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Are there age-dependent effects of diet on prostate cancer risk?

Summary

Objectives: To examine whether there are age-dependent effects of diet on prostate cancer risk.

Methods: We have postulated that nutritional factors that may affect the risk of initiation would be more likely to be identified among younger patients, whereas those that may affect the risk of progression would be more clearly identifiable among older patients. Study subjects were 320 patients with prostate cancer and 246 controls with no systematic disease, hospitalised in six major hospitals in Athens, Greece. Logistic regression models were fitted separately for men under 70 years and 70 years or older.

Results: Polyunsaturated lipids substantially increased the risk among younger subjects, but played little role among older ones (p for interaction 0.21). Cooked tomatoes had a strong protective effect among older persons, but not among younger subjects (p for interaction 0.009). Last, vitamin E was strongly inversely related to prostate cancer risk among younger subjects, but not among older subjects (p for interaction 0.15).

Conclusions: Even a simple straight forward interpretation of the data, i.e., that older cases of prostate cancer have a different dietary risk profile than younger ones, has potentially useful implications.

Key-Words: Prostate cancer – Diet – Age – Tomatoes – Fat – Vitamin E.

We have recently reported the results from a case-control study undertaken in Greece and concerning the dietary etiology of cancer of the prostate¹. None of the results of this study were new, but the overall findings were important in that they provided support to, or were compatible with several hypotheses on the nutritional etiology of prostate cancer, indicating that these hypotheses could be viewed as complementary rather than mutually exclusive. Thus, the collective evidence from epidemiologic investigations suggests that consumption of saturated fat of animal origin² and polyunsaturated lipids mostly from seed oils^{3,4} increase prostate cancer risk, whereas consumption of lycopene-rich cooked tomatoes⁵ and vitamin E intake⁶ reduce this risk. We have focused on nutrients, rather than foods. For lycopene, however, no database was available for Greek foods and we have used instead as a proxy cooked tomatoes, which contain very high quantities of lycopene that is released after cooking⁵.

Cancer is a long multi-stage process, the most distinct stages of which are considered to be the early one, that is initiation, and the late one, that is progression. It would have been important to determine at which stage does each nutritional factor act, but this would have required repeated dietary assessments of subjects in a large cohort study with several decades of follow-up, as well as the ability to reliably document the stage of carcinogenesis. Such results, however, have not been reported in the literature. A realistic alternative would be the use of the case-control design with a focus on changing dietary patterns over the various periods of life. Retrospective dietary assessments, however, mostly harvest the nutritional experience of the study subjects during the more recent past⁷.

We have postulated that nutritional factors that act early in life and are likely to affect the risk of initiation would be more likely to be captured in dietary records of younger

patients. In contrast, nutritional factors that may affect the risk of progression would be more clearly identifiable among older patients, among whom the initiation period is too remote to allow accurate recollection of relevant dietary exposures.

Patients and methods

Details concerning the case-control study have been previously reported^{1,8}. During a three-year period, from February 1994 to January 1997, all men newly diagnosed with prostate cancer who were residents of the Greater Athens area (population about four million) were identified in six major hospitals of this area. Discharge statistics indicate that these hospitals cover about $\frac{2}{3}$ of the newly diagnosed cases of prostate cancer in this area. 372 histologically confirmed cases were identified. It was not possible to interview 52 patients (14%) and 320 were eventually included in the study. Metastatic disease was present in 19 of the 320 cases of prostate cancer.

For each case, one control subject was to be selected from the same hospital and interviewed in the wards at the same date as the corresponding case. Controls had to be residents of the Greater Athens area, be of approximately the same age as the corresponding case (\pm three years), never have had cancer or been diagnosed with BPH, and have as current diagnosis a minor eye ailment, a minor injury or a minor ear, nose and throat condition. Controls were identified for 308 cases with prostate cancer, but for 62 of them (20%) a complete interview was not obtained. Of the 246 controls who were eventually included in the study, 209 had an eye ailment, 25 had a minor injury, and 12 had a minor ear, nose and throat condition.

Both cases and controls were interviewed in the hospital wards by specially trained public health visitors. The questionnaire was extensive and also included a semi-quantitative food frequency section previously validated⁹. Cases and controls were asked to indicate the average frequency of consumption, over a period of one year immediately preceding the recognition of symptoms or signs of the present disease, of about 120 food items or beverage categories per month, per week or per day. 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. 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 items¹.

The main statistical analysis was undertaken by modeling the data through multiple logistic regression. In all models, a set of core non-dietary variables was consistently included: age (in five-year groups), height (in five-cm groups), body mass index (in kg/m²) and years of schooling, as an indicator of socioeconomic status, (in three categories). Total energy intake (in kcal) was also included in the model, because this is considered as essential for the valid interpretation of nutritional associations with disease status¹⁰. In addition to the core variables, we have simultaneously evaluated four dietary variables that have been examined in previous investigations of the dietary etiology of prostate cancer²: saturated lipids, polyunsaturated lipids, vitamin E, and cooked tomatoes as a proxy of lycopene. For saturated lipids, polyunsaturated lipids, and vitamin E, increments were set as equal to the corresponding standard deviation among controls, whereas for cooked tomatoes the increment was set to one additional serving every other day, that is 15 servings per month.

In order to assess possible age-dependent effects of the nutritional factors, we have divided study cases and controls into two groups: less than 70 years and 70 years or more. We have chosen this cutoff point, because this age represents the round number closest to the median¹, but other cutoff points – 65 and 75 years of age – generated similar results with somewhat larger confidence intervals. Multiple logistic regression generates estimates of relative risks per specified increments, after controlling for all the other factors, nutritional and non-nutritional, included in the model. Differences between the relative risk estimates for prostate cancer with respect to a specific nutritional variable between the two groups (less than 70 years and 70 years or more) implies interaction of this variable with age in relation to prostate cancer risk. Because statistical documentation of interaction requires substantial statistical power, inferences can occasionally be made on the basis of simple arithmetic comparisons and the biomedical credibility of the emerging pattern. However, formal tests for interaction are available¹¹ and when one of the interacting variables has only two levels, as in this instance age below 70 and 70 years or more, the relative risk estimates concerning the second interacting variable in the two strata can be directly compared¹².

When the study objective is detection and quantification of interaction, use of the interacting factors (age, nutrient) as continuous variables increases the power, but complicates the interpretation of the regression coefficients. Moreover, use of different cutoff points for different nutrients, on the basis of *post hoc* arguments, challenges the interpretability of p values. In any case, interaction tests were performed with the age variable both in qualitative (<70, \geq 70) and continuous form.

Results

Table 1 shows representative values of the modelled demographic and dietary factors for younger and older prostate cancer cases and controls. The data in Table 1 provide the context of the study, but the information concerning the nutritional variables is not directly interpretable, because of the powerful confounding among these variables.

Table 2 presents multiple logistic regression-derived relative risk estimates for prostate cancer, among men under 70 years of age and 70 years or older, per 1 standard deviation

increase of selected nutrients and an additional serving every other day for cooked tomatoes. The relative risk estimates are fully adjusted. The results are as striking as they could possibly be in a study of moderate size. Polyunsaturated lipids are an important risk factor for younger subjects, but appear to play little, if any, role among older ones (p value for interaction 0.21). Cooked tomatoes have a strong protective effect among older persons, but they seem to be unrelated to prostate cancer risk among younger subjects (p value for interaction 0.009). Last, vitamin E appears

Cases										
	<70 years old (n = 146)					≥70 years old (n = 174)				
	Quartile cutoff points					Quartile cutoff points				
	mean	SD	1 st	2 nd	3 rd	mean	SD	1 st	2 nd	3 rd
Age (years)	63.9	3.8	62.0	65.0	67.0	77.1	5.1	73.0	77.0	80.0
Years of schooling	10	4.9	6.0	9.5	14.0	7.8	4.3	5.0	6.0	11.0
Height (cm)	170.7	5.7	167.0	170.5	175.0	170.0	6.3	165.0	169.5	173.0
Body mass index (kg/m ²)	26.5	3.2	24.7	26.3	28.4	25.8	3.4	23.7	25.2	28.0
Energy intake (kcal)	2999	1106	2188	2822	3362	2861	1094	2156	2607	3418
Saturated fat (g)	31.5	10.3	21.9	29.5	35.9	30.4	8.9	24.7	29.2	34.3
Polyunsaturated fat (g)	19.4	9.5	13.1	16.6	22.3	16.3	8.1	11.4	13.7	18.6
Cooked tomatoes (servings per month)	7.5	5.7	2.0	7.5	10.0	7.2	5.7	2.0	5.0	10.0
Vitamin E (mg)	10.7	3.5	8.3	10.2	12.2	9.8	3.4	6.1	9.1	11.4

Controls										
	<70 years old (n = 109)					≥70 years old (n = 137)				
	Quartile cutoff points					Quartile cutoff points				
	mean	SD	1 st	2 nd	3 rd	mean	SD	1 st	2 nd	3 rd
Age (years)	63.2	4.4	60.0	64.0	67.0	76.2	4.6	72.0	76.0	79.0
Years of schooling	7.8	4.5	5.0	6.0	10.0	6.4	3.4	4.0	6.0	8.0
Height (cm)	171.3	6.1	167.0	170.0	175.0	170.0	6.8	165.0	170.0	173.0
Body mass index (kg/m ²)	26.4	3.7	23.9	25.9	29.2	25.5	4.1	23.1	25.5	27.7
Energy intake (kcal)	3166	1293	2410	2922	3611	2789	868	2134	2650	3164
Saturated fat (g)	32.9	9.3	26.7	32.3	37.0	28.5	8.0	22.9	27.3	33.4
Polyunsaturated fat (g)	18.8	8.8	12.8	16.0	23.1	14.9	7.2	10.8	13.2	16.5
Cooked tomatoes (servings per month)	7.5	5.4	3.0	6.5	10.0	9.9	5.7	4.0	8.0	12.0
Vitamin E (mg)	11.0	3.8	8.2	10.4	13.2	9.4	3.0	7.5	9.1	10.5

Table 1 Descriptive statistics of demographic and dietary factors among 320 prostate cancer cases and 246 controls

	Subjects <70 years of age		Subjects ≥70 years of age		Two-tailed p for interaction	
	Relative risk	95%CI	Relative risk	95%CI	age dichotomous	age continuous
Polyunsaturated fat	2.11	1.07, 4.14	1.15	0.58, 2.25	0.21	0.23
Cooked tomatoes	1.14	0.54, 2.40	0.29	0.14, 0.59	0.009	0.006
Vitamin E	0.48	0.23, 0.99	1.02	0.49, 2.15	0.15	0.25
Saturated fat	1.02	0.69, 1.51	1.16	0.78, 1.74	0.60	0.34

Controlling for age, years of schooling, height, body mass index, and total energy intake, as well as mutually for the dietary variables

Table 2 Multiple logistic regression-derived relative risk estimates for prostate cancer, among men under 70 years of age and 70 years or older, per 1 standard deviation increase of selected nutrients and an additional serving every other day for cooked tomatoes^a

to be strongly inversely related to prostate cancer risk among younger subjects, whereas it has apparently no effect among older subjects (p value for interaction 0.15). Saturated fat had little overall effect on prostate cancer risk in these data, but it was examined because in other investigations it has been found to be a risk factor for prostate cancer. The little effect evident in our data is concentrated among older subjects. Interaction testing with age as a continuous variable generated the following two-tailed p values: 0.23 for polyunsaturated fat; 0.006 for cooked tomatoes; 0.25 for vitamin E; and 0.34 for saturated fat.

Discussion

This investigation has several strengths. Study size was sufficient for detection of main effects in the twofold range, although detection of interactions of similar magnitude requires four times as large study samples¹². The validity of the results is supported by the fact that cases and controls were derived from the same study base and the questionnaire administered had been validated⁹ and used with reasonable success in several previous investigations¹³. The validity of the results is also supported by the fact that both nutritional and non-nutritional findings of this case-control study^{1,8} were in line with those reported from other major investigations. The major weakness of the study was that its size was not large enough for documentation of genuine interactions. Indeed, among the nutritional variables evaluated for interaction, striking effect modification was found only for one (cooked tomatoes), whereas for two others, polyunsaturated lipids and vitamin E, the findings were simply suggestive.

Notwithstanding this limitation, the data appear to indicate that the beneficial effect of cooked tomatoes on prostate cancer risk is concentrated among older men, whereas the beneficial effect of vitamin E and the detrimental effect of polyunsaturated lipids are concentrated among younger men. Vitamin E is a powerful antioxidant¹⁴, likely to be active in the early stages of carcinogenesis. Similarly, polyunsaturated lipids have been reported to increase cancer

risk in experimental animals. This effect has been attributed to a large extent to their chemical composition (multiple double bonds) that makes them vulnerable to oxidative processes which play a major role during the early stages of carcinogenesis^{15,16}. There is no consensus about the mechanistic processes involved in the apparent protection conveyed by lycopene on prostate cancer risk, but the repeated demonstration of such an effect in several studies that mostly focus on diet proximal to the interview argues in favour of a late stage effect¹⁷.

Saturated fat was not an important overall predictor of prostate cancer risk in this investigation, but has been found to increase this risk in other studies². If it indeed affects the risk of prostate cancer, it is likely to act as a growth enhancer during the later stages of carcinogenesis^{2,18}. Concentration or limitation of the effect of saturated fat to people older than about 70 years of age has been reported by West and colleagues¹⁹ and Talamini and colleagues²⁰ and is only barely evident in these data.

We are aware, of course, that a correspondence between age at occurrence and proximity to age at initiation is tenuous and there is no clear distinction between constructive speculation and damaging over-interpretation. However, even a simple straight forward interpretation of the data, i.e., that older cases of prostate cancer have a different dietary risk profile than younger ones has potentially useful implications, for example targeted dietary advice. It is important to stress that secular changes of food consumption in Greece²¹ do not support the hypothesis that the observed pattern could reflect a generation (cohort) effect.

In conclusion, we have found evidence that, among men younger than 70 years of age, polyunsaturated lipids appear to considerably increase the risk of prostate cancer, whereas vitamin E considerably reduces this risk; in contrast, saturated fat and cooked tomatoes appear to play little if any role in the occurrence of this cancer. Among subjects 70 years of age or older, neither polyunsaturated fat nor vitamin E play an important role, but cooked tomatoes-related lycopene conveys substantial protection, whereas saturated fat could perhaps increase the risk of the disease.

Zusammenfassung

Sind die Effekte der Ernährung auf das Prostatakarzinom-Risiko altersabhängig?

Fragestellung: Es wurde untersucht, ob es altersabhängige Effekte der Ernährung auf das Risiko für Prostatakrebs gibt.

Methoden: Wir postulierten, dass Ernährungsfaktoren, die das Risiko einer Initiation beeinträchtigen, eher bei jungen Patienten feststellbar sind. Jedoch sind solche, die das Risiko einer Progression beeinflussen, eindeutiger bei älteren Patienten zu identifizieren. Probanden waren 320 an Prostatakrebs erkrankte Männer und 246 Kontrollfälle ohne entsprechende systematische Krankheitsmerkmale, die in sechs Krankenhäusern in Athen (Griechenland) hospitalisiert waren. Logistische Regressionsmodelle wurden jeweils für Männer unter bzw. im Alter von 70 Jahren und mehr angepasst.

Resultate: Mehrfach ungesättigte Fette erhöhten das Risiko bei jüngeren Personen erheblich, waren aber bei älteren nahezu unbedeutend (p für Interaktion 0,21). Gekochte Tomaten hatten einen deutlich schützenden Effekt bei älteren Personen, bei den jüngeren jedoch nicht (p für Interaktion 0,009). Die Vitamin-E-Aufnahme und das Risiko an Prostatakrebs zu erkranken, verhielt sich bei jüngeren Personen umgekehrt proportional, nicht aber bei älteren Personen (p für Interaktion 0,15).

Schlussfolgerungen: Auch eine ganz einfache und geradlinige Interpretation der Daten, dass ältere Betroffene ein Ernährungsrisikoprofil aufweisen, das von jenem junger Personen verschieden ist, ist von potentiell praktischer Bedeutung.

Résumé

Les effets de l'alimentation sur le risque des cancers de la prostate dépendent-ils de l'âge?

Objectifs: Examiner si les effets de l'alimentation sur le risque de cancer de la prostate sont dépendants de l'âge.

Méthode: Nous avons fait l'hypothèse que les facteurs nutritionnels qui peuvent modifier le risque d'initiation des cancers de la prostate pourraient être mieux identifiés chez des patients jeunes, alors que les facteurs nutritionnels qui modifient le risque de progression de la tumeur seraient plus clairement identifiables parmi les personnes plus âgées. Les sujets de l'étude sont 320 patients avec un cancer de la prostate et 246 témoins sans maladie systémique, hospitalisés dans les grands hôpitaux d'Athènes, Grèce. Les modèles de régression logistique ont été exécutés séparément pour les hommes de moins de 70 ans et pour ceux de 70 ans et plus.

Résultats: Les lipides polyinsaturés augmentent substantiellement le risque parmi les sujets plus jeunes, mais ne jouent que peu de rôle parmi les sujets plus âgés (p pour l'interaction = 0,21). Les tomates cuites ont un effet fortement protecteur parmi les personnes plus âgées, mais pas parmi les personnes plus jeunes (p pour l'interaction = 0,009). Finalement, la vitamine E était fortement et inversement associée au risque de cancer de la prostate parmi les plus jeunes sujets, mais pas parmi ceux qui sont plus âgés (p pour l'interaction = 0,15).

Conclusion: Même une interprétation simpliste des données, à savoir que les cas plus âgés de cancer de la prostate ont un profil de risque alimentaire différent des plus jeunes, a potentiellement des implications utiles.

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