I. INTRODUCTION

Cancer cells are influenced by the environment that they inhabit. They require nutrients, hormones, and growth factors, provided by the blood of their host, and receive paracrine signals from surrounding cells, in a similar manner to any other cell of the human body. These factors influence their growth and spread. The characteristics of cancer cells and the metabolic abnormalities of their host may influence how they survive, proliferate, and spread.

In 1926, Warburg et al. (192) reported that cancer cells have the ability to obtain energy both from aerobic respiration and anaerobic glycolysis with the formation of lactic acid, in the presence of oxygen (a characteristic known as the Warburg phenomenon). He reported that this ability to produce energy from aerobic respiration and glycolysis enhanced the survival of cancer cells in glucose- or oxygen-deprived conditions. In recent years, we have developed a greater understanding of the mechanisms that lead to the Warburg effect. In addition, it has emerged that changes in glucose uptake and metabolism are not the only metabolic idiosyncrasy of cancer cells. In fact, cancer cells are known to be influenced by the nutrients in the environment in which they reside, and the hormonal signals to which they are subjected. It is these interactions between an individual's metabolic status and the distinct characteristics of tumors that are believed to underlie the associations between obesity, diabetes, and cancer.

The association between obesity, diabetes, and cancer has recently received much attention due to the alarming increases in the prevalence of obesity and type 2 diabetes. However, the first reported case of diabetes associated with cancer has been attributed to the 19th century English physician Dr. Richard Bright. In 1832, he reported the case of a patient with polyuria, polydipsia, sweet urine, and carcinoma of the pancreas. This case was described years before the identification of the islets of Langerhans as the source of insulin secretion. In 1910, the South African epidemiologist Mr. George Darell Maynard reported that diabetes was associated with an increased risk of many cancers. His findings were controversial and disputed by many epidemiological and diabetes experts following his publication (132). By 1957, Dr. E. T. Bell, the renowned pathologist from the University of Minnesota, stated that it was “well known” that carcinoma of the pancreas was frequently associated with glycosuria and hyperglycemia; however, it was not known whether there was an increased incidence of “true” diabetes in subjects with pancreatic carcinoma, or if subjects with “true” diabetes demonstrated an increased incidence of carcinoma of the pancreas, a question that was debated subsequently for many years (15).

Obesity, calorie restriction, and cancer links have been explored in animal studies since the 1940s. An increase in toxin-induced cancers was found in obese animals, and a decrease in calorie-restricted animals (193). In the 1960s it...
was recognized that obese women had a greater incidence of endometrial cancer than their lean counterparts. This association was attributed to an increase in estrogen synthesis from adipose tissue in overweight/obese women (198), and weight loss was proposed by the authors as the most practical preventative measure for endometrial cancer.

Since the time of these groundbreaking clinical observations and research studies, much work has been done to understand the links between obesity, diabetes, and cancer. As type 2 diabetes and obesity are a global epidemic, an urgent need to understand the interactions between these metabolic conditions and cancer has emerged. In this review, we first discuss the epidemiological studies on obesity and cancer as well as diabetes and cancer. We then review the metabolic abnormalities that are associated with obesity and diabetes and could link obesity, diabetes, and cancer, specifically examining the in vitro and animal studies. Finally, we consider the lifestyle, surgical, and pharmacological treatments for obesity and diabetes that may reduce cancer risk.

II. EPIDEMIOLOGY

The initial clinical observations and studies discussed above paved the way for the many recent large cohort studies examining the links between obesity, diabetes, and cancer incidence and mortality.

A. Obesity and Cancer

The large cohort studies that have provided much of our knowledge today on the links between obesity and cancer have been performed since the 1990s. The Cancer Prevention Study II (CPS II) was one such study that followed patients from 1982 to 1996 and included over 1 million United States adults. The study examined the association between body mass index (BMI), calculated from patients self-reported height and weight, and cancer mortality. The authors found that the most obese men and women had a 40-80% increased risk of dying from cancer (28). The same group subsequently published a more detailed analysis of the CPS II cohort and the association between BMI and mortality from cancer at specific sites after 16 yr of follow up. They reported a linear trend of increased overall cancer mortality with increasing BMI, and for increased death from colorectal, liver, gallbladder, pancreatic, and kidney cancer, Non-Hodgkin’s lymphoma and multiple myeloma in both sexes; breast, endometrial, cervical, and ovarian cancer in women; and leukemia, esophageal, stomach, and prostate cancer in men. An inverse association was observed between lung cancer mortality and BMI in both sexes, while no association was found between melanoma, brain, or bladder cancer in either sex (27). Multiple subsequent studies and meta-analyses have been performed that have confirmed these findings that obesity is associated with greater mortality from specific cancers.

The incidence of certain cancers is also higher in obese individuals. A comprehensive meta-analysis was performed in 2007, including 221 datasets from different populations. The authors of this study found that in men, for every 5 kg/m² increase in BMI, there was an increased risk of esophageal, thyroid, colon, kidney, and rectal cancer, melanoma, leukemia, and multiple myeloma. In women, an increased risk of endometrial, gallbladder, esophageal, kidney, thyroid, postmenopausal breast, pancreatic, and colon cancer, multiple myeloma, non-Hodgkin lymphoma, and leukemia was detected. There was again an inverse association between lung cancer risk and BMI in men and women (161). While obesity is consistently associated with a greater risk of prostate cancer mortality (30), some studies have reported a decreased incidence of prostate cancer in obese men (66). Overall, it appears that obesity may decrease the risk of localized prostate cancer and increase the risk of more aggressive disease (43). Why this difference in prostate cancer incidence and mortality exists is not entirely understood. It is possible that lower testosterone levels in obese individuals reduce the risk of developing cancer, but when cancer develops, other factors such as endogenous insulin and lipids may contribute to the growth of the tumor. These factors are discussed in detail in section III.

Although BMI is generally used as a measure of obesity, it is well recognized in the field of endocrinology that when obesity is measured by BMI, a number of individuals who are metabolically unhealthy are classified as not obese. Waist circumference is preferred over BMI as a measure of obesity, as it correlates better with visceral adiposity and insulin resistance, as well as other markers of metabolic “unhealthiness” including dyslipidemia, glucose intolerance, and hypertension, which are all associated with the development of type 2 diabetes (6). Furthermore, specific populations including South-East Asian populations frequently have these metabolic abnormalities despite the fact that their BMI falls into the normal range (6). Fewer studies have specifically examined the contribution of waist circumference to cancer risk and mortality, compared with BMI. In the CPS II study of predominantly white women, waist circumference did correlate with postmenopausal breast cancer risk, but did not offer a greater predictive power than BMI in this population (63). However, in the Nurses’ Health Study population, it was found that waist circumference was associated with postmenopausal breast cancer risk, specifically in women who had never received postmenopausal hormone replacement therapy (84). A meta-analysis of studies reported that adjusting for BMI actually revealed that waist circumference may be specifically associated with breast cancer risk in premenopausal women while BMI was not (71). A 4% increased risk of colon cancer was found to be associated with every 2 cm
increase in waist circumference in a meta-analysis of studies (136). Interestingly, although multiple studies report that BMI is inversely associated with lung cancer risk, the Women’s Health Initiative revealed that waist circumference was positively associated with lung cancer risk in current and former smokers (94). These studies suggest that it is not simply obesity, but metabolic dysfunction even in people with normal BMI that is associated with the increased risk of certain cancers.

B. Weight Loss and Cancer

If obesity is associated with increased cancer incidence and mortality, then can intentional weight loss reduce the risk of cancer and cancer mortality? When evaluating the effect of weight loss on cancer risk and mortality, it is important to distinguish between intentional and unintentional weight loss, as cancer cachexia, associated with anorexia and weight loss, is associated with significant mortality (79). A review of 34 published articles covering this field was published by Birks et al. in 2012 (19). They separately examined the effects of intentional surgical weight loss, intentional nonsurgical weight loss, and weight loss that was unintentional or undefined on cancer incidence and mortality. The three studies examining the effect of surgical weight loss on cancer incidence found that there was a 24–78% reduction in overall cancer incidence in the bariatric surgery population compared with the obese control group (1, 35, 174). After further analysis, the Swedish Obesity Study (174) and the study from Utah in the United States (1) found that the decreased risk was only apparent in women. The Utah study also specifically examined the risk of obesity-related cancers and found a significant 38% risk reduction in the bariatric surgery group. The authors of this study also examined cancer mortality and found a 46% decrease in cancer mortality in the group who had undergone bariatric surgery (1). Birks et al. (19) examined three cohort studies investigating the effect of nonsurgical weight loss on the incidence and mortality from cancer. In these studies, 17–19% of the study populations achieved intentional weight loss, and the results were examined based on the degree of weight loss. One of the studies which included a cohort of men only from the CPS reported no significant difference in the risk of cancer mortality with intentional weight loss (196). However, women from the CPS with preexisting obesity-related illnesses did have a reduction in cancer mortality (195). The third study, which was a prospective cohort from the Iowa Women’s Health Study, reported a decrease in the incidence of all cancers, breast cancer, and obesity-related cancer in the population that lost ≥9 kg (153).

Currently, one in three Americans is overweight or obese, and excess body fat is estimated to be a cause of ~120,400 United States cancer cases every year, according to The American Institute of Cancer Research and the World Cancer Research Fund (http://www.aicr.org/learn-more-about-cancer/infographic-obesity-and-cancer.html, last accessed September 14, 2014). With the increasing global prevalence of obesity and the known increase in cancer risk and mortality in obese patients, these studies suggest that intentional effective weight loss through surgical or nonsurgical means may reduce cancer incidence and mortality in certain populations. The published studies find that the obese white female population benefit most from intentional weight loss by surgical or nonsurgical means. However, further studies on intentional weight loss should be performed in other obese populations to determine if weight loss is beneficial in reducing specific cancer incidence and mortality in other groups.

C. Diabetes and Cancer

1. Type 2 diabetes

Along with the increasing prevalence of obesity worldwide, there is an increasing prevalence of type 2 diabetes. Although it was recognized for many years that diabetes was associated with pancreatic cancer, large prospective cohort studies to reexplore Maynard’s initial observations on the association between diabetes and cancer were not performed until relatively recently. The National Health and Nutrition Examination Survey I (NHANES I) was one of the first of these Examination studies. The investigators analyzed the risk of all cancers, and specifically lung, colorectal, breast, and prostate cancers, in 14,407 men and women who were enrolled in the 1970s. The enrollees were followed until 1987. It was reported that men with diabetes had a 39% increased risk of developing cancer overall, specifically colorectal and prostate cancer (175). The Nurses’ Health Study enrolled women in 1976 and followed them biennially to determine potential risk factors for cancer, amongst other diseases. In 2003, the investigators reported a 17% increased risk of breast cancer incidence (HR 1.17, CI 1.01–1.35) in women with diabetes, compared with women without diabetes. This association remained after adjustment for multiple factors and was found to be independent of age and obesity. The researchers reported that the association was predominant among postmenopausal women and women with estrogen receptor (ER)-positive breast cancer (134). One of the largest cohorts with the longest duration of follow up is the CPS II cohort (29). After following these patients for 26 yr, an increased risk of death from liver, pancreatic, colon, and breast cancer was observed in diabetic men and women. In addition, an increased mortality was seen from endometrial cancer in women, oral cavity and pharyngeal cancer and bladder cancer in men (TABLES 1 and 2) (29). Many other studies and meta-analyses have been performed to examine cancer incidence and mortality in diabetic patients, compared with the general population. Overall, a consistent increase in the risk of pancreatic cancer, biliary tract cancer (159), and
esophageal cancer in men (83); breast and endometrial cancer in women (58, 108); and kidney and colorectal cancer in men and women (109, 110) have been reported. Furthermore, studies on cancer mortality have revealed that patients with diabetes have greater cancer mortality compared with their nondiabetic counterparts (12, 29).

In men, the studies examining the risk and mortality from prostate cancer in patients with diabetes have reported conflicting findings. The NHANES I study, for example, reported an increased risk of prostate cancer among men with diabetes. However, in many subsequent studies, diabetes has been associated with a reduced risk of developing prostate cancer (97). However, in men with diabetes who develop prostate cancer, they have a worse prognosis according to meta-analyses of studies (26). Genetic and endocrine reasons have been suggested as possible explanations for the decreased risk of prostate cancer in men with obesity and type 2 diabetes, although exactly why men with diabetes have a lower risk of developing prostate cancer, but a greater mortality from prostate cancer in most studies is not known. Genetics studies in the United States have reported that single nucleotide polymorphisms associated with type 2 diabetes were inversely associated with prostate cancer risk (126, 156). Obesity and diabetes are frequently associated with lower testosterone levels, which may protect from prostate cancer development. In addition, a recent study has reported that hyperglycemia leads to downregulation of the androgen receptor in an animal model using hormone-dependent prostate cancer xenografts (11). Therefore, lower circulating testosterone and a decrease in androgen receptor expression may explain the reduced risk. However, downregulation of the androgen receptor may make prostate cancer less responsive to androgen deprivation therapy in diabetic men. In addition, other metabolic abnormalities that occur with obesity and type 2 diabetes, and are discussed further below, may lead to the greater mortality observed in obese and diabetic men who develop prostate cancer.

### Table 1. Diabetes and cancer mortality in men

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Diabetes Risk Relative to No Diabetes (Men)</th>
<th>Age-adjusted RR (95% CI)</th>
<th>Multivariable-adjusted RR (95% CI) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity of pharynx</td>
<td></td>
<td>1.39 (1.04–1.87)</td>
<td>1.44 (1.07–1.94)</td>
</tr>
<tr>
<td>Colon</td>
<td></td>
<td>1.21 (1.08–1.35)</td>
<td>1.15 (1.03–1.29)</td>
</tr>
<tr>
<td>Liver or intrahepatic bile duct</td>
<td></td>
<td>2.40 (2.02–2.86)</td>
<td>2.26 (1.89–2.70)</td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td>1.42 (1.25–1.61)</td>
<td>1.40 (1.23–1.59)</td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td>1.23 (1.02–1.48)</td>
<td>1.22 (1.01–1.47)</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td>4.37 (2.32–8.24)</td>
<td>4.20 (2.20–8.04)</td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td>0.89 (0.80–0.98)</td>
<td>0.88 (0.79–0.97)</td>
</tr>
</tbody>
</table>

No significant difference in RR was found for cancer of the esophagus, rectum or anus, gallbladder or extracellular bile duct, larynx, lung, bronchus or trachea, connective tissue, other skin, melanoma, kidney or other urinary organs, brain or nervous system, lymphoma, multiple myeloma, and leukemia. *Adjusted for age, education, BMI, smoking, alcohol intake, vegetable intake, red meat intake, physical activity, and aspirin use. [Data from the Cancer Prevention II Study (28).]

### Table 2. Diabetes and cancer mortality in women

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Diabetes Risk Relative to No Diabetes (Women)</th>
<th>Age-adjusted RR (95% CI)</th>
<th>Multivariable-adjusted RR (95% CI) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td></td>
<td>1.42 (1.08–1.85)</td>
<td>1.24 (0.95–1.63)</td>
</tr>
<tr>
<td>Colon</td>
<td></td>
<td>1.29 (1.15–1.45)</td>
<td>1.18 (1.04–1.33)</td>
</tr>
<tr>
<td>Liver or intrahepatic bile duct</td>
<td></td>
<td>1.65 (1.25–2.18)</td>
<td>1.40 (1.05–1.86)</td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td>1.37 (1.19–1.58)</td>
<td>1.31 (1.14–1.51)</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td>1.24 (1.11–1.39)</td>
<td>1.16 (1.03–1.29)</td>
</tr>
<tr>
<td>Endometrial</td>
<td></td>
<td>1.72 (1.40–2.12)</td>
<td>1.33 (1.08–1.65)</td>
</tr>
<tr>
<td>Cervix</td>
<td></td>
<td>1.90 (1.19–3.03)</td>
<td>1.47 (0.91–2.37)</td>
</tr>
<tr>
<td>Kidney and other urinary organs</td>
<td></td>
<td>1.42 (1.09–1.87)</td>
<td>1.15 (0.88–1.52)</td>
</tr>
</tbody>
</table>

No significant difference in RR was found for cancer of the oral cavity or pharynx, esophagus, rectum or anus, gallbladder or extracellular bile duct, lung, bronchus or trachea, connective tissue, other skin, melanoma, brain or nervous system, lymphoma, multiple myeloma, and leukemia. *Adjusted for age, education, BMI, smoking, alcohol intake, vegetable intake, red meat intake, physical activity, and aspirin use. [Data from the Cancer Prevention II Study (28).]
2. Prediabetes

Type 2 diabetes is preceded by many years of prediabetes, which is defined as an elevated fasting glucose level or abnormal glucose tolerance, but without blood glucose levels in the diabetic range. Individuals with the metabolic syndrome, which is defined by increased waist circumference, dyslipidemia, hypertension, and glucose intolerance, are at greatest risk of developing type 2 diabetes. It has been noted in some studies that the incidence of cancer is greater within the first months to years following diabetes diagnosis (93). This included an increased risk of colorectal, lung, liver, cervical, endometrial, ovarian, pancreatic, and prostate cancers. The authors suggest that there is an increase in cancer diagnosis due to increased testing and screening of the newly diagnosed diabetic patient. After the initial period, the risk of some cancers remained elevated, including colorectal, liver and endometrial cancer, and pancreatic cancer, while after the initial 3 mo period, men with type 2 diabetes had a lower risk of prostate cancer diagnosis in this retrospective cohort (93). A similar observation was reported in a retrospective study of breast cancer incidence from Australia (150), and in a study from Canada that reported that 9.7% of 24,976 patients diagnosed with breast cancer were diagnosed with diabetes within 5.5 yr of follow up (118). The authors of these studies suggest that the increased incidence of breast cancer around the time of diabetes diagnosis is because of the risk of cancer being greatest in the prediabetes phase (118, 150). These results suggest that the metabolic abnormalities associated with prediabetes may contribute to breast cancer development.

3. Type 1 diabetes

In contrast to type 2 diabetes, type 1 diabetes has not been linked with the same increased risk of cancer. Type 1 diabetes is a condition of insulin deficiency due to autoimmune destruction of the pancreatic beta cells, rather than insulin resistance, and is not generally associated with the metabolic syndrome and obesity. However, if hyperglycemia associated with diabetes is an important contributing factor to the development of cancer in patients with type 2 diabetes, one would also expect an increase in cancer risk and mortality in patients with type 1 diabetes. Fewer studies have examined the association between type 1 diabetes and cancer. In one Swedish cohort, type 1 diabetes was associated with an increased risk of stomach, cervical, and endometrial cancer (210). A second Swedish study identified a 17% increased overall risk of cancer in hospitalized patients with type 1 diabetes (172) and a specific increase in gastric cancer, squamous cell skin cancer, and leukemia. Another study conducted in the United Kingdom reported no increased risk of cancer overall in patients with type 1 diabetes, but did find an increased risk of ovarian cancer incidence and mortality (181). Further prospective studies are needed to determine whether type 1 diabetes is associated with an increased incidence and mortality from specific cancers.

III. MECHANISMS LINKING OBESITY, TYPE 2 DIABETES, AND CANCER

Obesity, specifically abdominal obesity, and type 2 diabetes are frequently associated with metabolic abnormalities that may contribute to cancer progression. Abdominal obesity is associated with increased adipose tissue inflammation with the production of cytokines and changes in the circulating concentrations of adipokines (produced by fat). These changes can contribute to insulin resistance in metabolic tissues (fat, liver, and skeletal muscle), necessitating an increase in the production of insulin from the pancreatic beta cells to maintain normal glucose levels, leading to circulating hyperinsulinemia. Endogenous insulin acting on the liver increases insulin-like growth factor I (IGF-I) synthesis in response to growth hormone and leads to changes in circulating concentrations of IGF-binding proteins (IGFBPs). These changes in IGFBPs in response to insulin may also occur in individual tissues leading to changes in the local concentration of bioavailable IGF-I. In type 2 diabetes, the pancreatic beta cells eventually decompensate and hyperglycemia develops. Insulin resistance is also associated with lipid abnormalities, characterized by elevated very low-density lipoproteins (VLDL) and triglycerides, decreased high-density lipoprotein (HDL) cholesterol, and a decrease in the hepatic production of sex hormone binding globulin (SHBG), which may lead to an increase in the levels of free hormones (including estrogen and testosterone). Furthermore, excess adiposity may lead to increased local aromatization of androgens to estrogens, which may affect tumor growth. These mechanisms are summarized in Figure 1 and will be discussed in further detail below.

A. Insulin and Insulin-Like Growth Factors

1. Insulin and insulin-like growth factor signaling

Insulin resistance positively correlates with abdominal obesity (191). Of individuals with type 2 diabetes (who comprise 90% of all diabetes cases worldwide), almost all patients are insulin resistant (158). High circulating insulin levels correlate strongly with insulin resistance and have been found to do so in women with breast cancer (67). An increased interest in the role of hyperinsulinemia and insulin receptor signaling in cancers has recently occurred, in part due to the association between hyperinsulinemia and obesity and type 2 diabetes. Second, recent oncology clinical trials using IGF-1 receptor (IGF-IR) targeted therapy have emphasized the similarities between the insulin receptor and IGF-IR, and the potential role of the insulin receptor in driving tumor growth.

The insulin-like growth factor system consists of the insulin receptor (IR), IGF-IR, and insulin-like growth factor II re-
receptor (IGF-IIR), along with the ligands insulin, IGF-I, and IGF-II, and the IGFBPs that bind IGF-I and IGF-II, but not insulin. The IGF-IR was initially found to be overexpressed in a number of childhood cancers, such as Wilms’ tumor, osteosarcoma, and rhabdomyosarcoma (113), and subsequently found to be overexpressed in a number of other cancers including breast, colorectal, liver, and prostate cancers. In addition, many tumors overexpress IGF-II due to loss of imprinting, which signals through the IGF-IR and the mitogenic form of the IR (202). In addition, many tumors express IGF-I, which is the main ligand for the IGF-IR. The loss of tumor suppressor genes BRCA1, p53, and PTEN were found to lead to an increase in IGF-IR expression (201, 202, 214), and similarly IGF-I stimulation of tumor cells was found to downregulate tumor suppressor genes such as WT1 (18). In animal models, high doses of exogenous IGF-I have been found to increase tumor growth and metastases. Reduced tumor growth was seen in mice with liver-specific IGF-I deletion (LID) and low circulating IGF-I levels, and in the llt/lit mice that have low circulating IGF-I due to decreased growth hormone production (201). A number of epidemiological studies reported that circulating IGF-I levels in the upper quartile of the normal population range were associated with an increased risk of cancer.

In addition, a population of individuals from Ecuador with growth hormone receptor mutations, who have very low circulating IGF-I levels, appears to be protected from cancer development compared with the normal population (69). These human and animal data suggested that blocking the IGF-IR would be an effective target for anti-cancer therapy. However, clinical trials that targeted the IGF-IR have not been successful (205). The postulated reasons for their failure are numerous. First, the trials did not specifically target people with tumors that overexpressed the IGF-IR. In addition, inhibiting the IGF-IR leads to elevated circulating levels of IGF-I, which from in vitro and in vivo studies is known to be capable of activating the IR. Furthermore, inhibiting the IGF-IR leads to impaired feedback on growth hormone (GH) secretion, causing elevated circulating levels of GH, which causes insulin resistance and hyperinsulinemia. Hyperinsulinemia through activation of the IR on tumor cells may also contribute to tumor growth and progression (205).

The IR is expressed in many tissues, not only metabolic tissues. It is also expressed in the fetus, where insulin is important for growth, and hyperinsulinemia leads to macrosomia (96). Many tumors, including breast, colon, lung,
prostate, ovary, and thyroid cancers, overexpress the IR (14, 37). Insulin receptors are not downregulated in the fetus in response to hyperinsulinemia (96). Similarly in breast cancer, IR expression is not downregulated in tumors of hyperinsulinemic women (142). Although the IGF-IR has traditionally been thought of as a mediator of mitogenic signaling, and the IR as an activator of metabolic signaling, IR phosphorylation actually activates both metabolic and mitogenic signaling pathways (14). Furthermore, there are two splice variants of the IR, IR-A and IR-B. IR-A lacks exon 11 and is mainly expressed in fetal and cancer tissues, while IR-B is predominantly expressed in the liver, skeletal muscle, adipose tissue, and kidney. The expression of certain splicing factors in cells determines the ratio of IR-A to IR-B in the cell (14). Recent studies have found that activation of the epidermal growth factor receptor (EGFR)/mitogen-activated protein kinase (MAPK) pathway increases the IR-A/IR-B ratio in hepatocellular carcinoma cell lines by upregulating expression of certain splicing factors in the tumor cells, but not in regenerating normal liver (34). Alterations in expression of splicing factors such as SRSF3 lead to increased expression of IR-A and promote the growth of hepatocellular carcinoma (169). Studies in different cell lines have revealed that the different insulin receptor isoforms have different affinity for insulin, IGF-I, and IGF-II. IR-A has a 1.7-fold greater affinity for insulin than IR-B (139). IR-A binds IGF-II with ~40 times greater affinity than IR-B, and IGF-I with ~10 times higher affinity than IR-B (14). Signal transduction after ligand binding to IR-A or IR-B differs greatly, and differs depending on the ligand that is bound to the receptor isoform. In murine 32D hematopoietic cells, IR-A has been shown to activate mitogenic, anti-apoptotic signaling, while IR-B activation leads to cell differentiation. The differences between IR-A and IR-B signaling are highlighted in the condition known as myotonic dystrophy, which occurs due to a mutation leading to increased skeletal muscle ratio of IR-A to IR-B and is associated with insulin resistance (139). Therefore, in tumors, aberrant signaling leads to changes in the expression of splicing factors, leading to an increase in IR-A expression, and this is hypothesized to be responsible for the effects of hyperinsulinemia on tumor growth (14). For further details on insulin receptor ligands, signaling, and the insulin receptor isoforms, we refer readers to the comprehensive review written by Belfiore et al. in 2009 (14).

2. Epidemiology linking hyperinsulinemia and cancer

As discussed above, insulin resistance and hyperinsulinemia are common in individuals with obesity and type 2 diabetes. Large cohort studies have examined whether endogenous hyperinsulinemia is associated with cancer risk and mortality. These studies have examined insulin or C-peptide levels as markers of insulin secretion. C-peptide is cosecreted with insulin, has a longer half-life than insulin, and unlike insulin, it is not extracted by the liver (129) and is therefore a more stable marker of insulin secretion. The Nurses’ Health Study cohort found an association between C-peptide and invasive breast cancer, particularly estrogen receptor (ER)-negative disease (4). In the Healthy Eating, Activity, and Lifestyle (HEAL) Study, C-peptide was associated with a 33% increased risk of breast cancer death, particularly in women with ER-positive tumors (86). The European Prospective Investigation into Cancer and Nutrition (EPIC) study found a twofold increased risk of breast cancer in women over the age of 60 years with elevated C-peptide levels (188). Elevated C-peptide levels have also been correlated with a 37% increased risk of colorectal cancer (89) and a fourfold increased risk of endometrial cancer (123). Not all studies have reported a positive correlation between C-peptide and cancer risk. A recent meta-analysis did not find an increased risk of breast cancer in women with elevated serum insulin or C-peptide levels after adjusting for BMI, suggesting that insulin and C-peptide levels are not independent of BMI (9). In prostate cancer, some studies, including the Health Professionals Follow-Up Study and the CPS II Nutrition cohort, have reported no clear correlation between circulating C-peptide and either prostate cancer risk, or mortality, or in the risk of developing aggressive prostate cancer (107, 124, 177). However, the Physicians Health Study reported that obese men with elevated C-peptide levels were four times more likely to die from prostate cancer than men with normal C-peptide levels (124). Some of the variability in these studies is likely due to blood tests being drawn in an uncontrolled way relating to the length of time after the persons last meal, in addition to variations in adjustment for certain confounding risk factors, including BMI and medications. Overall, there is increasing evidence from both animal models and human studies to suggest a role for endogenous hyperinsulinemia, secondary to insulin resistance, in promoting breast cancer growth and metastases.

3. Animal models of hyperinsulinemia

A mouse model of hyperinsulinemia and type 2 diabetes was previously developed in the LeRoith lab using a transgenic approach (52). By overexpressing a dominant-negative IGF-IR specifically in skeletal muscle [named MKR for muscle (M) lysine (K) to arginine (R) substitution in the tyrosine kinase motif of the IGF-IR], the mice developed severe muscle insulin resistance, leading to beta cell compensation and hyperinsulinemia 2 wk after birth. Insulin resistance developed in fat and liver by 3–4 wk of age. At 6–8 wk of age, the male mice demonstrated a beta cell defect (loss of first phase insulin release) and the male mice became hyperglycemic and hyperlipidemic, but were not obese (52). The female MKR mice developed a similar degree of insulin resistance and hyperinsulinemia (2- to 3-fold higher insulin concentration than normal) but did not develop hyperglycemia. The female MKR mouse has normal circulating lipids, IGF-I, and levels of the inflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (55, 147). Therefore, the female MKR mice have
allowed for the study of the effect of hyperinsulinemia on breast cancer development, independent of hyperglycemia, dyslipidemia, and increased circulating inflammatory cytokines (147).

When mammary tumors were induced in the female MKR mice, by crossing them with mice expressing the polyoma virus middle T antigen (PyVmT) oncogene in mammary epithelium (a mouse model of luminal B type human breast cancer, Ref. 23), the MKR mice developed larger tumors (147). Similarly, when cells overexpressing the Neu (ortholog of human epidermal growth factor receptor 2, HER2) or c-myc/vegf oncogenes were injected orthotopically into mammary glands, the tumors grew more rapidly in the hyperinsulinemic female MKR mice (51, 147). Reducing insulin levels in the MKR mice using a β-3 adrenergic receptor agonist (CL-316,243) or blocking the IR and IGF-IR using a tyrosine kinase inhibitor reduced the growth of the primary tumors in the female MKR mice; conversely, administration of a mitogenic insulin analog increased tumor growth and metastases in the MKR mice (51, 55, 59, 147). These results support the hypothesis that endogenous hyperinsulinemia enhances primary breast cancer growth by activation of the IR and/or IGF-IR. The phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway was consistently overactivated in all of the tumor types derived from the MKR mice, irrespective of the oncogene (51, 146), and inhibiting PI3K or mTOR reduced primary tumor growth to the level of the wild-type mouse (60).

The female MKR mice develop more numerous lung metastases than wild-type mice after orthotopic injection of c-myc/vegf overexpressing (MVT1) cells, or induction of transgenic Her2/Neu overexpressing tumors (50, 51). Reducing the insulin levels using the β-3 adrenergic agonist CL-316,243 reduced the number of metastases to the number seen in the wild-type mice (28).

Another method of inducing hyperinsulinemia in mouse models is through diet-induced obesity. High-fat diet feeding of mice induces obesity, and elevations in circulating cytokines, including TNF-α, IL-1β, and IL-6 (119). It is also associated with increased circulating IGF-I, decreased IGFBP-3, glucose intolerance, increased leptin, resistin, and decreased adiponectin in mice (149). An increase in growth of colon, thyroid, breast, and gastric cancer has been found in diet-induced obesity models (64, 104, 117, 119). Therefore, while hyperinsulinemia is an important contributing factor to tumor progression in high-fat diet fed models, other metabolic and inflammatory abnormalities could also be contributing.

B. Hyperglycemia

Hyperglycemia is the hallmark of diabetes, occurring in type 2 diabetes due to a relative insulin deficiency, and in type 1 diabetes due to an absolute insulin deficiency. As discussed in section I, Warburg initially identified that cancer cells are glucose avid and generate more energy from glycolysis and lactate production compared with oxidative phosphorylation than noncancerous cells. Metabolic tissues including skeletal muscle and adipose tissue take up glucose in response to insulin, an effect mediated by the translocation of glucose transporter 4 (GLUT4) to the plasma membrane. In contrast, most cancers predominantly express the glucose transporter GLUT1, although other glucose transporters have been detected in tumor tissues (2, 125). GLUT1 has a high affinity for glucose and is responsible for basal glucose uptake in tissues. Cells transformed by oncogenes, such as ras, src, and c-myc have been shown to activate GLUT1 and GLUT3 expression (40, 125). GLUT12 was more recently discovered and is expressed in human breast and prostate cancer and rodent fetal tissues, as well as adult insulin-sensitive tissues, including skeletal muscle, heart, and adipose tissue. GLUT12 plays a role in glucose uptake in cancer cells distinct from GLUT1 and GLUT3 (125). The increased aerobic glycolysis observed in many tumors is thought to be due to the upregulation of glycolytic genes by oncogenes and the mutation of tumor suppressor genes (186). The three rate-limiting enzymes of glycolysis are hexokinase, phosphofructokinase, and pyruvate kinase. Their regulation has been found to be altered in cancer cells by oncogenes, loss of tumor suppressors, the activity of hormones, including insulin, and activation of PI3K/Akt signaling (72, 186). The increase in aerobic glycolysis in tumor cells provides the precursors necessary for nucleotide, amino acid, and lipid synthesis, and thus for cancer cell proliferation (186).

Knowing that cancer cells avidly take up glucose and utilize this glucose for energy production and synthesis of building blocks, and that in uncontrolled diabetes circulating glucose is abundant, an appropriate question would be, does hyperglycemia provide tumor cells with more glucose and add to tumor proliferation? Some clinical studies have examined the association between glycemic control, evaluated by hemoglobin A1c (HbA1c), and cancer risk and mortality. A meta-analysis of 14 studies examined the association between HbA1c and the risk of various cancers in patients with diabetic range and prediabetic range HbA1c levels. They reported an increased risk of breast cancer associated with a HbA1c above 8.5% and for colorectal cancer above 6.5%, and an increased risk of gastric, pancreatic, and hepatic cancer with HbA1c levels in the diabetic range. A trend to a decreased risk of prostate cancer incidence with increasing HbA1c was also observed (42). These epidemiological studies cannot account for the other metabolic and dietary factors associated with poor glycemic control. Therefore, animal models have been used to study the effect of hyperglycemia on tumor growth using the chemical streptozotocin that is toxic to pancreatic beta cells. Streptozotocin leads to hyperglycemia without hyperinsulinemia.
and has been used to study the effect of hyperglycemia and cancer growth in animal models. A decrease in human prostate cancer cell growth was observed in a mouse model of streptozotocin-induced diabetes (11). Given the inverse relationship between prostate cancer and HbA1c, this result may not be surprising. However, streptozotocin-induced diabetes also leads to inhibited growth of pancreatic and breast cancers in animal models (16, 36, 170). These results suggest that although tumors avidly take up glucose, delivering more glucose to tumors in the setting of hyperglycemia does not increase tumor growth.

Hyperglycemia can contribute to the formation of advanced glycation end products (AGEs), which have been implicated in the microvascular and macrovascular disease in patients with diabetes (22). AGEs are formed when glucose or other sugars react nonenzymatically with the free amino group on proteins, lipids, or nucleic acids. The initial product is known as a Schiff base, and it spontaneously rearranges itself into an Amadori product. Although the initial reaction is reversible, a series of subsequent irreversible reactions lead to the production of AGEs (22). While the generation of AGEs is a normal part of metabolism, older individuals, those with type 1 and type 2 diabetes, and obese individuals have high levels of AGEs in the circulation that accumulate in tissues (190). The receptor for AGEs (RAGE) is a member of the immunoglobulin family of cell surface receptors (163). The expression of RAGE is increased with increased levels of AGEs. The interaction of RAGE with its ligands has been reported to lead to oxidative stress and increased inflammation, which promotes tumor growth, angiogenesis, and metastases (163). Soluble RAGE (sRAGE) is a soluble form of RAGE that is found in the human circulation. sRAGE can also bind AGEs and therefore competitively inhibits the binding of AGEs and other ligands to RAGE. A small epidemiological study from Italy reported that circulating sRAGE is lower in diabetic patients than controls and lower in diabetic patients with higher HbA1c (13). One recent study has reported that individuals with the higher circulating levels of sRAGE had a lower risk of colorectal and hepatic cancer, although no association was found between sRAGE and pancreatic cancer in the EPIC cohort (68, 91, 140). Therefore, elevated HbA1c in patients with diabetes could be a marker for an increase in circulating and tissue levels of AGEs which may be contributing to tumor growth through their proinflammatory effects. Studies to further understand the role of AGEs and other ligands for RAGE and sRAGE in cancer development in obesity and type 2 diabetes are ongoing.

C. Dyslipidemia

Dyslipidemia is common in patients with obesity and type 2 diabetes. Obesity is associated with increased low-density lipoprotein (LDL) cholesterol (56). Obese and diabetic patients also frequently have dyslipidemia with elevated circulating very low-density lipoprotein (VLDL) cholesterol and triglycerides, an increase in small dense LDL cholesterol, and a decrease in HDL cholesterol (31). Elevated cholesterol, particularly elevated VLDL and low HDL cholesterol, was associated with a greater risk of cancer in the Framingham Offspring cohort (127, 133). A meta-analysis of studies found that elevated total cholesterol (>6.5 mM) was associated with an 18% increased risk of cancer, elevated triglycerides (>1.71 mM) was associated with a 20% increased risk, and decreased HDL cholesterol (<1.03 mM) was associated with a 15% increased risk (133). Genetic population studies have reported that polymorphisms in genes (ApoA-I and ApoE) that are associated with hyperlipidemia (elevated VLDL and LDL, respectively) are also associated with increased breast cancer risk, greater risk of developing estrogen receptor negative breast cancer, and a greater risk of breast cancer recurrence and mortality (32, 82, 141). Recent studies have reported that cholesterol-lowering therapy, with 3-hydroxy-3-methyl-glutaryl-CoA (HMG CoA) reductase inhibitors, is associated with a lower risk of overall cancer mortality (145), with some studies reporting a lowering risk of developing specific cancers, including hepatocellular carcinoma (173), and others report decreased recurrence and mortality from prostate cancer and breast cancer (5, 208). Not all studies have reported a protective effect of statins on cancer incidence (38, 183, 212, 213). Differences in study results may be partly related to the potentially protective effect of statin on cancer incidence, versus cancer metastasis, recurrence, and mortality, and not all cancer types or subtypes may be affected by cholesterol- or lipid-lowering therapy. In addition, duration of statin use has been cited in some studies to be an important contributing factor, while others have cited that the type of statin used is an important contributor to the potential statin effect. Different statins have different pharmacological properties, including their solubility in water, their hepatic uptake, and protein binding in the circulation (112). The statins simvastatin and lovastatin are lipophilic, are taken up by the liver, have 5% unbound drug in the circulation, and have been reported in rodents to have higher HMG CoA reductase inhibition in the liver than other statins. In contrast, pravastatin has 50% unbound fraction in the circulation and has been shown to inhibit HMG CoA reductase in nonhepatic tissue more than other statins (112). Statins have been hypothesized to potentially reduce cancer mortality by decreasing circulating cholesterol levels, through directly inhibiting cholesterol synthesis in tumor cells, by their anti-inflammatory properties, or by other tumor specific mechanisms, such as by downregulation of HER2 expression (215). However, not all statin studies have demonstrated beneficial effects (185). The apparently conflicting results suggest that not all subtypes of cancers may be responsive to the growth-stimulating effects of high cholesterol and further that not all statins inhibit the growth and progression of all breast cancers (197). No prospective randomized controlled trials have yet...
been performed to examine the effect of statins on cancer risk or progression.

If cholesterol is contributing to cancer growth and progression directly, then what mechanisms may contribute to this effect? The LDL receptor (LDLR) is widely expressed on cancer cells (178) and is a major site of cholesterol uptake into cells from LDL, VLDL, and VLDL remnant (33, 189). Higher expression of the LDLR in breast cancer pathological specimens has been correlated with more advanced disease, poor response to chemotherapy, and increased mortality (164, 184). Triple negative breast cancer cell lines have greater expression of the LDLR than ERα positive (MCF7) cells (178). LDL cholesterol increases the proliferation of breast and prostate cancer cell lines in vitro, and downregulating the LDLR in prostate cancer cell lines impairs this pro-proliferative effect of LDL (168). In normal cells, cholesterol levels are tightly regulated by sterol regulatory element-binding protein-2 (SREBP-2) and liver X receptors (LXRs), which downregulate cholesterol uptake via the LDLR and increase cholesterol efflux (92, 130). In human ERα-negative breast cancer cells (MDA-MB-231) and prostate cancer cell lines however, this downregulation of the LDLR does not occur, and no increase in cholesterol efflux gene transcription occurs, resulting in increased intracellular cholesterol (8, 209). Cholesterol has been shown to increase phosphatidylinositol 3-kinase (PI3K)/Akt signaling in vitro in breast, colon, and prostate cancer cell lines and increased cell proliferation (7, 167, 218). Cholesterol is a precursor for progesterone, estrogen, and androgen synthesis in normal physiology. In human prostate cancers, it has been demonstrated that the enzymes necessary for testosterone and dihydrotestosterone synthesis are expressed, suggesting that prostate cancers are capable of synthesizing androgens from cholesterol (138, 154) and therefore could promote their own growth through androgen stimulation of the androgen receptor activation, even in the setting of androgen deprivation therapy.

Animal studies have been used to examine the effect of hyperlipidemia on tumor growth. The ApoE−/− mouse has elevated total, VLDL, intermediate-density lipoprotein (IDL), and LDL cholesterol (41). The LeRoith lab has previously found an increase in the growth and metastasis of orthotopic murine ERα negative mammary tumors in the ApoE−/− mice on a high-fat/high-cholesterol diet (7). The Frank lab has used high-cholesterol diets to study the effect of hypercholesterolemia on ERα-positive breast and prostate cancer. They report that the hyperlipidemia resulting from a high-fat diet promotes the growth of these tumors (121, 122). Increased ERα-positive murine breast tumor growth was also seen in the hyperlipidemic ApoE3 mice fed a high-fat diet (143). In addition to its direct effects and its use to synthesize steroid hormones, cholesterol is also metabolized into biologically active oxysterols, one of which is 27-hydroxycholesterol. 27-Hydroxycholesterol is a selective ERα modulator and has recently been shown to promote the growth of primary ERα-positive human and murine breast cancers in mice (143). Inhibiting ERα reduced primary tumor growth in response to 27-hydroxycholesterol. Oxysterols such as 27-hydroxycholesterol are also agonists of LXR in murine ERα-negative breast cancers and inhibiting LXR activity reduced metastasis in this model (138, 154). Oxysterols have also been shown to increase inflammatory cytokines in macrophages in atherosclerotic lesions (102), and therefore, cholesterol may also have indirect effects on tumor growth by increasing inflammation.

D. Adipose Tissue Factors

Adipose tissue is an important organ for the production of adipokines, inflammatory cytokines, and enzymes that are dysregulated in obesity and type 2 diabetes and potentially contribute to tumor growth and metastases. While there are large adipose tissue deposits, including subcutaneous and visceral adipose tissue, there is adipose tissue surrounding many organs, and it is also abundant in many organs where cancers develop, for example, the breast. Therefore, the changes in adipose tissue related to obesity and type 2 diabetes may lead to the release of tumor promoting factors into the circulation. In addition, adipose tissue may exert an important influence on cancer cells in the local tumor environment.

1. Adipokines

Adipokines refer to the factors produced by adipocytes. In obesity and type 2 diabetes, inflammatory cells, including macrophages and lymphocytes, frequently invade adipose tissue and secrete factors, known as cytokines. The main factors secreted by adipose tissue and adipose tissue macrophages that have been studied in relation to cancer include leptin, adiponectin, resistin, lipocalin 2, NAMPT, TNF-α, and IL-6. The roles of these factors in obesity and inflammation have recently been reviewed in detail (20, 148, 152). Adipokines are being investigated as pharmacological strategies for the treatment of obesity and metabolic disease. We will discuss how changes in these adipokines have been associated with cancer development and progression in the setting of obesity and type 2 diabetes.

Leptin is a regulator of appetite through its effects on the brain. Leptin deficiency leads to hyperphagia, obesity, and insulin resistance, as seen in the ob/ob mice. However, in humans with obesity, elevated leptin levels are seen, without any reduction in appetite, due to leptin resistance (152). Leptin binds to the leptin receptor, ObR, a member of the class I cytokine receptor family. There is a full-length leptin receptor, ObRb, and short isoforms. Leptin binding to its full-length receptor activates numerous intracellular signaling pathways that promote tumor cell growth and metastases, including the Jak/Stat, MAPK, PI3K/Akt, and SOCS
pathways. ObR expression has been detected in human breast cancers, most notably in human breast cancer subtypes that carry a worse prognosis. High expression of ObR in breast tumors is associated with a poor prognosis particularly in patients with elevated circulating leptin levels (180). Its expression has also been found in gastrointestinal cancers, and in some tumors, it is associated with a worse prognosis. Ongoing research into the effects of leptin and leptin receptor signaling and their inhibition is necessary to further understand the role of this adipokine in cancer progression.

Adiponectin is reputed to be an anti-inflammatory adipokine. Plasma levels of adiponectin are lower in obese individuals than lean individuals, while weight loss increases adiponectin levels. Adiponectin knockout mice exhibit increased expression of proinflammatory genes, including TNF-α, IL-6, and MCP-1, while treatment of mice with adiponectin induces the expression of anti-inflammatory mediators including arginase-1, IL-10, and macrophage galactose/N-acetyl-galactosamine-specific lectin-1 in peritoneal macrophages. Adiponectin is secreted as a monomeric protein that can oligomerize to form a low-molecular-weight, high-molecular-weight, or multimeric complex or can be cleaved by leukocyte elastase to form a globular oligomeric complex. There are two receptors for adiponectin, AdipoR1 and AdipoR2. Globular adiponectin preferentially binds AdipoR1, while the full-length and multimeric adiponectin binds preferentially to AdipoR2. Adiponectin signaling leads to increased phosphorylation of AMPK and antagonizes leptin signaling. Epidemiological studies have reported that low circulating adiponectin levels are associated with an increased risk of cancer, and cancer progression, while mouse studies have demonstrated that adiponectin knockout mice have increased tumor formation in the liver and colon, but interestingly decreased tumor growth in polyoma virus middle T antigen-induced mouse mammary tumors (187). Therefore, whether adiponectin has cancer-protective or cancer-promoting effects remains controversial (73).

Resistin is also a proinflammatory adipokine that induces resistance to insulin and is elevated in obesity and type 2 diabetes (176). It mediates its effects on insulin resistance by activating suppressor of cytokine signaling 3 (SOCS3) that interferes with insulin signaling (176). In humans, resistin is primarily secreted by macrophages and is induced by IL-1, IL-6, and TNF-α. Its role in cancer development and progression has been less well studied than leptin and adiponectin. Some studies have reported an increase in serum resistin concentrations in patients with cancer, and an increased risk of cancer in individuals with higher levels of serum resistin. However, as elevated serum resistin correlates with insulin resistance, these associations do not demonstrate that resistin itself plays a direct role in cancer development or progression (39, 78). Only a few studies have examined the direct effects of resistin on cancer cells. Resistin has been reported to be expressed in human prostate cancer cell lines and stimulated prostate cancer cell proliferation by activation of PI3K/Akt signaling (101), while other studies have reported that it induces stromal derived derived factor-1 through activation of Toll-like receptors, p38 MAPK, and NFκB (81). It has also been found to be expressed in poor prognosis breast cancer tissues and in high-grade prostate cancer tissue (101, 111). Much remains to be discovered about the potential role of resistin in cancer.

Lipocalin-2 is a recently identified adipokine (211). Circulating lipocalin 2 levels are increased in obese rodents, and it has been reported to have anti-inflammatory properties (211). Elevated circulating levels of lipocalin-2 have been found in patients with pancreatic cancer (98). Some studies have reported that high expression of lipocalin-2 is associated with a good prognosis in pancreatic cancer, leading to a less aggressive phenotype with higher expression of the epithelial marker E-cadherin, and lower expression of the mesenchymal marker vimentin, which is associated with tumor metastasis (200). Other studies however have reported that lipocalin-2 expression in oral and lung cancers is associated with resistance to radiotherapy and increased VEGF expression in breast cancer cell lines (204). Therefore, further studies are needed to understand the potentiating or protective effects of this newly discovered adipokine on cancer growth and progression.

Nicotinamide phosphoribosyltransferase (Nampt)/visfatin is also secreted from adipose tissue and other tissues in humans. It converts nicotinamide to nicotinamide mononucleotide and regulates the activity of sirtuins (20, 62). Administration of Nampt to a mouse model of obesity and type 2 diabetes increased NAD+ biosynthesis and improved glucose intolerance and insulin sensitivity (207). Circulating levels of Nampt have been found to be higher in obesity and type 2 diabetes, and decreases after exercise in human studies (62). The conversion of nicotinamide to NAD+ is essential for cellular metabolism and energy production. Inhibiting Nampt using a small molecule inhibitor, FK866, leads to the attenuation of glycolysis due to the reduced availability of NAD+, necessary for the glyceraldehyde 3-phosphate dehydrogenase step. Inhibiting NAMPT in cancer cells led to the inhibition of tumor growth in rodent bearing tumors derived from human colon and ovarian cancer cell lines (182). Nampt has also been reported to increase the expression of proinflammatory cytokines and inhibit apoptosis in response to endoplasmic reticulum stress (62). Therefore, Nampt has the potential to increase tumor growth by promoting tumor cell glycolysis and increasing inflammation, and inhibiting Nampt has the potential to decrease tumor growth.
Multiple inflammatory cytokines are known to be dysregulated in obesity, type 2 diabetes, and cancer. TNF-α, IL-6, and IL-1β have been widely studied in obesity and type 2 diabetes and are increased in the adipose tissue and in the circulation of obese individuals (70). In obesity and type 2 diabetes, adipose tissue is infiltrated by macrophages and T cells, and these inflammatory cells lead to a state of chronic low-grade inflammation. The systemic induction of inflammatory cytokines and local production of inflammatory cytokines in the peritumoral stroma have been associated with increased tumor growth and metastasis. The tumor-promoting effects of inflammatory cytokines are chiefly mediated by the activation of NFκB and Stat3 signaling pathways and contribute to angiogenesis and changes to the cancer cells that allow them to change from an epithelial to a mesenchymal cell phenotype that has more metastatic properties (128).

Increased adiposity is also associated with increased aromatization of androgens to estrogen. Insulin resistance is associated with decreased synthesis of hepatic sex hormone binding globulin (SHBG). These two effects lead to an increase in the circulating levels of bioavailable estrogen, are associated with obesity and type 2 diabetes, and have been proposed to lead to the greater risk of estrogen-dependent breast and endometrial cancer. Adipose tissue macrophages have been shown to form crownlike structures, which have been observed in the breast adipose tissue from obese women and in animal models. An increase in aromatase expression is induced by the inflammatory cytokines from these crownlike structures. Aromatase increases the conversion of androgens to estrogens locally in the breast adipose tissue, leading to an increase in ERα signaling in breast cancer (80). A similar interaction between endometrial cancer and its surrounding stroma has been observed (131). Therefore, in obesity and type 2 diabetes, an increase in systemic and local estrogen production may occur and contribute to the risk of hormone-dependent cancers.

E. Gut Microbiome in Obesity, Diabetes, and Cancer

The relationship between the microbes that live in the human gut and metabolism has recently emerged. Changes in the gut microbiome are seen in obesity and type 2 diabetes and are believed to alter metabolism and potentially contribute to obesity and type 2 diabetes. Animal studies have shown that transplanting the microbes from an obese animal into the gut of a germ-free mouse leads to increased adiposity, compared with transplantation of the microbes from a lean mouse. In obese humans and mice, an increase in genes involved in carbohydrate metabolism has been seen in the gut microbiota. In patients with type 2 diabetes, a decrease in the proportion of butyrate-producing Clostridiales was observed, and other studies have reported an increase in E. coli and Proteobacteria. Changes in gut microbiota have been seen in humans after gastric bypass surgery. Precisely how the gut microbiome contributes to insulin resistance and type 2 diabetes is the subject of ongoing research. Some studies report that certain bacteria increase the production of lipopolysaccharides that lead to chronic inflammation and insulin resistance, while other bacteria produce protective factors, including butyrate, that can activate intestinal gluconeogenesis or cobalamin and folic acid that have been shown to improve metabolism (100).

Similarly, alterations in the gut microbiome have been reported to increase the risk of certain cancers. It is now well established that eradication of Helicobacter pylori reduces the risk of gastric cancer. As the microbacteria in the gut are in direct interaction with the gastrointestinal tract, one of the major cancers associated with altered gut bacteria is colorectal cancer. Different studies have reported different bacteria to be associated with colorectal cancer risk. One bacteria associated with colorectal cancer in a number of studies is Fusobacterium nucleatum. The microbiome has also been associated with other gastrointestinal cancers. The microbiome has also been reported to contribute to the development of other cancers, including pancreatic, laryngeal, gallbladder, and hepatocellular carcinoma (162, 171). The potential mechanisms are still the subject of much research. Whether the increased risk of cancer associated with certain gut bacteria is due to an increase in inflammation, or whether it is associated with the production of protective factors or toxic factors by some bacteria, or a combination of these factors is currently unclear. Interestingly, butyrate has anti-cancer effects, leading to decreased proliferation and inducing apoptosis, and thus may form a link between the protective effect of some bacteria against metabolic disease and cancer (171).

IV. DIABETES MEDICATIONS THAT POTENTIALLY REDUCE CANCER

Due to the associations between obesity, diabetes, and cancer and the renewed interest in the role of metabolism in cancer progression, studies have recently examined whether insulin-sensitizing medications, primarily metformin and thiazolidinediones, could be protective against cancer risk or progression. At the present time there are no results from prospective randomized controlled clinical trials; therefore, we will discuss the available epidemiological, clinical, and preclinical data that explain why these therapeutic agents may have anti-cancer effects.

A. Metformin

Metformin was initially hypothesized to have anti-cancer potential in diabetic patients in a paper by Evans et al. (47). Although metformin, and similar medications in the class of biguanides including phenformin, derived from French li-
lac, had been used to treat diabetes for many years, the mechanism of action was elusive until it was discovered that metformin led to decreased hepatic gluconeogenesis by activating or phosphorylating AMP kinase (AMPK) in the liver (216). Peutz-Jeghers syndrome, an autosomal dominant inherited condition that predisposes to cancer, is associated with mutations leading to loss of function of the tumor suppressor gene LKB1, an activator of AMPK. Therefore, when it was discovered that metformin led to AMPK phosphorylation, it was hypothesized that it may be protective against cancer. In the study by Evans et al. (47), and in multiple subsequent epidemiological studies, diabetic patients taking metformin had a lower mortality from cancer than diabetic patients on no therapy, on insulin secretagogues (sulfonylureas), or on insulin therapy. Prospective clinical trials are ongoing to determine if metformin has beneficial effects as an adjuvant therapy in patients with breast cancer.

Following the publication of these epidemiological studies, a number of groups have studied the in vitro and in vivo effects of metformin on cancer growth and metastasis to determine the mechanism of action by which metformin may inhibit cancer progression. There are two main hypotheses that explain the mechanism of metformin activity on cancer growth (FIGURE 2). The first is that metformin improves systemic insulin resistance, thus lowering circulating insulin and glucose levels. This effect has been seen in diabetic patients and underlying its therapeutic effects for treating type 2 diabetes. In one human study, patients without diabetes, with newly diagnosed breast cancer were given 1,500 mg metformin for a median of 18 days. Their circulating insulin levels and HOMA-IR (homeostasis model assessment of insulin resistance) were assessed before and after taking metformin. Metformin treatment led to a decrease in HOMA-IR, indicating a decrease in insulin resistance, as well as a decrease in circulating insulin levels. These findings suggest that metformin could reduce tumor growth by decreasing the effect of insulin on the tumor cells.

The second hypothesis is that metformin acts directly on the tumor cells. This hypothesis is supported by in vitro and animal studies using large doses of metformin; however, the direct effect of metformin on tumor growth in human tumors in clinically relevant doses remains to be proven. Metformin is taken up into the liver by the organic cation trans-
porters OCT1, OCT2, and OCT3/4 (75, 103). Therefore, if metformin acts directly on cancer cells, then Oct expression in the tumor cells would be necessary. Studies have shown that Oct-1, Oct-2, and Oct-4 are expressed in a variety of human cancers (3, 90, 103). Oct-4 is expressed in cancer stem-like cells and is regulated by IL-6 (103). The importance of these Oct transporters in the direct effects of metformin have been found in the mouse model of tuberous sclerosis and renal carcinoma (203). Metformin was found to be ineffective in reducing tumor growth in this model and did not inhibit mTORC1 signaling in the tumors, while it did in normal tissue. It was found that the expression of the Oct1, Oct2, and Oct3/4 genes was suppressed in the renal tumors, highlighting the need for these transporters to be expressed for metformin to be taken up into the tumor cells (203). Metformin has been shown in vitro and in animal models to increase AMPK activation (46), which inhibits signaling through the mTOR pathway by activating tuberous sclerosis complex 2, and thus prevent tumor cell proliferation. Metformin increases AMPK activation by augmenting the AMP-to-ATP ratio. It does so by inhibiting mitochondrial complex 1 of the respiratory chain, which decreases ATP synthesis (46). Other studies have shown that phosphorylation of Ser-428/431 in the long isoform of LKB1 by protein kinase C (PKC)-ε is essential for the metformin-mediated activation of AMPK (199).

Recent studies have reported that activation of AMPK by metformin inhibits lipid synthesis in cancer cells (114) and suppresses RAGE expression, thus inhibiting AGE/RAGE effects on tumor cell proliferation (87). However, studies on the metabolic effects of metformin demonstrated that metformin inhibits gluconeogenesis in an LKB1- and AMPK-independent fashion (57). Metformin also appears to exert some of its anti-neoplastic properties through AMPK-independent effects. Metformin has been shown to inhibit mTOR by increasing expression of REDD1, a p53 target in a manner dependent on p53 (17). It has recently been reported to inhibit cell proliferation by impairing cancer cell glycolysis (49, 88, 166). Metformin has been reported to directly inhibit hexokinase activity, thus impairing glucose uptake into tumor cells (166). In cells undergoing transformation, metformin prevented the increase in glycolytic intermediates, decreases tricarboxylic acid (TCA) cycle intermediates, and depleted nucleotide triphosphates, thus impairing nucleotide synthesis (88). Metformin inhibits inflammatory signals in cancer cells, including the nuclear translocation of NFkB and Stat3 phosphorylation and reduces the growth of inflammatory tumor xenografts in mice (76). It inhibits angiogenesis (151) and therefore may reduce cancer metastasis. Finally, metformin may selectively kill breast cancer stem cells and prevent tumor recurrence in mouse xenografts (77). Overall, these studies suggest that metformin may reduce tumor progression by improving systemic metabolism, or by direct effects on tumor cells. We await the results of clinical trials to determine whether the findings of these preclinical studies will translate into clinical benefit for patients with cancer.

B. Thiazolidinediones

The other major class of insulin-sensitizing medications, used to treat and prevent type 2 diabetes, is the thiazolidinediones (TZDs). The TZDs in current clinical use in the United States include rosiglitazone and pioglitazone. Troglitazone was another member of this drug class that was in clinical use in the 1990s, but was withdrawn due to adverse hepatic effects. TZDs are activators of peroxisome proliferator-activated receptor (PPAR)-γ, a transcription factor predominantly expressed in adipocytes (157). PPAR-γ is a nuclear receptor and forms a heterodimer with retinoid X receptor (RXR), regulating the expression of genes involved in insulin action, adipocyte differentiation, inflammation, and lipid metabolism (157). Activation of PPAR-γ by TZDs leads to the release of corepressors bound to the receptor and the recruitment of coactivators that lead to gene transcription. TZD activation of PPAR-γ leads to the differentiation of adipocytes; decreased release of free fatty acids from adipocytes; decreased production of prostaglandins, TNF-α, IL-6, leptin, and resistin by adipocytes; increased adiponectin production; and increased glucose disposal by adipocytes, and insulin sensitivity is thereby improved (FIGURE 3) (157).

The first animal studies that revealed the potential anti-neoplastic effects of TZDs were performed with troglitazone in prostate cancer models (105). Multiple in vitro studies in a variety of cancer cell lines demonstrated the anti-proliferative effects of troglitazone; however, phase II clinical studies of troglitazone on metastatic colorectal and refractory metastatic breast cancer failed to demonstrate a therapeutic benefit (25, 106). After the withdrawal of troglitazone, clinical and preclinical studies were performed using rosiglitazone and pioglitazone. A phase II clinical trial of rosiglitazone in patients with thyroglobulin-positive and radioiodine-negative differentiated thyroid cancer found that rosiglitazone improved radioiodine uptake in the tumors and decreased serum thyroglobulin levels in some patients but did not result in a clinically significant response (99). In women with early-stage breast cancer, 2–6 wk of treatment with rosiglitazone failed to alter cell proliferation, determined by Ki67 expression, but serum insulin levels decreased and serum adiponectin levels increased (206). A meta-analysis of randomized clinical trials using rosiglitazone found that the incidence of malignancies was significantly lower in the rosiglitazone-treated patients than the control patients (137). Animal studies have supported a potential role for rosiglitazone as an adjuvant therapy in pancreatic and lung cancer (24, 65).

Initial preclinical studies on pioglitazone in vitro and in animal models also supported an anti-neoplastic effect of
pioglitazone. However, in 2011, an interim analysis of a cohort study from the Kaiser Permanente Northern California diabetes registry reported that after more than 2 yr of therapy there was a 40% increased risk of bladder cancer in diabetic patients treated with pioglitazone (115). However, another group of investigators published their analysis of the same cohort and found no increased risk of cancer in those using pioglitazone (53). A subsequent flurry of studies were published also reporting an increased risk of bladder cancer associated with pioglitazone. These studies included data from an adverse events reporting database (155), a nested case control study (10), a retrospective cohort study (144), and two meta-analyses of studies (54, 217). However, reanalysis of the United Kingdom Clinical Practice Research Datalink did not find an increased risk of bladder cancer with pioglitazone use (194). Further analysis of the Kaiser Permanente Northern California cohort study found that adjusting for albuminuria attenuated the risk of bladder cancer in pioglitazone users. Further data have been uploaded to the European Medicines Agency’s European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) website, and report that the increased risk of bladder cancer may have been due to a detection bias, due to increased urinary screening of patients with albuminuria, and greater detection of subclinical bladder cancer (44), although the authors of the initial Kaiser Permanente study report that proteinuria testing does not fully explain the association between pioglitazone and bladder cancer (116). Prospective studies are ongoing to determine whether there is an increase in the risk of bladder cancer in patients treated with pioglitazone.

C. Insulin Therapy

All individuals with type 1 diabetes, and many individuals with type 2 diabetes, require exogenous insulin therapy to prevent and treat hyperglycemia. The advent of recombinant DNA technology allowed for the production of recombinant human insulin, which largely replaced porcine and beef insulin in clinical use in the 1980s (61). A number of insulin analogs were developed to create a more physiological meal-related insulin profile and to reduce hypoglycemia (48, 95). In broad terms, these insulin analogs fall into two categories: those with a more rapid onset of action and peak effect than human insulin, and those with a longer duration of action. A number of such analogs are in clinical use today. One such analog that is not in clinical use is known as AspB10, as it has an amino acid substitution of aspartic acid in place of histidine at position 10 on the B chain of insulin. Other analogs include lispro, aspart, glulisine, glargine, and detemir. These insulin analogs have been shown to have benefits in reducing hypoglycemia and improving glycemic control.
insulin. This insulin analog was found to induce spontaneous mammary tumors in rats and has subsequently been shown to be mitogenic in human breast cancer cells in vitro (135) and in animal models of breast and colon cancer (59, 85). Human registry studies and retrospective cohort studies published in 2011–2012 reported that other insulin analogs may increase the risk of certain cancers, including breast cancer (74, 163, 179). However, a number of methodological flaws have been found in these studies (160). A follow up publication to one of the studies that initially reported an increased risk of cancer with insulin glargine use during the 3-yr follow-up study found that in the 4-yr follow-up study no increase in breast cancer was found (120). Furthermore, in the only prospective study to date of insulin glargine, no increase in the risk of developing cancer was found in those being treated with insulin glargine compared with the standard treatment group (21). These studies raised an important question: Why is AspB10 more mitogenic than human insulin, while other insulin analogs are not? New insulin analogs are currently in development, and understanding the mitogenic activity of AspB10 is important so that other analogs that come into clinical use do not have this effect.

In vitro and in vivo studies have been performed to understand the mechanisms mediating the mitogenic effects of AspB10 insulin. Initially it was hypothesized that the mitogenic effects of AspB10 were mediated through its binding to the IGF-IR with greater affinity than human insulin. Compared with IGF-I, AspB10 still had relatively low affinity for the IGF-IR. AspB10 also had greater affinity for the IR than human insulin, with greater affinity for both IR-A and IR-B isoforms than human insulin. Additionally, AspB10 led to more prolonged IR phosphorylation and a greater phosphorylation of downstream proteins than human insulin in human breast cancer cell lines. In vivo studies using murine colon and breast cancer cell lines also demonstrated that AspB10 increased the growth of these tumors in animal models of diet-induced obesity and nonobese hyperinsulinemia, respectively. In the murine breast tumors, AspB10 was found to lead to IR phosphorylation in vivo, rather than IGF-IR phosphorylation. These findings suggest that the mitogenic effects of AspB10 may be mediated by its greater affinity for the IR as well as its prolonged phosphorylation of the IR and downstream signaling proteins. Therefore, in the development of new insulin analogs, not only should affinity for the IGF-IR be tested, but also activation of IR signaling.

D. Limitations of Retrospective Studies on Diabetes Treatments and Cancer

Although there is a wealth of literature on the different diabetes treatments and their potentially beneficial or detrimental links to cancer, most of these studies are retrospective and should be interpreted with caution. Many of these studies do not account for comorbidities, or other medications being prescribed that may also have beneficial or harmful effects on cancer risk. Furthermore, when prescribing diabetes medications for a patient with type 2 diabetes, the choice of medication is based on multiple factors, including diabetes severity, the patients’ comorbidities, risk of side effects, and cost. Therefore, a patient who is prescribed metformin is less likely to have as many comorbidities as a patient prescribed an insulin analog. This allocation bias may influence the results of retrospective studies. Some retrospective cohort studies have attempted to account for these comorbidities using propensity score methods. However, prospective randomized trials of diabetes medications, such as those that are in progress to study metformin, are necessary to determine if diabetes medications are truly increasing or decreasing cancer risk and mortality.

V. Conclusions

Individuals with obesity and type 2 diabetes are at greater risk of developing and dying from multiple cancers. There are multiple potential metabolic abnormalities that occur in obesity and type 2 diabetes that may explain the increased risk. These metabolic factors linking obesity and type 2 diabetes with cancer have been discussed in this review. Which of these metabolic factors is most important, or whether they in concert promote the growth of specific cancer subtypes, is the subject of ongoing research. Currently there are no specific guidelines for cancer screening in patients with obesity and type 2 diabetes, despite their higher risk of cancer. Further studies should be performed to determine whether specific screening strategies to target this population would lead to a decrease in their cancer mortality.

Many of the links between obesity, diabetes, and cancer are currently emerging. Developing fields of research include the following: the role of the insulin receptor signaling in cancer; the contribution of lipids to breast cancer growth and metabolism; how changes in the intestinal microbiome may lead to obesity, type 2 diabetes, and cancer; the formation of advanced glycation end products; and the role of newly discovered adipokines in cancer progression. Understanding more about how these factors contribute to metabolic disease and cancer will identify which factors should be therapeutically targeted to reduce cancer growth. In addition, understanding which types of cancers are most susceptible to the growth-promoting factors associated with obesity and type 2 diabetes is being studied. We hypothesize that not all cancers are susceptible to the growth-promoting effects of obesity and type 2 diabetes, but specific subtypes of cancers will respond to the metabolic abnormalities found in these conditions. It will be important to identify if there are specific cancer mutations that make them more susceptible to progress in a person with metabolic dysfunction. Understanding this further would enable us to identify...
which cancers are more likely to respond to treatment of metabolic abnormalities.

Additional areas of current and future research include understanding if treatment strategies for obesity (including bariatric surgery) and diabetes medications that improve metabolic abnormalities will reduce tumor progression in clinical trials. As diabetes and obesity become worldwide epidemics, it is imperative that we rapidly develop strategies to reduce cancer development and mortality in these patients.

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REFERENCES


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