Sirs—The innovative analysis by Giovannucci et al. may be interpreted as further confirmation for the thesis that plasma levels of insulin and free insulin-like growth factor-I (IGF-I) are key determinants of risk for ‘Western’ cancers among Western populations. Indeed, this formulation is consistent with our emerging understanding of the molecular biology of these hormones. Insulin and the free fraction of IGF-I are the chief systemic hormones that activate the PI3K-Akt and ras-MAPK signalling pathways in a wide range of tissues—pathways which work in various complementary ways to accelerate mitosis and suppress apoptosis, while also compromising the efficiency of DNA repair and free radical defences. These hormonal activities can also promote cancer induction less directly by modulating hepatic production of IGF binding proteins, by up-regulating free sex hormone levels, and by accelerating the onset of sexual maturity. Conceivably, these effects may interact in an additive or multiplicative fashion, such that a feasible down-regulation of insulin/IGF-I, sustained over a lifetime, could translate into a substantial reduction in cancer risk.

Giovannucci and colleagues conclude that risk for Western cancers could be cut by about 50% if the entire population had an adult height and C-peptide score comparable to those values seen in the lowest decile of the population. Yet it should not go unnoticed that Western cancer risk in this low-risk decile is still at least severalfold higher than that enjoyed by certain rural Asian and African populations while following their traditional pre-Western lifestyles. Is the insulin/free IGF-I model capable of rationalizing the comparatively very low risks for Western cancers noted in these populations? I suspect that it is, providing that the following two propositions can be sustained: (1) the very low fat intake of many traditional Third World diets (10–15% of total calories) has a markedly favourable impact on the insulin sensitivity of skeletal muscle, such that diurnal insulin secretion is notably down-regulated; (2) the relatively low protein content of such diets—most notably, the near absence of ‘high-quality’ animal protein—decreases hepatic IGF-I secretion while increasing that of its functional antagonist insulin-like growth factor binding protein type 1 (IGFBP-1), and also possibly blunts diurnal insulin secretion.

Indeed, the insulin-sensitizing activity of genuinely low fat diets has been demonstrated repeatedly, and likely reflects a favourable impact of such diets on intramyocellular triglyceride levels. There may be an interaction between regular physical activity—(characteristic of most Third World cultures) and very low fat diets in suppressing muscle triglyceride accumulation—thus explaining the rapid favourable impact of the ‘Pritikin regimen’ on insulin sensitivity. However, within the range of fat intake typical of Western society—almost invariably in excess of 20% of calories—the quality of fat may have a more important impact on insulin sensitivity than the quantity of fat, thus accounting for the fact that increased intakes of unsaturated fats sometimes emerge as protective (or at least not harmful) in Western prospective epidemiology. The fact that plant-derived unsaturates are the chief fats in most low fat Third World diets may further contribute to the insulin-sensitizing activity of such diets. In the longer term, very low fat diets tend to promote lifelong leanness—another key factor in the excellent insulin sensitivity enjoyed by traditional Third World peoples.

Epidemiological analyses examining British vegans found that their plasma IGF-I levels were modestly but significantly lower than those noted in omnivores or lacto-ovo-vegetarians, this finding is concordant with evidence that low protein diets—or diets that feature ‘lower quality’ plant proteins that are relatively low in certain essential amino acids—down-regulate hepatic IGF-I secretion in rodents. Low protein diets also up-regulate hepatic production of IGFBP-1 in rodents, and IGFBP-1 was about 40% higher in the British vegans.

Protein restriction may also influence diurnal insulin secretion. Although ingested protein per se usually has a modest impact on insulin secretion, it can markedly potentiate this insulin response to co-ingested carbohydrate. When Remer et al. added 32 g per day of egg protein to a low protein (50 g daily) lacto-vegetarian diet (isocalorically substituted for dietary fat), 24-hour urinary C-peptide rose by 60%, a more recent study by this group likewise observed a markedly lower 24-hour urinary C-peptide when subjects followed a quasi-vegan low-protein diet. A portion of this disparity might be attributable to increased glomerular filtration associated with omnivore diets, but this effect is modest and seems unlikely to offer a full explanation. On the other hand, plasma fasting levels of C-peptide and sex hormone binding globulin (SHBG) did not differ significantly between vegans and omnivores in the previously cited cross-sectional British study. More studies are needed to determine whether restricting the quantity and quality of protein intake does indeed down-regulate diurnal insulin secretion.

A role for animal protein in cancer induction is consistent with the findings of the China Health Project; in provinces of quasi-vegan rural China, risks for most cancers tend to correlate with the extent to which animal products are incorporated into the local traditional diet. This thesis also squares well with trans-national ecologic epidemiology correlating Western cancer rates with intakes of saturated fat and animal protein.

It should be noted that the diets of Western vegans tend to be far higher in fat (approximately 30% of calories) and protein than those of Third World vegetarians. The higher protein content can reflect frequent consumption of soy-protein-derived...
food products designed to mimic animal products. The ability of soy protein supplements to boost circulating IGF-I has been demonstrated,33 and increased soy intake correlates with increased plasma IGF-I in British vegans.21 These factors may help to explain why Western vegans are neither so lean nor so protected from Western cancers as are Third World vegans. (Lower physical activity, and the fact that few Western vegans have been vegan throughout early life, likely also contribute in this regard.)

Recent clinical studies by Barnard and colleagues demonstrate that a very low fat wholefood diet, coupled with daily aerobic exercise, rapidly decreases plasma levels of insulin and of IGF-I, while boosting that of IGFBP-1; these trends are even more prominent in those who have adhered to such a programme for years.36 The functional significance of these changes is demonstrated by the fact that human prostate cancer-derived cell lines grow less avidly, and are much more prone to apoptosis, when cultured in serum derived from subjects engaged in this diet–exercise programme.36–39 Since Barnard’s regimen was not strictly vegan (it included modest amounts of low fat animal products), it is conceivable that even larger effects might have been achieved if animal products had been wholly excluded.

These considerations encourage the hypothesis that prolonged consumption of wholefood vegan diets genuinely low in both protein and fat (e.g. 10% protein, 10% fat) will be associated with relatively low diurnal plasma levels of both insulin and free IGF-I—particularly if complemented by regular exercise—and that this phenomenon is largely responsible for the exceptionally low risks for Western cancers observed in many traditional Third World societies. Further clinical studies along the lines of those initiated by Barnard, coupled with appropriate epidemiological investigations targeting Asian populations in the process of transition to a more Western lifestyle, would be useful for evaluating this hypothesis.

In some respects, this thesis may seem at odds with the findings of Western epidemiology—thus, total fat and total protein intakes do not emerge as important determinants of cancer risk in many Western case-control studies. However, this may simply reflect that fact that Third World intakes of fat and high quality protein are usually far lower than the range encountered among free-living Western subjects; rather stringent restriction of fat (especially saturated fat) and protein may be required to achieve substantial down-regulation of insulin and free IGF-I levels. Of course it should be acknowledged that additional independent factors may contribute to the lower rates of Western cancers in the rural Third World—for example, increased sunlight exposure, earlier age at first childbirth, and increased phytochemical intakes from a relatively unrefined plant-based diet, may play a role in this regard.

Analysis of Western prospective epidemiology suggests that certain rather simple and practical measures—eating poultry and fish in preference to red meat, emphasizing whole grains and unsaturated oils as opposed to refined grains and saturates, consuming more fruits and vegetables, exercising more and getting more sun exposure—could achieve moderate but very worthwhile reductions in Western cancer rates. Achieving the far lower rates long prevalent in rural Asia and Africa evidently would require more stringent measures. The challenge is to determine precisely what those measures may be.

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