Insulin, insulin-like growth factors, insulin resistance, and neoplasia$^{1-4}$

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ABSTRACT
An accumulating body of epidemiologic and laboratory evidence suggests that insulin and insulin-like growth factors influence both the risk and the prognosis of cancer. In this brief review, I highlight topics covered in my lecture on research directions in this field, including the view that metformin deserves investigation as a potential adjunct in the treatment or prevention of cancer in persons with hyperinsulinemia. *Am J Clin Nutr* 2007;86(suppl): 820S–2S.

KEY WORDS Insulin, insulin-like growth factor-I, IGF-I, metformin, risk, prevention, treatment

In the late 1990s, we and other groups observed in prospective population studies that persons with circulating insulin-like growth factor-I (IGF-I) concentrations at the higher end of the broad normal range had an increased risk of a subsequent diagnosis of common epithelial cancers, such as those of the prostate, breast, or colon. These observations have been reproduced by many, but not all, subsequent follow-up studies (1–3). More recent work (for example, 4) has provided evidence that specific germline polymorphisms in certain genes encoding proteins involved in the IGF signaling pathway, including *IGF-I* itself, are associated with variation in cancer risk. In addition, a considerable body of circumstantial evidence relating IGF physiology to cancer risk has accumulated. For example, high mammographic breast density and high birth weight, both of which are known to predict increased breast cancer risk, have been associated with higher concentrations of circulating IGF-I (5) or umbilical cord IGF-I (reviewed in 6), respectively. Also, the weak but detectable positive correlation between height and risk of certain cancers may exist because height acts as a crude surrogate for adolescent concentrations of circulating IGF-I.

Laboratory experiments have yielded data consistent with some of the population findings. For example, crossing prostate cancer-predisposed TRAMP mice with mice that are genetically manipulated to have lower IGF-I concentrations (8). Population studies examining relations between fasting insulin concentrations (or C-peptide concentrations) and cancer risk and prognosis are ongoing. Results reported to date that involve analysis of samples obtained near the time of cancer diagnosis (eg, 9) suggest that higher concentrations are associated with worse prognosis of common epithelial cancers, whereas prospective studies of healthy subjects suggest that those with higher concentrations of these analytes are at increased risk of aggressive cancer or cancer with fatal outcome (J Ma, H Li, M Pollak, T Kurth, E Giovannucci, and M Stampfer, unpublished observations, 2006). These results suggest a possible mechanism underlying the association between obesity and adverse outcomes in prostate cancer, because obesity is often associated with hyperinsulinemia.

Although experimental data suggest that the well-known inhibition of rodent carcinogenesis associated with dietary restriction is related to the suppressive effect of diet restriction on IGF-I concentrations (10), emerging evidence suggests that in models in which accelerated carcinogenesis is associated with excess caloric intake, elevations in insulin concentrations may be involved (11).

The molecular and cellular biology underlying the observations reviewed above are the subject of ongoing research. The pathways downstream of the insulin and IGF-I receptors are well characterized. In general, pathway activation is associated with increased cell proliferation and increased cell survival. A hypothesis for increased cancer risk associated with increased IGF-I concentrations postulates that even a small increase in pathway activation in epithelial cells at risk of transformation would increase the probability of survival of cells accumulating genetic damage during the process of stepwise carcinogenesis, an effect that would increase the likelihood of accumulating sufficient damage for full transformation. It is also possible, particularly with respect to observations relating insulin concentrations to poor outcome, that the neoplastic behavior of transformed cells is directly stimulated by insulin.

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signaling by the use of anti-receptor antibodies or small-molecule tyrosine kinase inhibitors is receiving considerable attention in the context of cancer treatment, but these strategies are too early in development to be considered for prevention. The possibility that IGF-related germ line polymorphisms or concentrations of serum analytes related to IGF and insulin physiology may be clinically relevant in assessing absolute level of risk or the probability of successful risk reduction by specific lifestyle (eg, dietary, exercise) or pharmacologic (eg, tamoxifen or finasteride) interventions is under study. It is of interest that certain chemopreventive agents under study, such as retinoids (reviewed in 12) or silybinin (13) may act in part through mechanisms that involve reductions in IGF bioactivity.

Emerging evidence that hyperinsulinemia may be involved in the relation between obesity and cancer mortality suggests that lifestyle and possibly pharmacologic strategies to lower insulin concentrations in at-risk subjects or newly diagnosed cancer patients deserve investigation. This is important from a public health point of view given the worrisome population trends with respect to obesity.

Drugs such as metformin are known to have insulin-lowering actions and also to activate AMP kinase. In hepatocytes, AMP kinase activation leads to reduced glucose output, which results in a reduction in insulin concentrations (14). In epithelial cells, metformin-induced AMP kinase activation activates growth inhibitory pathways (15). Thus, metformin or other AMP kinase activators (16) may have direct as well as indirect (insulin-lowering) antiproliferative actions (15). Metformin is known to have a relatively favorable toxicity profile because it is in wide clinical use in the management of type 2 diabetes, which is associated with hyperinsulinemia and insulin resistance. Hypothesis-generating population studies (17, 18) suggest an unexpectedly low cancer burden in diabetic persons taking metformin compared with diabetic persons undergoing other therapies and justify further research. Insulin-lowering approaches using the currently available lifestyle and pharmacologic approaches may have potential in cancer prevention, particularly if targeted specifically to subpopulations with hyperinsulinemia.

Certain conspicuous gaps in our knowledge exist concerning the roles of metabolic syndrome and hyperinsulinemia in influencing cancer risk and cancer prognosis. One of these concerns is a lack of rigorous datasets concerning levels of expression of the insulin receptor on common epithelial cancers such as those of colon, breast, and prostate. Although some small sample sets have been studied, a clear need exists to use large-tissue microarray specimen sets and modern quantitative immunohistochemistry to study insulin receptor concentrations (as distinct from IGF-1 receptor concentrations) in common cancers to determine whether there are clinicopathologic correlates with receptor concentrations and to compare concentrations with those seen in classic insulin-sensitive tissues. It also will be important to make similar measurements on the normal epithelial cell populations of these organs that are at risk of transformation. The results of such investigations will either raise or lower enthusiasm for the hypothesis that insulin can act directly at physiologic in vivo concentrations to influence carcinogenesis or neoplastic progression. A finding of receptor concentrations comparable with those seen in classic insulin-sensitive tissues would be compatible with the hypothesis that hyperinsulinemia is a critical component of the metabolic syndrome and obesity that influences cancer behavior, whereas the absence of insulin receptors would increase interest in other plausible mediators such as leptin, for example. If insulin receptors are present in the epithelial cells of tissues such as breast, lung, colon, or prostate, understanding their normal physiologic role in these cell types would become a key research goal. They clearly are not expressed in these cells to regulate systemic carbohydrate metabolism in the manner seen in classic insulin-sensitive tissues.

A second important gap in knowledge related to insulin resistance in neoplasia concerns the question of insulin resistance within the neoplastic cells of a cancer patient with metabolic syndrome. This question is clinically relevant because of the increasing number of cancer patients with the full metabolic syndrome or with hyperinsulinemia in association with either obesity or the “lean, metabolically obese” phenotype (19). If the insulin resistance seen in classic insulin-sensitive tissues in metabolic syndrome is absent or reduced in neoplastic cells, then hyperinsulinemia-induced activation of signaling pathways downstream of the insulin receptor in neoplastic cells could be significant. The effects of pathway activation in promoting cell survival and proliferation might explain certain clinical observations, such as (for example) the relation between obesity and the aggressiveness of prostate cancer (reviewed in reference 20). This topic is also important because of the increasing appreciation of the fact that castration, which is commonly used in the treatment of steroid hormone–dependent cancers, leads to hyperinsulinemia (21). Might this aspect of classic endocrine therapies of steroid-dependent cancers underlie at least in part the well-known phenomenon of increased aggressiveness of cancer after the initial gratifying response to steroid hormone–targeting therapeutic strategies?

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