COMMENTS AND RESPONSES

Prospective Study of Hyperglycemia and Cancer Risk

Response to Bowker and Johnson

There are many possible mechanisms underlying the association between hyperglycemia and cancer risk (1); however, they were not discussed in our recent article (2), due to format limitations. At a cellular level, glucose may lead to activation of energy sensing mechanisms, which in turn favor cellular growth and proliferation. Additionally, elevated glucose concentrations may also stimulate cancer growth through increased formation of advanced glycation end products. As noted by Bowker and Johnson (3), increased insulin is also likely to contribute to the observed positive association of hyperglycemia and cancer. Insulin is key to the regulation of energy metabolism and may affect cell proliferation and apoptosis through its receptor (by increasing the bioactivity of IGF-I) and by increasing energy provision to cancer cells (1). Leptin, as well as other adipocytokines, may also be links between a high-energy state and increased cancer risk (4).

Insulin is not measured as part of the check-up health examination in the Västerbotten Intervention Project, although C-peptide (a marker of pancreatic synthesis of insulin), leptin, and glycated hemoglobin were assayed in cryopreserved specimens for a subset of subjects, as a part of a series of ongoing studies on the metabolic syndrome and cancer risk nested within the Västerbotten Intervention Project. In the largest of these studies (5), fasting and postload glucose were only weakly correlated between themselves ($r_s = 0.25$) and also with C-peptide ($r_s = 0.24$ and 0.11), BMI ($r_s = 0.17$ and 0.07), leptin ($r_s = 0.14$ and 0.13) and A1C ($r_s = 0.28$ and 0.09), respectively. In the present study, adjustment for BMI had virtually no effect on risk estimates, even though BMI has been consistently associated with an increased overall risk of cancer in many studies, including ours (1,6). Likewise, adjustments for C-peptide did not materially change relative ratios for glucose in our study on prostate cancer (5). Studies on multiple factors in the metabolic syndrome in relation to cancer will be instrumental to understand their separate and joint effects on risk.

Finally, it is unlikely that the use of sulfonylureas, metformin, or exogenous insulin by some participants in our cohort could have substantially affected risk estimates, given that the study was done mainly in nondiabetic subjects.

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DOI: 10.2337/dc07-0653

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