGF) receptors form a complex network of cell surface receptors; homodimers and heterodimers have been described, and all function to mediate insulin and IGF responses (49). Most cancer cells express insulin and IGF-I receptors; the A isoform

of the insulin receptor is commonly expressed. The A receptor isoform can stimulate insulin-mediated mitogenesis, even in cells deficient in IGF-I receptors (50). In addition to its metabolic functions, the insulin receptor is also capable of stimulating cancer cell proliferation and metastasis. Because most glucose uptake in cancer cells is constitutively high and independent of insulin binding to its receptor (51), the effects of insulin receptor activation on neoplastic cells may relate more to cell survival and mitogenesis than to enhanced glucose uptake.

Multiple signaling pathways are activated after insulin receptors or IGF-I receptors interact with their ligands. By phosphorylating adaptor proteins, most notably the insulin receptor substrate (IRS) family, the initial kinase event is linked to downstream signaling pathways (52). Once activated, these signaling pathways may stimulate multiple cancer phenotypes including proliferation, protection from apoptotic stimuli, invasion, and metastasis, potentially enhancing promotion and progression of many types of cancer cells. It is also clear that insulin/IGF may stimulate normal cells that are involved in cancer progression. For example, hyperglycemia allows IGF-I to stimulate vascular smooth muscle cell proliferation and migration (53). While this process has been linked to the pathophysiology of atherosclerosis, abnormal vasculature growth is also a hallmark of cancer.

Apart from direct effects of insulin on cancer cells, it is possible that hyperinsulinemia could promote carcinogenesis indirectly through its effects on IGF-I (54). Insulin reduces the hepatic production of IGF binding protein (IGFBP)-1 (55,56) and possibly IGFBP-2 (57) with resultant increases in the levels of circulating free, bioactive IGF-I. IGF-I has more potent mitogenic and anti-apoptotic activities than insulin (58) and could act as a growth stimulus in preneoplastic and neoplastic cells that express insulin, IGF-I, and hybrid receptors (49). Human tumors commonly over-express these receptors, and many cancer cell lines have been shown to be responsive to the mitogenic action of physiological concentrations of IGF-I.

As has been found in other cancers, insulin receptors are frequently expressed by breast cancer cells (59). Compared with the ligand (i.e., insulin), higher levels of insulin receptor have been associated with favorable breast cancer

prognosis in some studies (60,61). While these findings may seem to be contradictory, they are consistent with other hormone-dependent pathways in breast cancer. Elevated serum levels of estradiol are weakly associated with increased breast cancer risk (62), while expression of estrogen receptor (ER)- $\alpha$  is a favorable prognostic factor (63). Just like ER, insulin receptor may be a marker of breast cancer cell differentiation and identify cells with a potentially less aggressive phenotype. On the other hand, a recent larger study (64) concluded that high insulin receptor levels are related to adverse prognosis; further research is needed. Moreover, the relationship between serum levels of insulin and regulation of insulin receptor levels in neoplastic tissues has never been established. Since growth factors may downregulate the expression of their cognate receptors, it is possible that tumors with low insulin receptor levels are the most insulin-stimulated. Thus, there are biologically plausible models and correlative human clinical studies suggesting that insulin acting through insulin receptors might affect breast cancer risk and progression.

### **Effect of hyperinsulinemia on other hormones**

Increased circulating insulin has a number of indirect effects including a reduction in the hepatic synthesis and blood levels of sex hormone binding globulin, leading to increases in bioavailable estrogen in both men and women and increased levels of bioavailable testosterone in women but not in men (65). Androgen synthesis in the ovaries and possibly the adrenals is increased by hyperinsulinemia in premenopausal women. Elevated endogenous sex steroid levels are associated with a higher risk of postmenopausal breast, endometrial, and possibly other cancers.

### **Hyperglycemia and cancer**

In considering the complexity of interactions between diabetes, diabetes treatments, and cancer, it is important to not overlook glucose as a potentially relevant mediator. The recent resurgence of interest in the Warburg hypothesis and cancer energetics (66) emphasizes the dependence of many cancers on glycolysis for energy, creating a high requirement for glucose (or even "glucose addiction"), since ATP generation by glycolysis requires far more glucose than oxidative phosphorylation. Indeed, this forms the

basis for FDG-PET imaging of cancers, which detects tissues with high rates of glucose uptake. The possibility that untreated hyperglycemia facilitates neoplastic proliferation therefore deserves consideration. Direct data concerning dose-response characteristics of cancers to glucose are sparse, but it is relevant that most cancers have highly effective up-regulated, insulin-independent glucose uptake mechanisms (67) and therefore may not derive a further growth advantage from hyperglycemia.

In vivo models showing reduced tumor growth in the setting of type 1 diabetes (68) suggest that hyperglycemia does not lead to increased neoplastic growth, at least in the setting of insulin deficiency. Studies relating hyperglycemia to cancer do not necessarily indicate that glucose mediates the relationship; rather, hyperglycemia may serve as a surrogate for a causative factor such as hyperinsulinemia. Given the molecular heterogeneity of cancers, one cannot at this point exclude the possibility that there exists a subset of tumors for which hyperglycemia confers a growth advantage and appropriate therapy for diabetes therefore limits tumor growth, but the aggregate data suggest that insulin receptor activation may be a more important variable than hyperglycemia in determining tumor growth.

### **Inflammatory cytokines, diabetes, and cancer risk**

In addition to the direct effects of insulin, type 2 diabetes and/or the related obesity might enhance other pathways resulting in malignant progression. As recently reviewed, adipose tissue is an active endocrine organ producing free fatty acids, interleukin-6 (IL-6), monocyte chemoattractant protein, plasminogen activator inhibitor-1 (PAI-1), adiponectin, leptin, and tumor necrosis factor- $\alpha$  (69). Each of these factors might play an etiologic role in regulating malignant transformation or cancer progression. In some cases, the role for these molecules is well known. For example, the plasminogen system has been linked to cancer with expression of PAI-1 linked to poor outcome in breast cancer (70). Activation of signal transducer and activator of transcription protein (STAT) signaling, via cytokines such as IL-6, is known to enhance cancer cell proliferation, survival, and invasion while also suppressing host anti-tumor immunity (71).

Similarly, animal studies of energy balance support epidemiologic results re-

lating obesity with cancer mortality. Certain experimental cancers tend to behave more aggressively when animals overeat and less aggressively when animals are calorically restricted (72–74). These studies provide evidence that diet-induced changes in IL-6 and/or insulin may mediate the effect of diet on neoplasia and indicate that differences between tumors with respect to specific signaling pathways determine the extent to which diet influences tumor behavior (75).

### **Major unanswered questions**

As previously outlined, there is a growing body of epidemiologic evidence supporting a link between diabetes and the incidence and/or prognosis of some cancers. It is recognized the association may not be causal; diabetes and cancer may be associated simply because they share common predisposing risk factors such as obesity. However, a number of plausible biologic mechanisms have been described that may account for this link, including effects of hyperglycemia, hyperinsulinemia, and inflammation on cancer etiology and progression. Mechanisms by which these factors interact with cancer risk require further study. Another important area for investigation concerns the issue of insulin resistance in type 2 diabetes in cells of non-classic insulin target organs, such as the breast, colon, or prostate. The assumption that in the setting of insulin resistance of classic insulin target organs (liver, muscle, adipose tissue) at least a subset of cancers remain insulin-sensitive, or that insulin insensitivity to metabolic pathways does not extend to resistance to growth-promoting properties, needs to be more closely examined. How common is this? And what are the dose-response characteristics of insulin stimulation of such cancers?

Research is ongoing to provide a clearer understanding of these possible links, and this information may be relevant for prevention and optimal patient management. Most of the supporting evidence on biologic mechanisms comes from in vivo and in vitro studies. Since multiple pre-diagnostic biospecimens are rarely available on cohorts large enough for studies of cancer, many epidemiologic studies are only able to evaluate a single time point when measuring levels of insulin, glucose, or other analytes. The risk of long-term exposure to high levels of insulin is relatively underexplored and has direct relevance to the cancer risk associated with diabetes duration and use of

exogenous insulin. In addition, most of the large studies have only fasting levels; postprandial (area under the curve) insulin levels have not been adequately examined.

#### 4. Do diabetes treatments influence cancer risk or cancer prognosis?

Improved glucose control remains one of the central goals of effective diabetes management, which strives to minimize morbidity and mortality by reducing the risk of diabetes-associated complications. Several factors are considered by clinicians and patients when selecting pharmacologic diabetes therapies. These include the type of diabetes being treated, the glucose-lowering potential of a given agent, known acute and chronic adverse effects of treatment (such as weight gain, hypoglycemia, fluid retention, gastrointestinal intolerance), treatment costs, and patient comorbidities and characteristics. Only recently has the issue of cancer risk with diabetes treatments been considered.

Individuals with type 1 diabetes represent ~5% of the diabetes population worldwide. The autoimmune destruction of the pancreatic  $\beta$ -cells results in the loss of insulin production and the need for immediate and lifelong insulin therapy. In contrast, type 2 diabetes is much more common and accounts for ~95% of the diabetes population. Type 2 diabetes is generally associated with overweight and obesity (in an estimated 80% of cases) and commonly advances from a pre-diabetic state characterized by insulin resistance (hyperinsulinemia) to frank diabetes with sustained insulin resistance accompanied by a progressive reduction in insulin secretion. The resulting relative insulin deficiency gives rise to both fasting and postmeal hyperglycemia. Ongoing loss of insulin secretory capacity, along with a diminished incretin effect and several other pathophysiologic defects (76), makes the hyperglycemia of type 2 diabetes progressive. This results in increasing use of pharmacologic agents over time and the eventual need for insulin therapy in approximately half of all patients (77). The selection of the most appropriate pharmacologic agent(s) for each patient involves clinical decision-making process that includes an ongoing risk/benefit analysis (78).

#### Metformin

The biguanide metformin is the most commonly used therapy in patients with

type 2 diabetes, often prescribed as initial or combination therapy (79). While the mechanism of action of metformin in diabetes is only partially understood, metformin treatment generally reduces levels of both circulating glucose and insulin in patients with insulin resistance and hyperinsulinemia. The primary mode of action is through reduced hepatic glucose output (80).

In laboratory studies, metformin has been shown to inhibit cell proliferation, reduce colony formation, and cause partial cell cycle arrest in cancer cell lines (81–83). These studies suggest that metformin-induced activation of AMP-activated protein kinase (AMPK) in tumor cells may lead to growth inhibition, at least in part by inhibiting protein synthesis (84). Interestingly, in vivo studies show that metformin has less antineoplastic activity in mice on a control diet than it does in mice on a high-energy diet associated with hyperinsulinemia and accelerated tumor growth (74). This suggests that the insulin-lowering action of metformin may contribute to its anti-neoplastic activity, and that it may have less impact on cancers in less hyperinsulinemic patients. Other in vitro studies suggest that metformin may selectively kill cancer stem cells and enhance effectiveness of breast cancer treatment regimens (85–87). Metformin has also been shown to reduce mammary tumor growth in rodent models (88).

Results of a growing number of observational human studies suggest that treatment with metformin (relative to other glucose-lowering therapies) is associated with reduced risk of cancer (89–93) or cancer mortality (94). However, these studies have generally been limited in their ability to assess association with specific cancer types. Confounding by indication may limit the interpretation of results from observational studies, as metformin is most typically prescribed to those with short duration of diabetes and without contraindicating factors (advanced age, liver, or kidney disease) that also might impact risk of some cancers.

Additional observational data suggest that metformin might improve cancer prognosis. Metformin treatment was associated with higher pathologic complete response among early-stage breast cancer patients receiving neoadjuvant therapy (95). The potential effect of metformin on breast cancer cell proliferation (as measured by Ki67 index) is currently being evaluated in a clinical trial with a small

number of subjects (96), and other trials of metformin therapy in patients with breast cancer are planned.

#### Thiazolidinediones

Thiazolidinediones (TZDs) are insulin-sensitizing peroxisome proliferator-activated receptor (PPAR) $\gamma$  agonists that do not increase insulin secretion directly or cause hypoglycemia when used alone. Two drugs in this class, pioglitazone and rosiglitazone, are currently available. Unlike metformin, TZDs may be used in patients with renal insufficiency, although fluid retention is a potential adverse effect. TZDs are contraindicated in selected patients, most notably those with liver disease or with active untreated or unstable congestive heart failure.

In vitro studies indicate that PPAR $\gamma$  agonists have several anti-cancer activities, such as inhibiting growth and inducing apoptosis and cell differentiation (97), and PPAR $\gamma$  is currently considered a potential target for both chemoprevention and cancer therapy based on other pre-clinical studies (98,99). However, since recent in vitro studies indicate that the effects of PPAR $\gamma$  agonists on cell growth are often independent of the presence of PPAR $\gamma$  (100–102), the clinical relevance of findings of in vitro studies is unclear. Rodent studies also indicate that PPAR agonists can potentiate tumorigenesis, and they have been considered by some to be multi-species, multi-sex carcinogens (103). Therefore, it is possible that TZDs may increase, decrease, or have a neutral effect on the risk of cancer or cancer progression in humans.

Definitive human data on cancer risk associated with TZDs are not available. Three epidemiologic studies conducted among patients with diabetes focused on all cancers combined or only on a limited number of cancer sites, and results were inconsistent (104–106). Results of a recent meta-analysis of clinical trials of rosiglitazone showed no statistically significant increase or decrease in the risk of cancer at all sites combined or at the more common sites, although the numbers of cancer cases at these specific sites were small (107). The epidemiologic studies and the meta-analysis of trials were able to examine only short-term exposure, largely due to the relatively recent introduction of these medications and the shorter duration of many clinical efficacy trials.

Only a few clinical trials of TZDs for cancer treatment have been conducted,

and results have largely been negative (108). Other clinical trials are in progress (109) or are planned (99).

### Insulin secretagogues

Secretagogues, including sulfonylureas and the rapid-acting glinides, stimulate  $\beta$ -cells to release insulin by binding to specific cell receptors, resulting in  $\beta$ -cell depolarization and release of insulin stores. Sulfonylureas (e.g., glyburide, glipizide, glimepiride) have been used to treat type 2 diabetes for more than 50 years. While this class of agents is one of the more effective in lowering A1C, these drugs can cause hypoglycemia and weight gain. A small number of observational studies found a higher risk of cancer or cancer death among individuals with diabetes treated with sulfonylureas compared with those treated with metformin or other diabetes medications (90–92,110). However, most of these studies had very few cancer cases among users of sulfonylureas, and therefore power was limited to examine associations with specific cancer sites (91,111). Studies regarding dose, duration, recency, and persistence of use are limited.

While it is possible that the association of sulfonylureas and cancer risk is genuine, it is difficult to determine whether the findings reflect excess cancer among users of the secretagogues or reduced risk in those using comparator drugs, which often include metformin therapy. Furthermore, if the association were to be confirmed, it remains to be determined if the mechanism involves direct actions of the agents on transformed cells or cells at risk for carcinogenesis, as compared with indirect effects mediated by increased insulin levels. There are no published data that support an association between the glinide secretagogues and cancer risk, perhaps because they are newer and use of these agents is less common.

### Incretin-based therapies

Two recently developed classes of drugs either enhance or mimic the effect of gut-derived incretin hormones that improve glucose-dependent insulin secretion, suppress postprandial glucagon levels, and delay gastric emptying. The first of the incretin-based therapies introduced, exenatide, has ~50% homology with the incretin hormone glucagon-like peptide 1 (GLP-1), while the more recently approved liraglutide is an analog of human GLP-1. Both compounds bind to the

GLP-1 receptor to exert agonist activity. The oral dipeptidyl peptidase-4 (DPP-4) inhibitors inhibit the action of the ubiquitous enzyme that rapidly degrades many peptides including endogenous GLP-1.

Liraglutide increased risk of medullary thyroid cancer in rats and mice in preclinical tests and was associated with slight increases in serum calcitonin in human trials (U.S. Food and Drug Administration). Exenatide, liraglutide, and DPP-4 inhibitors increased  $\beta$ -cell proliferation in animal studies, and in one small study of a transgenic rodent model, the DPP-4 inhibitor sitagliptin was demonstrated to increase pancreatic ductal hyperplasia (112). No impact of incretin-based agents on human cancer incidence has been reported, likely due to the fact that these newer drugs have not been used in sufficient numbers of patients or for long enough periods of time to fully assess any possible effects on cancer risk.

### Insulin and insulin analogs

Insulin is required for all patients with type 1 diabetes. It is also necessary for many patients with type 2 diabetes to treat hyperglycemia, in part due to the progressive loss of  $\beta$ -cell function over time. Between 40–80% of individuals with type 2 diabetes will ultimately be considered for insulin therapy in an effort to achieve glycemic targets (77). Several formulations of insulin exist: short-acting human regular insulin, intermediate-acting human NPH insulin, and both rapid- and long-acting analogs of human insulin. Subcutaneous injection of insulin results in significantly higher levels of circulating insulin in the systemic circulation than endogenous insulin secretion, thereby possibly amplifying links between hyperinsulinemia and cancer risk.

Recently, a series of widely publicized epidemiologic analyses examined a possible association between insulin use and/or use of the long-acting insulin analog glargine (91,110,113,114) and an increase in risk of cancer. As noted below, insulin glargine may have a disparate impact on cancer risk through its binding to IGF-1 receptors. The potential strengths and weaknesses of these studies have been broadly debated and well detailed (115–117). For example, one concern is that insulin is more commonly prescribed in patients with longer duration of type 2 diabetes and is used more often in those with one or more comorbid conditions that preclude use of comparator medica-

tions. Rarely have these or other potential confounders (body mass, actual insulin dose, degree of glucose control, glucose variability, other patient characteristics) been fully accounted for in the study designs or analyses.

Randomized clinical trial data from an open-label 5-year trial of insulin glargine versus NPH insulin did not find evidence of excess cancer risk (all sites combined) in the insulin glargine arm (118), although among the ~1,000 subjects randomized, there was a very small number of cancer end points (57 cancer cases in the glargine arm and 62 cases in the NPH arm). The ongoing randomized ORIGIN trial (glargine versus placebo in patients with impaired fasting glucose or newly diagnosed type 2 diabetes) is much larger (~12,000 patients randomized and followed for 6–7 years) (119). Importantly, this trial was powered for cardiovascular outcomes and may still not provide definitive evidence regarding cancer incidence, especially for specific cancers.

### Possible mechanisms for the link between exogenous insulin, insulin analogs, and cancer

Potential mechanisms by which administration of insulin or insulin analogs might influence neoplastic disease include both direct and indirect actions. Direct actions have received the most attention and involve interactions of the administered ligands (or their metabolites) with cancer cells, partially transformed cells, or cells at risk for transformation. Indirect mechanisms have been less well studied but would involve interactions of signaling molecules whose levels (e.g., glucagon, adiponectin, or IGF-BPs) or activity are influenced by administered insulin on these target cells.

With respect to direct actions, one must consider not only the affinity of the administered agents for the various receptors involved, but also pharmacokinetic aspects. Substantial prior research has emphasized differences between human insulin and analog insulins with respect to binding affinity to the IGF-1 receptor, including evidence that insulin glargine has much higher affinity, and higher mitogenic potency, than human insulin or other analogs (120–122). The affinity of particular analog insulins for the IGF-1 receptor is an important issue, in view of evidence that knockdown of the IGF-1 receptor, but not the insulin receptor, abolished proliferation of malignant cell

Table 1—Summary and recommendations

- Diabetes (primarily type 2) is associated with increased risk for some cancers (liver, pancreas, endometrium, colon and rectum, breast, bladder). Diabetes is associated with reduced risk of prostate cancer. For some other cancer sites there appears to be no association or the evidence is inconclusive.
- The association between diabetes and some cancers may partly be due to shared risk factors between the two diseases, such as aging, obesity, diet, and physical inactivity.
- Possible mechanisms for a direct link between diabetes and cancer include hyperinsulinemia, hyperglycemia, and inflammation.
- Healthful diets, physical activity, and weight management reduce risk and improve outcomes of type 2 diabetes and some forms of cancer and should be promoted for all.
- Patients with diabetes should be strongly encouraged by their health care professionals to undergo appropriate cancer screenings as recommended for all people in their age and sex.
- The evidence for specific drugs affecting cancer risk is limited, and observed associations may have been confounded by indications for specific drugs, effects on other cancer risk factors such as body weight and hyperinsulinemia, and the complex progressive nature of hyperglycemia and pharmacotherapy in type 2 diabetes.
- Although still limited, early evidence suggests that metformin is associated with a lower risk of cancer and that exogenous insulin is associated with an increased cancer risk. Further research is needed to clarify these issues and evaluate if insulin glargine is more strongly associated with cancer risk compared with other insulins.
- Cancer risk should not be a major factor in choosing between available diabetes therapies for the average patient. For selected patients with very high risk for cancer occurrence (or for recurrence of specific cancer types), these issues may require more careful consideration.
- Many research questions remain, as described in the article.

lines in response to insulin glargine (120). However, the implicit assumption that an insulin or analog that retains specificity for the insulin receptor over the IGF-I receptor is unlikely to have important mitogenic effects or effects on neoplasia may be simplistic in the light of recent research results (64,123) that show that the insulin receptor is present on neoplastic cells and may itself influence neoplastic behavior in certain contexts.

Other pharmacokinetic issues must also be considered. It is not clear if there is a biologic difference between exposure of neoplastic cells to fluctuating levels of endogenous insulin seen under normal physiologic conditions, as compared with the levels of endogenous insulin in obesity, type 2 diabetes, and/or after administration of exogenous human or synthetic insulins. Classic subcutaneous therapy with subcutaneous human insulin involves transient exposures to very high insulin levels, while subcutaneous administration of some synthetic insulins results (by design) in longer-term exposure to higher insulin concentrations. As such, simple pharmacokinetics may not fully explain observed changes in the behavior of neoplastic tissues. It also is critical to recognize that cancer cells in type 2 diabetic patients may be exposed to abnormally high levels of endogenous insulin for many years prior to administration of exogenous insulin.

### Unanswered questions

There are several important limitations in human studies of diabetes treatment and cancer risk that require careful consider-

ation. First, most studies have had limited power to detect modest associations, particularly for site-specific cancers. Conducting studies with all sites combined might attenuate or even mask important associations with only specific cancer sites. Another limitation of observational studies is that most diabetic patients are treated with one or more anti-hyperglycemic medications. Indeed, the progressive nature of type 2 diabetes, requiring changes in pharmacotherapy over time, adds complexity to studies of a long-term outcome such as cancer incidence. Therefore, it is extremely difficult to assess the independent association of a specific medication on cancer risk relative to no medication. For example, if some medications increase risk, while other decrease or have no effect on risk, different comparator drugs will likely lead to different associations and may explain some of the observed inconsistencies across studies.

Because specific anti-hyperglycemic medications are associated with cancer risk factors, confounding by unmeasured or incompletely measured risk factors may at least in part explain the previously reported drug-cancer associations. Few studies examined risk associated with dose, duration, or recency of medication use, which might inform the biologic plausibility of observed associations. Many agents that affect carcinogenesis have long latencies or require a minimum exposure level, and risk associated with some agents may return to baseline after the exposure has been terminated for a period of time. Some diabetes medications have only recently come on the mar-

ket (e.g., TZDs, insulin analogs, incretin-based therapies). Therefore, studies of these agents will only assess cancer risk associated with relatively short-term use.

It is unlikely that the effect of diabetes therapies on cancer risk and progression—particularly at specific cancer sites—will be fully addressed with randomized controlled clinical trials, due to both cost- and follow-up time limitations. Such trials would also be confounded by the natural crossover and treatment escalation required to appropriately treat progressive hyperglycemia. Given these limitations, multiple well-conducted and appropriately designed prospective observational studies are needed. Results of in vitro and preclinical studies should inform design considerations for observational studies but by themselves cannot be considered conclusive.

**Acknowledgments**—The American Cancer Society and American Diabetes Association thank the following companies for their unrestricted support of the consensus development conference: Amylin Pharmaceuticals, Inc.; Lilly USA; Merck & Company, Inc.; Novo Nordisk A/S; and the sanofi-aventis Groupe.

The authors thank the researchers who presented their work at the conference: Rachel Ballard-Barbash, MD, MPH; Frederick Brancati, MD, MHS; Peter T. Campbell, PhD; Edwin Gale, MD; Hertz C. Gerstein, MD, MSc, FRCP(C); Edward L. Giovannucci, MD, ScD; Pamela Goodwin, MD, MSc, FRCP(C); Michael Goran, PhD; Jeffrey A. Johnson, PhD; Carol Koro, PhD; Larry Kushi, ScD; Derek LeRoith, MD, PhD; Karin B. Michels, MPH, MS, MSc, PhD, ScD; Alpa V. Patel, PhD; Andrew Renehan, PhD, FRCS; Ulf Smith, MD, PhD;

Kevin Struhl, PhD; and Henry Thompson, PhD.

Duality of interest statements: E.G., D.M.H., M.C.A., and S.M.G. report no duality of interest. R.M.B. has served on scientific advisory boards or as a consultant to Medtronic, Abbott, Bayer Diabetes Care, Eli Lilly, Intuity Medical, MannKind, Novo Nordisk, Roche, sanofi aventis, and Valeritas; has received research support from Amylin, Bayer Diabetes Care, Eli Lilly, Mannkind, Medtronic, the National Institutes of Health (NIH), Novo Nordisk, ResMed, and LifeScan; and is a joint stockholder in Merck. L.A.H. has received research support from Takeda, Merck, Genetech (Roche), and sanofi-aventis. M.P. has received research support from Pfizer and serves as a consultant to sanofi-aventis and Novo Nordisk. J.G.R. has received research support from NIH and the American Diabetes Association and has received honoraria from the University of Colorado, Denver. D.Y. has served on the advisory board of Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

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