

Height, early energy intake, and cancer

Evidence mounts for the relation of energy intake to adult malignancies

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Study of the relation between human body size and cancer risk has its origins in both human observational studies and animal experiments. In his late 19th century treatise *Air, Food, and Exercises* based on observations in England and continental Europe Rabagliatti concluded, "Overfeeding is the predisposing cause of cancer."¹ Since then the restriction of total energy intake has been shown over decades of research to be one of the most powerful nutritional interventions capable of lowering cancer rates in laboratory animals—and the only factor known actually to increase lifespan in these same systems.²⁻³ Such rodent experiments resulted in lighter, leaner animals—that is, with decreased body weight and adiposity—and in many instances, depending on the timing of the energy restriction, stunted growth and shortened overall animal length. Although lifelong dietary restriction has had the greatest impact, reduced food consumption early during development also effectively inhibits tumorigenesis.³ Human data are available from epidemiological studies of the relation between energy intake, body size, and cancer rates or risk. In these, overweight and obesity are associated with higher overall incidences of cancer⁴ and, in particular, with cancer of the breast (after the menopause), prostate, large bowel, endometrium, ovary—that is, the major non-smoking related malignancies—and kidney.⁵

A growing number of investigations have also established greater adult height as a risk factor for several of these same cancers. Data provided by two reports in this week's issue corroborate the previously observed direct relation between height, in this instance assessed as adult stature or childhood leg length, and the development of cancer.⁶⁻⁷ Using nearly 30 years of follow up of the Whitehall study of London civil servants, and based on more than 2000 cancers, Davey Smith et al observed 36% more non-smoking related malignancies among men taller than 6 ft (1.8 m) than in men 5 ft 6 in (1.65 m) or shorter, with men of intermediate height having intermediate risk (p 1351).⁶ Similarly, Gunnell et al evaluated prepubertal height and leg length in the Boyd Orr cohort and found that during a 50 year follow up nearly 80% more deaths from cancers unrelated to smoking occurred for every 3-4 mm increment (age and trunk length corrected) in leg length (p 1350).⁷ Underlying both these prospective investigations is the view that height is a proxy for early nutrition (particularly of energy intake) and childhood growth and development, with taller people more likely to have been exposed to a

greater surfeit of dietary energy during maturation than shorter ones, notwithstanding the influence of heredity. This interpretation is bolstered by the fact that leg length may be the more nutritionally sensitive component of height.

Two other aspects of the studies deserve mention. Firstly, the relation between height and cancer was not evident for organ sites associated with tobacco smoking, a finding consistent with most previous studies, suggesting that the carcinogenic effects of smoking can overshadow those from other behavioural exposures such as early nutrition. Secondly, statistical adjustment was made for socioeconomic status, which greatly improves the likelihood that the observed associations reflect an independent effect of height and its other determinants, and are not confounded by other socioeconomic correlates—or consequences—of height.

Although controlled trials of early energy intake are not possible, natural experiments have occurred. For example, women subjected during puberty to wartime food deprivation experienced reduced lifetime breast cancer rates compared with younger and older cohorts.⁸ Furthermore, direct evidence for the role of childhood energy intake itself in human cancer risk was reported earlier this year from one of these cohorts, with a 20% higher rate of cancers not related to smoking observed for every megajoule increase in total energy intake.⁹ Taken together, the human data are consistent with the laboratory experiments and suggest that excess energy intake relative to requirements, manifest as increased height or early maturation (from early excess) or overweight (from cumulative excess), has negative consequences with regard to several major cancers.

Elucidation of the biological basis for these observations will both provide the plausibility needed to impute causality and improve our understanding of how nutrition affects the malignant transformation of cells. Candidate mechanisms include greater exposure to mitogenic factors such as growth hormone, insulin, insulin-like growth factors, and sex steroids that could result from accelerated maturation mediated by the hypothalamic-pituitary axis. Positive energy balance during development may lead to a higher subsequent risk of malignancy not only through increased cumulative cell proliferation but also by expanding organ specific stem cell populations.¹⁰ Effects of excess energy intake on oxidative stress, detoxification enzyme systems, or immune function are also possible.

Affluent industrialised populations have advanced beyond concerns about adequate energy intake that originated from uncertain sustenance and periods of starvation. Ironically, the new, highly prevalent threat is posed by overnutrition—or more specifically, energy consumption beyond that expended.¹¹ This hazard applies not only to the risk of cancer but also to cardiovascular disease as well as other chronic illnesses (such as type 2 diabetes). Although the risks appear to be understood by most clinical, public health, and research communities, they have yet to be fully acted on. This may be a function of the unpopularity and challenging nature of the inherent proscriptive message—eat less, be less inactive—when compared with the facility and palatability of their alternatives.

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Nuts to you (...and you, and you)

Eating nuts may be beneficial—though it is unclear why

A generation ago the prudent diet for preventing coronary disease was dominated by negative advice. Poverty and food rationing in the 1930-50s had led to the promised land of the 1960s, but it was a monotonous greasy landscape of cakes, pies, chips, sausages, and fry ups, dominated by dairy and processed foods. The “you never had it so good” life was bad for the heart. Prophets of doom emerged from communion with molecules, denouncing cholesterol and issuing dietary commandments, almost all phrased “Thou shalt not eat x.” They were less explicit on what should be eaten. It seemed to be what remained after eliminating the favourites or cutting off the fatty bits. Foods were judged in one dimension—what they did to blood cholesterol.¹ Meanwhile a vegetarian subculture, regarded as cranky and unscientific (as many of its adherents were), was promoting fresh and natural foods of vegetable origin.

The cholesterol monolith was evidence based, but confrontation with sceptics, and powerful unscrupulous elements of the food industry, led to a siege mentality among some adherents, reluctant to concede that the diet-heart story might be multidimensional. A key element in that concession, still not categorically established, was the antioxidant-vitamin theory. Fruit and vegetables had a role separate from providing low fat calories. Antioxidant-vitamins protected low density lipoprotein (LDL) cholesterol from oxidation to its atherogenic product.² Further dietary dimensions have been provided through haemostatic factors,³ non-vitamin antioxidants such as flavonoids,⁴ folic acid in green vegetables reducing blood levels of homocysteine,⁵ plant sterols,⁶ and alcohol.⁷ Popular health mythology has embraced red wine, garlic, and green tea. And now we have nuts.

Like food grains, nuts are concentrated sources of food energy and micronutrients, built to carry life forward into a new generation, but their dietary image has been mixed. Commonly eaten salted, as self indulgent

snacks, and containing significant quantities of fat, they figure in the “cut out...” diet lists for obesity and hypertension. Yet the nut roast is the archetypal vegetarian meal. In the naive stereotyping of foods, which belies the sophisticated doctrine that it is the variety and balance that determine a good diet, nuts could be classified as both healthy and unhealthy. This ambiguity could continue had we not the experience of 84 409 American nurses followed for 14 years in this week's *BMJ* (p 1341).⁸

Earlier work on Seventh Day Adventists suggested that nut eating was associated with diminished coronary risk.⁹ Feeding experiments tested the effect of dietary substitution of almonds and walnuts on serum lipid concentrations and blood pressure—still an essential initiation for foods wishing to be considered beneficial. What the nurses' health study has done is to relate nut consumption to subsequent coronary risk in a very large study.⁸

One nurse in 20 ate five or more helpings of nuts a week whereas a third hardly ever ate them. Fourteen year coronary risk in the first group was half of that in the latter after adjusting for age and remained significantly reduced by one third even after correcting for all available risk factors. Intermediate nut consumption groups had intermediate risk. Reduced risk from nut eating was maintained across subgroups stratified to test for major confounding factors. The effect therefore appears large and significant, as great or greater than that in the statin trials,¹⁰ and unexplained by anything else.

Is the effect causal, and if so, to what constituent of the nuts can it be attributed? Unfortunately an observational study lacks the power of a randomised controlled trial to determine causality, as there is always the worry of residual confounding. Frequent nut eaters differed in many respects from the others. Of the four demarcated consumption groups, the high consumption group came out most favourably for 16 of 23

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