Dietary fat intake and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition[1–3]

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ABSTRACT

Background: Findings from early observational studies have suggested that the intake of dietary fat might be a contributing factor in the etiology of prostate cancer. However, the results from more recent prospective studies do not support this hypothesis, and the possible association between different food sources of fat and prostate cancer risk also remains unclear.

Objective: The objectives were to assess whether intakes of dietary fat, subtypes of fat, and fat from animal products were associated with prostate cancer risk.

Design: This was a multicenter prospective study of 142 520 men in the European Prospective Investigation into Cancer and Nutrition (EPIC). Dietary fat intake was estimated with the use of country-specific validated food questionnaires. The association between dietary fat and risk of prostate cancer was assessed by using Cox regression, stratified by recruitment center and adjusted for height, weight, smoking, education, marital status, and energy intake.

Results: After a median follow-up time of 8.7 y, prostate cancer was diagnosed in 2727 men. There was no significant association between dietary fat (total, saturated, monounsaturated, and polyunsaturated fat and the ratio of polyunsaturated to saturated fat) and risk of prostate cancer. The hazard ratio for prostate cancer for the highest versus the lowest quintile of total fat intake was 0.96 (95% CI: 0.84, 1.09; P for trend = 0.155). There were no significant associations between prostate cancer risk and fat from red meat, dairy products, and fish.

Conclusion: The results from this large multicenter study suggest that there is no association between dietary fat and prostate cancer risk.

INTRODUCTION

Worldwide, there is considerable diversity in the incidence of prostate cancer (1), and the weight of evidence indicates that a large proportion of prostate cancer risk is modifiable (2). Although dietary risk factors for prostate cancer are not yet established, findings from international comparison studies suggest that certain components (3, 4), such as the intake of fat, may be positively related to the risk of prostate cancer (5–7). Several biologically plausible mechanisms may underlie the association between dietary fat intake and prostate cancer risk, including the possible effect of dietary fat on hormone concentrations and other nonhormonal effects (8–10). Notwithstanding such evidence, the investigators of more recent observational studies have not been able to demonstrate a strong association between dietary fat and prostate cancer risk. In a meta-analysis of case-control and prospective studies, a higher intake of total fat was associated with only a slightly greater risk of prostate cancer (11) and, subsequently, results from 2 large prospective studies showed no association between dietary fat intake and prostate cancer risk (12, 13). Information regarding the association between dietary fat from animal foods such as meat, dairy products, and fish and the risk of prostate cancer in prospective studies has not been widely reported.

The lack of a strong association between dietary fat intake and risk of prostate cancer may be due to a number of reasons. For instance, the majority of observational studies have tended to involve a rather homogeneous group of participants with a limited range of dietary fat intakes (11, 13). Moreover, the use of a

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wide variety of dietary assessment techniques and nutrient databases may create significant heterogeneity between studies, which makes it questionable whether results should be combined in a meta-analysis (11).

The objective of this study was *1*) to investigate the association between dietary fat and fat from specified animal foods and the risk of prostate cancer in men with a variety of dietary patterns participating in the European Prospective Investigation into Cancer and Nutrition (EPIC), and *2*) to evaluate the associations by stage and grade of disease.

SUBJECTS AND METHODS

Study cohort

EPIC is a multicenter prospective study designed to investigate the relations between cancer and diet, lifestyle, and environmental factors. More details of the recruitment and study design have been published elsewhere (14). The total cohort comprises ≈500 000 men and women recruited in 28 centers from 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. This article includes data for men from 19 centers in 8 of these countries: Denmark, Germany, Greece, Italy, the Netherlands, Spain, Sweden, and the United Kingdom. No data are presented for France, Norway, Naples (Italy), and Utrecht (Netherlands) because only women were recruited in these countries and centers.

The men included in this analysis were recruited from the population residing in defined geographical areas in each of the 8 countries (general population in most centers and blood donors in Ragusa and Turin in Italy and in the Spanish centers), except for those in the Oxford, United Kingdom, "health conscious" subcohort, who were recruited throughout the United Kingdom to enroll a large number of vegetarians. Study participants were almost all white Europeans. Eligible subjects were invited to participate in the study, and those who accepted gave informed consent and completed questionnaires on their diet, lifestyle, and medical history. Study subjects were also invited to their local center, where a blood sample and anthropometric measurements were taken. Approval for this study was obtained from the ethical review boards of the International Agency for Research on Cancer (IARC) and from all local institutions from where the subjects had been recruited.

Men were not eligible for this analysis if they had previously been registered as having cancer at the time of completing the baseline questionnaire (other than nonmelanoma skin cancer), if they had missing dates on prostate cancer diagnosis or follow-up, or if they had no dietary or nondietary data ($n = 2889$). Individuals were also excluded if they were in the top or bottom 1% of the distribution of the ratio of reported energy intake to energy requirement ($n = 2876$) (15). Complete data on diet and follow-up for prostate cancer were available for 142 520 of the 148 372 men in the original data set.

Diet and lifestyle questionnaires

Dietary intake during the year before recruitment was measured with country-specific validated food-frequency questionnaires (FFQs) or diet histories that were designed to capture local dietary patterns (14, 16). For portion sizes, Germany, Italy, the Netherlands, and Spain used estimated individual average portions; Denmark, Greece, the United Kingdom, and Umeå (Sweden) assigned standard portion sizes; and Malmö (Sweden) used a combination of methods for estimating portion sizes. Estimated daily fat intakes were calculated by multiplying the fat content of each food of the specific portion size by the frequency of consumption as stated on the FFQ using country-specific national food tables. In this analysis, fat from meat refers to fat from red meat (beef, veal, pork, mutton/lamb, horse, and goat) and processed meats. Fat from dairy products includes fat from milk, milk beverages, yogurt, cheese, and butter. Fish and shellfish include fat from fish, crustaceans, mollusks, fish products, and fish in crumbs. Greece was not included in the analyses of fat from meat, dairy products, and fish, and Umeå was not included in the analyses of fat from meat because there was limited information for these particular food items in the central database for Greece and in the dietary questionnaire used in Umeå.

To correct for any systematic under- or overestimation of dietary intake between the study centers and to reduce attenuation bias in the risk estimates, a dietary calibration study was conducted. A random sample of 13031 men (9%) completed a 24-h dietary recall, and nutrient intake was calculated by using a common food-composition database (17).

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Participants completed a nondietary questionnaire that included information relating to education, socioeconomic status, occupation, history of previous illness and disorders or surgical operations, lifetime history of the consumption of tobacco and alcoholic beverages, and physical activity. Height and weight were measured at recruitment according to standard techniques, except for men in the Oxford "health-conscious" subcohort, among whom height and weight were self-reported and used to calculate Quetelet's body mass index (BMI; in kg/m^2). Information on family history of prostate cancer was not available.

Follow-up and identification of cancer cases

Follow-up is provided by population-based cancer registries in 6 of the participating countries: Denmark, Italy, the Netherlands, Spain, Sweden, and the United Kingdom. In Germany and Greece, follow-up was via self-completed questionnaires, and self-reported incident cancers were verified through medical records. By March 2007, complete follow-up data had been reported to the IARC up to December 2003 or December 2004 for most centers. For Germany and Greece, the censoring date was considered to be the date of the last known contact or the date of diagnosis or death, whichever came first. The 10th Revision of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD) was used to code cancer site, and cancer of the prostate as analyzed here was defined as code C61.

Data on TNM stage and Gleason grade were collected from each center, whenever possible. Of the 2727 cases, 1672 (61%) had information on stage and 1630 (60%) had information on grade. Tumors were classified as localized (TNM staging score of T0 or T1 or T2 and N0 or NX and M0, or stage coded in the recruitment center as localized; $n = 1131$), advanced (T3 or T4 and/or N1+ and/or M1, or stage coded in the recruitment center as metastatic; $n = 541$), or unknown. Disease was classified as low grade (Gleason sum <7 or equivalent; cases were coded as well differentiated or moderately differentiated; $n = 982$), high grade (Gleason sum ≥ 7 or equivalent; cases coded as poorly differentiated or undifferentiated; $n = 648$), or unknown. We were not able to establish whether the information on stage of disease was based on clinical or pathological reports. For the grade of disease, results from the pathological report were used when available, and the World Health Organization grading system was used if the Gleason sum was not available.

Statistical analysis

Analyses of the association of dietary fat and covariates with prostate cancer risk were conducted by using Cox regression. Data were stratified by center, and age was used as the underlying time variable in all models. Age-standardized rates in each national cohort were calculated as the weighted average of the ratio of cases to person-years in each of 4 attained age groups (50–54, 55–59, 60–64, and 65–69 y at recruitment) in that cohort, for whom the weights were based on the European standard population.

Dietary fat intakes estimated from the dietary questionnaires were expressed as a percentage of total energy and were analyzed as a categorical variable, based on quintiles of the distribution among all men. Tests for linear trend were conducted by using continuous values for dietary fat, with increments based on an increase in intake of 10% of total energy for total fat; 5% of total energy for saturated, monounsaturated, and polyunsaturated fat from red and processed meat; fat from dairy products; 1% of total energy for fat from fish and shellfish; and an increase of 0.2 in the ratio of polyunsaturated to saturated fat. All models were adjusted for height (<170, 170–174, 175–179, and ≥ 180 cm), weight (<70, 70–79, 80–89, and ≥ 90 kg), smoking (never, former, current, and unknown), educational level (no degree, degree or higher, and unknown), marital status (married/cohabiting, not married/cohabiting, and unknown), and energy intake (MJ/d; continuous).

Dietary intakes from the questionnaires were calibrated by using a fixed-effects linear model in which center and sex-specific 24-h recall data from a random sample of the cohort (17) were regressed on the FFQ intakes (18).

Separate analyses were conducted among men diagnosed with localized and advanced disease and also among men with low-grade and high-grade disease. Tests of heterogeneity between these subgroups were obtained by fitting stratified Cox models based on competing risks and comparing the risk coefficients and SEs in the subgroups of interest after excluding cases of uncertain stage and grade, by using the method described by Smith-Warner et al (19). To evaluate whether preclinical disease may have influenced results, additional analyses were conducted after the exclusion of cases diagnosed during the first 4 y of follow-up. Evidence of heterogeneity for the association between dietary fat intake and prostate cancer risk between countries was assessed by using chi-square tests of association.

To put the results of this study into context with previous relevant research, we performed a summary analysis of our results together with the results of previously published studies. Studies were identified by searching PubMed and the reference lists of relevant papers using the search terms *dietary fat*, *prospective*, *cohort*, and *prostate cancer*. Studies were restricted to those that had controlled for total energy intake ($n = 6$). Summary relative risks (RRs) were estimated as the weighted average of the study-specific RRs for men in the highest quantile of dietary fat intake compared with those in the lowest quantile, with weights determined by the inverse of the variance of each risk estimate using fixed-effects models.

All P values presented are 2-tailed, and P values <0.05 were considered statistically significant. All statistical analyses were carried out using STATA Statistical Software (release 9; StataCorp LP, College Station, TX).

RESULTS

There was a total of 2727 incident prostate cancer cases in 1 236 265 person-years of observation with a median follow-up time of 8.7 y. The incidence of prostate cancer and intake of dietary fat for each of the participating countries are shown in **Table 1**. The age-standardized incidence of prostate cancer varied 6-fold between the countries. Sweden had the highest age-standardized incidence of prostate cancer, and Greece had the lowest. The mean intake of total fat varied across the countries by 11% of total energy and contributed to the lowest percentage of total energy in Italy and the highest percentage in Greece. Sweden had the highest intake of saturated fat (% of total energy), and this value was lowest for Italy. The range in monounsaturated fat intake was 10% of total energy and was highest in Greece and lowest in the Netherlands. Germany had the highest intake of

TABLE 1
Characteristics of the European Prospective Investigation into Cancer and Nutrition (EPIC) study cohorts

	Denmark	Germany	Greece	Italy	Netherlands	Spain	Sweden	United Kingdom	Total
No. of men	26 267	21 567	10 593	14 009	9 782	15 150	22 299	22 853	142 520
Prostate cancer cases	368	420	40	145	59	206	1013	476	2727
Localized/advanced stage[1]	188/104	240/92	17/8	27/30	11/29	144/23	323/157	181/98	1131/541
Low/high grade[1]	78/112	215/95	16/8	58/30	45/13	121/44	313/176	136/170	982/648
Person-years	198 584	176 902	73 980	120 984	82 852	156 070	233 424	193 469	1 236 265
Age at recruitment (y)[2]	56 (50–64)	52 (41–63)	52 (33–72)	49 (38–62)	43 (23–58)	49 (40–63)	51 (30–68)	52 (28–73)	52 (33–67)
Age-standardized rate[3]	15.4	27.0	6.3	18.4	18.8	15.8	37.8	17.2	21.8
Total fat intake (% of total energy)[4]	36.5 ± 9.2	37.8 ± 9.6	40.8 ± 9.4	29.2 ± 7.8	35.0 ± 8.2	36.5 ± 8.4	37.1 ± 8.2	33.0 ± 8.9	36.2 ± 9.2
Saturated fat intake (% of total energy)[4]	15.0 ± 4.8	15.3 ± 5.1	11.9 ± 4.4	9.5 ± 3.2	13.6 ± 4.1	10.5 ± 3.4	16.1 ± 4.4	12.4 ± 4.7	13.5 ± 4.9
Monounsaturated fat intake (% of total energy)[4]	12.7 ± 3.8	13.0 ± 3.9	20.5 ± 7.1	13.9 ± 4.9	10.7 ± 3.3	17.3 ± 5.6	13.3 ± 3.3	11.8 ± 3.9	14.2 ± 5.3
Polyunsaturated fat intake (% of total energy)[4]	5.3 ± 2.3	7.0 ± 3.8	5.5 ± 3.4	4.0 ± 1.9	7.0 ± 2.9	5.9 ± 3.2	4.9 ± 1.7	6.2 ± 3.0	5.7 ± 3.0
P:S ratio[4,5]	0.39 ± 0.23	0.52 ± 0.37	0.54 ± 0.42	0.47 ± 0.28	0.56 ± 0.31	0.61 ± 0.41	0.33 ± 0.17	0.60 ± 0.44	0.48 ± 0.33
Fat from red and processed meat (% of total energy)[4]	7.4 ± 6.2	8.6 ± 7.4	3.1 ± 5.6	3.5 ± 4.4	7.2 ± 6.6	6.4 ± 6.5	6.5 ± 6.1	3.2 ± 5.0	6.2 ± 6.5
Fat from dairy products (% of total energy)[4]	7.4 ± 6.2	11.4 ± 9.2	7.7 ± 6.5	6.0 ± 4.6	7.6 ± 6.0	4.5 ± 4.4	7.5 ± 5.6	6.8 ± 6.7	7.6 ± 6.7
Fat from fish and shellfish (% of total energy)[4]	1.6 ± 3.3	0.7 ± 2.6	0.6 ± 1.6	0.6 ± 1.5	0.4 ± 1.5	1.4 ± 2.3	1.2 ± 2.6	0.7 ± 2.7	1.0 ± 2.4

[1] Stage and grade were unknown for some cases.
[2] All values are median (5th–95th percentiles).
[3] Age-standardized incidence rates per 10 000 person-years were calculated by using a weighted average of the incidence rates in each of 4 attained age groups (50–54, 55–59, 60–64, and 65–69 y), with weights based on the European standard population.
[4] All values are $\bar{x}$ ± SD based on 24-h recall data.
[5] Ratio of polyunsaturated to saturated fat.

polyunsaturated fat, meat, and dairy fat, and Spain had the highest ratio of polyunsaturated to saturated fat (P:S ratio) and the lowest intake of dairy fat.

When men were categorized into quintiles of increasing dietary fat intake (% of total energy), there was a trend for younger age at recruitment, a shorter height, and a greater weight and BMI across the quintiles (**Table 2**). The proportion of current smokers increased across the quintiles of total fat intake as did the proportion of men without an educational degree. Among men with known marital status, the proportion of married men was highest in the top quintile of fat intake and lowest in the bottom quintile of fat intake.

The results in **Table 3** show the hazard ratio (HR) and 95% CI for prostate cancer by quintile of dietary fat intake (% of total energy) stratified for study center and adjusted for height, weight, smoking, education, marital status, and energy intake. There were no statistically significant associations between intakes of total fat, the subtypes of fat, or the P:S ratio and risk of prostate cancer. Compared with the lowest quintile of total fat intake, men categorized in the highest quintile had an HR for prostate cancer of 0.96 (95% CI: 0.84, 1.09; *P* for trend = 0.155). Individuals categorized in the third quintile of total fat intake had a 15% (HR: 0.85; 95% CI: 0.76, 0.96) lower risk of prostate cancer in comparison with individuals categorized in the lowest quintile.

The association between the observed and calibrated intakes of dietary fat with total prostate cancer and prostate cancer subdivided by stage (localized or advanced) and grade (low or high) after adjustment for confounding variables are shown in **Table 4**. For the observed intake, each 10% increase in energy from fat was associated with a 5% (HR: 0.95; 95% CI: 0.89, 1.02) lower risk of prostate cancer, but this result was not statistically significant. There was no significant association between dietary fat intake and the risk of localized or advanced prostate cancer or low-grade prostate cancer. There was, however, a significant inverse association between the observed and calibrated intakes of total, monounsaturated, and polyunsaturated fats and the risk of high-grade prostate cancer. For each 10% increase in the observed intake of total fat, the risk of high-grade prostate cancer decreased by 17% (HR: 0.83; 95% CI: 0.72, 0.95). Each 5% increase in monounsaturated and polyunsaturated fat intake was associated with a lower risk of high-grade prostate cancer of 18% (HR: 0.82; 95% CI: 0.70, 0.97) and 23% (HR: 0.77; 95% CI: 0.62, 0.97), respectively. The tests for heterogeneity for the observed intakes of total, monounsaturated, and polyunsaturated fat by grade of prostate cancer were statistically significant, but after the intakes were calibrated they were no longer significant.

The results in **Table 5** show the risk of total prostate cancer and prostate cancer subdivided by stage and grade for the intake of fat from red and processed meats, dairy products, and fish and shellfish. There were no significant associations between the intake of fat from meat or fat from fish and the risk of overall prostate cancer. The associations between the intake of fat from dairy products and the risk of total, advanced, or high- or low-grade prostate cancer were not statistically significant. There was a significant inverse relation between fat from dairy products and risk of localized prostate cancer; each 5% increase in energy from dairy fat was associated with an 8% (HR: 0.92; 95% CI: 0.86, 0.99) and 10% (HR: 0.90; 95% CI: 0.82, 0.99) reduced risk of prostate cancer for the observed and calibrated intakes, respectively. There was significant heterogeneity between the risk of localized and advanced prostate cancer per 5% increase in energy from dairy fat for both the observed and calibrated intakes.

There was no evidence of heterogeneity between countries for the associations between the intakes of total, saturated, and polyunsaturated fat or the P:S ratio and risk of prostate cancer; however, there was significant heterogeneity between countries for

TABLE 2
Characteristics of men in the European Prospective Investigation into Cancer and Nutrition (EPIC) study by quintile of dietary fat intake

	Quintile of total fat intake (% of total energy)					
	1	2	3	4	5	*P* for trend[1]
No. of participants	28 551	28 530	28 467	28 503	28 469	
Age at recruitment (y)	52.4 ± 9.7[2]	52.0 ± 9.7	51.6 ± 9.9	51.4 ± 10.2	51.1 ± 11.0	<0.0001
Height (cm)	174.5 ± 7.1	175.0 ± 7.2	175.2 ± 7.3	175.1 ± 7.3	173.8 ± 7.6	<0.0001
Weight (kg)	80.2 ± 11.8	80.8 ± 11.7	80.9 ± 11.9	81.1 ± 11.9	81.3 ± 12.5	<0.0001
BMI (kg/m^2)	26.3 ± 3.6	26.4 ± 3.5	26.4 ± 3.6	26.4 ± 3.6	26.9 ± 3.9	<0.0001
Smoking [*n* (%)][3]						
Never	9200 (32.2)	9650 (33.8)	9808 (34.5)	9633 (33.8)	8627 (30.3)	<0.0001
Former	11 548 (40.4)	10 985 (38.5)	10 284 (36.1)	9838 (34.5)	9061 (31.8)	<0.0001
Current	7500 (26.3)	7609 (26.7)	8033 (28.2)	8679 (30.4)	10096 (35.5)	<0.0001
Unknown	303 (1.1)	286 (1.0)	342 (1.2)	353 (1.2)	685 (2.4)	<0.0001
Education [*n* (%)][3]						
Below degree level	19 424 (68.0)	19 617 (68.8)	19 713 (69.3)	20 251 (71.1)	21 891 (76.9)	<0.0001
Degree level	7924 (27.8)	7950 (27.9)	7875 (27.7)	7510 (26.4)	6088 (21.4)	<0.0001
Unknown	1203 (4.2)	963 (3.4)	879 (3.1)	742 (2.6)	490 (1.7)	<0.0001
Marital status [*n* (%)][3]						
Married	15 748 (55.2)	15 696 (55.0)	15 001 (52.7)	15 202 (53.3)	18 106 (63.6)	<0.0001
Not married	3998 (14.0)	3524 (12.4)	3653 (12.8)	3618 (12.7)	4032 (14.2)	<0.0001
Unknown	8805 (30.8)	9310 (32.6)	9813 (34.5)	9683 (34.0)	6331 (22.2)	<0.0001

[1] Trends for age, height, weight, and BMI were obtained by treating quintiles of total fat intake as a continuous variable, and chi-square tests of association were used for smoking, education, and marital status with the "unknown" category excluded.

[2] $\bar{x}$ ± SD (all such values).

[3] Percentages may not add up to 100 because of rounding.

TABLE 3
Multivariate-adjusted hazard ratios (HRs) (and 95% CIs) for prostate cancer by dietary fat intake among 142 520 men in the European Prospective Investigation into Cancer and Nutrition (EPIC) study

	Quintiles of dietary fat intake (% of total energy)[1]						
	1	2	3	4	5	*P* for trend	*P* for heterogeneity[2]
Total fat intake							
Mean (% of total energy)[3]	31.3	34.6	36.3	38.1	40.4		
No. of cases	592	571	509	544	511		
Multivariate-adjusted HR[4]	1.0	0.95 (0.84, 1.06)	0.85 (0.76, 0.96)	0.90 (0.80, 1.02)	0.96 (0.84, 1.09)	0.155	0.094
Saturated fat intake							
Mean (% of total energy)[3]	10.1	12.0	13.6	15.0	17.2		
No. of cases	443	472	559	551	702		
Multivariate-adjusted HR[4]	1.0	1.01 (0.89, 1.16)	1.09 (0.95, 1.24)	0.97 (0.85, 1.12)	0.97 (0.85, 1.11)	0.224	0.319
Monounsaturated fat intake							
Mean (% of total energy)[3]	11.4	12.5	13.3	14.3	18.2		
No. of cases	615	625	581	563	343		
Multivariate-adjusted HR[4]	1.0	0.96 (0.85, 1.07)	0.89 (0.80, 1.01)	0.89 (0.79, 1.01)	0.98 (0.84, 1.14)	0.348	0.247
Polyunsaturated fat intake							
Mean (% of total energy)[3]	4.3	5.0	5.7	6.3	7.4		
No. of cases	512	577	530	593	515		
Multivariate-adjusted HR[4]	1.0	1.07 (0.94, 1.21)	0.94 (0.83, 1.07)	0.97 (0.85, 1.10)	0.98 (0.85, 1.12)	0.413	0.310
P:S ratio[5]							
Mean (% of total energy)[3]	0.33	0.40	0.46	0.54	0.70		
No. of cases	622	569	528	569	439		
Multivariate-adjusted HR[4]	1.0	1.10 (0.98, 1.23)	1.02 (0.90, 1.15)	1.10 (0.98, 1.24)	0.94 (0.83, 1.08)	0.480	0.076

[1] Based on the distribution of dietary fat in all participants.
[2] Tests for heterogeneity between the HRs across the quintiles of fat intake.
[3] Based on 24-h recall data.
[4] Stratified by study center and adjusted for height, weight, smoking, education, marital status, and energy intake by using Cox regression.
[5] Ratio of polyunsaturated to saturated fat.

the observed and calibrated intakes of monounsaturated fat ($P = 0.005$ and $P = 0.01$, respectively; results not shown).

Exclusion of the first 4 y of follow-up to eliminate any possible influence of preexisting disease made no material difference to the associations between total fat intake, any of the subtypes of fat, or the P:S ratio and prostate cancer risk. Neither did it make any marked difference to the results whether total energy was excluded from the multivariate risk models (results not shown).

The summary RRs and 95% CI for prostate cancer for the highest compared with the lowest quantile of total, saturated, monounsaturated, and polyunsaturated fat intake from 7 prospective studies are presented in **Table 6**. None of the associations for total fat or the subtypes of fat were statistically significant, either for the individual studies or for the summary estimates. None of the *P* values for the tests of heterogeneity between studies were statistically significant.

DISCUSSION

In this large multicenter study, we showed that the P:S ratio and intakes of total, saturated, monounsaturated, and polyunsaturated fats were not associated with prostate cancer risk in European men. We found inverse associations between intakes of total, monounsaturated, and polyunsaturated fat and the risk of high-grade prostate cancer and a weak inverse association between dairy fat intake and the risk of localized prostate cancer. The strengths of our study include a population with diverse dietary patterns and a large number of prostate cancer cases to give the study adequate power to detect statistically significant associations between dietary fat intake and the risk of prostate cancer.

Findings from a recent meta-analysis of 15 observational studies showed that each 45-g increase in total fat intake was associated with a 12% greater risk of prostate cancer; however, for the 4 prospective studies included in this analysis, there were no significant associations between intakes of total, saturated, monounsaturated, or polyunsaturated fat and the risk of prostate cancer (11). Since this meta-analysis was published, Park et al (12) reported no significant association between dietary fat and risk of prostate cancer for men participating in the Multiethnic Cohort with >4000 cases of incident prostate cancer and Neuhouser et al (13) also reported a null association between total dietary fat and risk of prostate cancer among smokers participating in the Carotene and Retinol Efficacy Trial (CARET), whereas we reported that the risk of prostate cancer was reduced slightly in those with a higher intake of dietary fat. When the risk estimates from all 7 prospective studies were pooled, the RR for prostate cancer was not statistically significant (12, 13, 20–23). For the 6 studies that reported analyses of the subtypes of fat, none were associated with prostate cancer risk (12, 13, 20–22). Thus, the totality of the evidence indicates that a higher intake of dietary fat is not a risk factor for prostate cancer.

Our results did suggest that the intakes of total, monounsaturated, and polyunsaturated fat were inversely related to the risk of high-grade prostate cancer. This finding was unexpected and may have been due to chance because we conducted a large number of subgroup analyses. Moreover, there is limited evidence from observational studies (11–13) and no biologically

TABLE 4
Multivariate-adjusted hazard ratios (HRs) (and 95% CIs) for total prostate cancer and by stage and grade in association with dietary fat intake among men in the European Prospective Investigation into Cancer and Nutrition (EPIC) study[1]

	HR per unit increase in observed intake[2]	*P* for trend	*P* for heterogeneity[3]	HR per unit increase in calibrated intake[2]	*P* for trend	*P* for heterogeneity[3]
Total fat intake						
Total (n = 2727)	0.95 (0.89, 1.02)	0.155		0.90 (0.79, 1.02)	0.086	
Localized (n = 1131)	0.93 (0.84, 1.03)	0.190	0.376	0.89 (0.73, 1.08)	0.247	0.544
Advanced (n = 541)	1.01 (0.87, 1.17)	0.864		0.99 (0.75, 1.30)	0.937	
Low grade (n = 982)	1.00 (0.90, 1.12)	0.984	0.030	0.95 (0.77, 1.19)	0.681	0.073
High grade (n = 648)	0.83 (0.72, 0.95)	0.006		0.70 (0.55, 0.90)	0.006	
Saturated fat						
Total	0.96 (0.91, 1.02)	0.224		0.93 (0.84, 1.02)	0.140	
Localized	0.93 (0.85, 1.02)	0.130	0.174	0.91 (0.78, 1.06)	0.209	0.451
Advanced	1.04 (0.91, 1.19)	0.556		1.00 (0.81, 1.24)	0.980	
Low grade	0.97 (0.88, 1.07)	0.572	0.380	0.94 (0.79, 1.11)	0.458	0.306
High grade	0.90 (0.80, 1.02)	0.113		0.82 (0.67, 1.00)	0.045	
Monounsaturated fat						
Total	0.96 (0.89, 1.04)	0.348		0.89 (0.75, 1.06)	0.200	
Localized	0.97 (0.86, 1.09)	0.619	0.875	0.94 (0.72, 1.21)	0.613	0.863
Advanced	0.99 (0.83, 1.18)	0.886		0.97 (0.67, 1.42)	0.893	
Low grade	1.03 (0.91, 1.16)	0.693	0.035	1.02 (0.77, 1.36)	0.866	0.053
High grade	0.82 (0.70, 0.97)	0.019		0.66 (0.47, 0.93)	0.018	
Polyunsaturated fat						
Total	0.96 (0.86, 1.06)	0.413		0.93 (0.74, 1.16)	0.517	
Localized	0.95 (0.81, 1.11)	0.518	0.971	0.99 (0.72, 1.35)	0.934	0.663
Advanced	0.95 (0.75, 1.21)	0.697		0.87 (0.53, 1.41)	0.567	
Low grade	1.03 (0.87, 1.22)	0.737	0.047	1.04 (0.75, 1.44)	0.820	0.085
High grade	0.77 (0.62, 0.97)	0.025		0.63 (0.39, 1.00)	0.051	
P:S ratio						
Total	0.99 (0.95, 1.03)	0.480		0.99 (0.92, 1.06)	0.730	
Localized	0.98 (0.92, 1.04)	0.479	0.898	0.99 (0.89, 1.11)	0.904	0.941
Advanced	0.99 (0.90, 1.08)	0.753		1.00 (0.85, 1.17)	0.993	
Low grade	1.00 (0.94, 1.06)	0.909	0.705	1.00 (0.90, 1.12)	0.984	0.807
High grade	0.98 (0.90, 1.06)	0.563		0.98 (0.85, 1.13)	0.770	

[1] Stratified by study center and adjusted for height, weight, smoking, education, marital status, and energy intake by using Cox regression.
[2] For a 10% increase in energy from total fat; a 5% increase in energy from saturated, monounsaturated, and polyunsaturated fat; and an increase of 0.2 in the ratio of polyunsaturated to saturated fat.
[3] Tests of heterogeneity between trends for localized and advanced stages and high- and low-grade prostate cancer.

plausible mechanism to support a role for a high intake of fat in reducing the degree of cell differentiation associated with high-grade prostate cancer. Therefore, further research would be necessary to establish whether the inverse association between dietary fat and high-grade prostate cancer is causal.

We found no significant association between the intake of fat from dairy products and the overall risk of total prostate cancer; however, there was an inverse relation between dairy fat intake and the risk of localized prostate cancer that persisted when dairy fat intake was calibrated to account for between-center variation and measurement error. We examined the association between the intake of several subtypes and sources of fat and risk of prostate cancer by stage and grade; thus, the association between dairy fat intake and prostate cancer risk may have been due to chance rather than to a true differential effect of dairy fat intake on the risk of localized and advanced prostate cancer. Others have suggested that a higher consumption of dairy products may be a risk factor for prostate cancer (2, 5); however, on the basis of our analysis and that of Giovannucci et al (20), it may be nutrients other than fat in dairy products that are important predictors of prostate cancer risk.

Our results showed no evidence of an association between the intake of fat from fish and shellfish and the risk of prostate cancer, which is consistent with the results from other prospective studies that have reported intake of fat from fish (20) or intake of the 2 major n−3 long-chain polyunsaturated fatty acids—eicosapentaenoic and docosahexaenoic acids—for which fish fat is a rich source (22, 23). Although some findings from in vitro and animal studies have suggested a role for n−3 long-chain polyunsaturated fatty acids in lowering prostate cancer risk (24) and the association between biomarkers of n−3 long-chain polyunsaturated fatty acids and risk of prostate cancer has been investigated (25–29), only 2 observational studies have reported that a higher proportion of n−3 long-chain polyunsaturated fatty acids reduced the risk of prostate cancer (27, 29).

Proposed mechanisms that may underpin the association between dietary fat and prostate cancer risk include the influence of fat intake on concentrations of insulin-like growth factor I (8). The results from the majority of cross-sectional studies have shown a very weak or no association between the intake of total fat or any of the subtypes of fat and insulin-like growth factor I concentrations (30–38). The relation between dietary fat and

TABLE 5
Multivariate-adjusted hazard ratios (HRs) (and 95% CIs) for total prostate cancer incidence and by stage and grade in association with sources of dietary fat intake among men in the European Prospective Investigation into Cancer and Nutrition (EPIC) study[1]

	No. of cases	HR per unit increase in observed intake[2]	*P*	*P* for heterogeneity[3]	HR per unit increase in calibrated intake[2]	*P*	*P* for heterogeneity[3]
Fat from red and processed meat[4]							
Total prostate cancer	2401	0.98 (0.92, 1.04)	0.484		0.94 (0.83, 1.07)	0.345	
Localized prostate cancer	975	1.01 (0.92, 1.12)	0.759	0.403	1.03 (0.85, 1.24)	0.775	0.216
Advanced prostate cancer	485	0.94 (0.82, 1.09)	0.423		0.83 (0.63, 1.10)	0.192	
Low-grade prostate cancer	831	0.99 (0.90, 1.10)	0.893	0.384	0.97 (0.79, 1.18)	0.735	0.407
High-grade prostate cancer	576	0.92 (0.80, 1.05)	0.234		0.84 (0.64, 1.10)	0.195	
Fat from dairy products[5]							
Total prostate cancer	2687	0.99 (0.95, 1.03)	0.517		0.97 (0.91, 1.03)	0.343	
Localized prostate cancer	1114	0.92 (0.86, 0.99)	0.021	0.004	0.90 (0.82, 0.99)	0.035	0.038
Advanced prostate cancer	533	1.09 (0.99, 1.19)	0.065		1.07 (0.94, 1.22)	0.307	
Low grade prostate cancer	966	0.95 (0.88, 1.02)	0.128	0.198	0.95 (0.85, 1.05)	0.311	0.892
High grade prostate cancer	640	1.02 (0.93, 1.11)	0.699		0.96 (0.84, 1.09)	0.514	
Fat from fish and shellfish[5]							
Total prostate cancer	2687	1.00 (0.97, 1.04)	0.837		1.00 (0.93, 1.07)	0.977	
Localized prostate cancer	1114	1.01 (0.96, 1.07)	0.678	0.728	1.00 (0.90, 1.11)	0.959	0.587
Advanced prostate cancer	533	1.03 (0.95, 1.12)	0.468		1.05 (0.91, 1.21)	0.474	
Low grade prostate cancer	966	1.01 (0.95, 1.08)	0.682	0.418	0.99 (0.88, 1.12)	0.900	0.545
High grade prostate cancer	640	0.97 (0.89, 1.05)	0.481		0.94 (0.82, 1.07)	0.349	

[1] Stratified by study center and adjusted for height, weight, smoking, education, marital status, and energy intake by using Cox regression.
[2] For a 5% increase in energy from meat and dairy fat and 1% increase in energy from fish fat.
[3] Tests of heterogeneity between trends for localized and advanced stage and high- and low-grade prostate cancer.
[4] Dietary information not available for Greece and Umeå.
[5] Dietary information not available for Greece.

hormone concentrations is likely to be complex given the number of nutrient-hormone interactions and the influence of nondietary factors on hormone concentrations (39).

Our study has several potential limitations, including the use of dietary fat intake obtained from dietary assessment questionnaires, which are subject to random measurement error (40, 41) and may have attenuated the relation between dietary fat intake and the risk of prostate cancer. Nevertheless, the questionnaires in all EPIC centers have been validated and dietary intakes were calibrated with measures from a carefully standardized 24-h diet recall method. Although this calibration method does not account for intraindividual measurement error, adjustment for the analysis for energy intake and body weight should partially control for the measurement error related to dietary intake (42).

There was evidence that the effect estimate for the intake of monounsaturated fat and risk of prostate cancer differed between the countries. However, it is not clear whether this heterogeneity could be attributed to true biological differences between countries or random variation.

In conclusion, the results from this large prospective study showed that a high intake of dietary fat was not associated with an increased risk of prostate cancer. These findings add further evidence that the intake of dietary fat is not an important predictor of prostate cancer risk.

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TABLE 6
Summary of prospective studies assessing the association between dietary fat intake and prostate cancer risk[1]

Study	No. of cases	Total fat	Saturated fat	Monounsaturated fat	Polyunsaturated fat
Giovannucci et al (20)	279	1.32 (0.91, 1.92)	0.84 (0.48, 1.47)	1.86 (0.99, 3.51)	0.88 (0.55, 1.43)
Veierød et al (21)	72	1.30 (0.60, 2.80)	0.70 (0.30, 1.50)	1.40 (0.60, 3.00)	1.40 (0.60, 3.00)
Schuurman et al (22)	642	1.10 (0.80, 1.52)	1.19 (0.80, 1.75)	1.32 (0.82, 2.12)	0.78 (0.56, 1.10)
Chan et al (23)	233	1.10 (0.70, 1.70)	—	—	—
Park et al (12)	4404	0.99 (0.89, 1.09)	0.94 (0.85, 1.04)	1.01 (0.91, 1.12)	1.01 (0.91, 1.11)
Neuhouser et al (13)	890	1.19 (0.84, 1.67)	0.98 (0.71, 1.35)	1.05 (0.75, 1.45)	1.17 (0.88, 1.32)
Current study	2727	0.96 (0.84, 1.09)	0.97 (0.85, 1.11)	0.98 (0.84, 1.14)	0.98 (0.85, 1.12)
Summary[2]		1.01 (0.94, 1.09)	0.96 (0.89, 1.03)	1.03 (0.95, 1.11)	1.01 (0.94, 1.08)
P for heterogeneity	0.621	0.827	0.358	0.368	

[1] Values are risk ratios for the highest compared with the lowest quantile of dietary fat intake; 95% CI in parentheses.
[2] Summary estimates based on a fixed-effects model.

Cancer Registry and the Regional Cancer Registries Amsterdam, East, and Limburg for providing data on cancer incidence.

The authors' responsibilities were as follows—FLC, TJK, PNA, and RCT: responsible for drafting the manuscript; TJK: responsible for the study concept and design and for the recruitment and follow-up of the Oxford cohort; PNA: responsible for the statistical analyses; KO and MUJ: responsible for the recruitment and follow-up of the Aarhus cohort; AT and NFJ: responsible for the recruitment and follow-up of the Copenhagen cohort; JL and SR: responsible for the recruitment and follow-up of the Heidelberg cohort; HB and TP: responsible for the recruitment and follow-up of the Potsdam cohort; AT, PL, and DT: responsible for the recruitment and follow-up of the Greek cohort; CS, DP, RT, and VK: responsible for the recruitment and follow-up of the 4 Italian cohorts; HBB-d-M and LAK: responsible for the recruitment and follow-up of the Bilthoven cohort; M-DC, EA, M-JS, NL, CAG, and JRQ: responsible for the recruitment and follow-up of the 5 Spanish cohorts; JM and EW: responsible for the recruitment and follow-up of the Malmö cohort; PS and GH: responsible for the recruitment and follow-up of the Umeå cohort; K-TK and SB: responsible for the recruitment and follow-up of the Cambridge cohort; and PF, NS, MJ, and ER: responsible for the coordination of the entire EPIC collaboration. All authors contributed to the interpretation of the results and the revision of the manuscript and approved the final manuscript. No conflicts of interest were declared.

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