The insulin-like growth factor axis: a potential link between glycemic index and cancer

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The question of how diet affects cancer risk has been debated for many years. Dietary fiber is thought to decrease the transit time of food in the colon and to dilute carcinogens, thus minimizing the body’s exposure to toxins. The presence of certain compounds that induce the production of beneficial xenobiotic metabolizing enzymes may be important. In addition, high concentrations of antioxidants, which decrease free radical–induced damage, may play a role. At this time, however, the mechanism by which some foods promote and others protect against cancer remains largely unknown.

The novel dietary factor glycemic index (GI) has been linked to the risk of several types of cancer, including breast, ovarian, endometrial, pancreatic, and colorectal (1), although the mechanisms involved were not previously examined. The GI reflects the way in which a food (meal or diet) affects postprandial blood glucose and, consequently, insulin concentrations. Foods that are rapidly digested in the gut, including most refined-grain products and potato, have a high GI, whereas nonstarchy vegetables, fruit, and legumes tend to have a low GI (2).

In this issue of the Journal, Brand-Miller et al (3) suggest that a high-GI diet may increase cancer risk by modulating the insulin-like growth factor (IGF) axis. Using 10 healthy subjects, the authors compared the effects of a high-GI meal and a low-GI meal on glucose, insulin, and various components of the IGF axis in the serum over 4 h. The meals were well matched for macronutrient composition. As intended, the areas under the curve for glucose and insulin were 40% and 70% lower, respectively, after the low-GI meal than after the high-GI meal. There was no change in either free or total IGF-I. At 4 h, the high-GI meal reduced IGF-binding protein (IGFBP)-1 by 13 ng/mL and reduced IGFBP-3 by 110 ng/mL. The low-GI meal, on the other hand, reduced IGFBP-1 by 55 ng/mL and increased IGFBP-3 by 251 ng/mL. Thus, the low-GI meal produced a greater decrease in IGFBP-1 than did the high-GI meal and produced an increase, rather than a decrease, in IGFBP-3.

To understand the significance of these changes, it is important to consider the complexity of IGF-I signaling. IGF-I has powerful effects; it stimulates anabolic metabolism, cell proliferation, and cell differentiation and can also inhibit apoptosis. IGF-I in the serum is thought to be derived primarily from the liver and complexed to IGFBPs (4). IGFBP-3 is the major IGFBP in the serum, and most circulating IGF-I is present in ternary complexes with the acid-labile subunit and with either IGFBP-3 or -5. IGF-I in the ternary complex is sequestered in the plasma and hence has a prolonged half-life.

Circulating IGF-I is also found in binary complexes of IGF-I and IGFBP-1, -2, -4, or -6, all of which may exit the vasculature more freely. Only a small amount of IGF-I exists freely in the circulation. At the cellular level, IGF-I signals primarily through the IGF-I receptor, a tyrosine kinase, but it can also interact with the insulin receptor and the IGF-II receptor. The interaction of IGF-I with these receptors is also modulated by IGFBPs, which can either promote or attenuate IGF-I activity. Some IGFBPs are known to have effects on cell growth and proliferation that are independent of either IGF-I or its receptor. Furthermore, IGF activity is itself regulated by posttranslational modifications such as phosphorylation and by proteolysis.

Given the redundancy of the IGF system and its many layers of regulation, it is not surprising that IGFBPs are found to have varied biological effects. For example, IGFBP-1 promotes apoptosis of breast cancer cells under some conditions but not under others (5, 6). IGFBP-3 has been shown to promote apoptosis in most in vitro studies. Nonetheless the fact that transgenic mice overexpressing IGFBP-3 in the involuting mammary gland displayed decreased apoptosis suggests that factors other than the amount of IGFBP-3 determine its actions (7).

One finds similar inconsistencies in epidemiologic studies of the role of the IGFBPs in cancer. On the basis of in vitro data, it might be expected that high concentrations of IGFBP-3 would reduce the risk of cancer. Whereas some studies found such an association, a large meta-analysis failed to show any protective effect of serum IGFBP-3 concentrations on the risk of prostate, colorectal, or breast cancer (8). Similarly, IGFBP-1 concentrations have been shown to be both positively and negatively associated with cancer risk (5, 9).

Brand-Miller et al were the first, in the study reported in this issue of the Journal, to document the effects of GI on the IGF axis. Clearly, the magnitude of the changes they found was small: ≈6% for IGFBP-3. Moreover, there was no corresponding change in either total or free IGF-I. It is also surprising that IGFBP-1, which is known to be suppressed by insulin, was reduced to a greater extent after the low-GI challenge. This suggests that the GI may have effects on the IGF system that are independent of insulin.

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Despite these caveats, the fact that any change at all was noted is interesting, given the short duration of the study (4 h). Changes of this magnitude could conceivably affect IGF-I signaling significantly over time, through not only endocrine but also autocrine and paracrine pathways.

In summary, the powerful effects of IGF-I on cell growth and proliferation strongly argue for a role of the IGF system in cancer development. However, because of the complexity of the IGF axis, the exact roles of the different IGFBPs in modulating IGF-I function remain unclear. The study by Brand-Miller et al suggests that the GI can modulate IGF-I signaling within hours. These findings raise the possibility that, by lowering the dietary GI, we may be able to manipulate the IGF axis to prevent cancer.

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REFERENCES