

Interrelation of Energy Intake, Body Size, and Physical Activity with Prostate Cancer in a Large Prospective Cohort Study

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ABSTRACT

Energy restriction reduces prostate tumor growth in transplantable tumor models in rodents, which suggests that excessive energy intake may contribute to the risk of prostate cancer. The association of total energy intake across the normal range with prostate cancer has not been consistent in epidemiological studies. We prospectively evaluated the joint associations of energy intake and body size or physical activity with prostate cancer. Participants were 46,786 male health professionals ages 40–75 years at baseline in 1986 who were free of cancer diagnosis. Between 1986 and 2000, we documented 2896 incident prostate cancer cases (excluding stage T1a) by review of medical records and histopathology reports. Of these, 339 were metastatic or fatal cases. We used Cox proportional hazards regression to estimate the multivariate relative risk (RR) of prostate cancer associated with energy intake measured using a food frequency questionnaire, overall and stratified by body mass index, waist size, physical activity, as well as by age and family history of prostate cancer. There was no association between energy intake and total prostate cancer incidence. However, a modest increased risk of metastatic or fatal disease with energy intake was suggested [RR comparing extreme quintiles: 1.38, 95% confidence interval (CI) 0.96–1.98, $P(\text{trend}) = 0.06$]. This association was most pronounced in men with a lower body mass index (in stratum $< 24 \text{ kg/m}^2$: RR = 1.76, 95% CI 0.92–3.39; $P(\text{interaction}) = 0.04$), smaller waist size [in stratum ≤ 37 inches: RR = 1.91, 95% CI 0.83–4.36; $P(\text{interaction}) = 0.03$], and who were more physically active [in stratum \geq median: RR = 1.74, 95% CI 0.93–3.26; $P(\text{interaction}) = 0.09$]. Also, the association of energy intake with metastatic and fatal prostate cancer was restricted to men who were younger [in stratum ≤ 65 years old: RR = 2.60, 95% CI 1.26–5.39; $P(\text{interaction}) = 0.04$] or who had a positive family history [RR = 3.33, 95% CI 1.26–8.76; $P(\text{interaction}) = 0.04$]. Although energy intake is known to be imperfectly measured by questionnaire, we observed a positive association between energy intake and metastatic or fatal prostate cancer among men who were leaner, more physically active, younger, and who had a family history of prostate cancer. Our observations suggest the testable hypothesis that the elevated risk of clinically important prostate cancer in men with a high energy intake may be attributable to certain metabolic profiles that favor enhanced growth factor production over an increase in adiposity.

INTRODUCTION

Animal studies consistently show that diets with restricted total energy reduce tumor burden relative to *ad libitum* (i.e., free access) feeding (1, 2). In a transplantable prostate tumor model, moderate energy restriction reduced prostate tumor growth, lowered circulating concentrations of IGF-I⁴ and decreased expression of vascular endothelial growth factor (3). These effects, which may limit tumor

growth, were observed irrespective of whether fat, carbohydrate, or total diet was restricted. The effects of energy restriction on factors mediating greater proliferation relative to apoptosis and angiogenesis together suggest that excessive energy intake may act late in the carcinogenic pathway.

Whether excessive intake relative to expenditure adversely affects prostate cancer risk in humans is unclear. In comparisons among populations, per capita energy intake is positively correlated with national prostate cancer incidence and mortality rates (4–6). However, these studies are greatly limited because they are based on disappearance of food in a country rather than actual intake of food by individuals. Energy intake across the usual range also has been evaluated in relation to prostate cancer risk in 23 distinct analytic epidemiological studies, but findings have not been consistent. Among the studies reporting on associations, 9 of 15 retrospective studies support a positive relation, but none of four cohort studies do (7, 8). However, these epidemiological studies have not systematically considered the balance of energy input with body size and physical activity, the major determinants of variability in energy demand. Also, few of these studies have examined whether the energy association differs by whether the tumor was organ confined, which would suggest an influence on the initial development of the tumor, or metastatic, which would suggest an influence on the continued growth of the tumor. The four case–control studies that evaluated advanced disease suggested a higher risk with energy intake (odds ratio_{summary} = 1.6, 95% CI 1.2–2.0; Ref. 7). However, the one cohort study that evaluated advanced disease did not find an association (RR = 0.9, 95% CI 0.6–1.3; Ref. 9). Whether the positive findings in the case-control studies, but a null finding in the cohort study reflect bias in the case-control studies, is because of differential recall of past diet by case-control status (e.g., if cases overreport past intake or if controls underreport past intake) or reflects less error in the case-control studies in the assessment of energy intake because assessment was done closer in time to the etiologically relevant period is unknown.

Given these leads and uncertainties, we prospectively evaluated the association of energy intake summed over all food and beverage sources with prostate cancer overall and by disease stage in the HPFS. We examined whether total energy intake was associated with prostate cancer within categories of body size and physical activity.

MATERIALS AND METHODS

Study Population. Participants were members of the HPFS, an ongoing prospective study. At baseline in 1986, 51,529 men ages 40–75 years old completed a mailed questionnaire, which included questions on diet, lifestyle, and medical history. Lifestyle and medical history information, including diagnosis of prostate cancer, was updated every 2 years, and diet was updated every 4 years by mailed questionnaire. Deaths were identified through reports by family members or by the postal system in response to the follow-up questionnaires or were identified through a search of the National Death Index (10). We excluded 3647 men at baseline because they had been previously diagnosed with cancer (except nonmelanoma skin cancer) or because they did not return a valid food frequency questionnaire. We also excluded 1096 men who did not provide valid information on current weight and height. Thus, the

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⁴The abbreviations used are: IGF-I, insulin-like growth factor I; RR, relative risk; CI, confidence interval; HPFS, Health Professionals Follow-Up Study; BMI, body mass index; MET, metabolic equivalents/week; PSA, prostate-specific antigen.

analytic cohort included 46,786 men. The HPFS was approved by the Human Subjects Committee of the Harvard School of Public Health (Boston, MA).

Ascertainment and Classification of Prostate Cancer Cases. For each man who reported a prostate cancer diagnosis on a follow-up questionnaire, we asked for consent from the participant or his next-of-kin to request and review his medical records pertaining to his diagnosis. The response rate was 96% for nonfatal cases. We estimate having ascertained >98% of fatal cases. Medical records and pathology reports were successfully obtained for 90% of the cases. The remaining cases included in the analysis were based solely on self-report because the reporting of diagnosis of prostate cancer was found to be accurate in these health professionals. A study investigator blinded to exposure data reviewed the medical records and pathology reports to confirm a diagnosis of adenocarcinoma of the prostate. We abstracted pathological stage (or clinical stage, if a prostatectomy was not done) and Gleason histological grade (11) for the prostatectomy specimen (or biopsy, if prostatectomy was not done). We excluded from the analysis cases with incidental microscopic focal tumors (T1a). These tumors are generally indolent and are most susceptible to detection bias because of differential rates of undergoing surgery for benign prostatic hyperplasia. From 1986 through January 31, 2000, we confirmed a total of 2896 incident nonstage T1a prostate cancer cases. Of these, 99 were regionally invasive (C2 or T3 or T4 and N0M0), 57 were regionally metastatic (D1 or any T, N1M0), 49 were distant metastatic (D2 or any T, any N, M1), and 233 were fatal.

Assessment of Energy Intake and Diet. In 1986, 1990, and 1994, the men completed a semiquantitative food frequency questionnaire requesting usual frequency of consumption over the past year of specified portion sizes of 131 food items. In this cohort, these foods accounted for >90% of the intake of the major nutrients (12). From the baseline food frequency questionnaire, we estimated intake of energy in kilocalories and other foods and nutrients that have been associated with prostate cancer or advanced disease in this cohort. Intakes of energy, calcium, total fructose (including fructose from sucrose), vitamin E, and α -linolenic acid were estimated by summing over foods the product of the frequency of consumption of each food, the stated reference serving portion size, and the energy or nutrient content/serving. The energy and nutrient content of the foods was obtained from United States Department of Agriculture sources (13), which was supplemented with manufacturer information and our own laboratory data. Intakes of tomato sauce (including from pasta and pizza), red meat, and fish were taken directly from the questionnaire. Because intake of foods and nutrients and intake of energy are correlated, we used the residual method to adjust for energy intake (14).

In a subset of 127 of the participants, the correlation in energy intake between two administrations of the food frequency questionnaire completed 1 year apart was 0.65 (12). The correlations in energy intake between the average of two 1-week diet records spaced 6 months apart, and the first and second administrations of the food frequency questionnaire were 0.27 and 0.40, respectively (12).

Assessment of Stratification Factors. Other covariates that previously were observed to be associated with prostate cancer overall or with advanced disease in this cohort were obtained or derived from the baseline questionnaire: age, major ancestry, BMI at age 21 years (BMI; weight in kilograms divided by the square of height in meters), height, vigorous leisure-time physical activity, and use of multivitamins and supplements containing vitamin E. In this cohort, higher BMI at age 21 years was associated with a lower risk of advanced prostate cancer (15). Vigorous activity was calculated as the sum of activity-specific MET-h/week for activities with 6.0+ METs (running, jogging, biking, swimming, and playing tennis, squash, and racquetball) as described previously (16). One MET-h is the metabolic equivalent of sitting at rest for 1 h (17). Intake of ≥ 15 mg of vitamin E/day was considered to be high vitamin E intake (mostly supplement users). On the 1990, 1992, and 1996 questionnaires, we asked the men whether they had a father or brother who was diagnosed with prostate cancer. In the analysis, men who reported a first-degree relative with prostate cancer on any questionnaire were considered to have a positive family history. Every 2 years, the men were asked to report whether they ever had a diagnosis of type 2 diabetes mellitus or if they had had a vasectomy. At baseline and every 2 years, the men were asked about their smoking history, from which pack-years of cigarette smoking in the prior 10 years was calculated. In 1994, 1996, 1998, and 2000, the men were asked if they had had a screening PSA test. For use as stratification factors, we obtained current BMI, total and vigorous leisure-time physical activity from the baseline

questionnaire, and waist size (measured to the nearest 1/4" and available for two-thirds of the men) from the 1987 questionnaire. Self-report of height and weight (used for the calculation of BMI) and waist size (18) and physical activity (17) by questionnaire were shown to be valid and reliable in this cohort.

Statistical Analysis. Because energy intake decreases with age in this cohort, we calculated directly age-standardized means and proportions for the demographic, dietary, and lifestyle factors by quintile of energy intake. Quintile cut points were based on the distribution of energy intake among the men included in the analysis. To evaluate the age-adjusted association between quintiles of energy intake and prostate cancer, we calculated Mantel-Haenszel summary rate ratios of total prostate cancer; regionally invasive, metastatic, or fatal disease (T3 or worse, which is referred to as regionally invasive or worse throughout); and metastatic (N1 or M1) and fatal disease and corresponding 95% CIs. We used Cox proportional hazards regression to estimate multivariate RRs for each end point adjusting for family history of prostate cancer, major ancestry (Scandinavian, Southern European, other ancestry *versus* other white), BMI at age 21 years (kg/m^2 – ordinal), height (inches – ordinal), current type 2 diabetes mellitus, current vasectomy, vigorous physical activity (MET-h/week – ordinal), current cigarette smoking in the past 10 years (pack-years, >0–5, 5+), energy-adjusted intake (servings/day – ordinal) of red meat, fish, tomato sauce, calcium (energy-adjusted from diet plus supplements, mg/day), fructose (g/day) and α -linolenic acid (mg/day), and high intake of vitamin E. To account for any lack of proportionality in the hazards across follow-up, we fit separate baseline hazards for groups defined by age and calendar period. To test for trend, we entered a single ordinal variable corresponding to the median of the quintile of energy intake into the model, the coefficient for which was evaluated using the Wald test.

We compared the results using baseline energy intake to that for energy updated every 4 years (simple updating) and the average of the prior years' energy intakes (cumulative average updating; Ref. 19). The cumulative average intake is the mean of the reported intakes for all food frequency questionnaires preceding the time period of risk (19). We present as the main results those for baseline energy intake, which is less susceptible to bias than simple updating, although the effect of energy may be underestimated if recent intake is more important than past intake.

In an alternate analysis, we included as noncases only men who had ever had a PSA test by the year 2000 to limit the opportunity for detection bias. Because men with undiagnosed metastatic disease could have begun to consume more food to counter disease-associated weight loss, when using baseline energy intake, we repeated the analysis excluding cases that were diagnosed during the first 2-year follow-up period. In a subanalysis, we excluded those men who most greatly under reported energy intake relative to their predicted basal metabolic rate estimated from age-specific formulae that are a function of weight and height as given in Schofield (20).

Variability in energy intake is, in part, determined by body size and activity level. Thus, within strata of current BMI (<24 , ≥ 24 kg/m^2), current weight [<180 , ≥ 180 lbs. (81.8 kg)], waist size [≤ 37 , >37 inches (94 cm)], total physical activity (≤ 12 , >12 MET-h/week), and vigorous physical activity (≤ 3 , >3 MET-h/week), we evaluated the association of energy intake with prostate cancer. We also tested whether current age (≤ 65 , >65 years old) or family history of prostate cancer modified the association of energy with prostate cancer by entering the cross-product term for energy (continuous) and age (continuous) or family history (binary) along with the main effects terms for each. We used the same approach to evaluate effect modification by other previously identified prostate cancer risk factors in this cohort. We evaluated the coefficients for the cross-product terms using the Wald test. All hypothesis tests were two-sided, and associations were considered to be statistically significant if the *P* was <0.05 . All analyses were conducted using SAS release 8.2 (SAS Institute, Cary, NC).

RESULTS

We included in the analysis 2896 men diagnosed with prostate cancer (excluding stage T1a) through 2000 during 585,477 person-years of follow-up. The median age at prostate cancer diagnosis was 69.3 years (range, 45.0–88.2 years). Age-standardized baseline characteristics of the cohort by quintile of energy intake are shown in

Table 1. Taking into account baseline age, as would be expected, men who had higher total energy intakes were taller and were more physically active.

Overall, there was no association between quintile of energy intake at baseline and prostate cancer after adjusting for age or after adjusting for suspected prostate cancer risk factors (Table 2). However, men in the top four quintiles of energy intake at baseline appeared to have a modest increased risk of prostate cancer that was regionally invasive or worse (438 cases) or was metastatic or fatal (339 cases), although these associations were not statistically significant (Table 2).

Because some men may have changed their energy intake over time and because we hypothesize that recent energy intake may be more important than past intake, we used simple and cumulative updating of energy intake. For total prostate cancer, the findings using simple and cumulative updating of energy intake remained null (data not shown). However, for prostate cancer that was regionally invasive or worse, the associations were slightly stronger using simple updating [RR of metastatic or fatal disease comparing extreme quintiles: 1.47, 95% CI 1.02–1.63, $P(\text{trend}) = 0.07$] or cumulative updating [RR of metastatic or fatal disease comparing extreme quintiles: 1.63, 95% CI 1.12–2.38, $P(\text{trend}) = 0.04$].

For total prostate cancer cases, no association with energy intake at baseline was observed when we conducted subanalyses in which we excluded (a) the first follow-up period, (b) noncases that had never had a PSA test through 2000, or (c) the 20 or 40% of men who most under reported intake relative to predicted energy requirement (data not shown). Making these same exclusions for the analyses for regionally invasive or worse disease produced small numbers of cases within each quintile of energy intake, although suggestions of modest positive associations remained (data not shown).

We evaluated whether the association of energy intake at baseline with prostate cancer varied by the major determinants of variability in energy intake – body size and physical activity. Energy intake was not associated with total prostate cancer within strata of BMI (Table 3), weight (data not shown), waist size (Table 4), or total (data not shown) or vigorous physical activity (Table 5). However, energy intake appeared to be positively associated with regionally invasive or worse disease or with metastatic or fatal disease primarily among men who were leaner, either a BMI < 24 kg/m² (Table 3) or waist

Table 2 RR of prostate cancer in relation to baseline energy intake

Quintile of energy intake	Cases	Person-Years	RR (95% CI)	
			Age-adjusted	Multivariate ^a
Total cases				
1	571	116,603	1.00 (ref)	1.00 (ref)
2	609	116,925	1.07 (0.96–1.20)	1.06 (0.94–1.19)
3	624	117,053	1.11 (0.99–1.24)	1.10 (0.98–1.23)
4	568	117,330	1.05 (0.93–1.18)	1.04 (0.92–1.17)
5	524	117,567	1.00 (0.89–1.13)	0.99 (0.88–1.12)
<i>P</i> (trend)			0.81	0.74
Regionally invasive or worse cases ^b				
1	67	117,073	1.00 (ref)	1.00 (ref)
2	95	117,381	1.43 (1.05–1.96)	1.36 (0.99–1.87)
3	98	117,525	1.50 (1.10–2.04)	1.44 (1.05–1.98)
4	89	117,760	1.43 (1.04–1.96)	1.29 (0.93–1.78)
5	89	117,959	1.47 (1.07–2.02)	1.37 (0.99–1.89)
<i>P</i> (trend)			0.06	0.17
Metastatic or fatal cases				
1	54	117,088	1.00 (ref)	1.00 (ref)
2	66	117,405	1.24 (0.86–1.77)	1.16 (0.80–1.67)
3	73	117,547	1.39 (0.97–1.95)	1.33 (0.93–1.91)
4	75	117,774	1.50 (1.05–2.12)	1.37 (0.96–1.96)
5	71	117,974	1.46 (1.02–2.09)	1.38 (0.96–1.98)
<i>P</i> (trend)			0.03	0.06

^a RR adjusted for current age, family history of prostate cancer (1990, 1992, 1996), major ancestry, BMI at age 21 years, height, diabetes mellitus (ever), vasectomy (ever), vigorous physical activity (baseline), pack-years of smoking in the past 10 years, energy-adjusted intake at baseline of red meat, fish, tomato sauce, calcium, fructose, α -linolenic acid, and high intake of vitamin E.

^b Includes regionally invasive, regionally metastatic, distant metastatic, and fatal cases.

size ≤ 37 inches (Table 4), and possibly among men who were more physically active (Table 5). The results were similar when stratifying by weight rather than BMI (for metastatic or fatal disease when comparing top to bottom quintile of energy intake among weight < 180 lbs. RR = 2.00, 95% CI 1.18–3.40; among weight ≥ 180 lbs. RR = 0.97, 95% CI 0.57–1.65). In all of these stratified analyses, the age-adjusted estimates were not substantially different from the multivariate estimates. Additional adjustment for current BMI slightly attenuated the energy association in men with a smaller waist circumference (comparing top to bottom quintile of energy intake: odds ratio = 1.82, 95% CI 0.80–4.15) and slightly strengthened the energy association in men who were more physically active (comparing top to bottom quintile of energy intake: odds ratio = 1.86, 95% CI 0.98–

Table 1 Selected characteristics in relation to energy intake at baseline in 1986^a

	Quintile of energy intake				
	1 803–1446	2 1449–1759	3 1760–2066	4 2067–2469	5 2470–4200
Participants (<i>n</i>)	9350	9388	9374	9336	9338
Mean age in 1986 (years)	54.9	54.7	54.6	54.0	53.5
Mean BMI at age 21 years (kg/m ²)	23.1	23.1	23.0	22.9	23.0
Mean current BMI (kg/m ²)	25.6	25.5	25.4	25.4	25.6
Mean height (inches)	69.8	70.0	70.1	70.3	70.4
Mean waist size ^b (inches)	37.4	37.3	37.3	37.3	37.6
Family history of prostate cancer (%)	10.9	11.9	12.1	12.5	12.1
Type 2 diabetes mellitus (%)	3.3	3.3	3.4	2.9	2.7
Vasectomy (%)	21.5	22.0	21.2	21.4	20.3
Routine screening for PSA by 2000 (%)	76.4	78.3	78.6	76.9	76.0
Smoked in the past 10 years (%)	21.2	21.4	21.0	21.5	22.8
Vigorous physical activity (METs)	12.0	12.4	12.9	13.0	13.5
Mean intakes ^c					
Calcium (mg/day)	911	901	903	894	882
Fructose (g/day)	50.1	49.4	48.7	48.9	49.2
Tomato sauce (servings/day)	0.19	0.20	0.20	0.21	0.23
α -Linolenic acid (g/day)	1.08	1.07	1.07	1.07	1.07
Red meat (servings/day)	1.94	1.89	1.92	1.93	1.99
Fish (servings/day)	0.32	0.33	0.34	0.34	0.35
High vitamin E intake ^d (≥ 15 mg/day)	88.1	87.8	85.8	82.1	78.1

^a All values (except age) are standardized to the age distribution of the study population.

^b Available for 64% of men.

^c Nutrients and foods are adjusted for total energy intake.

^d Mostly supplement users.

Table 3 Multivariate^a RR of prostate cancer in relation to baseline energy intake according to categories of adult BMI

Quintile of energy intake	BMI at baseline	
	<24 kg/m ²	≥24 kg/m ²
Total cases		
Cases/PY	952/181,115	1,944/404,361
1	1.00 (ref)	1.00 (ref)
2	0.86 (0.70–1.07)	1.14 (0.99–1.32)
3	0.89 (0.72–1.09)	1.21 (1.05–1.39)
4	0.96 (0.78–1.18)	1.06 (0.92–1.23)
5	0.84 (0.67–1.04)	1.07 (0.93–1.25)
P (trend)	0.26	0.72
	P(interaction) ^b = 0.42	
Regionally invasive or worse cases ^c		
Cases/PY	153/181,855	285/405,843
1	1.00 (ref)	1.00 (ref)
2	1.62 (0.90–2.92)	1.27 (0.86–1.87)
3	1.51 (0.63–2.74)	1.44 (0.99–2.11)
4	1.54 (0.85–2.77)	1.21 (0.82–1.81)
5	1.68 (0.93–3.05)	1.22 (0.82–1.82)
P (trend)	0.19	0.51
	P(interaction) ^b = 0.24	
Metastatic or fatal cases		
Cases/PY	120/181,881	219/405,907
1	1.00 (ref)	1.00 (ref)
2	1.30 (0.66–2.55)	1.15 (0.74–1.79)
3	1.50 (0.77–2.90)	1.33 (0.86–2.06)
4	1.60 (0.84–3.06)	1.35 (0.87–2.10)
5	1.76 (0.92–3.39)	1.23 (0.78–1.93)
P (trend)	0.07	0.32
	P(interaction) ^b = 0.04	

^a RR adjusted for current age, family history of prostate cancer (1990, 1992, 1996), major ancestry, BMI at age 21 years, height, diabetes mellitus (ever), vasectomy (ever), vigorous physical activity (baseline), pack-years of smoking in the past 10 years, energy-adjusted intake at baseline of red meat, fish, tomato sauce, calcium, fructose, α -linolenic acid, and high intake of vitamin E.

^b From the Wald test of the coefficient for the cross-product term for BMI (continuous) and energy intake (continuous), which was entered into the model along with the main effects terms for each.

^c Includes regionally invasive, regionally metastatic, distant metastatic, and fatal cases.

3.55). The interactions for energy and BMI [$P(\text{interaction}) = 0.04$] and waist size [$P(\text{interaction}) = 0.03$] were statistically significant for metastatic or fatal disease. Shown in Fig. 1 is the joint association of energy intake and BMI with metastatic or fatal prostate cancer all compared with men with both lower BMI and low energy intake. With more extreme cut points for BMI (cut points at 23 or 22 kg/m²) and waist size (cut points at 36 or 35 inches), the RRs for regionally invasive or worse disease in the leaner groups were even larger comparing the top to bottom quintiles of energy intake; however, within increasing severity of the cut point, the diminished sample size led to wide confidence intervals (data not shown).

We also evaluated whether the association of energy intake at baseline with prostate cancer varied by age and family history of prostate cancer and also by other suspected prostate cancer risk factors. Risk of regionally invasive or worse disease or metastatic or fatal disease associated with energy intake was limited to men who were currently younger. Among men who were ≤65 years old, the RR for metastatic or fatal disease comparing extreme quintiles was 2.60 [95% CI 1.26–5.39; $P(\text{trend}) = 0.02$, $P(\text{interaction}) = 0.04$]. This result was not changed after additionally adjusting for current BMI. No association for energy was observed in older men [in men > 65 years: RR = 1.03; $P(\text{trend}) = 0.53$]. In addition, the risk of regionally invasive or worse disease or metastatic or fatal disease associated with higher energy intake was greater in men with a family history of prostate cancer. The RR for metastatic/fatal disease comparing extreme quintiles was 3.33 [95% CI 1.26–8.76; $P(\text{trend}) = 0.02$, $P(\text{interaction}) = 0.04$] in men with family history, whereas the RR was 1.16 [95% CI 0.77–1.74; $P(\text{trend}) = 0.39$] in men without a family history. The association of energy with regionally invasive or worse disease or

metastatic/fatal disease did not differ by height, cigarette smoking in the past decade, intake of tomato sauce, red meat, fish, calcium, fructose, α -linolenic acid, and vitamin E or other prostate cancer risk factors observed in this cohort [all $P(\text{interaction}) \gg 0.05$].

DISCUSSION

In this large prospective study, no association was observed between energy intake and total prostate cancer. However, we observed a positive association between energy intake and regionally invasive or worse disease, in particular in men who were leaner and possibly in men who were more physically active. Also, stronger associations for energy and regionally invasive or worse prostate cancer were observed among younger men and men with a family history of prostate cancer.

Our finding of no association of energy intake with total prostate cancer is consistent with four other prospective cohort studies that have evaluated this relation (9, 21–23). The one cohort study that evaluated advanced disease did not find an association (RR = 0.9, 95% CI 0.6–1.3; Ref. 9). None of the published cohort studies considered the interrelation of energy intake and body size or physical activity.

Energy restriction influences a broad spectrum of cellular and tissue activities and many of its effects plausibly could ameliorate carcinogenesis, in particular, the promotion and progression phases. Energy restriction appears to decrease cellular proliferation by impedance of progression through the cell cycle (2) and to enhance apoptosis (24, 25). Studies also indicate that the greatest benefit of energy restriction is later in the natural history of tumorigenesis, possibly influencing the

Table 4 Multivariate^a RR of prostate cancer in relation to baseline energy intake stratified by adult waist size

Quintile of energy intake	Waist size in 1987 ^b	
	≤Median (29–37 inches)	>Median (37.25–68.25 inches)
Total cases		
Cases/PY	1,036/107,795	1,027/179,728
1	1.00 (ref)	1.00 (ref)
2	0.98 (0.80–1.20)	1.12 (0.90–1.38)
3	0.98 (0.81–1.20)	1.22 (0.99–1.50)
4	0.96 (0.78–1.18)	1.04 (0.84–1.28)
5	0.85 (0.69–1.06)	1.09 (0.88–1.35)
P (trend)	0.14	0.76
	P(interaction) ^c = 0.50	
Regionally invasive or worse ^d		
Cases/PY	142/206,357	171/180,479
1	1.00 (ref)	1.00 (ref)
2	1.91 (0.99–3.68)	1.18 (0.68–2.03)
3	1.78 (0.92–3.43)	1.12 (0.65–1.94)
4	1.54 (0.78–3.03)	1.27 (0.75–2.17)
5	1.51 (0.75–3.01)	1.15 (0.67–2.00)
P (trend)	0.72	0.60
	P(interaction) ^c = 0.89	
Metastatic or fatal cases		
Cases/PY	103/206,391	128/180,519
1	1.00 (ref)	1.00 (ref)
2	1.58 (0.69–3.62)	1.06 (0.57–1.99)
3	1.89 (0.85–4.20)	1.01 (0.53–1.91)
4	1.90 (0.85–4.28)	1.32 (0.72–2.44)
5	1.91 (0.83–4.36)	1.02 (0.53–1.96)
P (trend)	0.17	0.76
	P(interaction) ^c = 0.03	

^a RR adjusted for current age, family history of prostate cancer (1990, 1992, 1996), major ancestry, body mass index at age 21, height, diabetes mellitus (ever), vasectomy (ever), vigorous physical activity (baseline), pack-years of smoking in the past ten years, energy-adjusted intake at baseline of red meat, fish, tomato sauce, calcium, fructose, α -linolenic acid, and high intake of vitamin E.

^b Available for 64% of men.

^c From the Wald test of the coefficient for the cross-product term for waist circumference (continuous) and energy intake (continuous), which was entered into the model along with the main effects terms for each.

^d Includes regionally invasive, regionally metastatic, distant metastatic, and fatal cases.

Table 5 Multivariate^a RR of prostate cancer in relation to baseline energy intake stratified by level of vigorous leisure-time physical activity

Quintile of energy intake	Vigorous leisure-time physical activity at baseline ^b	
	≤Median (0 to 3 MET-hours/week)	>Median (>3 MET-hours/week)
Total cases		
Cases/PY	1,729/310,802	1,167/274,675
1	1.00 (ref)	1.00 (ref)
2	1.03 (0.86–1.22)	1.04 (0.82–1.32)
3	1.10 (0.92–1.30)	1.07 (0.84–1.35)
4	1.01 (0.85–1.21)	1.16 (0.92–1.46)
5	1.03 (0.86–1.24)	1.00 (0.78–1.28)
P (trend)	0.35	0.81
	P(interaction) ^c = 0.65	
Regionally invasive or worse cases^d		
Cases/PY	281/312,129	157/275,570
1	1.00 (ref)	1.00 (ref)
2	1.21 (0.78–1.69)	1.24 (0.65–2.37)
3	1.31 (0.85–2.01)	1.44 (0.75–2.78)
4	1.29 (0.83–1.99)	1.18 (0.59–2.34)
5	1.08 (0.67–1.72)	1.26 (0.64–2.48)
P (trend)	0.61	0.12
	P(interaction) ^c = 0.12	
Metastatic or fatal cases		
Cases/PY	221/312,181	118/275,607
1	1.00 (ref)	1.00 (ref)
2	1.12 (0.72–1.75)	1.32 (0.68–2.56)
3	1.39 (0.90–2.14)	1.27 (0.66–2.47)
4	1.44 (0.94–2.20)	1.22 (0.63–2.37)
5	1.16 (0.73–1.85)	1.74 (0.93–3.26)
P (trend)	0.36	0.11
	P(interaction) ^c = 0.09	

^a RR adjusted for current age, family history of prostate cancer (1990, 1992, 1996), major ancestry, body mass index at age 21, height, diabetes mellitus (ever), vasectomy (ever), vigorous physical activity (baseline), pack-years of smoking in the past ten years, energy-adjusted intake at baseline of red meat, fish, tomato sauce, calcium, fructose, α -linolenic acid, and high intake of vitamin E.

^b Includes leisure-time physical activities with MET values of 6.0+ (running, jogging, biking, swimming, and playing tennis, squash, and racquetball).

^c From the Wald test of the coefficient for the cross-product term for vigorous leisure-time physical activity (continuous) and energy intake (continuous), which was entered into the model along with the main effects terms for each.

^d Includes regionally invasive, regionally metastatic, distant metastatic, and fatal cases.

transition from preneoplastic lesions to patent adenocarcinoma, which in some cases may result in an accumulation of preneoplastic lesions (25, 26). Our findings of a positive association only for regionally invasive and worse prostate cancer and for the association being stronger when considering recent energy intake compared with baseline energy intake are consistent with recent energy intake influencing the later stages of carcinogenesis.

Energy intake is determined primarily by the basal metabolic rate but also by activity level and body size (27). In epidemiological studies, excessive energy intake is perhaps best captured by high BMI. If excessive energy intake did increase the risk of prostate cancer, then it would be expected that obesity would be associated with prostate cancer. However, no consistent association of high BMI with prostate cancer is supported in the literature (28). In the HPFS, obesity in adulthood is not associated with total prostate cancer risk or with metastatic and fatal disease (15). However, in younger men and those with a family history of prostate cancer, obesity is inversely associated with prostate cancer (29). Multiple physiological systems are perturbed in overweight and obese men such as insulin and glucose control and the balance of sex steroids. Some of these perturbations may be predicted to increase the risk of prostate cancer (e.g., high circulating insulin and glucose) or decrease the risk (e.g., high circulating estrogen relative to androgen). Taken together, our previous finding of an inverse association between obesity and prostate cancer in a subset of men and our present finding of an increased risk of regionally invasive or worse prostate cancer in lean men may suggest that it is more difficult to isolate the adverse effect of excessive energy

intake in obese men because that effect is balanced by the sequelae of obesity that decrease the risk of prostate cancer.

The specific mechanisms underlying how high energy intake might adversely affect the balance of proliferation with apoptosis and enhance angiogenesis and thus advanced prostate cancer remain to be resolved. Because circulating concentrations of IGF-I decline with energy restriction (3, 30, 31), it has been implicated as a mediator of the adverse effects of excessive energy intake. In addition to its endocrine production by the liver (32), IGF-I also acts as a paracrine growth regulator, including in the prostate where it is produced by the stroma (33). In prostate tumors, epithelial cells also may produce IGF-I (34). Plasma IGF-I concentration was not clearly correlated with energy intake, obesity, or physical inactivity in a cross-sectional study (35). However, fasting (10 days) reduces plasma IGF-I concentrations in adult men (36), including restriction of protein and total energy (37). In the HPFS, energy intake was not correlated with IGF-I concentration overall (38). However, in men with lower BMI (<25 kg/m²), IGF-I concentrations tended to be higher in men who had greater energy intake [P(trend) = 0.03; Ref. 38]. The finding of a positive association between energy intake and IGF-I only in leaner men in this cohort coupled with the finding that IGF-I is positively associated primarily with advanced prostate cancer in another large cohort (39) together lend support to our finding of a positive association for energy intake for regionally invasive or worse prostate cancer primarily in leaner men.

We also evaluated the association between energy intake and prostate cancer that was regionally invasive or worse in the subgroup of men enriched for an underlying susceptibility to prostate cancer. We observed even stronger associations for energy intake in men who were young at diagnosis or who had a positive family history of prostate cancer. That we observed opposing effects of energy intake and obesity (29) on risk of clinically important prostate cancer strongly among men with a young age at diagnosis or with a positive family history may possibly suggest that some men with an underlying susceptibility to prostate cancer may be more prone to the effects of certain metabolic or hormonal profiles.

Alternative explanations for our findings should be considered. It is possible that we could only detect the positive association of energy with regionally invasive or worse prostate cancer in lean men because the extent of error in the measurement of energy intake was lower in lean men. Food frequency questionnaires have been reported to underestimate energy intake by 10–30% relative to diet records (27).

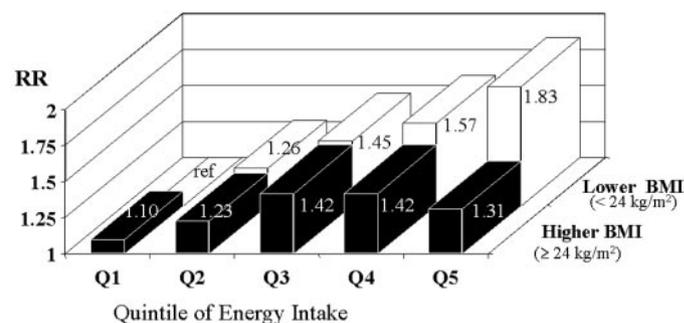


Fig. 1. Multivariate RR of metastatic or fatal prostate cancer in relation to combinations of baseline energy intake and BMI. Compared with men with lower BMI (<24 kg/m²) and low energy intake (lowest quintile), risk of metastatic or fatal prostate cancer increases with increasing energy intake, in particular in men who have a lower BMI and who have high energy intake [P(interaction) = 0.04]. The RR for comparing men with lower BMI and the highest quintile of energy intake to men with lower BMI and the lowest quintile of energy intake was 1.83 (95% CI 0.97–3.45). The number of cases in each joint category are: lower BMI, Q1 energy (Ref) 15; lower BMI, Q2 energy 22; lower BMI, Q3 energy 25; lower BMI, Q4 energy 29; lower BMI, Q5 energy 29; higher BMI, Q1 energy 39; higher BMI, Q2 energy 44; higher BMI, Q3 energy 48; higher BMI, Q4 energy 46; and higher BMI, Q5 energy 42.

However, in the validation study in this cohort, mean energy intake reported by food frequency questionnaire differed from diet records by <10% (12). In any case, it would be expected that individuals of similar body size and activity level would be ranked correctly on energy intake. However, obese individuals tend to underreport energy intake to a greater extent than normal weight individuals (40). If measurement error were profound in men who had greater adiposity, then the association between energy and prostate cancer might not have been detectable in that subgroup. However, we did not find evidence to support less measurement error when comparing the correlation coefficients for energy intake measured by food frequency questionnaire and diet records in men with lower and higher BMIs in this cohort. Second, although our findings appear to fit well with existing experimental and observational data in the literature, as with any epidemiological finding, in particular for subgroups, we also cannot preclude that some of these are chance findings.

Our study has a number of important strengths. Our analysis was prospective and included >3.5 times the number of cases included in any of the other cohort studies reporting on energy intake in relation to prostate cancer. Because of the large size of the HPFS, the number of regionally invasive or worse cases was adequately large to examine associations and two-way interactions in detail. However, we did not have adequate power to evaluate three-way interactions, *e.g.*, among energy, body size, and physical activity or among energy, family history, and body size. We controlled for a number of known and suspected risk factors for prostate cancer. In addition, we adjusted food covariates for energy intake using residual analysis to be able to observe the full effect of energy intake. Because this analysis was conducted prospectively, the extent of error in the assessment of energy intake should not be differential with respect to diagnosis of prostate cancer.

Other strengths of the study include increasing the accuracy of usual energy intake in an alternative analysis using simple and cumulative updating of energy intake from three food frequency questionnaires collected 4 years apart. When using simple or cumulative updating, the association of energy intake with prostate cancer that was regionally invasive or worse was somewhat stronger. Whether recent diet is more important, which would be compatible with energy intake influencing later stages in carcinogenesis or whether this finding reflects bias because of yet undiagnosed disease-influencing current diet (19), cannot be determined from these data. To address whether our finding for cases that were regionally invasive or worse and baseline energy intake is an artifact of extensive disease producing weight loss and compensatory increase in energy intake in the interval before diagnosis, we excluded cases that were diagnosed in the first 2 years of follow-up. Our findings did not change appreciably.

Finally, to help rule out that the lack of an association between energy intake and total prostate cancer was because of a difference among quintiles of energy intake in the opportunity to have occult prostate cancer detected, we ran a subanalysis that included as non-case person-time only those men who had had a screening PSA test. The result for total prostate cancer remained null.

In summary, we observed that higher energy intake is associated with a higher risk of prostate cancer that was regionally invasive or worse in lean and more physically active men and especially for cases with a young age at diagnosis or a positive family history. Our observations lead to the testable hypothesis that men who remain lean despite high energy intake may have a higher risk of clinically important prostate cancer because of a metabolic profile that favors enhanced production of growth factors and their antiapoptotic and proangiogenic activities over an increase in adiposity and its sequelae.

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