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Lycopene intake and prostate cancer risk in men at high cardiovascular risk: a prospective cohort study

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Abstract

Background Intake of lycopene has been proposed as a protective dietary factor against prostate cancer development. Cardiovascular disease and prostate cancer share risk factors, which may modulate the effect of lycopene in high-risk individuals. This study aimed to examine the association between lycopene intake and prostate cancer risk in a Mediterranean population at high cardiovascular risk.

Methods A prospective cohort analysis was conducted among 2970 men aged 55–80 years at high cardiovascular risk from the PREDIMED trial, a multicenter study in Spain. Lycopene intake was assessed using repeated food frequency questionnaires. Prostate cancer cases were identified through medical records and death certificates. Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) across lycopene intake quartiles.

Results Over a mean follow-up of 5.8 years, 104 prostate cancer cases were identified. Participants in the highest quartile of lycopene intake had a significantly lower risk of prostate cancer than those in the lowest quartile (HR: 0.46; 95% CI: 0.23–0.95; p-trend = 0.035). A nonlinear dose–response relationship was observed, with a significant inverse association emerging at intakes above 4.9 mg/day (HR: 0.36; 95% CI: 0.13–0.98).

Conclusions Higher lycopene intake suggested a protective association with a lower incidence of prostate cancer in men at high cardiovascular risk. These findings support the role of lycopene-rich diets in prostate cancer prevention, which may be particularly relevant for high cardiovascular risk populations.

Trial registration ISRCTN registry: ISRCTN35739639 (PREDIMED trial).

Keywords Lycopene, Prostate cancer, Nutrition, Cancer prevention, Cardiovascular risk

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Background

Prostate cancer is the second most frequently diagnosed cancer in men worldwide and represents a significant public health challenge due to its impact on men's life expectancy and quality of life [1]. Although its mortality is lower compared to other cancers, prostate cancer globally accounts for more than 7% of cancer mortality among men, with 396,792 deaths reported in 2022 [1].

Established risk factors for prostate cancer include age, family history, African ethnicity, and certain genetic polymorphisms, while the influence of modifiable lifestyle factors such as diet is inconclusive [2]. Intake of lycopene, a carotenoid predominantly found in tomatoes and watermelon, has been associated with a reduced risk of prostate cancer in cohort and supplementation studies [3, 4], which is biologically plausible due to its antioxidant and anti-inflammatory properties [5]. Preclinical studies also suggest that lycopene promotes apoptosis in cancer cells, modulates gene expression and immune responses, inhibits the activity of sex steroid hormones, and affects mitochondrial function, which may contribute to its potential role in prostate cancer prevention [5–8]. In addition, lycopene might be particularly relevant for prostate protection because it has been reported to accumulate in testicular tissue [9].

Still, the modest inverse association between lycopene intake and prostate cancer risk found in epidemiological studies [3, 4] is limited by heterogeneity among studies and the fact that dietary exposure is usually examined at baseline and is not periodically reassessed using repeated dietary measurements during follow-up [4]. This may be critical because prostate cancer has a long preclinical phase before a formal diagnosis is made, which increases the possibility of reverse causation (i.e., individuals that went on to develop prostate cancer might have neglected their diet and had lower lycopene intake for this reason). Measurements of circulating lycopene concentrations improve exposure assessment [10], but they remain vulnerable to selection bias, and again, usually lack repeated measurements during follow-up.

Therefore, there is a need for high-quality prospective studies with repeated dietary assessments and more robust methodology [11]. Likewise, given the known interplay between cardiovascular and cancer pathways, we hypothesized that lycopene intake might enhance prostate cancer protection in subjects at high cardiovascular risk [12–14]. In the present study, we tested this hypothesis using comprehensive dietary data collected annually from high cardiovascular risk participants in the PREDIMED intervention trial [15]. This study is the first to investigate the association between lycopene intake and prostate cancer risk in a Mediterranean population at high cardiovascular risk.

Methods

Study design

This study is a secondary analysis using a cohort design within the frame of the PREDIMED (PREvención con DIeta MEDiterránea) trial (ISRCTN35739639). The PREDIMED trial was a large-scale, multicenter, parallel group, randomized controlled trial designed to evaluate the effects of the Mediterranean diet (MedDiet) on the prevention of cardiovascular disease [15]. Eligible participants were individuals with either type 2 diabetes or at least three major cardiovascular risk factors, including smoking, hypertension, dyslipidemia, overweight or obesity, and family history of premature coronary heart disease. The recruitment period was from June 2003 to June 2009, and participants were randomly assigned to one of three dietary interventions: MedDiet supplemented with extra-virgin olive oil, MedDiet supplemented with mixed nuts, or a control group who received advice to adhere to a low-fat diet. After the active intervention trial (December 2010), the register of incident cases of prostate cancer continued through review of medical records and consultation of the National Death Index. Cases were participants who developed prostate cancer during the active trial and an extended follow-up period until June 2012.

Study participants and data collection

From 3165 male participants, we excluded 94 due to implausible energy intake (<800 or >4000 kcal/day), 93 with baseline cancer diagnoses, three who did not attend any follow-up visits after baseline and had no follow-up information available through medical record review, and five who developed prostate cancer as a second malignancy. The final analysis included 2970 men (Additional file 1: Fig. S1).

Dietary assessment and lycopene intake

At baseline and annually during follow-up, trained personnel collected data on diet, medical history, and physical activity using validated questionnaires, including a 14-item MedDiet adherence screener [16], a 137-item food frequency questionnaire (FFQ) [17], a general medical questionnaire, and the Minnesota Leisure-Time Physical Activity Questionnaire [18].

Energy and nutrient intake were calculated from the FFQ by multiplying the frequency of consumption by the average portion size, using Spanish food composition tables [19]. Lycopene, as well as other carotenoids (β-carotene, α-carotene, β-cryptoxanthin, lutein, and zeaxanthin), intake was estimated using the FFQ data, with carotenoid content in foods obtained from the FoodData Central database of the United States Department of Agriculture [20]. Individual intakes were determined by multiplying the carotenoid content of each food item (mg/g) by the daily consumption of that item (g/day) and summing the values for all food items.

Lycopene, carotenoids (β-carotene, α-carotene, β-cryptoxanthin, lutein and zeaxanthin), and nutrient intakes were energy-adjusted using the residuals method [21]. Lycopene and other carotenoid intakes were analyzed from available FFQs over follow-up using weighted cumulative averages, calculated as the mean of current and previous years' intake. Total carotenoid intake was the sum of all individual carotenoid intakes.

Outcome

New prostate cancer diagnoses during the follow-up period were considered incident cases. The follow-up period was defined as the interval from study enrolment to the diagnosis of prostate cancer, the last follow-up contact, or death, whichever occurred first until June 2012. Incident cases were identified using two sources: a review of participants' medical records by a panel of physicians who were blinded to the intervention (i.e., The Clinical Event Committee of the PREDIMED trial) or death certificates (coded as C61 according to the International Classification of Diseases, 10th Revision) through an agreement of the University of Navarra with the Spanish National Institute of Statistics. The Clinical Event Committee, also blinded to the intervention and dietary information, adjudicated all outcomes based on predefined criteria. All prostate cancer cases were adenocarcinomas, confirmed through pathological examination of prostate biopsy specimens.

Statistical analyses

Participants were categorized into quartiles (Q) based on cumulative averages of energy-adjusted lycopene intake. Baseline characteristics of the participants across quartiles of energy-adjusted lycopene intake were compared using one-way analysis of variance for continuous variables and Pearson's chi-square tests for categorical variables.

For survival analyses, participants were categorized into three groups: Q1 (reference), Q2–Q3 combined, and Q4. This classification provided a clearer distinction between low and high intake than tertiles, while Q2–Q3 were merged into an intermediate category because neither was significantly associated with prostate cancer risk compared with Q1. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using time-dependent Cox proportional hazards models, stratified by recruitment center. The first model was adjusted for age (continuous) and intervention group (three categories). The second model was additionally adjusted for education level (primary, secondary, higher), body mass index (BMI, continuous), physical activity (quartiles, MET-min/day), total energy intake (quartiles, kcal/day), alcohol consumption (abstainers, ≤ 20 g/day, > 20 g/day), and smoking habit (never, former, current). The third model was further adjusted for weighted cumulative averages intake of fruit, vegetables, and dairy products (all in quartiles). Adjustments for baseline diabetes, hypertension, and statin use were tested but showed no effect on the models.

Kaplan–Meier survival curves were generated to illustrate prostate cancer-free survival according to the three lycopene intake groups. The proportional hazards assumption was tested using Schoenfeld residuals. Restricted cubic spline regression models were used to evaluate the dose–response relationship between cumulative lycopene intake and prostate cancer risk.

Stratified analyses were used to show the interactions between lycopene intake and both key risk factors and other carotenoids, using likelihood ratio tests for the statistical significance of interaction terms. Stratified analyses were performed using the median for age, alcohol consumption, physical activity, and carotenoids intake, while smoking status was grouped as never/former vs. current smokers, MedDiet adherence was categorized as low (≤ 8 points) or high (> 8 points) based on the 14-item screener, and cardiovascular risk factors (diabetes, hypertension, dyslipidemia) were classified as present or absent. Sensitivity analyses were performed by (1) excluding participants with < 2 years of follow-up; (2) removing extreme lycopene intake values (1st–99th and 5th–95th percentiles); and (3) including participants who developed prostate cancer as a second malignancy. Analyses were also conducted across tertiles of cumulative lycopene intake from the main dietary sources.

Missing values of educational level were considered a separate category ($n = 52$), and the only missing value of physical activity was imputed with the median; absent family cancer history data were coded as negative ($n = 205$; coding them as categorized separately did not change the results). Statistical analyses were performed using Stata software, version 15, with significance set at p-values < 0.05.

Results

Participants classified according to average intake of lycopene in quartiles had similar baseline characteristics (Table 1). Participants in the highest quartile reported greater consumption of fruits, vegetables, and total carotenoids compared to those in the lower quartiles ($p < 0.001$ for all comparisons). Moderate alcohol intake (≤ 20 g/day) was more common in the highest quartile, while higher intake (> 20 g/day) was less frequent. Hypertension was more prevalent in the lowest quartile. Tomato and tomato products were the main

Table 1 Baseline characteristics of the study participants by quartiles of cumulative lycopene intake

	Lycopene intake [a]			
	Q1 (*n* = 743)	**Q2 + Q3 (*n* = 1485)**	**Q4 (*n* = 742)**	***p* value***
Cumulative lycopene intake, mean (SD), mg/day	1.7 (0.6)	3.3 (0.5)	6.1 (1.9)	
Age, mean (SD), years	66.6 (6.5)	65.9 (6.4)	65.7 (6.8)	0.011
BMI, mean (SD), kg/m^2	29.1 (3.1)	29.3 (3.4)	29.5 (3.5)	0.050
Intervention group (%)				0.063
MedDiet with extra-virgin olive oil	223 (30.0)	508 (34.2)	266 (35.9)	
MedDiet with nuts	262 (35.3)	535 (36.0)	252 (34.0)	
Control diet	258 (34.7)	442 (29.8)	224 (30.2)	
Education (%)				0.421
Primary	475 (63.9)	981 (66.1)	489 (65.9)	
Secondary	169 (22.8)	311 (20.9)	149 (20.1)	
Higher	89 (12.0)	161 (10.8)	94 (12.7)	
Missing	10 (1.4)	32 (2.2)	10 (1.4)	
Physical activity, mean (SD), METs-min/day	311.4 (280.3)	316.5 (298.7)	289.9 (288.2)	0.121
Family history of cancer (%)	305 (41.1)	669 (45.1)	345 (46.5)	0.084
Smoking, (%)				0.400
Never	197 (26.5)	388 (26.1)	198 (26.7)	
Former	303 (40.8)	665 (44.8)	320 (43.1)	
Current	243 (32.7)	432 (29.1)	224 (30.2)	
Alcohol consumption, (%)				0.002
Abstainers	119 (16.0)	230 (15.5)	129 (17.4)	
> 0 to ≤ 20 g/day	375 (50.5)	787 (53.0)	432 (58.2)	
> 20 g/d	249 (33.5)	468 (31.5)	181 (24.4)	
Total energy intake, mean (SD), kcal/day	2423.7 (557.9)	2390.5 (559.6)	2435.7 (573.8)	0.152
Total cumulative carotenoid intake, mean (SD), mg/day [a]	10.3 (3.4)	13.4 (3.4)	17.5 (4.2)	< 0.001
Cumulative fruit consumption, mean (SD), g/day [a b]	226.0 (120.7)	241.3 (107.4)	277.5 (125.6)	< 0.001
Cumulative vegetable consumption, mean (SD), g/day [a b]	215.2 (79.7)	253.9 (81.5)	280.4 (100.2)	< 0.001
Cumulative dairy products consumption, mean (SD), g/day [a]	336.3 (189.5)	334.1 (166.6)	347.0 (164.4)	0.237
Diabetes, (%)	409 (55.1)	788 (53.1)	433 (58.4)	0.061
Hypertension, (%)	595 (80.1)	1164 (78.4)	550 (74.1)	0.016
Dyslipidemia, (%)	486 (65.4)	994 (66.9)	492 (66.3)	0.771
Family history of CHD, (%)	114 (15.3)	249 (16.8)	145 (19.5)	0.088

Q, quartile; *BMI*, body mass index; *SD*, standard deviation; *MedDiet*, Mediterranean diet; *CHD*, coronary heart disease

* *p* value for comparisons across quartiles of lycopene intake. Data normality was assessed using the Kolmogorov–Smirnov test. Differences between groups were analyzed using one-way ANOVA for continuous variables and chi-square tests for categorical variables

[a] Adjusted for total energy intake

[b] Major sources of lycopene (tomato, watermelon, and grapefruit) excluded

lycopene sources in this population (69.6%: tomatoes 55.3%, gazpacho 9.6%, tomato sauce 4.7%), followed by watermelon (30.1%) (Additional file 1: Fig. S2).

Over the total follow-up time (mean follow-up 5.8 years), 104 cases of prostate cancer were documented. Participants in the highest quartile of lycopene intake displayed a significant 54% lower risk of prostate cancer compared to the lowest quartile (HR: 0.46; 95% CI: 0.23–0.95, *p*-trend = 0.035) in the fully adjusted model (Table 2, Fig. 1).

Restricted cubic spline analyses suggested a non-linear relationship between lycopene intake and prostate cancer risk (*P* non-linearity = 0.0307). A significant risk reduction was apparent at lycopene intakes above 4.9 mg/day, corresponding to a 64% decrease in prostate cancer risk (HR: 0.36; 95% CI: 0.13–0.98) (Fig. 2).

Stratified analyses did not reveal any statistically significant interactions between lycopene intake and prostate cancer risk across subgroups (Fig. 3; Additional file 1: Tables S1–S3). The inverse association between lycopene

Table 2 Cox hazard ratios for prostate cancer by quartiles of cumulative lycopene intake ($N = 2970$)

	Quartiles of cumulative lycopene intake			
	Q1	**Q2 + Q3**	**Q4**	***p*-trend**
Incidence of prostate cancer	32	57	15	
No. of person-years	4264	8673	4222	
Intervention group and age-adjusted HR (95% CI) [a]	1.00	0.80 (0.51 to 1.26)	0.45 (0.23 to 0.88)	0.020
Multivariable-adjusted HR (95% CI) [b]	1.00	0.81 (0.52 to 1.28)	0.45 (0.23 to 0.89)	0.021
Multivariable-adjusted HR (95% CI) [c]	1.00	0.78 (0.49 to 1.25)	0.46 (0.23 to 0.95)	0.035

Q, quartile; *HR*, hazard ratio; *CI*, confidence interval; *MedDiet*, Mediterranean diet

All the estimations are stratified by recruitment center

Lycopene intake adjusted for total energy intake

[a] Model 1: Adjusted for age (continuous) and intervention group (MedDiet + extra virgin olive oil, MedDiet + nuts, control diet)

[b] Model 2: Further adjusted for education level (primary, secondary, higher), body mass index (continuous), physical activity (quartiles), total energy intake (quartiles), alcohol consumption (abstainers, ≤ 20 g/day, > 20 g/day), smoking habit (never, former, current), and family history of cancer

[c] Model 3: Additionally adjusted for cumulative consumption of fruits, vegetables, and dairy products (all in quartiles)

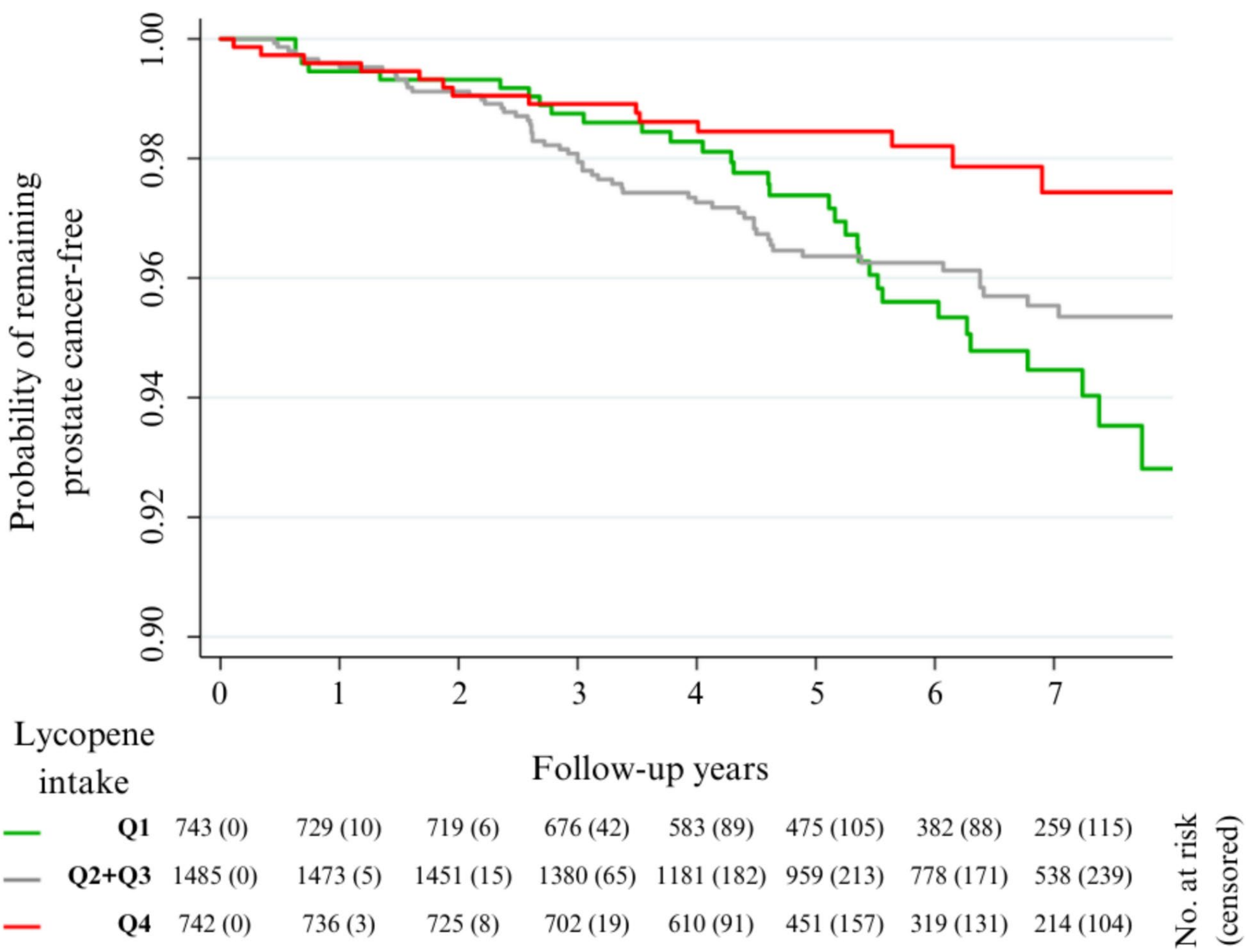

Fig. 1 Kaplan–Meier curves for prostate cancer incidence across quartiles of cumulative lycopene intake

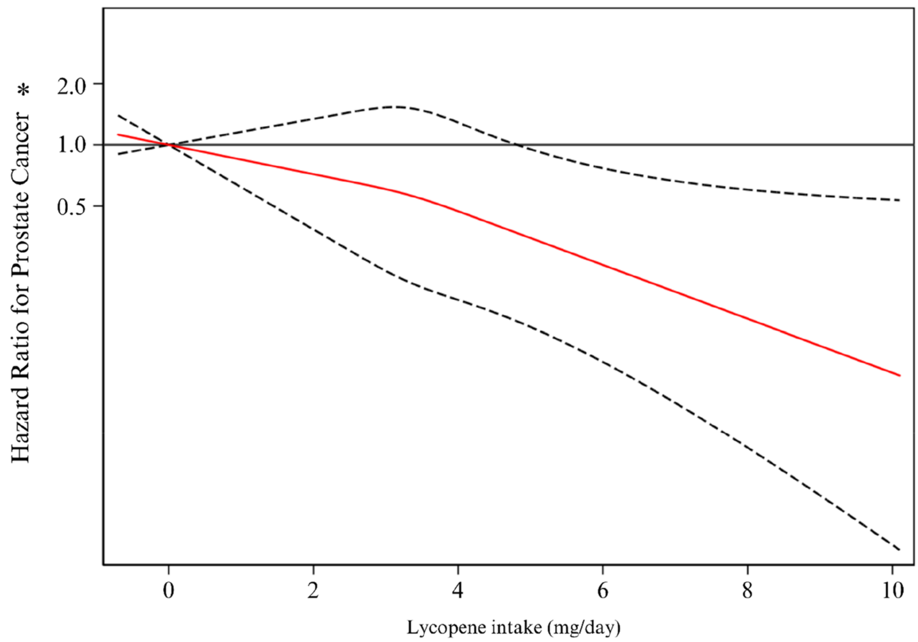

Fig. 2 Association between lycopene intake and prostate cancer risk: Restricted cubic spline analysis. Participants consuming 4.9 mg of lycopene per day show a 64% reduced risk of prostate cancer (HR = 0.36; 95% CI: 0.13–0.98). Non-linear association: $p = 0.0307$. * Hazard ratio adjusted for age, intervention group, education level, body mass index, physical activity, total energy intake, alcohol consumption, smoking habit, family history of cancer, cumulative fruit consumption, cumulative vegetable consumption, and cumulative dairy products consumption, and stratified by recruitment center. Knots were placed at the 25th, 50th, and 75th percentiles of lycopene intake (corresponding to 2.5, 3.3, and 4.3 mg/day, respectively)

intake and prostate cancer risk remained robust across multiple sensitivity analyses, including exclusions based on follow-up duration, extreme lycopene intake values, and the presence of secondary cancers (Additional file 1: Table S4), and similar trends were observed when considering lycopene intake from different dietary sources (Additional file 1: Table S5).

Discussion

In this analysis of 2970 participants from the PREDIMED trial considered as a prospective cohort, higher lycopene intake was associated with a 54% reduction in prostate cancer risk when comparing the highest to the lowest quartiles. The association between lycopene intake and prostate cancer risk was nonlinear, with significant protective associations emerging at intake levels exceeding 4.9 mg/day (equivalent to approximately 175 g of tomato or 110 g of watermelon).

These results provide new insights into the previously controversial association between lycopene intake and prostate cancer risk [11, 22], aligning with recent meta-analyses that support a protective association [3, 4]. Similar associations have been reported in other cohorts, with risk reductions ranging from 9 to 53% [23–27]; however, other studies found no association [28–30], and a single study from Japan reported a detrimental relation [31].

Mixed findings from prior research on the association of lycopene's intake with prostate cancer can be explained by several key limitations. Most studies relied on single measurements of lycopene intake [27–32], missing potential dietary changes over time, and used self-reported dietary questionnaires [23–31], which often lead to inaccurate reporting of food intake [33]. Also, several studies included men under 50 years of age [23–27, 30, 31], when there is a low risk of prostate cancer, which may limit the ability to detect meaningful associations. These studies also covered different geographic regions, mainly North America [23–28, 30], with few from Europe and Asia [29, 31, 32], where genetic backgrounds and lifestyle factors differ. Reported studies of lycopene intake varied considerably; in some studies, the highest intake groups consumed less than 4.9 mg/day [29, 30], while others started with relatively high baseline intake levels [28], making it difficult to observe additional benefits. Furthermore, most studies focused on processed food sources of lycopene [25, 27, 28, 30]; in contrast, our study primarily evaluated fresh food sources, particularly raw or cooked tomatoes, which are present in traditional recipes of the MedDiet. The Mediterranean context is distinctive, characterized by fresh rather than processed sources of lycopene, traditional cooking methods, the use of olive oil, and a broader dietary pattern, which may

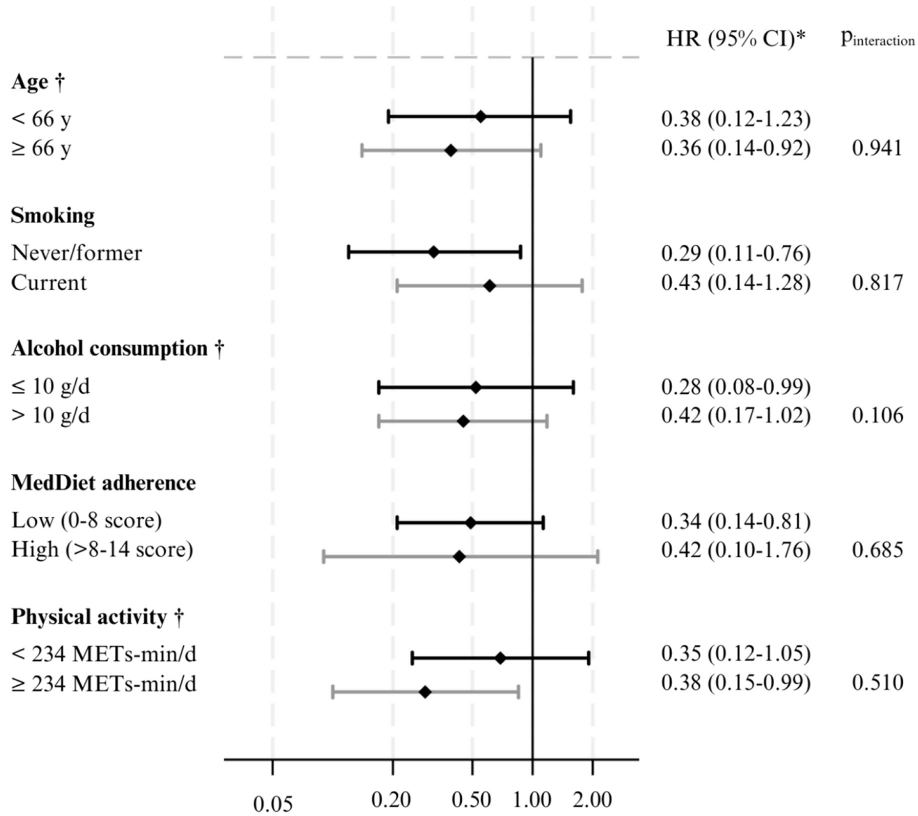

Fig. 3 Stratified analysis of prostate cancer according to quartiles of cumulative lycopene intake (Q4 vs. Q1). Q = quartile; HR = hazard ratio; CI = confidence interval; MedDiet = Mediterranean diet. * HR adjusted for age, intervention group, education level, body mass index, physical activity, total energy intake, alcohol consumption, smoking habit, family history of cancer, cumulative fruit consumption, cumulative vegetable consumption, and cumulative dairy products consumption, and stratified by recruitment center. † Categorized above and below the median

modify lycopene's bioavailability [34] and influence prostate cancer risk.

Preclinical evidence on potential anticancer mechanisms of lycopene supports the findings of observational research [5–8]. However, evidence from randomized controlled trials specifically conducted in a preventive setting, either on prostate cancer incidence or on biomarker changes in men without cancer, is scarce, with inherent methodological limitations that may contribute to inconsistent results [35, 36]. These trials are mainly constrained by short follow-up, small sample sizes, and restriction to populations with conditions strongly related to prostate cancer development (e.g., high-grade prostatic intraepithelial neoplasia), thus precluding firm conclusions about the preventive effect of lycopene in broader populations.

Our study has strengths, such as the fact that dietary intake was assessed using annual measurements with a validated FFQ administered face-to-face by trained dietitians, allowing cumulative intake calculations, which enhances the validity of self-reported data and is the most accurate approach to reduce measurement error in nutritional epidemiology [37]. Additionally, all other measurements followed a higher level of methodological rigor compared to typical cohort studies, as this analysis was nested within a clinical trial, ensuring greater control over data collection and quality. Indeed, after adjusting for multiple potential confounders, our estimates remained largely unchanged, reflecting minimal residual confounding.

We also acknowledge limitations. First, prostate cancer was a secondary outcome in the PREDIMED trial. As in any observational study and despite comprehensive adjustment for confounders, residual confounding cannot be excluded. This is particularly relevant because men with higher lycopene intake are likely to engage in overall healthier behaviors, which may not be fully accounted for in the multivariable models. The ~ 6-year follow-up may not capture longer latency. The relatively small number of prostate cancer cases limited the statistical power, particularly in stratified analyses and prevented analysis by cancer subtypes. Our focus on total cancer incidence, without consideration of cancer severity or staging, provides an incomplete picture of lycopene's potential protective effects. Lastly, since our study population consisted of older adults at high cardiovascular risk, the findings may not be generalizable to younger or healthier populations, where dietary patterns, lifestyle factors, lycopene intake, and prostate cancer incidence may differ.

Conclusions

In a Mediterranean population of older adults at high cardiovascular risk, higher lycopene intake was associated with a reduction in prostate cancer risk. These findings, although based on limited case numbers and an observational design, suggest a potential protective role of lycopene as a dietary component for individuals at high cardiovascular risk. Larger-scale investigations are needed to evaluate the associations within specific population subgroups. Additionally, further experimental research is warranted to elucidate the underlying mechanisms by which lycopene might protect against prostate cancer, and to better understand how the Mediterranean context and cardiovascular status may modify this association.

Abbreviations

BMI	Body mass index
CI	Confidence intervals
FFQ	Food frequency questionnaire
HR	Hazard ratio
MedDiet	Mediterranean diet
Q	Quartiles
SD	Standard deviation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04440-0.

Additional file 1: Fig. S1. Flow chart of the study population. Fig. S2. Major food contributors to total lycopene intake in the study population. Table S1. Stratified analysis of prostate cancer according to quartiles of cumulative lycopene intake. Table S2. Stratified analysis of prostate cancer according to quartiles of cumulative lycopene intake across cardiovascular risk factors. Table S3. Interactions between lycopene and the other carotenoids. Table S4. Sensibility analysis. Table S5. Cox hazard ratios for prostate cancer across tertiles of cumulative lycopene intake from different sources.

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Authors' contributions

Conceptualization, RLS, SCB, MC, CAR, ER, and RMLR; methodology, RLS, SCB, CAR, ER, and RMLR; formal analysis, RLS, SCB, and CDV; validation, RE, MAMG, JSS, MF1, and ER; resources, XP, MAMG, JVS, JSS, JL, EGG, MF2, LSM, ER, and RE; data curation, XP, MAMG, JVS, JSS, JL, EGG, MF2, LSM, NB, ER, and RE; writing—original draft preparation, RLS, SCB, CDV, MC, ER, and RMLR; writing—review and editing, MAMG, JSS, MF1, MF2, EGG, JL, JVS, LSM, XP, JBRS, NB, ET, and RE; visualization, RLS and CDV; supervision, ER and RMLR; project administration, ER and RMLR.; funding acquisition, MAMG, JSS, ER, XP, MF1, and RE. All authors have read and agreed to the published version of the manuscript.

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The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Data availability

The dataset generated and/or analyzed during the current study are not publicly available due the lack of authorization from PREDIMED participants. Requestors wishing to access the PREDIMED trial data used in this study can make a request to the corresponding author and it will then be passed to members of the PREDIMED Steering Committee (predimed-steering-committe@googlegroups.com) for deliberating.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of the Hospital Clínic of Barcelona (reference ID 1244; approval date: July 16, 2002), and by the Institutional Review Boards of the participating centers (Universities of Barcelona, Valencia, Rovira i Virgili, Málaga, and Las Palmas; Municipal Institute for Medical Research; Primary Care Divisions of Barcelona and Sevilla; Institute of Research in Health Sciences at Palma de Mallorca; Hospital Txagorritxu of Vitoria; and University Hospital of Bellvitge). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

RMLR reported personal fees from Cerveceros de España, UNIDECO, Adventia, Wine in Moderation, and Ecoveritas S.A., all outside the submitted work. ER reported grants, personal fees, non-financial support, and other support from the California Walnut Commission during the conduct of the study; and grants, personal fees, non-financial support, and other support from Alexion, all outside the submitted work. RE reported grants from the Fundación Dieta Mediterránea and Fundación Cerveza y Salud, as well as personal fees for lectures from Brewers of Europe, Fundación Cerveza y Salud, Instituto Cervantes (Albuquerque, Milan, Tokyo), Pernod Ricard, and the Wine and Culinary International Forum. He also received non-financial support for the organization of a national nutrition congress and for feeding trials with products from Grand Fountain and Uriach Laboratories (Spain). JSS reported receiving consulting fees or travel expenses from Instituto Danone Spain; non-financial support from Hojiblanca, Patrimonio Comunal Olivarero, the Almond Board of California, Pistachio Growers and Borges S.A.; serving on the board of, and receiving grant support through his institution from, the International Nut and Dried Fruit Foundation; and serving on the Scientific Board of the Danone Institute International (nonpayed member). The remaining authors declared no competing interests.

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