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The Links Between Insulin Resistance, Diabetes, and Cancer

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Abstract

The growing epidemic of obesity has resulted in a large increase in multiple related diseases. Recent evidence has strengthened the proposed synergistic relationship between obesity-related insulin resistance (IR) and/or diabetes mellitus (DM) and cancer. Within the past year, many studies have examined this relationship. Although the precise mechanisms and pathways are uncertain, it is becoming clear that hyperinsulinemia and possibly sustained hyperglycemia are important regulators of not only the development of cancer but also of treatment outcome. Further, clinical decision-making regarding the treatment of choice for DM will likely be impacted as we learn more about the non-metabolic effects of the available hyperglycemic agents. In our review, we endeavored to synthesize the recent literature and provide a concise view of the journey from macro-level clinical associations to specific mechanistic relationships being elucidated in cell lines and animal models.

Keywords

Apoptosis; Caloric Restriction; Cancer; Chemotherapy Resistance; Glargine; Insulin; Insulin Resistance; Metabolic Syndrome; Metformin; Obesity; Proliferation; Diabetes

Introduction: A Divergence in Paths

Concern regarding a potential association between diabetes mellitus (DM) and cancer risk first arose at the turn of the previous century [1] based on clinical observations of the coincident disease processes. This was supported by the simultaneous and sustained increase in the incidence of both diseases until recently [2;3]. Despite frequent convergence of the diagnoses in individuals, a divergence is now present in the incidence of the two diseases. The latest estimates show increased incidence and prevalence of DM in both the United States and globally [3;4], with a forecast of over 500 million individuals with diabetes by the year 2030 [5;6]. In contrast, the incidence of cancer which had been steadily increasing since the 1970's has currently plateaued. There is even a decreased incidence being reported for some malignancies, such as breast and colorectal cancer--two cancers strongly associated with the presence of DM [2;7;8]. The question facing clinicians therefore is: are these

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independent processes whose parallel rise is a result of similar responses to external forces (i.e. changes in the sensitivity of diagnosis, environmental influences, host changes in activity, nutrition, and other currently unknown factors) or does a true physiological link exist between the two diseases that will again accelerate the incidence of cancer? Furthermore, if a connection is present, do the existence of diabetes and the choices made in the treatment of the disease affect the development of, and/or outcome from, the various types of cancer? With the surge in publications within the field over the past year, this review will critically address these primary questions to help better understand the relationship between diabetes and cancer.

The Association between Diabetes and Risk for Developing Cancer

New evidence does, in fact, support an association between diabetes and cancer, albeit of a far more granular nature than the broad strokes of early reports. To be more precise, as displayed in Table 1, multiple meta-analyses and other large cohort studies published over the past year support an association between the presence of Type 2 DM (T2DM) and an increased incidence of many site-specific malignancies, including colorectal [9], hepatic [10], pancreatic [11], breast [12], endometrial [13], and urinary tract malignancies [14]. Most compelling is the persistence of this association across multiple international populations and the full spectrum of age and ethnic groups while controlling for all known confounders (e.g. smoking, body mass index, hormonal influences/menopause where relevant).

Yet, despite these strong statistical associations, many questions remain unanswered. For instance, if this is a broad physiologic oncologic effect as a result of T2DM, why does a protective association exist solely for prostate cancer? Adults with T2DM appear to actually have a 25–40% reduced lifetime risk of developing prostate cancer versus those without DM [15]. Similarly, while many hormonally-mediated tumors such as breast and endometrial cancers demonstrate an increased incidence in patients with T2DM, others such as ovarian cancer show no such increase in incidence [16]. Finally, common methodology constraints due to the observational cohort design lead to the presence of (A) detection bias (i.e. increased detection of cancer because of heightened levels of general health surveillance through treatment for T2DM) and/or (B) reverse causality (i.e. T2DM developing as a result of the malignancy). Two new studies help to shed light on the latter through accounting for the relative timing of diagnosis of T2DM and the malignancy. They found that while the association may not be as extreme as previously thought, the association between T2DM and certain cancer types is still present even when accounting for length of diagnosis of T2DM prior to diagnosis of malignancy and remains significant even with long periods of follow-up after diagnosis of the cancer [11;17]. A further understanding of the relationship between T2DM and malignancy is necessary through studies designed to specifically address causality, a question that has remained strictly beyond the purview of the trials to date.

Treatment for Type 2 Diabetes Mellitus and Cancer Incidence

Two primary hypotheses have been formulated regarding the potential mechanism of this relationship. The first such hypothesis combines the known episodic or continued hyperglycemia due to DM with the Warburg effect [18]; cancer's reliance for energy on anaerobic metabolism requires high levels of glucose to fuel the reaction and therefore cancer growth may be facilitated by high levels of available glucose. Clinical studies supporting this idea are inconsistent. While a high glycemic load even in non-diabetic patients has been associated with increased risk for developing endometrial cancer [19], the association was not consistent across all malignancies [20]. Further, studies of intensive

versus standard glycemic control in patients with diabetes failed to affect cancer incidence as would have been expected if the process is mediated by hyperglycemia [21]. The second proposed etiology attributes increased cancer incidence on the growth promoting effects of insulin [22]. Clinical examination of this theory can be drawn from studies of various oral agents and whether a difference in cancer incidence is present between oral agents that operate via heightened levels of insulin (i.e. sulfonylureas and meglitinides) and those that do not (i.e. glucosidase inhibitors, biguanides, thiazolidinediones). Studies comparing metformin, the most commonly used biguanide, to other hyperglycemic drugs are the clinical cornerstone of this theory. Use of metformin has been consistently associated with a reduced risk for developing a malignancy as compared to other oral drugs [23;24]. Conversely, and also consistent with the theory, a new study has reported sulfonylureas to be associated with greater incidence of cancer than metformin although not as high an incidence as with exogenous insulin [25]. Two new studies, however, challenge the relevancy of this clinical evidence for the insulin hypothesis through their identical finding that insulin-sensitizing thiazolidinediones are also associated with increased incidence of bladder and colorectal cancer despite the fact that they do not raise insulin levels [26;27]. Metformin continues to be tested as both an anti-cancer therapeutic agent in addition to whether it contributes to decreased incidence. Pending further information as to whether a true difference exists, the recommendation continues to be choosing the drug best clinically indicated for the treatment of the patient's hyperglycemia.

Exogenous insulin has also been studied in the context of the hypothesized insulin-mediated oncogenic effect. The alarm over exogenous insulin causing cancer was first raised in 2004 in the context of colorectal carcinoma [28]; in 2009, the concern became more widespread through a landmark cohort study by Hemkens *et al* that found that insulin dose and use of the long-acting insulin analogue, glargine, both correlated with increased risk for malignancy [29•]. From the time of publication, this finding raised a storm of controversy, with conflicting reports concurrently extracted from registry studies [30;31]. It is notable that the initial corroboratory study from the Swedish cohort reported by Jonasson *et al*, was reported this past year to show no further evidence of association now that the cohort has been expanded to include the intervening years since the initial report [32]. Contemporary studies predominantly show no association between insulin glargine and site-specific malignancies although certain exceptions exist for particular subsets such as pancreatic and prostate cancer [33–35]. The strongest evidence to date supporting the absence of a relationship between insulin and cancer was recently published in the *New England Journal of Medicine* [36]. It reports the results of a large prospective clinical trial (“The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial”) in which a subset of individuals were randomized between insulin glargine and standard of care to determine its impact on cardiovascular outcomes. The study also measured the incidence of overall and site-specific cancers and showed no differences between the two study groups. Unfortunately, as cancer incidence was only a secondary outcome, interpretation of the results remains complicated by the use in both study groups of a mixture of insulin, metformin and other oral glycemic agents, which as describe above, may directly influence cancer incidence. In summary, the ideal prospective studies specifically targeting the relationship between insulin and cancer have yet to be done and are unlikely to be performed due to issues of cost and feasibility caused by the necessity of complicated clinical regimens such as those found within the ORIGIN trial. Therefore, while current evidence supports the safety of insulin glargine, the concern over the oncogenic potential of insulin glargine will likely remain inconclusive.

Diabetes and Cancer Outcomes

Earlier cohort studies also raised the concern that DM was related not just to cancer incidence but cancer survival too. Around this time, a large cohort study also reported DM to be associated with increased mortality across a wide variety of site-specific malignancies including colon, pancreatic, breast, liver, and bladder cancers [37••]. The deleterious effect of pre-existing DM on survival continues to be validated across multiple cohorts and the full spectrum of cancer types [38;39] and appears to potentially be correlated even with the degree of hyperglycemia itself [40]. Similar to the evidence regarding choice of glycemic agent and incidence of cancer, multiple reports implicate metformin as the lone drug that consistently improves cancer survival across multiple cancers [41;42] although it should be noted a lack of benefit has been reported in a few cancers as well [41;43].

Insulin Resistance, Metabolic Syndrome & Cancer Incidence

Hyperinsulinemia and/or hyperglycemia are central components to current theories regarding the link between diabetes and cancer; elevated insulin levels due to insulin resistance (IR) in so-called “pre-diabetic” individuals has the potential to shed further light on the nature of this hypothesized relationship. To examine the potential association between IR and cancer across large cohorts and time periods is difficult, however, without an associated clinical diagnosis. Metabolic syndrome (MetS) supplies the key to this doorway. MetS is the definition for a group of diagnoses strongly associated with IR and may therefore be a potential surrogate marker of IR that can be found in clinical studies. In fact, a vast pooled cohort study titled the “Metabolic Syndrome and Cancer Project” or “Me-Can Study” provides exactly this opportunity to examine a connection between IR and cancer. The cohort consists of nearly a million subjects assembled from various Europe prospective studies over the course of the past 40 years and analyzes a collection of self-reported risk factors and clinical measurements for any association with various site-specific cancers [44]. Contemporary publications from this large cohort and others describe metabolic syndrome to be closely associated with the increased incidence of and/or mortality from a broad range of site-specific malignancies (including colorectal [45] cervical [46], liver [47], bladder [48], breast [49;50], and pancreatic cancer [45]) along with similar exceptions (ovarian and lung cancers) [51;52]. Interestingly, both skin and brain cancer, whose association with DM remains currently unexplored, showed no relationship with metabolic syndrome [53;54].

The MetS literature is complicated, however, by its clinical definition remaining a loosely-defined entity causing vast discrepancies in the diagnosis of MetS and reports of its prevalence [55]. This variation must be recognized in analysis of the above historical cohorts. Recent estimations have become more precise due to a composite definition disseminated in 2009 that will facilitate ongoing investigation [56]. Despite these limitations, the large cohorts included and the consistent effect found across multiple populations supports the existence of an association between MetS and cancer. The similarity in the associated oncogenic findings between MetS and clinical DM also promotes the concept that this is in fact mediated by a common factor, whether it is hyperinsulinemia, hyperglycemia, or some currently unrecognized feature.

In summary, a large number of prospective observational trials support the relationship between T2DM and increased cancer incidence and mortality. The strength of this association was formally recognized by the American Diabetes Association and the American Cancer Society in a joint statement in 2010 [57••]. Much remains to be learned regarding the nature of the connection between DM and cancer that can guide clinical decision making. An urgent need exists for further in-depth trials targeted at answering the

question of causality as well as any differences in incidence or mortality due to different glucose-lowering strategies.

Laboratory Evidence & the Basis for Further Clinical Trials

Despite the well-established epidemiological links between obesity, DM, IR, and cancer, the mechanisms linking these phenomena remain unclear. In vitro and animal models help provide some hint to this complex relationship and provide information regarding potential therapeutic targets for intervention.

The Role of Insulin in Cancer

Insulin is secreted by the beta cells of the pancreas in response primarily to glucose and other fuels. Obesity-induced IR is compensated for by an increase in insulin secretion, leading to fasting and post-prandial hyperinsulinemia. For individuals in whom IR progresses to T2DM, treatment frequently includes insulin secretagogues, insulin, or insulin analogues, which often requires achieving elevated levels of insulin to maintain appropriate glycemia in the face of continued IR. Thus, many patients with MetS and/or frank T2DM live in a persistent state of hyperinsulinemia.

In fact, insulin's role extends beyond glucose metabolism. The insulin receptor is a tyrosine kinase which exists in two isoforms: IR-A and IR-B. IR-B is expressed primarily in insulin-sensitive tissues and signals its metabolic effects through activation of the phosphoinositide 3-kinase (PI3K) pathway. IR-A is expressed in fetal tissue and cancer cells, and signals cell survival and proliferation through the Ras-mitogen-activated protein kinase (MAPK) pathways [58]. Both receptors signal through activation of insulin receptor substrate (IRS) family proteins, including IRS-1.

The involvement of insulin signaling in cancer pathogenesis has become evident from studies that show expression of insulin signaling proteins are poor prognostic markers. Recently, insulin receptor expression was found to be an independent, albeit weak, predictor of decreased overall survival in non-small cell lung cancer (NSCLC) [59]. Insulin receptor phosphorylation and/or IRS1 expression have been implicated in risk for metastases in colorectal [60] and endometrial [61] cancer.

Further, Morvan et al. showed that culturing human melanocytes at twice the standard glucose and insulin concentrations for 3 weeks was associated with carcinogenesis, as shown by increased rates of proliferation, DNA content, chromosomal aberrations, p-Akt, and c-Myc [62]. IRS-1 overexpression has also been shown to have oncogenic effects through promoting cell proliferation, inhibiting basal and oxidative stress-induced autophagy, and ultimately decreasing cell death in NIH/3T3 fibroblasts [63]. Conversely, insulin's cancer-promoting role is also demonstrated through studies in which insulin signaling is blocked. Indole-3-Carbinol (I3C), a hydrolysis product of glucobrassicin which is found in cruciferous vegetables, arrests proliferation of breast cancer cells through decreased expression of both the IGF1 receptor and IRS1 [64]. Dual inhibition of the insulin and IGF-1 receptors enhances breast cancer sensitivity to doxorubicin [65] and decreases hormone-independent growth [66]. All of these associations between insulin signaling and cancer demonstrate its important role in cancer cell pathogenesis.

Although insulin signaling via both the PI3K and MAPK pathways can contribute to cancer cell proliferation [67], several recent studies across multiple cancer types highlight the importance of the PI3K/AKT pathway in cancer pathogenesis. Insulin stimulates proliferation and migration of breast and colon cancer, and these effects are reversed by AKT inhibitor A6730 and PLC γ inhibitor U73122 [68]. IRS-1 and -2 overexpression also

prevents glucose-induced caspase 3 cleavage in human neuroblastoma cells, and this effect is reversed by PI3K inhibition [69]. Inhibiting PI3K similarly reduces the growth of Met-1 and MCNeuA mammary tumor orthografts in the MKR mouse model [70].

In addition to outright hyperinsulinemia, individuals with IR and T2DM have elevated circulating levels of proinsulin, thought to be due to impaired beta cell processing [71]. Since proinsulin binds to the IR-A isoform and stimulates receptor phosphorylation, it too can potentially contribute to the IR-cancer link [72].

Although most studies support the cancer-promoting effect of insulin signaling, there are a couple recent exceptions which highlight the complexity of these pathways. Cao et al. showed that α PGG, an insulin receptor activator, induces apoptosis in cancer cells [73]. Porter and colleagues found that IRS1 expression in 32D myeloid cells actually enhances sensitivity to chemotherapy induced apoptosis, an effect mediated through Annexin A2 [74]. While these exceptions may be from differences in experimental techniques, they also raise the concern that the effects of insulin signaling may not be uniform and likely vary between cancer cell types and subtypes.

insulin analogues

Diabetes treatment is becoming more reliant on the use of insulin analogues, which allow patients to attain more physiological pharmacodynamic patterns of insulin action. Glargine, a basal insulin analogue, has come under recent scrutiny, as discussed above. Glargine does exhibit similar effects on cancer cells as endogenous insulin, as one would expect. For example, glargine promotes proliferation and suppresses apoptosis in the MCF-7 breast cancer cell line [75]. However, there is little mechanistic evidence that glargine has disproportionate cancer promoting activity. One recent study showed that glargine may stimulate the insulin receptor/IGF-1 receptor hybrid with more potency than insulin and similar potency to IGF-1. However, the EC_{50} of this stimulation was well above (~50–100 times) levels normally obtained in vivo, and the primary breakdown products of glargine actually had less potency than insulin [76]. Another study found that glargine can upregulate expression of miRNAs in pancreatic cancer cells which promote cell proliferation; however, this was at concentrations roughly 1000 times physiological levels. [77]. In contrast, Pan et al. found that glargine at a near-physiological concentration of ~350 pM increased proliferation of ALL cells by 20–30%, which was slightly higher than equimolar regular insulin and aspart insulin [78]. Glargine also appeared to cause ALL resistance to daunorubicin in this study. Since peak glargine concentration is on the order of 200 pM [79], these findings are concerning, and should stimulate further work in this area.

Metformin

A number of in vitro and animal studies have addressed whether metformin has a direct anti-cancer effect, and have shown some promising results. For example, metformin enhances UVB-induced DNA repair in skin, which could potentially prevent malignant transformation [80]. In addition, metformin decreases leukemia cell proliferation rates and enhances sensitivity to daunorubicin [78]. These effects appear to be mediated via a variety of mechanisms, including inhibition of growth via NF κ B and mTOR pathway inhibition [81], increasing mitochondrial ROS production [82], targeting of STAT3 [83], and direct cytotoxicity via both caspase-dependent and PARP-dependent mechanisms [84]. Earlier studies had found metformin to selectively target cancer stem cells [85], with recent studies extending these findings to ovarian [86], pancreatic [87], and thyroid cancer [88]. Cufi et al. showed that breast cancer initiating cells resistant to Trastuzumab are particularly susceptible to metformin cytotoxicity [89]. Similarly, Appleyard et al. showed that

metformin can slow xenograft breast cancer cells, and phenformin can do so more potently [90].

In all, there is exciting in vitro evidence supporting the epidemiological finding of metformin's direct, anti-cancer effects. Given the beneficial safety profile of metformin, further work is certainly justified to continue exploring its potential use as adjunctive therapy.

Insulin-like Growth Factor-1 (IGF-1)

IGF-1 is a potent growth factor with a role in cancer pathogenesis, which has been linked in epidemiological studies to cancer. In obese individuals, total IGF-1 levels are often normal or even low due to decreased concentrations of IGF binding proteins, though the free/active IGF-1 levels are generally higher than in the non-obese. IGF-1 signals some of the same pathways as insulin, including PI3K, ERK, AKT, and mTOR, which as described above could increase cancer cell proliferation and impair apoptosis. IGF-1 can also increase normal cell cycling, leading to increased risk of mutation and malignant transformation. Most circulating IGF-1 is produced by the liver, though paracrine secretion of IGF-1 occurs at the growth plate, and perhaps other tissues [91]. Although a thorough review of the links between IGF-1 and cancer are beyond the scope of this article (see [92] for a recent review) we will describe some of the basic understanding of the role of IGF-1 in cancer, as well as highlight some recent findings of interest in this area.

IGF-1 receptor expression has been linked to poor prognosis in a number of cancers. Increased IGF-1 receptor expression in NSCLC is associated with poor prognosis [93], and IGF-1 receptor expression was noted to be higher in hepatocellular carcinoma cancer stem cells [94]. Cisplatin resistant lung cancer cells were found to have increased IGF-1 receptor signaling [95].

IGF-1 has recently been shown in vitro to enhance proliferation in prostate cancer cells [96]. Interestingly, adipocyte secretion of IGF-1 has been demonstrated to directly stimulate breast cancer cell proliferation in vitro [97••]. IGF-1 similarly modulates colon tumor cell growth via stimulation of NF κ B signaling and inflammatory response [98]. Lau et al. showed that IGF-1, perhaps via an autocrine signal, represses E-cadherin expression in ovarian cancer cells [99], which could thereby increase the risk of metastasis.

As with insulin, inhibition of IGF-1 signaling has anti-cancer effects. Knockdown of the IGF-1 receptor enhances chemotherapy sensitivity in some studies [95;100]. IGF-1 receptor antibody has been explored as a treatment, and recently shown to have in vitro efficacy against a small subset of gastric cancer and hepatocellular carcinoma cells, specifically those that express a high level of IGF-1R/Insulin Receptor heterodimer [101]. A few recent studies have explored the role of miRNA in IGF-1R expression in cancer. IGF-1 receptor expression was shown to be downregulated by miR-497 [102] and miR-139 [103] in colorectal cancer, and miR-7 in gastric cancer [104], both highlighting the potential roles of these miRNAs as anticancer agents and reaffirming IGF-1's apparent oncogenicity.

Given the cross-talk between signaling of the IGF-1 receptor, insulin receptor, and other growth receptors, some have hypothesized that IGF-1 signaling could represent a mechanism of resistance to therapies targeting signaling pathways [105]. For example, Qi et al demonstrated that IGF-1 receptor blockade acts synergistically with gefitinib, an epidermal growth factor receptor (EGFR) inhibitor, in gefitinib-resistant NSCLC [106]. In addition, Kim et al. showed that an IGF-1 receptor tyrosine kinase inhibitor was cytotoxic to NSCLC cells which expressed wild-type, but not those with EGFR mutations [107]. Conversely, immunohistochemistry measured expression of IGF-1 receptor in NSCLC from

patients previously treated with gefitinib was not associated with prognosis, and in fact co-expression of IGF-1 receptor and EGFR appeared to be associated with improved outcome [108]. A recent Phase II clinical trial of erlotinib (EGFR antibody) and R1507 (IGF1-R antibody) in patients with NSCLC showed no significant benefit of IGF1R targeting [109], while another Phase II trial showed no effect of the small molecule IGF1R inhibitor nordihydroguaiaretic acid to decrease prostate specific antigen levels in patients with non-metastatic, hormone sensitive prostate cancer [110].

In addition to EGFR, IGF-1 may also impair targeting of other signaling pathways. In ovarian cancer xenografts, increased IGF-1 expression was shown to be a potential mechanism of resistance to bevacizumab, an anti-VEGF therapy [111]. IGF1 increased protein expression of the G-protein coupled estrogen receptor (GPR30) in breast and endometrial cancer cells [112], a protein which has been implicated in tamoxifen resistance. Further, IGF-1 was shown to directly impair tamoxifen cytotoxicity of ER+ breast cancer cells by a mechanism requiring MEK activation [113].

Thus, the preponderance of evidence shows that IGF-1 is associated with increased incidence and poor prognosis in a number of cancers and has direct effects on cancer cells in vitro. Further studies examining modulation of IGF-1 pathway will hopefully lead to therapeutic advances in the near future.

Adipose Tissue and Metabolic Fuels

Obesity is a central component of the metabolic syndrome, and much recent literature has focused on the role of adipose tissue in cancer progression and treatment resistance. There are a number of potential mechanisms whereby adipose tissue could impair cancer prognosis. Excess adiposity makes appropriate chemotherapy dosing difficult, particularly for lipophilic drugs [114], but we have also shown that adipocytes protect acute lymphoblastic leukemia cells from chemotherapy via secretion of one or more soluble factors [115]. Adipokines, such as leptin and IL-6, have been shown in vitro to have cancer promoting activity [116].

Cancer cells have high metabolic requirements to maintain cell proliferation rates, and can utilize “metabolic fuels” present in obese and insulin resistant patients. In particular, in vitro evidence has been reported for the relationship between the Warburg Effect and hyperglycemia. A recent study by Tomas et al. found that diabetic levels of glucose in culture were associated with an increase in Akt expression, proliferation rate, and migratory activity of MB-468 breast cancer and SW480 colon cancer cells [68].

In addition to glucose, cancer cells appear to be exquisitely dependent on free fatty acids (FFA). FFA are needed to produce plasma and organelle membranes, as metabolic fuels, and can act as signaling molecules. A landmark study by Nomura et al. demonstrated that expression of monoacylglycerol lipase, an enzyme which releases a FFA chain from monoacylglycerol, is associated with worse prognosis in a number of different cancer types [117•]

Glutamine is another metabolic fuel that plays a central role in cellular metabolism, with importance as a contributor to the Krebs cycle, nucleic acid synthesis, and as a nitrogen source. Cancer cells appear to have higher glutamine needs than most other tissues, which has led some to explore this as a potential exploitable pathway. In particular, neural tumors and leukemia cells exhibit high glutamine utilization rates. As adipose tissue is a significant contributor to the whole body glutamine pool, we have investigated the role of adipocyte glutamine release in leukemia proliferation and resistance to chemotherapy. Although obese individuals do not appear to have higher plasma glutamine levels, glutamine concentrations

at the site of adipocytes (e.g. adipose tissue, bone marrow, breast tissue) are likely to be elevated. However, little work has yet been done to evaluate the role of adipocyte glutamine production in other cancers.

Caloric restriction

If the insulin resistant state can increase cancer, then it stands to reason that treatments that enhance insulin sensitivity could improve cancer. Caloric restriction has been shown to improve cancer survival, and it is thought that this could be in part through decrease in insulin and IGF1 concentrations [118]. Fine et al showed that low carb diet/ketosis induced disease stabilization or partial remission in some patients. However, disease progression was measured with PET scanning, which depends on glucose uptake and therefore might be confounded by a low carb diet and decreased insulin levels [119].

Conclusion

The landmark study by Eugenia Calle and colleagues in 2003 highlighted the substantial effect of obesity to increase cancer mortality [120]. Since that time, much epidemiologic and bench research has been done to elucidate the mechanisms of this link. Some themes have emerged, such as the importance of insulin resistance and IGF-1 to cancer prognosis, which have led to the recent evaluation of therapies targeting these pathways. Other questions, such as how best to adjust chemotherapy doses for increasingly obese patients have received less attention. It is clear that the obesity epidemic is not going away any time soon. More concerning is the fact that our youth are becoming more and more obese, which in time will yield an adult population with a high prevalence of lifelong obesity and IR—people who are likely to be at the highest risk of obesity-related cancer. It is imperative that we continue to clarify the effects of the metabolic syndrome on cancer, while at the same time strive to reverse the obesity epidemic to help our and future generations.

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Table 1

Association of Insulin Resistance and Site-Specific Cancer Incidence

	Association With Specific Categories of Malignancy		
	Increased Incidence within Malignancy Category	Decreased Incidence or No Effect	Controversial or Unknown
Non-Insulin Dependent Diabetes Mellitus (Type 2 DM)	Esophageal Colorectal Pancreatic Hepatocellular Carcinoma Renal Carcinoma Breast Endometrial Urinary System	Prostate Lung Ovarian	Lymphoma Acute & Chronic Leukemia Bone Sarcomas Soft Tissue Sarcomas Thyroid Brain Skin
Metabolic Syndrome (MetS)	Pancreatic Hepatocellular Carcinoma Breast Endometrial Cervical	Lung Ovarian Brain Skin Thyroid	Lymphoma Acute & Chronic Leukemia Bone Sarcoma Soft Tissue Sarcoma Prostate Urinary System