Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis

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Summary

Background **Excess body-mass index (BMI) has been associated with adverse outcomes in prostate cancer, and hyperinsulinaemia is a candidate mediator, but prospective data are sparse. We assessed the effect of prediagnostic BMI and plasma C-peptide concentration (reflecting insulin secretion) on prostate cancer-specific mortality after diagnosis.**

Methods **This study involved men diagnosed with prostate cancer during the 24 years of follow-up in the Physicians' Health Study. BMI measurements were available at baseline in 1982 and eight years later in 1990 for 2546 men who developed prostate cancer. Baseline C-peptide concentration was available in 827 men. We used Cox proportional hazards regression models controlling for age, smoking, time between BMI measurement and prostate cancer diagnosis, and competing causes of death to assess the risk of prostate cancer-specific mortality according to BMI and C-peptide concentration.**

Findings **Of the 2546 men diagnosed with prostate cancer during the follow-up period, 989 (38·8%) were overweight (BMI 25·0–29·9 kg/m²) and 87 (3·4%) were obese (BMI ≥30 kg/m²). 281 men (11%) died from prostate cancer during this follow-up period. Compared with men of a healthy weight (BMI <25 kg/m²) at baseline, overweight men and obese men had a significantly higher risk of prostate cancer mortality (proportional hazard ratio [HR] 1·47 [95% CI 1·16–1·88] for overweight men and 2·66 [1·62–4·39] for obese men; p_{trend}<0·0001). The trend remained significant after controlling for clinical stage and Gleason grade and was stronger for prostate cancer diagnosed during the PSA screening era (1991–2007) compared with during the pre-PSA screening era (1982–1990) or when using BMI measurements obtained in 1990 compared with those obtained in 1982. Of the 827 men with data available for baseline C-peptide concentration, 117 (14%) died from prostate cancer. Men with C-peptide concentrations in the highest quartile (high) versus the lowest quartile (low) had a higher risk of prostate cancer mortality (HR 2·38 [95% CI 1·31–4·30]; p_{trend}=0·008). Compared with men with a BMI less than 25 kg/m² and low C-peptide concentrations, those with a BMI of 25 kg/m² or more and high C-peptide concentrations had a four-times higher risk of mortality (4·12 [1·97–8·61]; $p_{interaction}$=0·001) independent of clinical predictors.**

Interpretation **Excess bodyweight and a high plasma concentration of C-peptide both predispose men with a subsequent diagnosis of prostate cancer to an increased likelihood of dying of their disease. Patients with both factors have the worst outcome. Further studies are now needed to confirm these findings.**

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Introduction

Prostate cancer and obesity are major public health concerns for middle-aged and older men. Excess bodyweight, measured by the body-mass index (BMI), has been associated with increased risk of prostate cancer progression, although it seems to be unrelated to the risk of incident prostate cancer in most prospective studies.[1–5] Some studies have shown that a higher BMI, measured before disease onset, is associated with a lower risk of localised prostate cancer, but a higher risk of lethal cancer.[5] Most studies,[6–13] but not all,[14,15] suggest that obesity at the time of prostate cancer diagnosis is associated with a higher risk of biochemical failure. In one study, obesity (BMI ≥30 kg/m²) assessed retrospectively at ages 25 years and 40 years was a stronger predictor for risk of biochemical failure than obesity assessed at diagnosis.[10] Up to now, in five studies that have assessed the risk of prostate cancer-specific mortality,[11,16–19] three reported a positive association for BMI at the time of treatment or for recall of BMI in the year before diagnosis.[11,17,19] Taken together, these data suggest that obesity before or at a prostate cancer diagnosis predisposes men to an increased risk of dying from the disease.[20] However, to our knowledge, no long-term prospective study of prostate cancer-specific mortality with a concomitant assessment of the biological mechanism(s) has been done.

Obesity causes many metabolic changes that might mediate the association with increased prostate cancer mortality. Hyperinsulinaemia is a candidate mediator. In

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a recent laboratory study, mice fed a high-energy diet had increased weight gain, hyperinsulinaemia, accelerated growth of prostate cancer xenografts, and increased signalling downstream of the insulin receptor in neoplastic prostate tissue.[21] Additionally, we noted abundant expression of the insulin receptor in human prostate cancer tissue.[22] To our knowledge, no studies have reported an association between plasma concentrations of insulin or C-peptide, a marker of insulin secretion,[23] before prostate cancer diagnosis and the risk of prostate cancer mortality.

We assessed the role of prediagnostic BMI and plasma C-peptide concentration in prostate cancer-specific mortality in a well-defined cohort of US male physicians diagnosed with prostate cancer during the 24 years of follow-up. We also assessed the potential effect of known clinical predictors of prostate cancer progression, including age at diagnosis, Gleason grade, and clinical stage, on these associations.

Methods

Study population and baseline questionnaire

This study involved men diagnosed with prostate cancer during the 24 years of follow-up in the Physicians' Health Study (median follow-up between diagnosis and death or end of follow-up was 7 years [range 1 day–24 years]), a randomised trial of aspirin and beta carotene in 22 071 US male physicians, aged 40–84 years in 1982, without a history of heart disease, cancer, or major chronic diseases.[24] At baseline, participants reported height and bodyweight and, at the eighth year of follow-up, the participants reported bodyweight again, from which baseline and the eighth-year BMI were calculated and categorised as healthy weight (BMI <25 kg/m²), overweight (BMI 25–29·9 kg/m²), or obese (BMI ≥30 kg/m²). Cigarette smoking (never, past, current) and history of diabetes were also ascertained at baseline. Between August, 1982, and December, 1984, 14 916 men provided blood samples. In a subgroup of patients selected for

	BMI <25 kg/m²	BMI 25·0–29·9 kg/m²	BMI ≥30 kg/m²	p value
Total patients with prostate cancer, n (%)	1470/2546 (57·7)	989/2546 (38·8)	87/2546 (3·4)	..
Pre-PSA era (1982–1990), n (%)	237/415 (57·1)	165/415 (39·8)	13/415 (3·1)	0·88
PSA era (1991–2007), n %	1233/2131 (57·9)	824/2131 (38·7)	74/2131 (3·5)	..
Deaths due to prostate cancer, n (%)	134/1470 (9·1)	129/989 (13·0)	18/87 (20·7)	0·0001
Median overall follow-up (range), years				
Baseline to diagnosis	14·3 (0·0–23·9)	14·0 (0·2–23·8)	13·1 (0·5–23·0)	..
Diagnosis to end of follow-up	7·5 (0·0–22·7)	7·3 (0·1–24·3)	6·2 (0·5–17·4)	..
Mean age at baseline (SD), years	56·7 (9·3)	57·2 (8·4)	55·9 (7·5)	0·31
Mean age at diagnosis (SD), years	70·6 (7·7)	70·8 (7·2)	69·2 (6·7)	0·13
Smoking status at baseline, n (%)				
Non-smoker	774/1470 (52·7)	464/989 (46·9)	35/87 (40·2)	0·02
Past smoker	572/1470 (38·9)	421/989 (42·6)	42/87 (48·3)	..
Current smoker	124/1470 (8·4)	104/989 (10·5)	10/87 (11·5)	..
Baseline diabetes, n (%)	23/1470 (1·6)	15/989 (1·5)	0/87 (0·0)	0·50
Clinical stage, n (%)*				
T1/T2	1141/1270 (89·8)	767/852 (90·0)	58/74 (78·4)	0·0010
T3/T4	87/1270 (6·9)	48/852 (5·6)	7/74 (9·5)	..
N1/M1	42/1270 (3·3)	37/852 (4·3)	9/74 (12·2)	..
Gleason score, n (%)†				
2–6	897/1422 (63·1)	569/955 (59·6)	49/81 (60·5)	0·06
7	343/1422 (24·1)	269/955 (28·2)	16/81 (19·8)	..
8–10	182/1422 (12·8)	117/955 (12·3)	16/81 (19·8)	..
Baseline PSA (ng/mL), n (%)‡				
4·0–9·9	87/419 (20·8)	62/277 (22·4)	6/22 (27·3)	0·71
≥10	63/419 (15·0)	46/277 (16·6)	5/22 (22·7)	0·58
PSA at diagnosis (ng/mL), n (%)§				
4·0–9·9	580/1090 (53·2)	421/722 (58·3)	30/57 (52·6)	0·09
≥10	375/1090 (34·4)	224/722 (31·0)	22/57 (38·6)	0·22
Median plasma C-peptide concentration (10th–90th percentile), ng/mL¶	1·5 (0·7–3·9)	1·9 (0·8–4·5)	2·8 (1·4–4·7)	<0·0001

PSA=prostate specific antigen. *350 of 2546 men (14%) had unknown clinical stage. †88 of 2546 men (3%) had unknown Gleason grade. ‡Data for plasma PSA concentrations at baseline were available for 718 men. §Data for plasma PSA concentrations at diagnosis were available for 1869 men. ¶Data for plasma C-peptide concentrations at baseline were available for 827 men.

Table 1: **Characteristics of 2546 patients with prostate cancer (1982–2007) by baseline body-mass index (BMI)**

nested case–control biomarker studies, we assayed plasma C-peptide concentrations for 827 men and prostate specific antigen (PSA) concentrations for 718 men, by use of baseline blood samples. All patients provided written informed consent for inclusion in this study. This study was approved by the Human Subjects Committee of the Brigham and Women's Hospital and Harvard School of Public Health, MA, USA.

Follow-up and confirmation of prostate cancer death

Follow-up questionnaires to ascertain disease outcomes were sent out to physicians at 6 months and 12 months after randomisation and yearly thereafter. Of 2751 reported prostate cancer diagnoses, 2549 were confirmed by medical records and pathology reports; all except three (patients who reported BMI <18·5 kg/m²) of the confirmed cases were included in the analysis. Prostate cancer stage was recorded according to the Tumour Node Metastasis (TNM) staging system or converted from a modified Whitmore-Jewett classification scheme (for prostate cancer diagnosed during the early years of follow-up). We used clinical stage and Gleason grade whenever the information were available. PSA concentrations at diagnosis were also extracted from medical records. Deaths were ascertained by repeated mailings, telephone calls to non-respondents, and searches of the National Death Index. We used medical records to assess the cause of death, and assignment of prostate cancer-specific death was blinded to questionnaire and laboratory data and was based on consensus of the three physicians, who form the End Point Committee, by use of medical records and all available information. Follow-up for morbidity and mortality to March 30, 2007, is 97% complete.

C-peptide assay

Plasma C-peptide concentrations were measured in blood that had been frozen at –82°C, by use of standard ELISA and a single production lot of reagents (Diagnostic Systems Limited, Webster, TX, USA) at MP's laboratory. Blinded embedded quality control samples showed a within-assay coefficient of variance of 5% and a between-assay variability of 9%.

Statistical analyses

We characterised the clinical predictors of lethal prostate cancer and other potential confounding variables, according to the three BMI categories, by use of χ^2 tests and analysis of covariance. A competing risk analysis by use of Cox proportional hazards regression[25] was done to assess associations of baseline and the eighth-year follow-up BMI (three categories as the major exposure) with the risk of prostate cancer-specific mortality (the major outcome), using proportional hazard ratios (HR) and 95% CI. This competing risk model is a semiparametric multiplication hazard model assuming that the log-relative hazard is linearly related to covariates. The implementation of the model is based on a stacked dataset technique that allows some covariates to have identical effects for several causes. In our analysis, we assume that no covariates have identical effects on the two types of failure types (ie, prostate cancer death and death due to other causes).[26] Person-years were counted from the date of prostate cancer diagnosis until the date of prostate cancer death (event), death due to other causes, or the end of follow-up (March 31, 2007; censored), whichever came first. We also estimated the HR in association with a one-unit

	Healthy BMI (<25 kg/m²)			Overweight (BMI 25·0–29·9 kg/m²)			Obese (BMI ≥30 kg/m²)			Per-unit increase in BMI		p trend	
	Patients, n	HR (95% CI)*	HR (95% CI)†	Patients, n	HR (95% CI)*	HR (95% CI)†	Patients, n	HR (95% CI)*	HR (95% CI)†	HR (95% CI)*	HR (95% CI)†	HR (95% CI)*	HR (95% CI)†
BMI measured in 1982 (n=2546)													
All patients with prostate cancer (1982–2007), n‡	134/1470	1·00 (ref)	1·00 (ref)	129/989	1·47 (1·16–1·88)	1·26 (0·98–1·62)	18/87	2·66 (1·62–4·39)	1·95 (1·17–3·23)	1·09 (1·05–1·14)	1·07 (1·02–1·12)	<0·0001	0·0042
Patients diagnosed with prostate cancer in pre-PSA era (1982–1990)	68/237	1·00 (ref)	1·00 (ref)	63/165	1·44 (1·02–2·04)	1·06 (0·73–1·53)	9/13	3·15 (1·52–6·51)	1·55 (0·74–3·24)	1·10 (1·03–1·18)	1·06 (0·99–1·13)	0·0045	0·1113
Patients diagnosed with prostate cancer in PSA era (1991–2007)	66/1233	1·00 (ref)	1·00 (ref)	66/824	1·45 (1·03–2·05)	1·57 (1·11–2·24)	9/74	2·41 (1·19–4·89)	2·50 (1·22–5·13)	1·09 (1·02–1·16)	1·08 (1·02–1·15)	0·0064	0·0146
BMI measured in 1990 (n=2078)													
Patients diagnosed with prostate cancer in PSA era (1991–2007)	59/1094	1·00 (ref)	1·00 (ref)	66/877	1·49 (1·05–2·13)	1·61 (1·12–2·32)	9/107	2·24 (1·09–4·57)	2·23 (1·07–4·64)	1·09 (1·03–1·15)	1·10 (1·04–1·16)	0·0033	0·0015

HR=hazard ratio. Ref=reference group. PSA=prostate specific antigen. *Adjusted for age at diagnosis (<65 years, 65–69 years, 70–74 years, 75–79 years, ≥80 years), baseline smoking status (never, past, and current smoker) and time interval from BMI measurement to prostate-cancer diagnosis. †Adjusted for age at diagnosis (<65 years, 65–69 years, 70–74 years, 75–79 years, ≥80 years), baseline smoking status (never, past, and current smoker), time interval from BMI measurement to prostate-cancer diagnosis, clinical stage, and Gleason grade. ‡Number of prostate-cancer deaths per men diagnosed with prostate cancer.

Table 2: **Cox proportional hazard ratio and 95% CI of prostate-cancer-specific mortality according to body-mass index (BMI)**

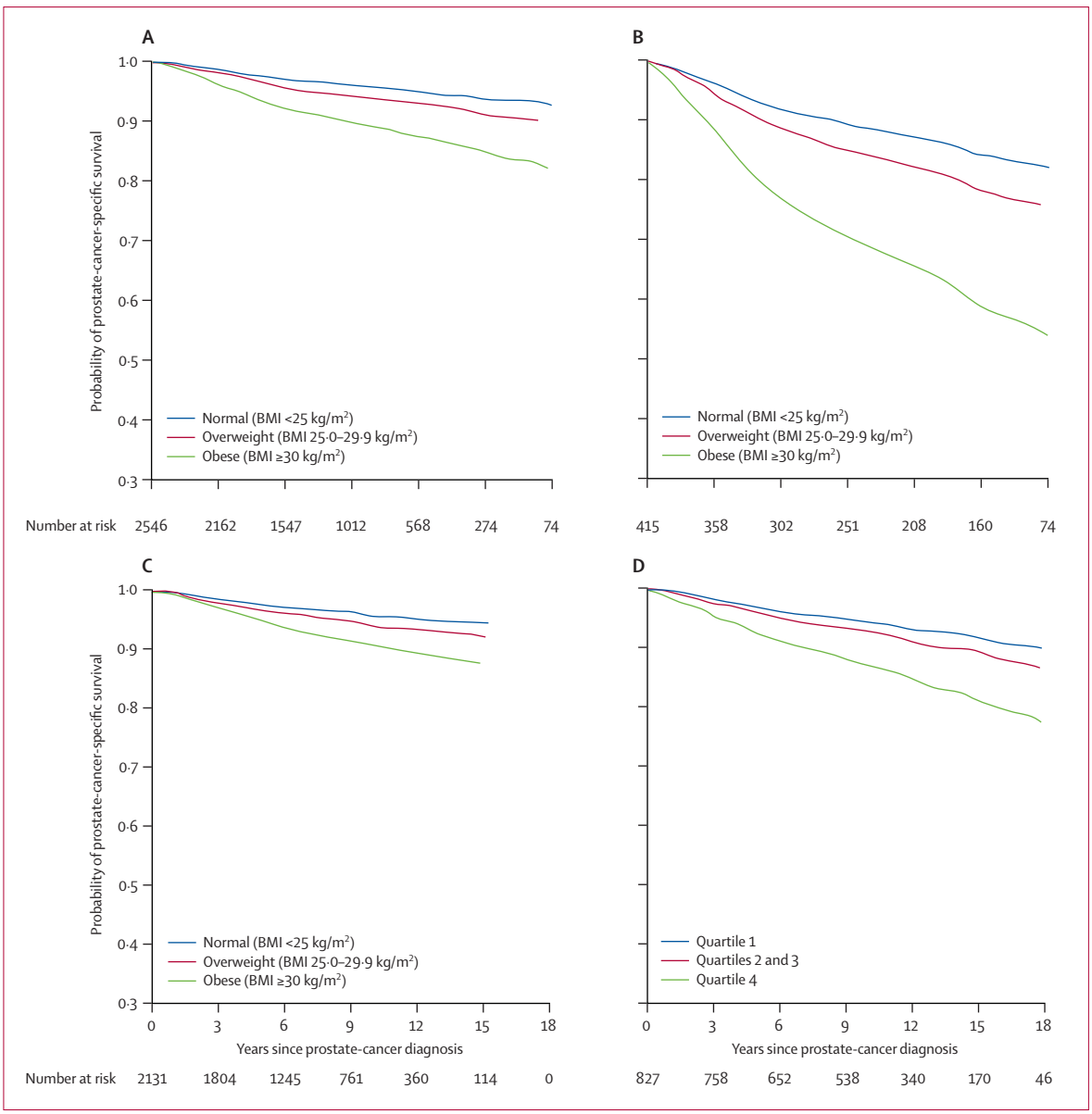

Figure: **Survival curves show the probability of prostate cancer-specific survival after diagnosis according to baseline BMI measured in 1982 and baseline C-peptide concentrations, controlling for age at diagnosis, smoking status, and time between BMI measurement or plasma C-peptide measurement and cancer diagnosis**

(A) Overall study period (1982–2007). 2546 patients diagnosed with prostate cancer, leading to 281 prostate cancer deaths. (B) Preprostate specific antigen (PSA) era (1982–90). 415 patients diagnosed with prostate cancer, leading to 140 prostate cancer deaths. (C) PSA era (1991–2007). 2131 patients diagnosed with prostate cancer, leading to 141 prostate cancer deaths. (D) Baseline plasma C-peptide concentrations during 1982–2007. 827 patients diagnosed with prostate cancer, leading to 117 prostate cancer deaths). p values for log-rank tests were all less than 0·023.

incremental increase in BMI and present the p values of the tests for trend.

In the basic model, we controlled for age at diagnosis, baseline cigarette-smoking status, and time between BMI measurement and prostate cancer diagnosis in all analyses. Controlling for the randomised trial components, aspirin and beta-carotene, had no effect, so these were not included in the analyses. To assess the independent effect of BMI, we further controlled for clinical stage and Gleason grade in some analyses. To assess the effect of PSA screening, we stratified the analysis by year of diagnosis (ie, before or after 1990, when PSA screening became widespread). In the subgroup analyses, we also controlled for baseline PSA (<4, 4–9, ≥10 ng/mL; n=718) or PSA at diagnosis (n=1869). To further decrease the potential effect of obesity or being overweight on PSA screening or treatment options, we did sensitivity analyses by excluding stage T1 or stage

N1/M1 cancer. We also assessed models excluding current smokers, men with a history of diabetes, non-white patients (less than 6% of the cohort), or men who died of any cause within the first 5 years of follow-up.

All analyses of plasma C-peptide concentrations (in quartiles) were controlled for baseline age and time since last meal, and subsequent analyses controlled for baseline BMI, or clinical stage and Gleason grade to assess the independent association of C-peptide. The median (10th-90th percentile) from the lowest to the highest quartile of C-peptide concentrations were: 0·8 (0·5–1·0), 1·3 (1·0–1·7), 2·1 (1·7–2·7), and 3·9 (2·8–5·9). Tests for trend were done by treating the median concentration for each quartile as a continuous variable. We also assessed the joint association between BMI (<25 kg/m² *vs* ≥25 kg/m²) and quartile of C-peptide concentration and tested the significance of the interaction by including a product term of the two variables with the main exposures. Because excluding 11 men with a history of diabetes at baseline did not change the findings materially, we presented data including all men with plasma C-peptide concentrations. We used Cox proportional hazards regression models adjusting for age at diagnosis and smoking categories to produce plots of prostate cancer-specific survival curves for the three BMI categories or for the quartiles of C-peptide concentration. Additionally, we did log-rank tests controlling for age at diagnosis and smoking status to test whether the survival curves estimated by the Kaplan-Meier method for the three BMI categories or for the quartiles of C-peptide concentration were equal. All statistics were calculated by use of SAS (version 9.1.3; SAS Institute Inc, Cary, NC, USA), with a two-sided significance level of 0·05.

Role of the funding source

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Results

Of the 2546 men diagnosed with prostate cancer during the follow-up period, 989 (38·8%) were overweight (BMI 25·0–29·9 kg/m²) and 87 (3·4%) were obese (BMI ≥30 kg/m²) at baseline (table 1). Overweight men had characteristics similar to men of a healthy weight. Greater proportions of obese men were past smokers, and were more likely to have extraprostatic or metastatic cancer, or a high Gleason grade (8–10) tumour at diagnosis. BMI was unrelated to PSA concentration, with Spearman correlation coefficients between BMI and baseline PSA concentration of 0·06 (p=0·09; n=718) and –0·03 between BMI and PSA concentration at diagnosis (p=0·25; n=1869). As expected, higher baseline plasma C-peptide concentrations were correlated with older age (Spearman partial correlation r=0·12, p=0·001, controlling for fasting status and assay batch) and higher BMI (r=0·25, p<0·0001, controlling for fasting, batch, and age).

	HR (95% CI)	p value
All patients with prostate cancer	1·09 (1·05–1·14)	<0·0001
Controlling for aspirin and beta-carotene	1·09 (1·05–1·14)	<0·0001
Excluding any deaths occurring during first 5 years of follow-up	1·10 (1·05–1·15)	<0·0001
Excluding current smokers	1·11 (1·06–1·16)	<0·0001
Excluding diabetes	1·09 (1·05–1·14)	<0·0001
Excluding non-white patients	1·11 (1·05–1·16)	<0·0001
Excluding stage T1	1·10 (1·05–1·15)	<0·0001
Excluding metastasis (N1/M1)	1·08 (1·02–1·13)	0·0039

*All adjusted for age at diagnosis, smoking status at baseline (past smoking for the analysis excluding current smokers) and time interval from baseline to prostate cancer diagnosis.

Table 3: **Cox proportional hazard ratio (HR)* and 95% CI of prostate-cancer-specific mortality according to one-unit increase in baseline body-mass index**

During the 24 years of follow-up, 281 of 2546 men (11%) subsequently died from prostate cancer and 485 men (19%) died from other causes. A higher baseline BMI was significantly associated with a higher risk of prostate cancer-specific mortality, independent of age at diagnosis and baseline smoking status, compared with a healthy BMI (table 2 and figure; HR 1·47 [95% CI 1·16–1·88] for overweight men and 2·66 [1·62–4·39] for obese men; p_{trend}<0·0001). Controlling for the two trial components, aspirin and beta-carotene, did not change the findings (table 3).

We further included clinical stage and Gleason grade in the multivariate model to assess the independent association between baseline BMI and fatal prostate cancer. Controlling for these clinical predictors somewhat attenuated the size of the association (HR 1·26 [95% CI 0·98–1·62] for overweight men and HR 1·95 [1·17–3·23] for obese men). However, the positive trend of increase in risk for each unit-increase in BMI remained statistically significant (HR 1·07 [1·02–1·12], p_{trend} = 0·0042; table 2). As expected, a high Gleason score (7 or 8–10) and regional (clinical stage T3/T4/N0/M0) and metastatic (N1/M1) disease at diagnosis were strong predictors of lethal prostate cancer (HR 2·25 [1·62–3·12] for patients with a Gleason score of 7 [80 prostate cancer deaths] and 4·70 [3·37–6·56] for those with a Gleason score of 8–10 [93 prostate cancer deaths], compared with those with a Gleason score of 2–6 [73 prostate cancer deaths]; HR 3·62 [2·61–5·02] for stage T3/T4/N0/M0 tumours [78 prostate cancer deaths] and HR 10·62 [7·45–15·14] for stage N1/M1

	Plasma C-peptide quartile				p*
	1	2	3	4	
Number of patients†	21/207	32/206	20/208	44/206	..
Median plasma C-peptide concentration (10th–90th percentile), ng/mL	0·8 (0·5–1·0)	1·3 (1·0–1·7)	2·1 (1·7–2·7)	3·9 (2·8–5·9)	..
Simple model‡	1·00	1·54 (0·87–2·71)	1·10 (0·58–2·09)	2·38 (1·31–4·30)	0·008
Simple model plus BMI	1·00	1·42 (0·80–2·51)	0·95 (0·50–1·82)	2·01 (1·11–3·66)	0·030
Simple model plus clinical stage and Gleason grade	1·00	1·15 (0·63–2·10)	1·08 (0·56–2·08)	1·93 (1·03–3·63)	0·090
Simple model plus BMI, clinical stage, and Gleason grade	1·00	1·01 (0·54–1·86)	0·97 (0·50–1·87)	1·72 (0·92–3·24)	0·110

*Test for trend by use of median concentration of C-peptide in each of the quartiles. †Number of prostate-cancer deaths per men diagnosed with prostate cancer. ‡Controlling for age, fasting status, and time interval from baseline to prostate-cancer diagnosis.

Table 4: **Cox proportional hazard ratio and 95% CI of prostate cancer-specific mortality according to baseline plasma C-peptide concentration**

disease [67 prostate cancer deaths], compared with localised [stage T1/T2/N0/M0] disease [105 prostate cancer deaths]). Further controlling for PSA at diagnosis (<4, 4–9, ≥10 ng/mL) in a subgroup of 1869 men (diagnosed in the PSA era) strengthened the association for being overweight (HR 1·80 [1·15–2·83]), but attenuated the association for obesity (1·61 [0·56–4·58]). Controlling for baseline PSA (<4, 4–9, ≥10 ng/mL; n=718 [most of whom were diagnosed during the pre-PSA era]) in the multivariate model with clinical predictors did not materially change the findings (HR 1·61 [1·11–2·34] for overweight men and HR 2·83 [1·31–6·11] for obese men).

Widespread PSA screening since the early 1990s has substantially changed the clinical presentation of prostate cancer. Because information on screening was not uniformly available, we used the period of 1982–1990 and 1991–2007 as a surrogate of the pre-PSA and PSA screening eras. In the 415 men diagnosed with prostate cancer during 1982–1990 (pre-PSA era), 140 (33·7%) died of prostate cancer. In the 2131 men diagnosed with prostate cancer during 1991–2007 (PSA screening era), 141 (6·6%) died of the disease. Although the overall prostate cancer-specific mortality was substantially different between the two periods (figure), the relative risk of prostate cancer-specific mortality in association with baseline BMI remained similar in the age-adjusted and smoking-adjusted model (table 2). Further controlling for clinical stage and Gleason grade significantly attenuated the association for prostate cancer diagnosed during 1982–90. However, for prostate cancer diagnosed during the PSA screening era, excess bodyweight many years before diagnosis was a strong and significant predictor of poor survival.

The median time between baseline BMI measurement and prostate cancer diagnosis was 14 years (table 1), we therefore controlled for time between BMI measurements to prostate cancer diagnosis in all the analyses. Additionally, BMI obtained in the eighth year of follow-up (1990) was highly correlated with baseline BMI in 1982 (correlation coefficient=0·8), suggesting strong tracking over time. The prospective association between prediagnostic BMI and prostate cancer-specific mortality in the PSA screening era (1991–2007) was similar using BMI obtained in 1982 or in 1990 (table 2), with or without controlling for clinical stage and Gleason grade, further showing this robust relation.

To assess potential confounding factors, we did a series of subgroup sensitivity analyses with baseline BMI as a continuous variable, which gives more statistical power (table 3), and controlling for age and smoking status. Compared with the overall risk of prostate cancer-specific mortality with a one-unit increase in BMI (HR 1·09 [95% CI 1·05–1·14]), the association remained virtually unchanged after each of the following exclusions: men who died of any cause during the first 5 years of follow-up; current smokers; men with a history of diabetes; or non-white patients. This suggests that these factors cannot explain the strong positive association between baseline BMI and prostate cancer mortality. Additionally, excluding men with stage T1 or stage N1/M1 prostate cancer at diagnosis did not materially change the

Plasma C-peptide quartiles	BMI <25 kg/m²		BMI ≥25 kg/m²	
	Patients, n*	HR (95% CI)	Patients, nn	HR (95% CI)
Simple model†				
1	13/148	1·00 (ref)	8/59	1·71 (0·71–4·15)
2	19/123	1·83 (0·89–3·76)	13/83	1·79 (0·81–3·94)
3	10/119	1·22 (0·52–2·88)	10/89	1·31 (0·56–3·03)
4	12/99	1·33 (0·57–3·13)	32/107	4·22 (2·10–8·48)
p, trend	..	0·380	..	0·007
p, interaction	0·017			
Simple model plus clinical stage and Gleason grade				
1	13/148	1·00 (ref)	8/59	2·07 (0·84–5·13)
2	19/123	1·64 (0·78–3·47)	13/83	1·04 (0·44–2·44)
3	10/119	1·15 (0·48–2·74)	10/89	1·56 (0·65–3·73)
4	12/99	0·97 (0·39–2·38)	32/107	4·12 (1·97–8·61)
p, trend	..	0·480	..	0·006
p, interaction	0·001			

ref=reference group. *Number of prostate cancer deaths per men diagnosed with prostate cancer. †Controlling for age, fasting status, and time interval from baseline to prostate cancer diagnosis.

Table 5: **Cox proportional hazard ratio (HR) and 95% CI of prostate cancer-specific mortality according to baseline body-mass index (BMI) and plasma C-peptide concentrations**

findings, suggesting that early cancer detection by PSA (stage T1) or delayed diagnosis (metastasis) had little effect on the association.

Baseline blood-sample data were available for a subgroup of 827 men; 634 of these blood samples were collected less than 8 h since their last meal (non-fasting). We therefore measured plasma C-peptide as a surrogate for insulin secretion, and assessed the link between C-peptide concentration and prostate cancer-specific mortality, adjusting for time between last meal and obtaining blood. Baseline characteristics and clinical features in this subgroup of men were similar to those in the overall study population (webtable). In the 117 men who died from prostate cancer, a significantly higher proportion (44 of 206 [21·4%]) had baseline C-peptide concentrations in the highest quartile compared with the lowest quartile (21 of 206 [10·1]%). After controlling for age, fasting status, and time interval from baseline to prostate cancer diagnosis, men with baseline C-peptide concentrations in the highest quartile had an HR of 2·38 (1·31–4·30) for prostate cancer mortality compared with the lowest quartile, p_{trend}=0·008 (figure and table 4). The increased risk was mainly in men in the highest quartile, suggesting a threshold effect (table 4). Inclusion of BMI in the model slightly attenuated the association for C-peptide (interquartile HR 2·01 [1·11–3·66]; p_{trend}=0·030), but BMI remained a strong predictor (HR 1·61 [1·10–2·35] for overweight men and HR 2·37 [1·04–5·37] for obese men; p_{trend}=0·023). The HR for the highest quartile of C-peptide concentration remained significant (HR 1·93 [1·03–3·63]; p_{trend}=0·090) after controlling for clinical stage and Gleason grade. However, inclusion of both BMI and clinical predictors in the same model attenuated the associations for both BMI (HR 1·76 [1·19–2·61] for overweight men and HR 1·87 [0·80–4·37] for obese men) and C-peptide concentration (interquartile HR 1·72 [0·92–3·24], p_{trend}=0·110). This finding suggests that part of the effect of BMI on prostate cancer prognosis is mediated by insulin (table 4).

When assessing the joint association between BMI and C-peptide concentration, we noted that the increased risk of prostate cancer mortality associated with higher concentrations of C-peptide was significant in men with a BMI ≥25 kg/m² or greater (p_{trend}=0·007), but not in men with a BMI of less than 25 kg/m² (p_{trend}=0·380; table 5). Overweight men with C-peptide concentrations in the highest quartile were over four-times (multivariate-adjusted HR 4·22 [2·10–8·48]; $p_{interaction}$=0·017) more likely to die from prostate cancer than men of a healthy weight and with C-peptide concentrations in the lowest quartile. Further controlling for clinical stage and Gleason grade did not change the finding (multivariate-adjusted HR 4·12 [1·97–8·61]; $p_{interaction}$=0·001).

Discussion

In this large cohort with long-term follow-up, men who are overweight or obese and who have a subsequent diagnosis of prostate cancer are at increased risk of prostate cancer-specific death. Compared with men of a healthy weight at baseline in 1982, overweight men and obese men had a significantly higher risk of dying of prostate cancer after initial cancer diagnosis. The size of the association increased monotonically (HR was 1·09 (95% CI 1·05–1·14) for each unit-increase in BMI [p_{trend}<0·0001]). The findings remained largely unchanged after further excluding current smokers at baseline, men with a history of diabetes, non-white patients, or those who died of any cause within 5 years of follow-up. Moreover, we noted that men with baseline C-peptide concentrations in the top quartile had a 2·4-times higher risk of dying of prostate cancer than those who had concentrations in the lowest quartile.

In the PSA screening era, obesity might delay a prostate cancer diagnosis, because a higher BMI has been associated with lower serum PSA concentrations.[27] A less sensitive PSA test in obese men could delay diagnosis and treatment, perhaps leading to a worse prognosis. However, we did not note a correlation between baseline BMI and PSA concentrations measured at baseline or PSA concentrations recorded at diagnosis. We assessed further the association separately by pre-PSA screening and PSA screening eras, controlling for clinical predictors (ie, disease stage, Gleason grade, and PSA concentration at diagnosis), or excluding stage T1 or stage N1/M1 prostate cancer from the analysis, and noted that the significant association between BMI and prostate cancer mortality remained largely unchanged. Thus, the positive associations between high BMI and poor prostate cancer outcomes are unlikely to be attributable to differences in cancer detection by PSA screening.

Another concern is whether the association between obesity and high prostate cancer mortality could be due to different choices of treatment in obese men, which might have affected the outcome. Although we cannot fully address this issue in view of the limited treatment information, our findings are in line with many previous clinical studies showing that, in patients receiving either prostatectomy or radiotherapy, obesity at diagnosis predicts subsequent PSA failure.[6–13] In addition to the relation with obesity, which accounts for only 3·4% of our study population, we noted that overweight men (38·8% of the study population) also had a significantly higher risk of prostate cancer-specific mortality. Although one could argue that obesity leads to treatment differences, this seems less plausible for overweight men with a BMI under 30 kg/m².

In our study, higher prediagnostic BMI and plasma C-peptide concentrations were both independent positive predictors of prostate cancer-specific mortality and men with both factors had the worst outcome. High insulin concentration might promote tumour progression via insulin receptors or the insulin-like growth factor type I receptor and downstream pathways.[28] Significantly increased insulin concentrations have been noted in

patients with prostate cancer versus healthy controls in a Chinese case–control study,[29] in men with high-risk prostate cancer versus those with low-risk cancer,[30] and in men who died of prostate cancer versus survivors.[31] Because these retrospective studies measured insulin concentration after the cancer diagnosis, it is unclear whether insulin concentrations were affected by disease severity or hormonal therapy, which affects hyperinsulinaemia or insulin resistance.[32,33] Two prospective studies reported a null association between fasting insulin or plasma C-peptide concentrations and risk of incident prostate cancer,[34,35] but neither specifically addressed the association with prostate cancer progression or survival.

Major strengths of this study are the prospective design, which avoids possible recall bias of BMI or effects of disease severity and treatment on blood biomarkers. The long follow-up allows us to assess independently the effect of both baseline BMI and BMI at the eighth year of follow-up on prostate cancer mortality. Additionally, we did a series of sensitivity analyses to assess potential biases and confounding factors. A limitation of our study is that no detailed information about PSA screening and cancer treatment was available. However, in view of the prospective design and the homogeneous study population of US physicians, confounding by PSA screening and treatment is unlikely to explain our findings. Another limitation is that, although plasma C-peptide concentration is a more reliable measurement of insulin secretion than insulin itself,[23] especially by use of non-fasting samples, we had only one C-peptide measurement at baseline, taken years before prostate cancer diagnosis. However, C-peptide is relatively stable; the within-person correlation coefficient for C-peptide measured 4 years apart in a similar cohort of men was 0·57, a correlation similar to blood-cholesterol measurements.[36] Participants in our study are not a representative sample of patients with prostate cancer in the general population; all are physicians in good health at baseline, and further selected by being trial participants. However, we believe that studying this more homogeneous population can avoid many unknown confounding factors, such as socioeconomic status, which might affect obesity, access to medical care, and cancer treatment options. Moreover, the biological relations of being overweight and prostate cancer prognosis noted in this population are broadly generalisable.

Our findings, taken together with other evidence, are consistent with the hypothesis that insulin and obesity-related metabolic factors affect prostate cancer prognosis. The findings further suggest that the "seed and soil" hypothesis proposed by Stephen Paget more than 100 years ago,[37] might apply to metabolic aspects of host–tumour interactions, and imply that the overweight or obese, hyperinsulinaemic host might provide an intrinsic microenvironment that favours aggressive neoplastic behaviour. The association of high C-peptide concentrations with prostate cancer mortality is also of interest in the context of evidence that the androgen ablation leads to hyperinsulinaemia, and might increase diabetic and cardiovascular morbidity in long-term prostate cancer survivors.[32,33] Our findings suggest the speculative possibility that hyperinsulinaemia might also favour aggressive androgen-independent disease progression.

Findings from this study have several implications for prostate cancer risk prediction, prevention, and treatment. First, men living in affluent societies are facing two epidemics, obesity and prostate cancer. In parallel with the obesity epidemic, the prevalence of hyperinsulinaemia has increased substantially in non-diabetic US adults.[38] The over-treatment of prostate cancer detected by PSA screening is a well recognised issue, and the need to identify prognostic factors that will improve our ability to identify men with life-threatening prostate cancer who might benefit from new and more aggressive treatment is clear. If confirmed, our prospective data provide evidence that being overweight or obese and having high C-peptide concentrations are adverse prognostic factors, and that they operate independently of clinical predictors. This provides further impetus for men to avoid becoming overweight and to decrease their risk of metabolic syndrome by physical activity and diet. Second, our data suggest that the recent progress in prostate cancer control might have been attenuated by the increased prevalence of obesity and hyperinsulinaemia. It also adds to the rationale for investigation of new therapeutic and prevention strategies, such as use of insulin-lowering or antidiabetic drugs,[39] and new agents that target the insulin/insulin-like growth factor-1 receptor family as an adjuvant therapy for prostate cancer.

Contributors

JM, MP, and MJS were responsible for the study concept, data interpretation, and the writing of the paper. JM also contributed to the study design, literature search, and design of the data analysis and MP also contributed to the assay measurement. HL and WQ contributed to the data analysis and EG and WQ contributed to the data interpretation. JMG was responsible for the study population and did the data collection with MJS, JM, LM, and PLN.

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