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Are dietary influences on the risk of prostate cancer mediated through the insulin-like growth factor system?

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Objectives To investigate whether dietary factors that appear to affect the risk of prostate cancer may be similarly associated with serum levels of insulin-like growth factor 1 (IGF-1).

Patients and methods In the context of a case-control study, 112 men were admitted to three teaching hospitals in Athens, Greece, for disorders other than cancer. Sociodemographic data and detailed histories of smoking, alcohol and coffee consumption were recorded. A validated food-frequency questionnaire was administered by an interviewer and serological measurements of IGF-1 and its binding protein-3 conducted.

Results IGF-1 declined significantly by almost 25% among men aged >75 years and there was a small reduction in IGF-1 levels with increased alcohol intake, with a mean (95% confidence interval, CI) change of -1.6 (-2.2 to -0.9)% for an increment of one drink per day. There was no evidence for an effect of either smoking or coffee consumption on IGF-1 level. Among foods, the consumption of cooked tomatoes was substantially and significantly inversely associated with IGF-1 levels, with a mean (95% CI) change of -31.5 (-49.1 to -7.9)% for an increment of one serving per day.

Conclusions The strongest known dietary risk factor for prostate cancer (lycopene deficit, as reflected in a reduced intake of cooked tomatoes) and an important endocrine factor in the aetiology of this disease (IGF-1) seem to be related in a way that suggests that at least one, and perhaps more, exogenous factors in the development of prostate cancer may be mediated through the IGF-1 system.

Keywords IGF-1, dietary factors, prostate cancer, risk, epidemiology

Introduction

During the last few years there has been considerable progress in the understanding of the hormonal causes of prostate cancer, particularly the IGF system. Specifically, all studies including a substantial number of patients with prostate cancer [1–5] have shown a positive association between IGF-1 and the incidence of prostate cancer, whereas the association was reversed after radical prostatectomy [6]. At the same time, several reports about the dietary components associated with prostate cancer have appeared [4,7–16]. These nutritional epidemiology studies had different objectives but the results appear to be convergent. The risk of prostate cancer seems to be inversely associated with vegetable intake [11], and the relationship is dominated by the strong inverse association with cooked tomatoes (and their products) which are very rich in lycopene [9]. A strong negative association of prostate cancer risk with selenium intake has also been reported [12–14]. In contrast, there is a positive association between the consumption of dairy products and prostate cancer risk, and this relationship is attributed to the high calcium content of these products [17,18]. Positive associations have also been reported between prostate cancer risk and meat consumption (mainly red meat), saturated lipids of animal origin, and polyunsaturated lipids (particularly α-linolenic acid) [7,8,11,15]. Finally, tobacco smoking and alcohol intake have not emerged as factors that increase prostate cancer risk and indeed some recent studies have indicated that alcohol may be weakly inversely correlated with this risk [19].

We investigated in a large sample of Greek men whether dietary factors that appear to affect the risk of prostate cancer may be similarly associated with serum levels of IGF-1. If these dietary factors were also found to affect IGF-1 in the same direction, this would lend biological plausibility to both the dietary factors and IGF-1 as component causes of prostate cancer. The Greek Food Composition Tables [20] contain no information

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about lycopene or selenium, but we evaluated the associations of IGF-1 with energy-generating nutrients and cooked tomatoes, the principal source of dietary lycopene. Sociodemographic and anthropometric factors were also evaluated as potential confounders, while IGF binding protein-3 (IGFBP-3), which is thought to modulate the effect of IGF-1, was also considered in the analysis.

Patients and methods

In the context of a study on the aetiology of liver cancer [21], 112 control patients were recruited during a 4-year period between January 1995 and December 1998. These individuals were admitted to three teaching hospitals in Athens (Hippokration, Western Attica and Laiko General Hospital) for injuries or for eye, ear, nose or throat conditions, i.e. disorders not involving cancer, usually requiring minor surgery and considered to be unrelated to smoking or alcohol consumption.

All the patients were interviewed in the hospital wards by three trained interviewers. Data on demographic, socio-economic and medical variables were recorded, and detailed histories of smoking habits, and alcohol and coffee consumption were taken. The interviewers also administered a validated food-frequency questionnaire [22].

Sera, which had been obtained from each subject and stored at -25°C, were transferred on dry ice to the internationally certified Biomedicine Laboratories in Athens, Greece, for serological measurements of IGF-1 and IGFBP-3. The former was measured using a chemiluminescence assay (Nichols Institute, San Juan Capistrano, CA). No cross-reactivity with IGF-2, proinsulin, insulin, thyroid-stimulating hormone or luteinizing hormone was detected. IGFBP-3 concentrations were measured using a commercially available RIA kit (Nichols Institute).

Dietary data

A validated, semiquantitative food-frequency questionnaire was used [22]. The patients were asked to indicate the average frequency of consumption of about 120 food items or beverage categories per month, per week or per day, over one year. For analysis, the frequency of consumption of different food items was quantified approximately in terms of the number of times per month the food was consumed. Thus, daily consumption was multiplied by 30, and weekly consumption by four; a value of zero was assigned to food items rarely or never consumed. Food items were considered in groups, as recommended by Davidson and Passmore [23], and regularly used in nutritional epidemiological studies in Greece [24]. Individual values for monthly consumption were added, and the sums approximately distributed into quintiles. The food groups formed were: cereals; starchy roots; sugars and syrups; pulses and nuts; vegetables; fruits; meats, fish and eggs; milk and dairy products; added lipids; and nonalcoholic beverages. Some cooked meals were allocated to two food groups; for instance, moussaka, a popular dish in Greece, was apportioned into both the vegetable and meat groups, while cheese pie was apportioned into cereals and milk products.

Nutrient intakes for individuals were estimated by multiplying the nutrient contents of a selected typical portion, for each specified food item, by the frequency that the food item was eaten, and adding these estimates for all food items. Estimates were based on a nutrient database applicable to the Greek population [20]. The estimate of portion size was based on the results from previous validation studies, and the nutrient content of dishes was calculated on the basis of Greek recipes [20,22]. Daily macronutrient intakes (in grams) were calculated for protein, saturated, mono-unsaturated and polyunsaturated lipids and carbohydrates, and total energy calculated in kilocalories.

Statistical analysis

Linear models were developed to evaluate dietary predictors of IGF-1; because the distribution of IGF-1 was positively skewed, log-transformed values of the dependent variable were used. In this way, partial regression coefficients, after exponentiation, express the relative change (e.g. percentage) of the dependent variable (IGF-1) corresponding to an increment of one unit in the specified independent variable, keeping all the other independent variables constant. IGFBP-3 binds IGF-1 and modulates its effect by reducing its availability. However, because IGF-1 and IGFBP-3 are strongly and positively associated, the identification of independent predictors of IGFBP-3 has limited value and thus the ratio of IGF-1/IGFBP-3 was used, as is frequently the case in biochemistry when two factors have functionally opposite effects. In all instances, models are presented with both log IGF-1 and IGF-1/IGFBP-3, alternatively, as dependent variables. In the core statistical models we adjusted for the potential confounding effect of age (in decades, categorically), total energy intake (kcal/day, continuously) and alcohol intake (glasses/day, continuously). We also evaluated body mass index (BMI), coffee intake and smoking as potential confounders, although their effect was later shown to be negligible. Food groups (servings per month), individual food items (servings per month), and nutrients (grams per day) were assessed continuously and introduced individually in the core model, always controlling for total energy intake.

Table 1 The demographic and lifestyle characteristics of the 112 male study participants

Characteristic	*N (%)*
Age group (years)	
<65	43 (38.4)
65–74	52 (46.4)
≥75	17 (15.2)
Current smoking habits (cigarettes/day)	
Non-smoker	33 (29.5)
1–10 cigarettes	13 (11.6)
11–20 cigarettes	32 (28.6)
≥21	34 (30.4)
Alcohol consumption (drinks/week)	
None	36 (34.6)
1–6	11 (10.6)
7–13	13 (12.5)
14–20	5 (4.8)
≥21	39 (37.5)
Coffee consumption (drinks/week)	
None	11 (9.8)
1–6	9 (8.0)
7–13	26 (23.2)
14–20	41 (36.6)
≥21	25 (22.3)
Body mass index (kg/m^2)	
<25.0	33 (29.5)
25.0–26.9	24 (21.4)
27.0–29.9	39 (34.8)
≥30.0	16 (14.3)

Results

Table 1 shows the distribution of study participants by demographic and lifestyle characteristics. In this group of middle-aged and elderly men, more than two-thirds were current smokers and regular drinkers, and >90% were regular coffee consumers. These patterns are typical of Greek men in these age groups. More than two-thirds of the study participants were also slightly or considerably overweight, again in line with what is known about the prevalence of obesity in this population group.

Table 2 shows descriptive characteristics of the principal study variables. The distributions of IGF-1 and IGFBP-3 were both slightly positively skewed and the Spearman correlation coefficient between the variables was + 0.74. For the intake of energy-generating nutrients, the pattern is typical of that prevailing in the Greek population, with energy from lipids being >40% of the total energy intake and energy from mono-unsaturated lipids being >25% of the total. Table 2 also shows the consumption of red meat and dairy products, both reported to be positively associated with IGF-1, and of cooked tomatoes, consistently found to be inversely associated with IGF-1.

The data in Table 3 were generated by multiple linear regression models in which serum log IGF-1 and the ratio of IGF-1/IGFBP-3 were alternatively used as the dependent variable. The factors indicated in Table 1 were used as independent variables, together with energy intake, an indispensable variable for evaluating nutritional associations. IGF-1 declined significantly by almost 25% among people aged >75 years and there was a small but significant reduction in IGF-1 levels with increased alcohol intake. There was no evidence for an effect of either smoking or coffee consumption on IGF-1 levels. Last, both the BMI and energy intake were positively associated with IGF-1 levels, but the respective associations were not significant. For the IGF-1/IGFBP-3 ratio no association was statistically significant; only for energy intake and alcohol consumption were the associations possibly suggestive.

Table 2 The serum concentration of IGF-1 and IGFBP-3, and daily intake of energy-generating nutrients, red meat, dairy products, and cooked tomatoes* among 112 male study participants

Variable	*Mean (SD)*
IGF-1 (ng/mL)	174.3 (62.1)
IGFBP-3 (μg/mL)	2.3 (0.93)
Total energy (kcal/day)	2698 (1775)
Saturated lipids (g/day)	37.9 (23.9)
Monounsaturated lipids (g/day)	78.7 (34.7)
Polyunsaturated lipids (g/day)	19.4 (11.8)
Carbohydrates (g/day)	188.0 (290.9)
Protein (g/day)	89.9 (60.4)
Red meat (servings/month)	7.0 (5.2)
Dairy products (servings/month)	47.0 (26.6)
Cooked tomatoes (servings/month)	13.2 (4.8)

*There are no data on lycopene content of foods in the Greek Food Composition Tables. Cooked tomatoes are the richest source of this retinoid.

Table 3 also shows the relationship of IGF-1 and IGF-1/IGFBP-3 ratio with energy-generating nutrients. No association was significant and a suggestive value for protein in relation to the ratio is difficult to interpret, given the multiplicity of tests and the absence of supportive biological evidence. However, Table 3 also shows substantial and significant inverse associations between cooked tomatoes and both IGF-1 and IGF-1/IGFBP-3. Moreover, the associations of both red meat and dairy products with both IGF factors are in biologically plausible directions, although only for red meat in relation to the IGF-1/IGFBP-3 ratio does the *P* value approach significance.

Discussion

IGF-1, which mediates the effects of growth hormone, is secreted mainly by the liver, but is also produced in several other tissues [25]. IGF-1 is tightly bound to a family of six proteins, the IGFBPs, of which IGFBP-3 is

Table 3 Percentage changes (generated by multiple linear regression) in serum IGF-1 and the absolute changes in the ratio of serum IGF-1/IGFBP-3 for the indicated increments of the predictor variables, energy-generating nutrients and food-group items

Predictor variables	*Category/ increment*	*IGF-1*		*IGF-1/IGFBP-3*	
		% change (95% CI)	P*	*Change (95% CI)*	P*
Lifestyle†					
Age (years)	<65			baseline	
	65–74	−4.0 (−14.0, +7.1)	0.47	−4.4 (−14.3, 5.5)	0.38
	≥75	−23.2 (−34.2, −10.3)	0.0012	−11.2 (−25.0, 2.6)	0.12
BMI	1 kg/m^2	+0.7 (−0.6, +2.1)	0.27	+0.3 (−0.8, 1.5)	0.58
Energy intake	500 kcal/day	+0.6 (−0.8, +2.0)	0.41	+1.0 (−0.2, 2.3)	0.17
Alcohol consumption	1 drink/day	−1.6 (−2.2, −0.9)	0.010	−0.8 (−1.9, 0.3)	0.16
Coffee consumption	1 cup/day	0.0 (−4.1, +4.1)	0.98	+1.4 (−2.4, 5.2)	0.47
Current smoking	10 cigarettes/day	−0.8 (−4.0, +2.4)	0.62	+1.2 (−1.6, 4.1)	0.40
Energy-generating nutrients‡§					
Carbohydrates	1775	0.1 (−10.9, 12.5)	0.98	3.8 (−6.8, 14.3)	0.49
Protein	60	1.4 (−11.4, 16.0)	0.84	−10.5 (−22.4, 1.4)	0.09
Saturated lipids	24	0.6 (−5.2, 6.7)	0.85	−3.3 (−8.6, 1.9)	0.22
Mono-unsaturated lipids	35	2.5 (−4.1, 9.6)	0.47	2.8 (−3.3, 8.9)	0.36
Polyunsaturated lipids	12	1.3 (−6.0, 9.3)	0.73	−1.6 (−8.3, 5.2)	0.65
Food group/item‡					
Red meat	1 serving/day	17.9 (−11.3, 56.7)	0.26	19.03 (−6.54, 44.59)	0.15
Dairy products	1 serving/day	2.4 (−3.2, 8.3)	0.41	0.12 (−4.93, 5.16)	0.96
Cooked tomatoes	1 serving/day	−31.5 (−49.1, −7.9)	0.014	−27.70 (−54.92, −0.48)	0.047

*Two-tailed; † For IGF-1, also controlling for serum IGFBP-3; ‡ for IGF-1, controlling for serum IGFBP-3, age, alcohol consumption and total energy intake, and for IGF-1/IGFBP-3, controlling for age, total energy intake and alcohol consumption; § the interval is one SD increase (rounded).

the most abundant in serum [26]. IGF-1 can act in an autocrine and paracrine manner to promote normal growth and malignant cellular proliferation [25,27]. The realization that IGF-1 has mitogenic and anti-apoptotic effects on prostate epithelial cells [28,29] prompted studies of the role of IGF-1 in human prostate carcinogenesis. In a case-control study in Greece an increment of of ≈ 1 SD in the serum IGF-1 level (60 ng/mL) was reported to double the risk of prostate cancer [3]. In a case-control study nested in a large cohort in the USA [4] a similar increase in prostate cancer risk was found, and in a population-based control study in Sweden [5] a 50% increase in risk per 100 ng/mL increment in IGF-1 was reported. Similar, although statistically not significant results, were reported from earlier and smaller clinical studies [1,2].

Because the IGF system is considered as potentially important in carcinogenesis in general, and in prostate carcinogenesis in particular, studies exploring the determinants of various components of this system are important. Several such studies have been undertaken and most have focused on IGF-1, which is thought to be the more important factor in the IGF system. We identified seven earlier studies [30–36] that explored anthropometric and lifestyle variables in relation to IGF-1, and three earlier studies that focused on dietary factors in relation to this hormone [33,35,36]. No previous investigation has examined the association between lycopene (or cooked tomatoes, which are by far the most important source of lycopene) in relation to IGF-1, and there has been no attempt to assess the role of diet as an early step in the postulated sequence from exogenous determinants through the IGF system to prostate cancer risk.

The present study has several strengths; it was considerably larger than other studies that examined nutritional factors among men, relevant in the context of prostate cancer risk. The academic units contributing to the present investigation were involved in several studies of IGF in relation to prostate cancer [3,5], as well as other forms of cancer [37–40], and reported results that were in agreement with similar studies previously or subsequently undertaken. Last, state-of-the-art laboratory and epidemiological methods were used. An important limitation is that the statistical power of the study may not be sufficient to ascertain weak associations that have traditionally characterized nutritional variables in cancer epidemiology [41]. However, it was not considered a disadvantage that the participants were not tested for subclinical prostate cancer; the crucial issue is that these men did not have clinical cancer, because these are the people to whom the present results apply [42].

There was a decline in IGF-1 serum levels with increasing age, in agreement with most previous reports [31,32,34,43]. Among the lifestyle factors examined, only alcohol intake appeared to reduce serum IGF-1

levels and the effect, although small, was statistically significant. A weak inverse association was also detected in an earlier study in a different sample of elderly Greek men [36]. This finding needs to be evaluated in other populations and more attention should be paid to occasional reports that alcohol intake may be inversely related to prostate cancer risk [15]. There was no evidence in the present, or any other earlier investigation, that BMI was associated with IGF-1, but the present data could not be used to confidently refute the possibility that energy intake is positively associated with serum IGF-1, an association suggested by other investigators [33].

There was no effect of tobacco smoking on IGF-1 levels in the present or in an earlier independent study among men in Greece [36]. This finding is in line with the well-established lack of association of tobacco smoking with prostate cancer risk. Two other published studies examined the effect of smoking on IGF-1; one reported a significant negative association [30] and the other a significant positive one [34]. The weight of evidence suggests no such association. There is also no evidence in this or any other study that coffee drinking may affect levels of IGF-1 or prostate cancer risk.

For diet, no macronutrient has been conclusively linked to prostate cancer risk and the evidence for total fat or saturated fat consumption has been judged as being no more than 'possible' [11]. In the present study, none of the energy-generating nutrients appeared to affect serum IGF-1 levels, and nor was there an indication for an association, positive or inverse, in two other earlier investigations [33,36]. In only one paper was there a report of associations between macronutrients and IGF-1, but it is difficult to interpret that evidence because the regression and correlation coefficients indicated different and conflicting directions of association [35].

We also examined the effects of food items or groups, notably red meat, dairy products and cooked tomatoes, that were repeatedly reported to be associated with prostate cancer risk [9,15,44–46]. Both red meat and dairy products were positively associated with IGF-1 levels and the indicator of bioavailable IGF-1, but none of these associations was statistically significant, possibly because the underlying associations are too weak to be documented in other than very large samples. In contrast, there were large and statistically significant associations between cooked tomatoes and both IGF-1 and IGF-1/IGFBP-3. To the extent that the inverse association of lycopene and its major dietary source, cooked tomatoes, is the best established nutritional association for prostate cancer [9,15,44,45], the clear inverse association of cooked tomatoes with IGF-1 conveys credibility to both lycopene deficit and IGF-1 as being important sequential links in the chain of causation of prostate cancer.

In conclusion, there is evidence that the strongest known dietary risk factor for prostate cancer, lycopene deficit, and the most likely endocrine factor in the aetiology of this disease, IGF-1, may be related in a way suggesting that at least one, and perhaps more, exogenous factors in the aetiology of prostate cancer may be mediated through the IGF-1 system. Alcohol intake was also inversely related to IGF-1, suggesting that the association of alcohol intake and prostate cancer should be carefully evaluated.

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