S9. Energy metabolism, cancer risk, and cancer prevention

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Large-scale population studies have established that excess body weight is associated with increased risk of subsequent cancer mortality. Further work has shown that this is not simply related to a relationship between body size and cancer risk. Rather, it involves for many cancers a combined increase in risk with a worsening of prognosis, such that the effect of obesity on cancer-specific mortality is for many cancer types greater than the effect on risk. Given the magnitude of the global "obesity epidemic", the relationship of body size to cancer mortality deserves our attention.

Obesity (energy intake in excess of energy expenditure) may influence neoplasia in many ways. There is only limited evidence that altered levels of glucose or lipids in the blood have a direct effect. There is more evidence that it is the changes in the endocrine environment which arise as a consequence of excess energy intake that influence carcinogenesis and cancer progression. These include increased tissue and circulating levels of inflammatory cytokines, alterations in adipokines such as leptin or adiponectin, and other changes.

We have recently been extending earlier work concerning the relationship of insulin-like growth factors to cancer risk by examining the role of insulin itself as a candidate mediator of the effect of obesity on cancer mortality. It is well known that obesity is associated with increased insulin resistance in classic 'target tissues' for insulin action such as fat, muscle, and liver, which leads to elevation in insulin levels. Recent results show that insulin receptors are perhaps unexpectedly commonly expressed on many cancer cell types. Thus insulin may directly stimulate cancer growth in obese subjects.

A review of older literature reveals that this is not a new concept; rather evidence from recent laboratory research (*example*: Venkateswaran V, Haddad AQ, Fleshner NE, Fan R, Sugar LM, Nam R, Klotz LH, Pollak M. Association of diet-induced hyperinsulinemia with accelerated growth of prostate cancer (LNCaP) xenografts. J Natl Cancer Inst. 2007 Dec 5; 99(23): 1793–800) is consistent with older studies that showed impressive inhibitory effects of insulin deprivation on neoplastic growth (*example*: Heuson JC, Legros N. Influence of insulin deprivation on growth of the 7,12-dimethylbenz(a)anthracene-induced mammary carcinoma in rats subjected to alloxan diabetes and food restriction. Cancer Res 1972 Feb; 32(2): 226–32).

Recent data from population studies provide further evidence consistent with a role for insulin: I will review data sets suggesting that higher insulin levels are predictive of adverse outcome among breast and prostate cancer patients. If these results are confirmed, we could speculate that both lifestyle modification and pharmacologic (eg metformin) strategies that lower insulin levels may be useful in cancer control. If this is the case, it is unlikely that the benefit of such interventions will not be homogeneous in the population, but rather selection of a subset of people who might benefit most might be based on each person's metabolic characteristics.