Published in final edited form as:

Eur J Cancer Prev. 2019 May ; 28(3): 212–219. doi:10.1097/CEJ.0000000000000438.

Body mass index and prostate cancer risk in the Carotene and Retinol Efficacy Trial

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Abstract

Objective—To investigate the association between body mass index (BMI, kg/m²) and prostate cancer risk. BMI is a modifiable lifestyle factor and may provide a unique opportunity for primary prevention of prostate cancer if a causal association exists.

Methods—Data from 11,886 men from the Carotene and Retinol Efficacy Trial (CARET, 1985–1996 with active follow-up through 2005) comprising current and former heavy smokers were analyzed. CARET was a multicenter randomized, double-blind placebo-controlled chemoprevention trial testing daily supplementation of 30 mg β -carotene + 25,000 IU retinyl palmitate for primary prevention of lung cancer. Prostate cancer was a secondary outcome. Non-aggressive disease was defined as Gleason <7 and stage I/II. Aggressive disease was primarily defined as Gleason 7 or stage III/IV, and secondly by excluding Gleason 3+4 from the first definition. BMI was calculated from measured weight and height. Cox proportional hazards regression models were used to estimate hazard ratios with 95% confidence intervals for cancer incidence between BMI-categories.

Results—During follow-up, 883 men were diagnosed with prostate cancer. In analysis of aggressive disease when Gleason 3+4 was excluded, men with a BMI ≥ 35 kg/m² had an increased rate of prostate cancer (HR: 1.80, 95%CI: 1.04–3.11, $P_{\text{trend}}=0.04$) compared to men with BMI 18–24.9 kg/m². No other differences were seen in risk estimates for overall, non-aggressive or aggressive prostate cancer including all Gleason 7 cases, between BMI-categories.

Conclusions—Our results show an association between having a BMI ≥ 35 kg/m² and an increased risk of aggressive prostate cancer (not including Gleason 3+4 tumors) but do not support an association between BMI and risk of overall, aggressive disease including all Gleason 7, or non-aggressive prostate cancer within a population of current and former heavy smokers.

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Conflict of interest
None declared.

Keywords

Body mass index; Epidemiology; Prostate cancer risk; Prostate neoplasms

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Introduction

Prostate cancer is the second most common cancer among men globally (Ferlay et al., 2013) and the most common cancer among men in the US today (American Cancer Society, 2014). While incidence rates have increased during previous decades, partly due to the implementation of prostate specific antigen (PSA) testing, they have stabilized on a high level over the past 10 years (Center et al., 2012). During the same time period, the prevalence of overweight and obesity has also increased worldwide (WHO, 2014).

The global prevalence of overweight and obesity among men has been estimated at 61% with even higher estimates in the United States where 72% of adult men were overweight or obese in 2014 (WHO, 2014). Both overweight and obesity, often measured as body mass index (BMI, kg/m²), and prostate cancer affect substantial proportions of the male population today. Body weight is related to metabolic and hormonal pathways, that may have an influence on tumorigenesis, and fat mass that plays an important role in the metabolism of sex hormones (Hsing et al., 2007). Prostate cancer is hormone dependent and likely linked to anthropometric factors which may affect, for example, pathways of insulin and insulin-like growth factors (IGFs), sex hormones and adipokine signaling (Roberts et al., 2010). The potential impact of overweight and obesity on prostate cancer is therefore important to clarify.

Results from two previous meta-analyses have shown weak (MacInnis and English, 2006) and non-statistically significant (Renehan et al., 2008) direct associations between BMI and overall risk of prostate cancer. The inconsistent and weak associations seen previously could possibly be explained by a non-linear biological association between BMI and overall prostate cancer risk (Bhaskaran et al., 2014). However, heterogeneity of the disease may be another explanation. A meta-analysis by Discacciati et al. (2012) showed an inverse relationship between BMI and localized disease and a positive association between BMI and advanced prostate cancer. A more recent study also showed a decreased risk of low-grade prostate cancer and an increased risk of high-grade prostate cancer among obese men (Vidal et al., 2014). While the association between BMI and prostate cancer risk appears complex, overweight and obesity prevention may provide a unique opportunity for primary prevention should a causal association be present.

The aim of the proposed study is to further investigate the association between BMI and risk of overall, aggressive and non-aggressive prostate cancer by examining the association between baseline BMI and subsequent prostate cancer risk among men in the Carotene and Retinol Efficacy Trial (CARET).

Methods

Study population

CARET is a multicenter randomized, double-blind placebo-controlled chemoprevention trial and has previously been described in detail (Thornquist et al., 1993). Briefly, the trial tested whether daily supplementation with 30 mg β -carotene and 25,000 IU retinyl palmitate would reduce the risk of lung cancer among 18,314 heavy smokers, former smokers, and asbestos-exposed workers.

Beginning in 1985, participants were recruited from six centers across the United States. Eligible for participation were both men and women aged 50–69 years who were current or former smokers (within the previous six years) with a history of at least 20 pack-years of cigarette smoking ($n=14,254$, 55.9% were male), and men aged 45–69 years ($n=4,060$) who were current or former smokers (within the previous 15 years) with evidence of extensive occupational exposure to asbestos. CARET participants were recruited from health insurance rolls, managed care organizations, labor unions, workmen's compensation programs and via occupational physicians. Recruitment ended in 1994. Participants attended yearly clinic visits and completed follow-up telephone calls every four months throughout the intervention period which was stopped 21 months early in January 1996 when interim analysis found evidence that the supplements increased the risk of lung cancer and total mortality in this high-risk population (Omenn et al., 1996). Although the CARET intervention ended in 1996, active follow-up continued until 2005, including the collection of endpoint data for 94% of all randomized participants. This report is, however, restricted to male participants only.

The Institutional Review Board of the Fred Hutchinson Cancer Research Center and each of the five other participating institutions approved all procedures for the study. Participants provided written informed consent at recruitment.

Exclusion criteria

All male CARET participants with the exclusion of those with a previous prostate cancer diagnosis before baseline ($n=25$) were included in the present study. Additional exclusions were made based on the exposure and men with missing information on BMI ($n=67$), or a BMI <18 kg/m² ($n=45$) or >60 kg/m² ($n=2$) were excluded as outliers. In total 11,886 men were included in final analysis. Additional self-reported information of physical activity was available from 6,594 (55.5%) of participants.

Exposure assessment

Measured weight and height from each participant's first CARET clinic visit was used to calculate BMI (kg/m²). Study participants were divided into categories of BMI 18–24.9 kg/m², 25–29.9 kg/m², 30–34.9 kg/m² and ≥ 35 kg/m² (Expert panel on the Identification, evaluation and treatment of overweight in adults, 1998). Information regarding age, sex, race/ethnicity, and general health history were also collected at the first clinic visit. Detailed data on smoking were collected at each CARET contact. This information consisted of

current smoking status and smoking history, including age at smoking initiation, total years smoked and average number of cigarettes smoked per day.

Dietary intake over the previous year was assessed at baseline and every two years using a self-administered food frequency questionnaire (FFQ). For this study, the baseline assessment was used when available; if the baseline FFQ was missing, the earliest available assessment was selected. Any reported energy intake <800 kcal/day or >5,000 kcal/day were considered unreliable and therefore not included in analysis. Family history of prostate cancer was self-reported and defined as having at least one first degree relative with prostate cancer. Participants also self-reported level of education.

Physical activity was assessed in 1996–1997 using a self-administered physical activity questionnaire previously described by Alfano et al. (2004). In brief, participants were asked to report their average daily hours within five activity categories; (1) sleeping, (2) sitting, and (3) light, (4) moderate and (5) vigorous physical activity. Time spent on weekdays and weekend days were reported separately and participants estimated their activity to the closest 0.25 hour. Total weekly hours within each activity category were summarized by multiplying reported weekday hours by 5 and adding reported weekend hours multiplied by 2. In the present study, weekly hours reported spent in moderate and vigorous activities were summarized into a variable of moderate-to-vigorous physical activity (MVPA).

Outcome assessment - Prostate Cancer Cases

At each CARET annual visit as well as during the quarterly follow-up telephone calls, participants were asked to report if they had been diagnosed with any new cancers. All endpoints, including prostate cancer, were verified by the CARET Endpoints committee. Prostate cancer was a secondary end-point of the trial. As part of this study, an augmented review of medical records and Surveillance Epidemiology and End Results (SEER) cancer registry files was made to obtain data on Gleason score and stage of disease at diagnosis. Medical records, including pathology reports, surgical reports, hospital records, and scan and radiography reports were obtained. Gleason score information was abstracted from the pathology reports of the diagnosing pathologist. Approximately 92% of the prostate cancer cases were adjudicated and confirmed. Aggressive prostate cancer was defined in two ways: primarily as Gleason score ≥ 7 and/or stage III/IV (distant) at diagnosis as in prior studies on prostate cancer in CARET (Neuhouser ML, 2007) and additionally by excluding men with a Gleason score of 3+4 from the previous definition. This was done as large differences on prostate cancer mortality has been seen for men with Gleason score 7 depending on if the tumor was diagnosed as a 3+4 or 4+3 Gleason score (Stark et al., 2009). Men with a Gleason score of 4+3 had a more than doubled rate of mortality compared to men with a score of 3+4. Non-aggressive disease was defined as Gleason score <7 and stage I/II at diagnosis. In total, 196 men did not have enough information, i.e. had missing data for Gleason score or stage, to classify disease. Widespread use PSA-screening was not in use when CARET began and information on serum PSA were therefore not available.

Statistical analysis

Distributions and means of characteristics were studied across categories of BMI. Associations were tested by using one-way ANOVA for continuous variables and χ^2 test for categorical variables. The Kaplan-Meier method was used to analyze unadjusted incidence rates for overall prostate cancer risk and risk of non-aggressive and aggressive disease, respectively.

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for prostate cancer incidence between different BMI-categories. Time from inclusion to CARET to cancer diagnosis, death or censoring at end of follow-up, whichever came first, was used as the underlying time scale. BMI 18–24.9 kg/m² was used as the reference category. The proportional hazards assumption was tested using Schoenfeld's residuals.

All Cox models were adjusted for age at enrollment as a continuous variable. A priori adjustments for additional specific CARET confounders were made for; intervention arm, study center, race/ethnicity and smoking at baseline (pack-years, continuous variable). The association between additional covariates (family history of prostate cancer, total energy intake, and education level) and the outcome was tested for by including covariates, one by one, in Cox proportional hazards models. Additional adjustments in multivariable models were thereafter made for family history of prostate cancer and total energy intake (kcal/day, continuous). Within the sub-group of study participants with data on physical activity (n=6,594), Cox models were additionally adjusted for MVPA (hours/wk, continuous). Men diagnosed with prostate cancer during follow-up prior to the physical activity assessment (n=173) were excluded from these models. Further, in additional sensitivity analysis, all models were run including only men in the sub-group with information on physical activity. To test for linear trends, the median value of each BMI-category was used as a numerical variable in the Cox-models. In order to examine whether pre-clinical symptoms of cancer might have affected BMI at baseline, leading to biased results, we excluded the first two years of follow-up from all analysis in sensitivity analysis.

P-values were considered significant if <0.05. All statistical analyses were performed using STATA 13.0 (Stata Corporation, College Station, TX, USA).

Results

Characteristics of study participants are presented in Table 1. Overall, 23.0 % of men had a BMI 18–24.9 kg/m², 47.9 % a BMI of 25–29.9 kg/m² and 29.1 % of men had a BMI 30 kg/m² at baseline. Significant differences between men in the different BMI-categories were observed for: age at baseline, smoking, total energy intake, moderate-to-vigorous physical activity, race/ethnicity, education level and study center. During the follow up, 883 (7.4 %) men were diagnosed with prostate cancer. Of these, 353 (40.0 %) were classified as aggressive disease when all Gleason 7 were included, 202 (22.9 %) as aggressive when Gleason 3+4 was excluded from the definition, and 334 (37.8%) were classified as non-aggressive disease. The mean age at diagnosis was 67.5 (±5.9) years. The mean follow-up time for all men was 11.4 (±3.9) years. The average follow-up times to diagnosis for all

prostate cancer cases, men diagnosed with aggressive, aggressive excluding Gleason 3+4, and non-aggressive disease were 7.2 (± 3.9), 6.8 (± 3.7), 6.5 (± 3.9), and 6.7 (± 3.9) years, respectively. The follow-up times differed significantly between all men and men diagnosed with prostate cancer during the follow-up ($P < 0.0001$) but not between men diagnosed with aggressive and non-aggressive disease ($P = 0.78$ and $P = 0.51$).

Incidence rates for overall, aggressive, aggressive excluding Gleason 3+4, and non-aggressive prostate cancer for all men in the cohort were: 6.5, 2.5, 1.5 and 2.5 per 1000 person-years. Kaplan-Meier curves of unadjusted incidence rates for overall prostate cancer risk and risk of non-aggressive and aggressive prostate cancer, respectively are shown in Figure 1.

Results from age adjusted and multivariable adjusted Cox proportional hazards models are presented in Table 2. No statistically significant differences were seen in incidence rates between the BMI-categories for overall, aggressive or non-aggressive prostate cancer. In analysis of aggressive prostate cancer when Gleason 3+4 was not included in the definition, a significantly increased incidence rate of disease was seen among men with BMI ≥ 35 kg/m² compared to the reference group with a BMI of 18–24.9 in both age-adjusted (HR: 1.78, 95%CI: 1.05–3.01), and multivariable adjusted models (HR: 1.77, 95%CI: 1.04–3.00 and HR: 1.80, 95%CI: 1.04–3.11).

Additional adjustment for physical activity restricted to only men with complete information from the physical activity questionnaire changed estimates slightly but no statistically significant results were seen (data not shown). However, point estimates for aggressive disease not including Gleason 3+4 in the definition still indicate an increased incidence rate, although not statistically significant, among men in the highest BMI-category (HR: 2.17, 95%CI: 0.84–5.57, $P_{\text{trend}} = 0.17$). Further, in sensitivity analysis where all models were restricted to only the sub-group with available information on physical activity, BMI estimates were more or less unchanged (data not shown). Results were also similar in sensitivity analysis where the first two years of follow-up had been excluded (data not shown). Additionally, a linear trend was seen across BMI-categories for aggressive disease excluding Gleason 3+4 ($P_{\text{trend}} = 0.04$). Analysis did not indicate any linear trends across BMI-categories for overall, aggressive disease when including all Gleason 7, or non-aggressive prostate cancer.

Discussion

Our results showed an increased incidence rate of aggressive prostate cancer among men in CARET with a baseline BMI ≥ 35 kg/m² compared to men with a BMI of 18–24.9 when Gleason score 3+4 was not included in the definition of aggressive disease. We did not demonstrate any associations between baseline BMI and risk of overall, aggressive (including all Gleason 7) or non-aggressive prostate cancer. The results are similar to those of previous meta-analyses that have shown only modest or non-significant associations between BMI and the risk of overall and less-aggressive prostate cancer (MacInnis and English, 2006; Renehan et al., 2008). While Renehan et al. (2008), did not distinguish between localized and advanced disease in their systematic overview and meta-analysis,

MacInnis and English (2006) did. Our results when not including men with Gleason 3+4 in the definition of aggressive disease are in line with the significantly increased risk of advanced disease shown with increasing BMI (RR: 1.12, 95%CI: 1.01–1.23 per 5 kg/m² increase in BMI) presented by MacInnis and English (2006). Additionally, an increased risk of advanced prostate cancer with increasing BMI was also seen in a meta-analysis by Discacciati et al. (2012) (RR: 1.08, 95%CI: 1.04–1.12). In contrast to our findings, Discacciati et al. (2012) also showed a significantly decreased risk of localized disease with increasing BMI, which is not supported in the present study. Our results further support the conclusion made in a report from the World Cancer Research Fund International stating that results from published studies constituted strong evidence for an increased risk of advanced prostate cancer among overweight and obese men (World Cancer Research Fund International, 2014).

In this study, aggressive disease was defined in two different ways; firstly, as Gleason score 7 and/or stage III/IV (distant) at diagnosis, and secondly by additionally excluding men with a Gleason score of 3+4 from the first definition. The first definition has been used in prior studies on prostate cancer in CARET while the second definition was included to take into account previous research indicating that cancer mortality may differ between men with a Gleason 3+4=7 compared to men with a Gleason 4+3=7. In Gleason 4+3 tumors, the prevalent pattern is that of poorly formed, fused and cribriform glands, whereas the most prevalent pattern in 3+4 tumors comprise well formed, individual glands. Studies have shown that a Gleason score 4+3 demonstrates both worse pathological stage and biochemical recurrence rates than Gleason 3+4 (Gordetsky2016). Gleason 4+3 cancers have also been associated with a more than doubled to three-fold risk of lethal prostate cancer compared to Gleason 3+4 cancers (Stark et al., 2009). Our results indicate that there might be a difference between Gleason 7 tumors depending on if pattern 3 or 4 is more prevalent and that a distinction of the different Gleason 7 categories may be important.

Adiposity affects both metabolic and hormonal pathways that may have an influence on tumorigenesis and the differentiation of tumor cells. Obesity can lead to altered levels of adipokines, with increased levels of leptin and decreased levels of adiponectin, which have been associated with tumor development (Roberts et al., 2010). Increased adiposity has also been associated with hyperinsulinemia that, through reduction of IGF-binding proteins, leads to increased serum levels of IGF-1 that may promote tumor development (Renehan et al., 2006). An explanation to differences in risk estimates between different BMI-categories and different prostate cancer subtypes may also be an effect of BMI on PSA-levels. Higher BMI has been consistently associated with decreased levels of serum PSA (Baillargeon et al., 2005; Banez et al., 2007), potentially leading to later detection among men in today's era of frequent PSA-testing. Nevertheless, a decreased risk of low-grade prostate cancer and an increased risk of high-grade prostate cancer have also been shown among obese men independent of PSA-level (Vidal et al., 2014).

There are several strengths and weaknesses of the present study that need to be acknowledged. The strengths include standardized data collection and excellent follow-up of participants during and after the trial with 92% of prostate cancer cases being adjudicated and confirmed. Further, the measured weight and height to compute BMI is also a strength.

Nevertheless, BMI is nonspecific and does not differentiate between fat free mass and fat mass and individuals with a high muscle mass and low fat mass may therefore be incorrectly classified as overweight and obese (Prentice and Jebb, 2001; Okorodudu et al., 2010). Additionally, BMI does not consider distribution and therefore cannot differentiate between more metabolically active abdominal fat and other fat (Schwenzer et al., 2010). Fat mass has been shown to play an important role in hormone metabolism that might influence tumorigenesis (Hsing et al., 2007). However, the limitations of BMI as a proxy for body composition are inherent to all studies using BMI if other measures of body composition are not available. Another limitation to this present study is the fact that CARET began before widespread use of PSA-screening was implemented and information on serum PSA was not available to distinguish between screen- and clinically-detected cases. The low sample size in analysis of low- and high-grade prostate cancer, respectively, due to missing data on Gleason score and stage, which creates uncertainty in estimates, is also a limitation. Nevertheless, information on tumor stage is likely missing at random.

Further, although detailed assessment of several lifestyle factors enabled controlling for confounders, residual or unmeasured confounding cannot be ruled out. The collection of information on physical activity on average about five years post baseline is another limitation. In addition, physical activity was self-reported and there is no assurance that even if a PA measure was available on the entire cohort, that it would be an assessment free of bias and measurement error. Nevertheless, although physical activity levels are generally stable in this age group (Smith et al., 2015) and the collected data therefore is a reasonable approximation of usual PA also at baseline, men responding to the physical activity questionnaire are conditioned on being alive at the time of response. Therefore, selection bias cannot be ruled out.

Since the CARET cohort is composed of current or former heavy smokers the generalizability of results to the general population may be limited. Additionally, the limited follow-up time restricted analysis to prostate cancer incidence and did not allow for analysis with mortality as an end-point. It has been suggested that BMI may play a greater role in the progression of prostate cancer tumors rather than in tumor development (Mistry et al., 2007) and a high BMI has been associated with an increased risk of both progression and mortality (Cao and Ma, 2011).

In conclusion, our results indicate an increased risk of aggressive prostate cancer among men with a high BMI when Gleason 3+4 were not included in the definition of aggressive disease, but do not support an association between BMI and risk of overall, aggressive disease including all Gleason 7, or non-aggressive prostate cancer risk within a cohort of current and former heavy smokers. Further studies should investigate differences between different Gleason 7 patterns.

Acknowledgments

This work was supported by the National Cancer Institute, National Institute of Health U01-CA63673, UM1-CA167462 and R01-CA96789. Additional funding was also received from the Robert Lundberg Memorial Foundation and the Gålö Foundation.

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Figure 1.

Kaplan-Meier survival curves for overall, non-aggressive (Gleason <7 and stage I/II) and aggressive (Gleason ≥7 and/or stage III/IV) and aggressive (not including Gleason 3+4) prostate cancer incidence and categories of body mass index (BMI, kg/m²). Time from inclusion in CARET to diagnosis, death or censoring at end of follow up is shown on the x-axis

Table 1
Baseline characteristics by BMI-category of men enrolled in the Carotene and Retinol Efficacy Trial (CARET)

	Body mass index category, kg/m ²								<i>p</i> ^d		
	All (n=11,886)	18 – 24.9 (n=2,735)	25 – 29.9 (n=5,695)	30 – 34.9 (n=2,545)	35 (n=911)						
						Mean	(SD)				
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)			
Age at baseline	58.1	(6.1)	58.7	(6.2)	58.2	(6.1)	57.7	(6.1)	57.0	(6.0)	<0.001
Smoking ^b , pack-years	49.1	(23.4)	49.6	(22.1)	48.5	(23.3)	49.8	(24.7)	49.8	(24.7)	0.04
Total energy intake (kcal)	1,848	(702)	1,850	(693)	1,830	(682)	1,859	(720)	1,924	(796)	0.003
MVPA ^c (h/wk)	37.8	(22.3)	38.3	(21.9)	38.6	(22.2)	36.5	(22.5)	34.1	(22.9)	<0.001
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Race/ethnicity											<0.001
White	10,952	(92.1)	2,504	(91.6)	5,287	(92.8)	2,353	(92.5)	808	(88.7)	
Black	447	(3.8)	110	(4.0)	183	(3.2)	100	(3.9)	54	(5.9)	
Other or unknown	487	(4.1)	121	(4.4)	225	(4.0)	92	(3.6)	49	(5.4)	
Education											<0.001
< High school level	1,551	(13.1)	344	(12.6)	702	(12.3)	358	(14.1)	147	(16.1)	
High school level	6,395	(53.8)	1,444	(52.8)	3,034	(53.3)	1,417	(55.7)	500	(54.9)	
> High school level	2,484	(20.9)	614	(22.5)	1,232	(21.6)	476	(18.7)	162	(17.8)	
Missing data	1,456	(12.3)	333	(12.2)	727	(12.8)	294	(11.6)	102	(11.2)	
Family history of PCa											0.47
Yes	419	(3.5)	88	(3.2)	203	(3.6)	100	(3.9)	28	(3.1)	
Intervention arm											0.74
Placebo	5,743	(48.3)	1,298	(47.5)	2,768	(48.6)	1,229	(48.3)	448	(49.2)	
Active vitamins ^d	6,143	(51.7)	1,437	(52.5)	2,927	(51.4)	1,316	(51.7)	463	(50.8)	
Study center											<0.001
Baltimore	807	(6.8)	91	(3.3)	384	(6.7)	231	(9.1)	101	(11.1)	
Irvine	2,362	(19.9)	599	(21.9)	1,086	(19.1)	487	(19.1)	190	(20.9)	
New Haven	1,022	(8.6)	175	(6.4)	467	(8.2)	275	(10.8)	105	(11.5)	

	Body mass index category, kg/m ²								<i>p</i> ^a	
	All (n=11,886)	18 – 24.9 (n=2,735)	25 – 29.9 (n=5,695)		30 – 34.9 (n=2,545)		35 (n=911)			
			Mean	(SD)	Mean	(SD)		Mean		(SD)
Portland	2,647	(22.3)	681	(24.9)	1,274	(22.4)	521	(20.5)	171	(18.8)
San Francisco	850	(7.2)	202	(7.4)	411	(7.2)	178	(7.0)	59	(6.5)
Seattle	4,198	(35.3)	987	(36.1)	2,073	(36.4)	853	(33.5)	285	(31.3)
Prostate cancer cases	883	(7.4)	199	(7.3)	426	(7.5)	193	(7.6)	65	(7.1)
Prostate cancer sub-type										0.96
Missing data	196	(22.2)	35	(17.6)	100	(23.5)	45	(23.3)	16	(24.6)
Non-aggressive ^e	334	(37.8)	78	(39.2)	163	(38.3)	74	(38.3)	19	(29.2)
Aggressive ^f	353	(40.0)	86	(43.2)	163	(38.3)	74	(38.3)	30	(46.2)
Aggressive ^{f,g}	202	(22.9)	41	(20.6)	95	(22.3)	45	(23.3)	21	(32.3)
Gleason Score										0.28
2–6	415	(47.0)	90	(45.2)	209	(49.1)	91	(47.2)	25	(38.5)
7–10	305	(34.5)	78	(39.2)	137	(32.2)	64	(33.2)	26	(40.0)
Missing data	163	(18.5)	31	(15.6)	80	(18.8)	38	(19.7)	14	(21.5)
Stage of disease										0.79
I/II	520	(58.9)	123	(61.8)	249	(58.5)	114	(59.1)	34	(52.3)
III/IV	148	(16.8)	33	(16.6)	74	(17.4)	28	(14.5)	13	(20.0)
Missing data	215	(24.4)	43	(21.6)	103	(24.2)	51	(26.4)	18	(27.7)

^aFrom ANOVA for continuous and Chi-2-tests for categorical variables;

^bMissing data for n=7;

^cInformation on Moderate-to-Vigorous Physical Activity was self-reported in a questionnaire in 1996–1997 and data was available for a sub-group (n=6,594);

^d30mg β-carotene + 25,000 IU retinyl palmitate/day;

^eGleason score <7 and stage I/II at diagnosis;

^fGleason score 7 or stage III/IV at diagnosis;

^gExcluding Gleason 3+4

Table 2

Associations of BMI with prostate cancer risk in the Carotene and Retinol Efficacy Trial (CARET)

		Age-adjusted	Multivariable adjusted ^a	Multivariable adjusted ^{a,b}
		HR (95% CI)	HR(95% CI)	HR(95% CI)
		(n=11,886)	(n=11,879)	(n=11,229)
All prostate cancer				
Cases (n)		883	883	851
BMI (kg/m²)	18-<25 (ref)	1.00	1.00	1.00
	25<30	1.01 (0.85–1.20)	1.01 (0.85–1.19)	1.01 (0.85–1.20)
	30<35	1.07 (0.88–1.30)	1.06 (0.87–1.30)	1.06 (0.87–1.30)
	35	1.11 (0.84–1.47)	1.10 (0.83–1.45)	1.09 (0.81–1.45)
	<i>P for trend</i>	<i>0.35</i>	<i>0.41</i>	<i>0.45</i>
Non-aggressive prostate cancer^c				
Cases (n)		334	334	323
BMI (kg/m²)	18-<25 (ref)	1.00	1.00	1.00
	25<30	0.99 (0.76–1.30)	0.99 (0.75–1.29)	0.98 (0.75–1.30)
	30<35	1.05 (0.76–1.44)	1.04 (0.76–1.44)	1.05 (0.76–1.45)
	35	0.82 (0.50–1.36)	0.81 (0.49–1.34)	0.80 (0.47–1.34)
	<i>P for trend</i>	<i>0.83</i>	<i>0.81</i>	<i>0.77</i>
Aggressive prostate cancer^d				
Cases (n)		353	353	341
BMI (kg/m²)	18-<25 (ref)	1.00	1.00	1.00
	25<30	0.90 (0.69–1.17)	0.89 (0.69–1.16)	0.89 (0.68–1.17)
	30<35	0.95 (0.70–1.30)	0.94 (0.69–1.29)	0.95 (0.69–1.30)
	35	1.18 (0.78–1.79)	1.16 (0.77–1.77)	1.12 (0.73–1.73)
	<i>P for trend</i>	<i>0.58</i>	<i>0.62</i>	<i>0.71</i>
Aggressive prostate cancer^{d,e}				
Cases (n)		202	202	202
BMI (kg/m²)	18-<25 (ref)	1.00	1.00	1.00
	25<30	1.11 (0.77–1.60)	1.09 (0.76–1.58)	1.13 (0.76–1.66)
	30<35	1.23 (0.81–1.88)	1.21 (0.79–1.86)	1.25 (0.81–1.94)
	35	1.78 (1.05–3.01)	1.77 (1.04–3.00)	1.80 (1.04–3.11)
	<i>P for trend</i>	0.04	0.04	0.04

^a Multivariable adjusted for age, study center, study arm, race/ethnicity and smoking (pack-years), missing data on pack-years (n=7);^b Additionally adjusted for family history of PC, total energy intake, missing data on total energy intake (n=652);^c Gleason score <7 and stage I/II at diagnosis;^d Gleason score ≥7 or stage III/IV at diagnosis;^e not including men with Gleason 3+4 (n=151)