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Height, predictors of C-peptide and cancer risk in men

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Background Excessive energy intake tends to increase circulating levels of insulin and free insulin-like growth factor-1 (IGF-I), which may increase risk of some cancers that are common in Western countries. However, the relative importance of these hormonal factors during pre-adulthood and adulthood is unknown.

Methods We prospectively examined height, as a marker of pre-adult IGF-I bioactivity, and modifiable adult determinants of insulin secretion, in relation to risk of cancer, particularly Western-related cancers (colon, pancreas, kidney, and aggressive prostate cancers) in 47 690 male health professionals. Information about dietary and lifestyle factors for these men was collected at baseline (1986) and was updated periodically. A C-peptide score, representing insulin secretion, was created by using body mass, physical activity, and diet in a stepwise linear regression to predict C-peptide level, in a sample of 263 cohort members.

Results From 1986 to 1998, we documented 3270 incident cancers (excluding the less aggressive prostate cancers). Greater body mass index, lower physical activity, and a Western dietary pattern were independent predictors of higher plasma C-peptide levels in the sample. A C-peptide score, based on these variables, was positively related to risk of Western-related cancers, but not to other cancer types in the entire cohort. Height was also only related to Western-related cancers. For Western-related cancers, 29% (95% CI: 16%, 48%) were attributed to C-peptide scores above the first decile, 30% (95% CI: 11%, 58%) to heights ⩾66 inches, and 49% (95% CI: 30%, 69%) to both factors combined. For total cancers, 29% (95% CI: 16%, 46%) were attributable to both factors.

Conclusions Maximal growth in the pre-adult period and hyperinsulinaemia during adulthood may largely underlie the excess risk of some cancers that are common in Western populations. A substantial proportion of these cancers may be modifiable in adulthood, through alterations in body weight, sedentary behaviour, and dietary patterns that stimulate hyperinsulinaemia.

Several types of epithelial cancers have a relatively high incidence in economically developed countries and increase in incidence in populations that become 'Westernized.' These carcinomas include colon, pancreatic, and renal cancers, in addition to prostate cancer in men, and breast and endometrial cancers in women. Their consistently high frequency in Western populations and association with height and body mass index (BMI) suggest a common underlying risk factor, generally believed to be nutritional.[1] Many explanatory hypotheses have focused on specific components of the diet, including fat, fibre, antioxidants, and vegetables, but recent prospective studies and randomized trials[2–4] have not supported that these individual factors are the primary causes for these cancers.

An alternative hypothesis, rather than concentrating on single nutrients or food groups, has considered the integrated influence of nutrition and lifestyle on the levels of circulating insulin and

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insulin-like growth factors.[5,6] A cancer-enhancing influence of insulin and insulin-like growth factor-1 (IGF-I) is supported by their mitogenic and anti-apoptotic properties,[7–9] by animal models in which reductions in insulin and IGF-I through energy restriction[10] or other means [11–13] result in fewer tumours, and by epidemiological studies in which circulating insulin[14–17] and IGF-I[18,19] or related factors such as tallness,[20] obesity,[21] physical inactivity,[22] type 2 diabetes mellitus,[23] and acromegaly[24] are associated with greater cancer incidence. In sedentary populations with ready access to energy-dense foods, excessive energy intake leads to increased body mass and obesity and to insulin resistance and hyperinsulinaemia.[25] Insulin levels influence the IGF axis. Growth hormone (GH) is the primary regulator for hepatic production of IGF-I, and hepatic GH receptor concentration is partly regulated by insulin level.[26,27] Additionally, short-term increases in circulating insulin reduce hepatic secretion of insulin-like growth factor binding protein-1 (IGFBP-I),[28] a protein that binds IGF-I with high affinity and inhibits IGF-I action *in vitro*,[29] and long-term increases in insulin secretion decrease IGFBP-II.[30,31] In individuals with insulin-dependent diabetes mellitus, infusion of insulin increases hepatic production of IGF-I, but not IGFBP-III, and lowers IGFBP-I production.[32] By its stimulating actions on IGF-I and its inhibiting effects on IGF binding proteins, insulin increases free IGF-I, increasing IGF-I bioactivity.[31,33]

Although exposure to high insulin and IGF-I levels may influence cancer risk throughout the lifespan, their relative importance during pre-adulthood and adulthood is unknown. The proportion of cancer risk that may be altered in these time periods is important to establish because the public health implications are quite different for each. Thus, we examined height, a marker of pre-adult IGF-I bioactivity,[34] and modifiable adult determinants or markers of insulin secretion in relation to risk of cancer, particularly Western-related cancers, in the Health Professionals Follow-Up Study (HPFS), a large cohort of men. We then estimated the proportion of cancers potentially attributable to either or both pre-adult and adult factors combined.

Methods

Study population

The HPFS is an ongoing prospective investigation of the causes of chronic disease. The cohort consists of 51 529 US male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians, aged 40–75 years in 1986.[35] Through the baseline mailed questionnaire in 1986, these men provided information on age, marital status, height and weight, ancestry, medications, smoking history, medical history, physical activity, and diet. We updated non-dietary exposures and medical history every 2 years, and dietary information every 4 years. The study was approved by the Institutional Review Board of the Harvard School of Public Health. Completion of the self-administered questionnaire was considered to imply informed consent to participate in the cohort. Men provided informed consent to allow us to review medical records regarding diagnoses of cancer.

Assessment of diet

Semiquantitative food-frequency questionnaires, described in detail previously,[36] were administered in 1986, 1990, and 1994. The self-administered questionnaires contained a list of about 130 food and beverage items, each with a specified commonly used unit or portion size, and an open-ended section for unlisted foods. The men reported how often, on average, over the past year, they typically consumed each item. They also reported the brand of breakfast cereal, brand, duration and frequency of vitamin supplements, and types of fat commonly used. We computed nutrient intakes by multiplying the consumption frequency of each unit of food by its nutrient content, based on composition values from US Department of Agriculture sources, supplemented with other data. The mean correlation coefficients between intakes determined by two one-week diet records and the dietary questionnaire (adjusting for week-to-week variation in the diet records) among a sample of 127 cohort members were 0.65 for nutrients and 0.63 for specific foods.[36,37]

Assessment of physical activity and anthropometric variables

In 1986 we asked participants to report the average time per week that they engaged in the following activities during the past year: walking or hiking outdoors (including walking while playing golf), jogging, running, bicycling (including stationary machine), lap swimming, tennis, squash or racquet ball, calisthenics, or rowing. We also asked about the number of flights climbed daily and walking pace. To generate the total leisure-time physical activity score, we summed activity-specific MET-hours/week, using MET values based on a compendium of activities. One MET-hour is the metabolic equivalent of sitting at rest for one hour. Vigorous activities were those with MET values exceeding 6. In a sub-study of 238 study participants, the correlation between the questionnaire assessment of vigorous activity with four one-week diary records was 0.58; reported vigorous activity was also a strong predictor of resting heart rate.[38] We also asked the men to report height and weight in 1986. In a sub-study, the correlation between self-report and technicians' measurements was 0.97 for height and 0.97 for weight.[39] Physical activity and weight were assessed every 2 years.

C-peptide analyses

In 1993 and 1994, 18 018 HPFS members provided blood samples, chilled by ice, through overnight mail. Upon receipt at our laboratory, samples were separated into plasma, buffy coat, and erythrocytes. The vast majority of samples were frozen within 29 hours of venipuncture, and stored in liquid nitrogen freezers from −196 °C to −130 °C. C-peptide analyses were conducted in a sample of 263 men in this cohort. Plasma levels of C-peptide were assayed in the laboratory of Dr Nader Rifai by radioimmunoassay (Linco Research, St Charles, MO), an assay with little or no cross-reactivity with proinsulin.[40] Insulin is synthesized in the beta cells of the pancreas as proinsulin, which is cleaved to form insulin and C-peptide. Because C-peptide and insulin are secreted in equimolar amounts from pancreatic beta cells, circulating C-peptide levels provide a measure of insulin secretion.[41] Because of the lack of hepatic extraction and a much slower metabolic clearance rate, C-peptide measurements provide an excellent long-term estimate of insulin secretion.[41] The mean coefficient of variation for C-peptide levels from blinded quality control specimens was <10%.

Ascertainment of cancers

We asked for written permission to acquire relevant medical records and pathology reports from men who reported a cancer on our biennial questionnaires. For deceased participants, we asked the next-of-kin for additional information and permission. The follow-up rate with respect to the incidence of cancer was 97% of the total potential person-years, and death follow-up rate was over 98%. Approximately 90% of cases were confirmed by medical record review, and the remaining cases were confirmed with information from the participant or family member, or by death certificate. Up to 1998, excluding non-aggressive prostate cancer, we confirmed 3270 cases of total cancers, 1029 Western-related carcinomas (colon, n = 494; pancreas, n = 134; and kidney, n = 149; and aggressive prostate cancer, n = 259), 1601 other (non-Western) carcinomas, and 672 non-epithelial cancers. Among the non-Western carcinomas, the most common were lung cancer (n = 342), melanoma (n = 333), and bladder cancer (n = 299). Among the non-carcinomas, most were haematopoietic malignancies (n = 529). The sum of Western-related carcinomas, other carcinomas, and non-carcinomas exceeds total cancers because of multiple cancers in some individuals. In this analysis, we included only aggressive prostate cancer (those that were fatal, or had spread to distant or adjacent organs) because of the high number of prostate-specific antigen (PSA)-detected organ-confined prostate cancers with excellent prognosis, and because nutritional factors appear to influence progression rather than overall incidence.[42] If we included all of the prostate cancers diagnosed (n = 2481), these would have comprised about half of total cancers, whereas in US men prostate cancer accounts for about 10% of fatal cancers. Aggressive prostate cancers (n = 347) comprised 10.7% of total cancer (excluding non-aggressive prostate cancer).

Statistical analysis

To determine the modifiable predictors of C-peptide, we used a sample of 263 HPFS men without cancer, cardiovascular disease, or diabetes mellitus, who had provided fasting blood samples and had C-peptide measured as part of another sub-study. Using stepwise linear regression, with C-peptide as the dependent variable, we examined as independent variables body mass index (BMI) (kg/m^2), waist circumference, waist-to-hip ratio, leisure-time physical activity level, glycaemic index, fibre, and other selected food groups and nutrients. We also considered a dietary pattern score termed 'Western diet' (characterized in part by higher intakes of red meat, processed meat, high-fat dairy products, sweets, and refined grains) that was previously identified by factor analysis (principal components) in this cohort, and which correlated with C-peptide levels.[43] Additionally, we considered a diet score with high risk characterized by a diet low in cereal fibre and polyunsaturated fat and high *in trans* fat and glycaemic load, because this dietary pattern had been shown to predict type 2 diabetes mellitus risk in a similar cohort of women.[44] Then, based on the predictors' regression coefficients from the sample, we calculated an empirical C-peptide score for each cohort member every 2 years based on the most recent available physical activity, BMI, and dietary data. To reduce random within-person variation and best assess long-term exposure, we used cumulative average C-peptide scores from our repeated measures. Although tobacco use and alcohol have moderate influences on insulin resistance, these were not included in the score because their overall influence on cancer risk is likely to be far exceeded by other mechanisms, and thus their inclusion could lead to residual confounding.

We examined height in 1986 and the computed C-peptide score in relation to cancer risk in the 47 690 men who provided dietary, physical activity, and anthropometric data, and were free of diagnosed cancer in 1986. We calculated incidence rates of total cancer and sub-groups of cancer for each category of height and quintile of predicted C-peptide score. The relative risks (RR) were computed as the incidence rate among men in each of the four upper categories divided by the rate among men in the lowest category. We used Cox proportional hazards regression to control for age, race, alcohol intake, and smoking history, and to compute 95% CI. We additionally controlled for total and saturated fat, protein, fibre, and total fruits and vegetables, nutritional factors frequently hypothesized to contribute to the aetiology of Western-related cancers. We tested for trends across categories by modelling the median for each exposure category as a continuous variable. All reported *P*-values are two-sided.

We calculated the population attributable risk per cent (PAR%), an estimate of the percentage of cancer cases in this population that theoretically would not have occurred if all men had been in the low risk category.[45,46] We calculated the partial PAR% and 95% CI holding other risk factors constant using the method described by Bruzzi *et al*.[47] We assume either a causal association, or the considered factor as a marker of the causal factor, specifically height as a surrogate of pre-adult insulin and IGF-I bioactivity.[34,48] All statistical analyses were done using the SAS 6.12 statistical package (SAS Institute).

Results

First, we determined predictors of C-peptide in the sample of 263 men. Using stepwise regression, we identified BMI, physical activity, and Western diet as defined by factor analysis as independent predictors of age-adjusted plasma C-peptide levels. For example, a 60 year old man with a BMI of 23 kg/m^2, in the top quintile of physical activity, and with a low Western diet score (1 SD below the mean) had a predicted C-peptide level of 1.13 ng/ml. In contrast, a relatively inactive man with a BMI of 29 kg/m^2 and a high Western diet score (1 SD above the mean) had a predicted C-peptide level of 2.33 ng/ml. These factors explained 26% of the variance of C-peptide. Waist circumference and waist-to-hip ratio were not predictors of C-peptide independent of BMI and physical activity in this sample. The Western diet defined by factor analysis appeared to most effectively capture the dietary influences, and selected individual food groups and nutrients were not predictors of C-peptide independent of BMI, physical activity, and Western diet score. The alternative empirical diet score defined by cereal fibre, polyunsaturated and trans fat, and glycaemic load did predict C-peptide, but not as strongly as the Western diet score did. Thus, for the primary analyses we used the Western diet predictor score. In regard to the factors contributing to the C-peptide score, the 263 men in the sample were similar to the entire cohort (mean BMI [kg/m^2]: 25.6 [sample], 25.7 [cohort]; mean MET-hours of physical activity: 33.6 [sample], 30.5 [cohort]; mean Western diet score [normal standard]: 0.08 [sample], 0.00 [cohort]).

Table 1 shows age-standardized selected factors in relation to predicted C-peptide score. Those with greater C-peptide scores had a higher BMI, lower physical activity level, and higher consumption of red meat, dairy fat, refined grains, saturated and trans fat, and lower consumption of whole grain foods and fibre. Table 1 also shows generally weak associations between height and other variables, except for a higher percentage of Asian-American men at the lowest category of height. Taller men had greater intakes of most dietary factors, concordant with their overall large body size and lean body mass and thereby higher energy requirements.

Table 2 displays the association between height and cancer risk. A positive association was observed between taller height and total cancers. This association was largely attributable to an association with Western-related carcinomas. A suggestive but non-significant association was observed between height and non-Western-related carcinomas, but this was limited primarily to men with height <68 inches. No trend was observed for men ⩾68 inches. Height was unrelated to non-carcinomas, nor to either of the major subgroups of this category, including the haematopoietic malignancies, lymphoma, and leukaemia, which made up 529 of 672 (79%) non-carcinomas.

Table 3 displays the association between predicted C-peptide score and risk of cancer. Among carcinomas, a positive monotonic association was observed only for Western-related carcinomas, but not for other types of carcinomas. A modest association was also noted for non-carcinomas, but this was not monotonic. The association between C-peptide score and Western-related carcinomas was only slightly attenuated in the multivariate analysis. In addition to age, smoking, race, and alcohol intake, in a model that additionally included intakes of total fat, saturated fat, protein, fibre, and total fruits and vegetables, the results for height or C-peptide score did not change appreciably.

For the individual Western-related cancers, the patterns we observed for height and C-peptide score generally held, although the results were strongest for colon cancer (Figure 1). Height was significantly related to risk of aggressive prostate cancer, but C-peptide score was not appreciably related to risk. Because increasing BMI is related to higher oestrogen and lower total and free testosterone levels,[49,50] which may decrease risk of prostate cancer,[51] we computed an alternative C-peptide score based only on physical activity and dietary pattern but not BMI. This alternative C-peptide score was related to higher risk of aggressive prostate cancer, controlling for BMI (multivariate RR = 1.47; 95% CI: 1.02, 2.14, for high versus low quintile; *P*[trend] = 0.05).

Table 4 shows the PAR% of cancers, interpreted as the per cent of cancers that theoretically would not have occurred if all men had been in the low-risk categories of height and C-peptide scores. We show results for two levels of low-risk categories for each of height and C-peptide. Of Western carcinomas, 29% were attributable to C-peptide scores above the low decile, and 30% to heights ⩾66 inches. We also estimated that 29% of total cancers and 49% of the Western-related carcinomas were attributable to the combined influence of taller height and higher C-peptide.

Discussion

Excessive energy intake raises insulin and free IGF-I levels. During pre-adulthood, high circulating insulin and IGF-I levels

Table 1 Age-standardized characteristics of selected factors by predicted C-peptide score and height in 1986 in men of the Health Professionals Follow-Up Study (n = 47 690)

	C-peptide score[a]			Height (in.)		
	Quintile 1	Quintiles 2–4	Quintile 5	<66	66–71.9	⩾72
Body mass index (kg/m^2)	22.0	25.0	29.8	26.4	25.5	25.4
Height (in.)	70.2	70.2	70.2	64.1	69.1	73.1
Physical activity (MET-h/wk)	32.8	19.0	12.8	17.9	20.1	20.7
Current smokers (%)	4.3%	6.0%	7.6%	5.4%	6.0%	6.2%
Multivitamin use (%)	48.9%	41.7%	35.7%	41.4%	41.5%	42.2%
Alcohol (g/day)	10.0	11.6	11.7	8.5	11.1	12.2
Red meat (servings/day)	0.39	0.60	0.82	0.55	0.60	0.63
High fat dairy (servings/day)	0.69	0.95	1.20	0.82	0.94	1.01
Refined grains (servings/day)	1.0	1.2	1.5	1.3	1.2	1.2
Whole grains (servings/day)	1.8	1.4	1.2	1.2	1.4	1.5
Total fat (g/day)[b]	64.5	71.5	76.3	69.6	71.2	71.7
Saturated fat (g/day)[b]	21.4	24.5	26.7	23.6	24.4	24.7
Trans-unsaturated fat (g/day)[b]	2.4	2.8	3.1	2.7	2.8	2.8
Fibre (g/day)[b]	23.6	20.9	19.4	21.2	21.1	21.0
Caucasian (%)	88.6%	91.1%	92.2%	78.0%	90.6%	92.5%
African-American (%)	1.0%	1.0%	1.1%	1.6%	0.9%	1.1%
Asian-American (%)	3.4%	1.6%	0.6%	13.9%	1.9%	0.3%

[a] C-Peptide score is based on β-coefficients on body mass index, physical activity level, and 'Western' dietary pattern for the entire cohort determined by regression analysis with C-peptide as the dependent variable in a sub-sample of 263 men.

[b] Energy-adjusted.

Table 2 Relative risk (RR) and 95% CI for cancers according to height in 1986 in male health professionals (1986–1998)

	Height (in.)					
	<66	66–67.9	68–69.9	70–71.9	≥72	P (trend)
Total cancer (n = 3270)	108	422	801	980	959	
Age-adjusted RR	1.0	1.17	1.28	1.26	1.41	0.0005
Multivariate RR[a]	1.0	1.16	1.25	1.23	1.36	0.003
95% CI	—	0.94, 1.43	1.02, 1.54	1.00, 1.50	1.11, 1.67	—
Western carcinoma[b] (n = 1029)	30	131	234	310	324	
Age-adjusted RR	1.0	1.31	1.36	1.47	1.82	0.0001
Multivariate RR[a]	1.0	1.29	1.33	1.43	1.74	0.0002
95% CI	—	0.87, 1.93	0.91, 1.96	0.98, 2.09	1.19, 2.55	—
Non-Western carcinoma (n = 1601)	47	201	406	491	456	
Age-adjusted RR	1.0	1.28	1.49	1.45	1.52	0.05
Multivariate RR[a]	1.0	1.26	1.45	1.40	1.46	0.14
95% CI	—	0.92, 1.74	1.07, 1.97	1.03, 1.89	1.07, 1.98	—
Non-carcinoma (n = 672)	32	93	168	189	190	
Age-adjusted RR	1.0	0.86	0.88	0.78	0.88	0.82
Multivariate RR[a]	1.0	0.86	0.88	0.79	0.88	0.92
95% CI	—	0.57, 1.29	0.60, 1.29	0.54, 1.15	0.60, 1.29	—

[a] Multivariate RR controlled for age, racial group, C-peptide score, smoking history, and alcohol intake.
[b] Western carcinomas include colon, pancreatic, kidney, and aggressive prostate cancer.

Table 3 Relative risk (RR) and 95% CI for cancers according to predicted C-peptide score in male health professionals (1986–1998)

	C-peptide score[a] (quintiles)					
	1	2	3	4	5	P (trend)
Total cancer (n = 3270)	586	650	658	686	690	
Age-adjusted RR	1.0	1.09	1.09	1.12	1.19	0.006
Multivariate RR[b]	1.0	1.07	1.05	1.08	1.13	0.05
95% CI	—	0.95, 1.19	0.94, 1.18	0.97, 1.21	1.01, 1.26	—
Western carcinoma[c] (n = 1029)	161	196	226	214	232	
Age-adjusted RR	1.0	1.18	1.34	1.24	1.43	0.006
Multivariate RR[b]	1.0	1.17	1.32	1.22	1.38	0.01
95% CI	—	0.95, 1.45	1.08, 1.62	0.99, 1.49	1.13, 1.69	—
Non-Western carcinoma (n = 1601)	304	307	330	349	311	
Age-adjusted RR	1.0	1.05	1.06	1.22	1.09	0.30
Multivariate RR[b]	1.0	0.96	1.00	1.03	0.95	0.63
95% CI	—	0.82, 1.12	0.85, 1.17	0.89, 1.21	0.81, 1.11	—
Non-carcinoma (n = 672)	123	156	107	131	155	
Age-adjusted RR	1.0	1.24	0.84	1.02	1.26	0.06
Multivariate RR[b]	1.0	1.25	0.85	1.03	1.28	0.04
95% CI	—	0.98, 1.58	0.65, 1.10	0.81, 1.32	1.01, 1.63	—

[a] C-peptide score based on body mass index, physical activity, and 'Western' dietary pattern weighed by regression analysis (See text).
[b] Multivariate RR controlled for age, racial group, height, smoking history, and alcohol intake.
[c] Western carcinomas include colon, pancreatic, kidney, and aggressive prostate cancer.

may accelerate physical development and accentuate linear growth,[34] and in adulthood, excessive energy intake causes obesity, which is the strongest modifiable determinant of insulin resistance.[25] Physical activity improves insulin sensitivity[52–54] by reducing visceral adiposity[55] and by increasing glycogen synthesis in muscle.[56] In addition, some aspects of the Western diet accentuate insulin resistance and hyperinsulinaemia. As discussed in the introduction, data from *in vitro*, animal, clinical, and epidemiological studies support a cancer-promoting role of high IGF-I and insulin bioactivity. Data on impaired glucose tolerance in relation to cancer risk have been mixed,[57–61] but this may reflect the complex temporal relation between

hyperglycaemia and hyperinsulinaemia. Because these hormonal factors could act both early and late in life, we examined tallness as a marker of insulin and IGF-I exposure in pre-adulthood, and the combined influence of obesity, physical inactivity, and Western diet in adulthood in relation to cancer risk in men.

In our study of US males, we estimated that 18% of total cancers were attributable to factors associated with tallness, and 14% were attributable in adulthood to modifiable determinants of hyperinsulinaemia, and 29% to both factors combined. This reduction was mostly in Western-related cancers, for which 29% were attributable to adult hyperinsulinaemia and 49% to tallness and hyperinsulinaemia combined. We controlled for major cancer risk factors, including age, race, smoking, and alcohol intake. Additional control for other nutritional factors hypothesized to influence carcinogenesis, including total fat, saturated fat, protein, fibre, and total fruits and vegetables did not change the results for height and C-peptide score. These results suggest that insulin and IGF-I may mediate a substantial proportion of the estimated nutritional influence on cancers observed in excess in Western countries and that energy balance may be the most important component.

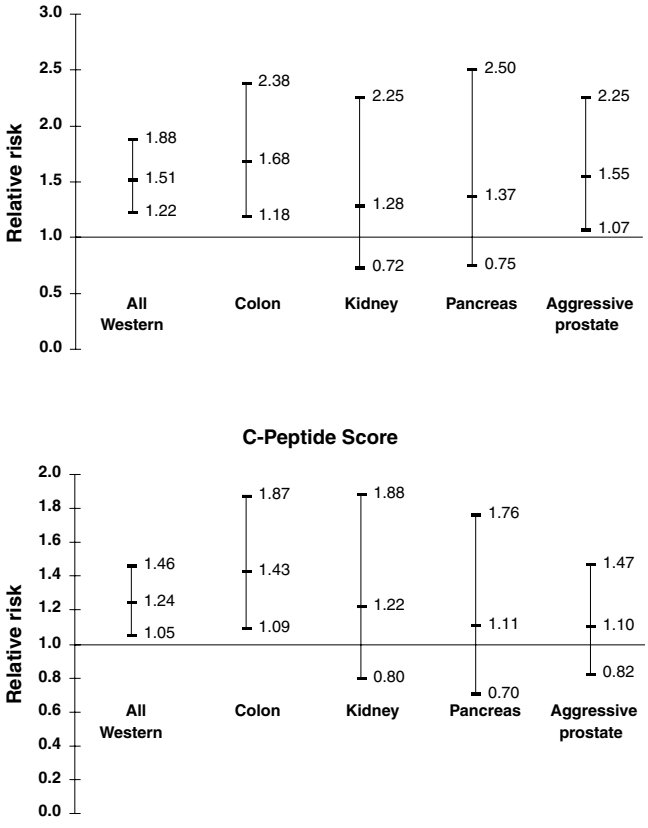

Figure 1 Multivariate relative risks and 95% CI for all Western cancers and each type for a 9-inch increment in height and a 2 standard deviation increase in predicted C-peptide score from a continuous variable model, controlling for age, racial group, smoking history, and alcohol intake

The results were generally consistent for each of the Western-related cancer types, but weakest for adult factors for aggressive prostate cancer. Consistent with this finding, most studies do not support a strong association between BMI and prostate cancer risk.[62] However, a recent case-control study of prostate cancer in Shanghai, China, a low-risk area, found higher risk associated with a larger waist-to-hip ratio and with higher serum insulin levels.[17] With the average BMI only 21.9 kg/m^2, most of the Chinese men would have fallen within the lowest BMI quintile in our study population. Possibly in Western populations, the higher oestrogen and lower testosterone levels associated with obesity,[49,50] which may decrease risk of prostate cancer,[51] offset the potential risk increase related to obesity-induced hyperinsulinaemia. This speculation was consistent with our finding that C-peptide score was associated with a higher risk of prostate cancer only after we removed the BMI component for the C-peptide score. These findings support further studies that directly measure insulin exposure, and that account for the potentially confounding effects of steroid hormones in relation to prostate cancer.

The definition of Western-related cancer is somewhat arbitrary, but we selected *a priori* cancers that are consistently higher in Western countries, and relatively consistently related to taller height and/or obesity. Some cancers (e.g. brain, testicular) arguably could be included, but the numbers of cases are so low as to not influence the results. Haematopoietic cancers, especially non-Hodgkin's lymphoma, have been inconsistently associated with tallness. However, this association in some populations may reflect a lower infection load in childhood, which may lead to shorter height and susceptibility for infections in older ages, which would be related to haematological malignancy.[20] In any case, tallness was not related to risk of haematopoietic malignancies in this cohort.

We did not directly measure insulin or C-peptide levels for the entire cohort, but focused instead on the known modifiable

Table 4 Population attributable risk per cent (PAR%)[a] and 95% CI of total cancers and Western carcinomas by C-peptide score and height in male health professionals (1986–1998)

		Height (in.)		C-peptide score		Height ⩾66 in. + C-peptide score
		Quintiles	Deciles	Quintiles	Deciles	
		⩾68	⩾66	2–5	2–10	(deciles 2–10)
Total cancer	PAR%	9%	18%	7%	14%	29%
(n = 3270)	95% CI	4–19%	7–38%	2–18%	6–28%	16–46%
Western carcinoma	PAR%	15%	30%	19%	29%	49%
(n = 1029)	95% CI	6–31%	11–58%	10–34%	16–48%	30–69%

[a] The population attributable risk is the percentage of cases of cancer that would theoretically not have occurred if all men had been in the low-risk category for these factors (for example, low decile of C-peptide score or height <66 inches). The model was also adjusted for age, smoking history, alcohol intake, and racial group.

determinants of C-peptide. Even lean and reasonably active individuals experience a wide range in insulin sensitivity and insulin levels due to genetic factors and unidentified environmental exposures. Thus, if hyperinsulinaemia is one of the causal factors underlying our observations, we likely underestimated the full influence of long-term, average insulin levels on cancer risk. Nonetheless, our approach directly estimates the potentially known modifiable proportion of cancer risk through this mechanism in adulthood. In addition, although a direct measure of C-peptide would capture additional variation (e.g. genetic), even a single measure of C-peptide would mismeasure long-term exposure somewhat. In contrast, we measured average BMI, physical activity, and diet over a relatively long time period.

We did not specifically incorporate the influences of nutritional modifiers of total IGF-I in adulthood, although the component of IGF-I bioactivity related to modifiable determinants of insulin is accounted for through the C-peptide score. In this cohort, nutritional modifiers of total IGF-I level, primarily protein and mineral intake, were not strong.[63] For example, modifiable predictors in this cohort predicted a 106% higher insulin level in those with higher compared with lower predictor scores, but the difference was only about 25% for IGF-I and 10–15% for IGF-I/IGFBP-III ratio. Other evidence suggests that insulin and IGFBP-I levels are relatively modifiable, whereas total IGF-I level is primarily genetically determined,[64] at least outside extreme situations (e.g. severe calorie or protein restriction). Our results suggest that, although total IGF-I level, as shown by other studies,[15,18,19] is likely to be an independent risk factor for Western-related cancers, the component of risk related to insulin resistance and hyperinsulinaemia (e.g. influence of IGF binding proteins on free IGF-I) may be potentially more modifiable by feasible dietary and lifestyle alterations. This requires confirmation in other studies, especially in women.

In our study, a Western diet score identified by factor analysis, possibly by taking into account complex interactions and synergy among relevant dietary factors, was the best dietary predictor of C-peptide. The use of an alternative pre-specified diet score that incorporated cereal fibre, trans and polyunsaturated fat, and glycaemic load instead of the Western score yielded similar but marginally weaker results in regards to predicting C-peptide level and Western-related carcinoma risk. For practical purposes, this dietary pattern is characterized by higher intakes of red meat, processed meat, high-fat dairy products, sweets, and refined grains, and less whole grains and fibre. A similar pattern has been identified in other US populations.[65] Further study of the relevant hyperinsulinemic components, which may include processed carbohydrates, saturated and trans fat, and low polyunsaturated fats and fibre, micronutrients, and their interactions,[5] may facilitate translating this pattern to other populations.

Adult height is a complex variable because of its multiple determinants, including genetic, nutritional, and health-related factors. For individuals to attain their maximal genetically determined height, intake of energy, protein, minerals, and vitamins must be optimal, and extended periods of illness must be avoided.[66–68] As populations undergo economic development, nutrition and health in childhood usually improves and the average height attained increases. Nutrition in the first few years of life may be of particular importance for final achieved adult height. Variation in average height among populations worldwide will be largely due to nutritional and health-related factors, but variation among individuals in economically developed populations reflects mostly genetic factors. Whether comparing cancer rates to average heights across diverse populations, or cancer risk within relatively homogenous populations such as US health professionals, tallness is a strong risk factor.[20] This pattern is consistent with the underlying causative factors being sensitive to both genetic and to environmental influences, being important determinants of height, and mitogenic in diverse organs. Insulin and IGF-I have these properties.

Our results suggest that a substantial proportion of cancers in economically developed countries are attributable to excessive energy intake, a sedentary lifestyle, and hyperinsulinaemic aspects of diet. This excess risk of cancer is conferred partly in the growth period and partly in adulthood. The adult component has relatively clear public health implications. Besides cancer, the reduction of obesity, increases in physical activity, and avoidance of insulin-stimulating components of diet have other benefits on cardiovascular disease, diabetes, hypertension, and other conditions. The public health implications of the component of risk related to childhood exposure are more complex. It is not feasible, nor necessarily desirable, to reduce maximal potential height. However, the relationships among childhood and adolescent obesity, physical inactivity, hyperinsulinaemic dietary pattern, early maturity, accelerated growth rate, insulin, and IGF-I levels should be studied in the context of cancer risk.

In conclusion, our findings support the hypothesis that components of a Western lifestyle related to hyperinsulinaemia, including obesity, excessive caloric intake, sedentary behaviour, and dietary pattern are the major factors underlying the excess of some cancers seen in developed countries. While part of the risk is conferred in the pre-adult period, our findings indicate that a substantial proportion may potentially still be preventable through diet and lifestyle modifications in adulthood.

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KEY MESSAGES

- Maximal growth in the pre-adult period and hyperinsulinaemia during adulthood may largely underlie the excess risk of some cancers common in Western countries, where energy intake relative to requirements tends to be excessive.

- In a study of men, components of a Western lifestyle related to hyperinsulinaemia in adulthood, including obesity, sedentary behaviour, and diet pattern are major factors underlying the excess of these Western-related cancers.
- While part of the risk is conferred in the pre-adult period, a substantial proportion of these cancers may potentially still be preventable through diet and lifestyle modifications in adulthood.

References

[1] Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 1981;**66:**1191–308.

[2] Schatzkin A, Lanza E, Corle D *et al*. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. *N Engl J Med* 2000;**342:**1149–55.

[3] Smith-Warner SA, Spiegelman D, Adami HO *et al*. Types of dietary fat and breast cancer: a pooled analysis of cohort studies. *Int J Cancer* 2001;**92:**767–74.

[4] Smith-Warner SA, Spiegelman D, Yaun SS *et al*. Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. *JAMA* 2001;**285:**769–76.

[5] Giovannucci E. Insulin and colon cancer. *Cancer Causes Control* 1995;**6:**164–79.

[6] Gerber M, Corpet D. Energy balance and cancers. *Eur J Cancer Prev* 1999;**8:**77–89.

[7] Aaronson S. Growth factors and cancer. *Science* 1991;**254:**1146–53.

[8] DiGiovanni J, Kiguchi K, Frijhoff A *et al*. Deregulated expression of insulin-like growth factor 1 in prostate epithelium leads to neoplasia in transgenic mice. *Proc Natl Acad Sci USA* 2000;**97:**3455–60.

[9] Cohen P, Peehl DM, Rosenfeld RG. The IGF axis in the prostate. *Horm Metab Res* 1994;**26:**81–84.

[10] Hursting SD, Lavigne JA, Berrigan D, Perkins SN, Barrett JC. Calorie restriction, aging, and cancer prevention: mechanisms of action and applicability to humans. *Ann Rev Med* 2003;**54:**131–52.

[11] Corpet D, Jacquinet C, Peiffer G, Taché S. Insulin injections promote the growth of aberrant crypt foci in the colon of rats. *Nutr Cancer* 1997;**27:**316–20.

[12] Tran TT, Medline A, Bruce R. Insulin promotion of colon tumors in rats. *Cancer Epidemiol Biomarkers Prev* 1996;**5:**1013–15.

[13] Lee WM, Lu S, Medline A, Archer MC. Susceptibility of lean and obese Zucker rats to tumorigenesis induced by N-methyl-N-nitrosurea. *Cancer Let* 2001;**162:**155–60.

[14] Schoen RE, Tangen CM, Kuller LH *et al*. Increased blood glucose and insulin, body size, and incident colorectal cancer. *J Natl Cancer Inst* 1999;**91:**1147–54.

[15] Kaaks R, Toniolo P, Akhmedkhanov A, *et al*. Serum C-peptide, insulin-like growth factor (IGF)-1, IGF-binding proteins, and colorectal cancer risk in women. *J Natl Cancer Inst* 2000;**92:**1592–600.

[16] Yang G, Lu G, Jin F *et al*. Population-based, case-control study of blood C-peptide level and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2001;**10:**1207–11.

[17] Hsing AW, Chua S Jr, Gao YT *et al*. Prostate cancer risk and serum levels of insulin and leptin: a population-based study. *J Natl Cancer Inst* 2001;**93:**783–89.

[18] Ma J, Pollak MN, Giovannucci E *et al*. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-1 and IGF-binding protein-3. *J Natl Cancer Inst* 1999;**91:**620–25.

[19] Chan JM, Stampfer MJ, Giovannucci E *et al*. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science* 1998;**279:**563–66.

[20] Gunnell D, Okasha M, Davey Smith G, Oliver SE, Sandhu J, Holly JM. Height, leg length, and cancer risk: a systematic review. *Epidemiol Rev* 2001;**23:**313–42.

[21] Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med* 1999;**341:**1097–105.

[22] Colditz G, Cannuscio C, Frazier A. Physical activity and reduced risk of colon cancer: implications for prevention. *Cancer Causes Control* 1997;**8:**649–67.

[23] Strickler HD, Wylie-Rosett J, Rohan T *et al*. The relation of type 2 diabetes and cancer. *Diabetes Technol Ther* 2001;**3:**263–74.

[24] Orme SM, McNally RJ, Cartwrigh RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. *J Clin Endocrinol Metab* 1998;**83:**2730–34.

[25] Bjorntorp P. Metabolic implications of body fat distribution. *Diabetes Care* 1991;**14:**1132–43.

[26] Jones J, Clemmons D. Insulin-like growth factors and their binding proteins: biological actions. *Endocr Rev* 1995;**16:**3–34.

[27] Underwood LE, Thissen JP, Lemozy S, Ketelslegers JM, Clemmons DR. Hormonal and nutritional regulation of IGF-I and its binding proteins. *Horm Res* 1994;**42:**145–51.

[28] Powell DR, Suwanichkul A, Cubbage ML, DePaolis LA, Snuggs MB, Lee PD. Insulin inhibits transcription of the human gene for insulin-like growth factor-binding protein-1. *J Biol Chem* 1991;**266:**18868–76.

[29] Katz LEL, Cohen P, Rosenfeld R. Clinical significance of IGF binding proteins. *Endocrinologist* 1995;**5:**36–43.

[30] Argente J, Caballo N, Barrios V *et al*. Disturbances in the growth hormone-insulin-like growth factor axis in children and adolescents with different eating disorders. *Horm Res* 1997;**48(Suppl.4):**16–18.

[31] Nam SY, Lee EJ, Kim KR *et al*. Effect of obesity on total and free insulin-like growth factor (IGF)-I and their relationship to IGF-binding protein (BP)-1, IGFBP-2, IGFBP-3, insulin, and growth hormone. *Int J Obes Relat Metab Dis* 1997;**21:**355–59.

[32] Brismar K, Fernqvist-Forbes E, Wahren J, Hall K. Effect of insulin on the hepatic production of insulin-like growth factor-binding protein-1 (IGFBP-1), IGFBP-3, and IGF-1 in insulin-dependent diabetes. *J Clin Endocrinol Metab* 1994;**79:**872–78.

[33] Wong WW, Copeland KC, Hergenroeder AC, Hill RB, Stuff JE, Ellis KJ. Serum concentrations of insulin-like growth factor-1, and insulin-like growth factor binding proteins are different between white and African American girls. *J Pediatr* 1999;**135:**296–300.

[34] Juul A, Bang P, Hertel NT *et al*. Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. *J Clin Endocrinol Metab* 1994;**78:**744–52.

[35] Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Intake of carotenoids and retinol in relation to risk of prostate cancer. *J Natl Cancer Inst* 1995;**87:**1767–76.

[36] Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of a expanded self-administered

semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol* 1992;**135:**1114–26.

[37] Feskanich D, Rimm EB, Giovannucci EL *et al*. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. *J Am Diet Assoc* 1993;**93:**790–96.

[38] Chasan-Taber S, Rimm EB, Stampfer MJ *et al*. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. *Epidemiology* 1996;**7:**81–86.

[39] Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology* 1990;**1:**466–73.

[40] Bonser AM, Garcia-Webb P. C-peptide measurement: methods and clinical utility. *Crit Rev Clin Lab Sci* 1984;**19:**297–352.

[41] Hovorka R, Jones RH. How to measure insulin secretion. *Diabetes Metab Rev* 1994;**10:**91–117.

[42] Clinton SK, Giovannucci E. Diet, nutrition, and prostate cancer. *Ann Rev Nutr* 1998;**18:**413–40.

[43] Fung TT, Rimm EB, Spiegelman D *et al*. The association between dietary patterns and plasma biomarkers of obesity and cardiovascular disease risk. *Am J Clin Nutr* 2001;**73:**61–67.

[44] Hu FB, Manson JE, Stampfer MJ *et al*. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 2001;**345:**790–97.

[45] Rothman KJ, Greenland S. *Modern Epidemiology. 2nd Edn*. Philadelphia: Lippincott-Raven Publishers, 1998.

[46] Wacholder S, Benichou J, Heineman EF, Hartge P, Hoover RN. Attributable risk: Advantages of a broad definition of exposure. *Am J Epidemiol* 1994;**140:**303–09.

[47] Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. *Am J Epidemiol* 1985;**122:**904–14.

[48] Caprio S. Insulin: the other anabolic hormone of puberty. *Acta Paediatr Suppl* 1999;**433:**84–87.

[49] Pasquali R, Casimirri F, Cantobelli S *et al*. Effect of obesity and body fat distribution on sex hormones and insulin in men. *Metabolism* 1991;**40:**101–04.

[50] Field AE, Colditz GA, Willett WC, Longcope C, McKinlay JB. The relation of smoking, age, relative weight, and dietary intake to serum adrenal steroids, sex hormones, and sex hormone-binding globulin in middle-aged men. *J Clin Endocrinol Metab* 1994;**79:**1310–16.

[51] Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. A prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst* 1996;**88:**1118–26.

[52] Koivisto VA, Yki-Jarvinen H, DeFronzo RA. Physical training and insulin sensitivity. *Diabetes Metab Rev* 1986;**1:**445–81.

[53] Schneider SH, Amorosa LF, Khachadurian AK, Ruderman NB. Studies on the mechanism of improved glucose control during regular exercise in type 2 (non-insulin-dependent) diabetes. *Diabetologia* 1984;**26:**355–60.

[54] Burstein R, Polychronakos C, Toews CJ, MacDougall JD, Guyda HJ, Posner BI. Acute reversal of the enhanced insulin action in trained athletes. Association with insulin receptor changes. *Diabetes* 1985;**34:**756–60.

[55] Ross R. Effects of diet- and exercise-induced weight loss on visceral adipose tissue in men and women. *Sports Med* 1997;**24:**55–64.

[56] DeFronzo RA, Jacot E, Jequier E, Maeder E, Wahren J, Felber JP. The effect of insulin on the disposal of intravenous glucose. Results from indirect calorimetry and hepatic and femoral venous catheterization. *Diabetes* 1981;**30:**1000–07.

[57] Saydah SH, Loria CM, Eberhardt MS, Brancati FL. Abnormal glucose tolerance and the risk of cancer death in the United States. *Am J Epidemiol* 2003;**157:**1092–100.

[58] Davey Smith G, Egger M, Shipley MJ, Marmot MG. Post-challenge glucose concentration, impaired glucose tolerance, diabetes, and cancer mortality in men. *Am J Epidemiol* 1992;**136:**1110–14.

[59] Levine W, Dyer AR, Shekelle RB, Schoenberger JA, Stamler J. Post-load plasma glucose and cancer mortality in middle-aged men and women. *Am J Epidemiol* 1990;**131:**254–62.

[60] Shaw JE, Hodge AM, de Courten M, Chitson P, Zimmet PZ. Isolated post-challenge hyperglycaemia confirmed as a risk factor for mortality. *Diabetologia* 1999;**42:**1050–54.

[61] Pyorala M, Miettinen H, Laakso M, Pyorala K. Plasma insulin and all-cause, cardiovascular, and noncardiovascular mortality: the 22-year follow-up results of the Helsinki Policemen Study. *Diabetes Care* 2000;**23:**1097–102.

[62] Nomura AM. Body size and prostate cancer. *Epidemiol Rev* 2001;**23:**126–31.

[63] Giovannucci E, Pollak M, Liu Y *et al*. Nutritional predictors of insulin-like growth factor I and their relationships to cancer in men. *Cancer Epidemiol Biomarkers Prev* 2003;**12:**84–89.

[64] Hong Y, Pedersen NL, Brismar K, Hall K, De Faire U. Quantitative genetic analyses of insulin-like growth factor-I (IGF-I), IGF-binding protein-1, and insulin levels in middle-aged and elderly twins. *J Clin Endocrinol Metab* 1996;**81:**1791–97.

[65] Slattery ML, Boucher KM, Caan BJ, Potter JD, Ma KN. Eating patterns and risk of colon cancer. *Am J Epidemiol* 1998;**148:**4–16.

[66] Proos LA. Anthropometry in adolescence—secular trends, adoption, ethnic and environmental differences. *Horm Res* 1993;**39(Suppl.3):** 18–24.

[67] Hauspie RC, Vercauteren M, Susanne C. Secular changes in growth and maturation: an update. *Acta Paediatr Suppl* 1997;**423:** 20–27.

[68] Cole TJ. Secular trends in growth. *Proc Nutr Soc* 2000;**59:**317–24.