Review Article

Cancer Prevention Research

Body Mass Index, Prostate Cancer–Specific Mortality, and Biochemical Recurrence: a Systematic Review and Meta-analysis

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Abstract

Increasing evidence suggested obesity, measured by body mass index (BMI), was associated with prostate cancer–specific mortality, and its impact on biochemical recurrence was also inconclusive. We systematically searched MEDLINE, EMBASE, and bibliographies of retrieved studies up to January 5, 2010. We used random-effects meta-analysis to assess the relative risks (RR) of prostate cancer-specific mortality and biochemical recurrence associated with a 5 kg/m^2 increase in BMI. Among the six population-based cohort studies in 1,263,483 initially cancer-free men, 6,817 prostate cancer deaths occurred; a 5 kg/m^2 increase in BMI was associated with 15% (RR: 1.15, 95% confidence interval (CI): 1.06–1.25, $P < 0.01$) higher risk of dying of prostate cancer. In the six postdiagnosis survival studies on 18,203 patients with 932 prostate cancer deaths, a 5 kg/m^2 increase in BMI was associated with 20% higher prostate cancer–specific mortality (RR: 1.20, 95% CI: 0.99–1.46, $P = 0.06$). In the sixteen studies which followed 26,479 prostate cancer patients after primary treatment, a 5 kg/m^2 increase in BMI was significantly associated with 21% increased risk of biochemical recurrence (RR: 1.21, 95% CI: 1.11–1.31 $P < 0.01$). Elevated BMI is associated with risk of prostate cancer–specific mortality in prospective cohort studies and biochemical recurrence in prostate cancer patients. Its association with prostate cancer–specific mortality in diagnosed patients needs to be further evaluated. *Cancer Prev Res; 4(4); 486–501. ©2011 AACR.*

Introduction

Obesity, a growing epidemic in all over the world, has been linked to mortality of several cancers (1), but only in the past 5 to 10 years, body mass index (BMI) as a surrogate of adiposity has been extensively evaluated for prostate cancer incidence and mortality.

Higher BMI in mid/late adult life is weakly associated with higher risk of incident prostate cancer (2), but recently, the pattern that obesity is associated with lower risk of low-grade prostate cancer and higher risk of aggressive prostate cancer has emerged (2–5). Increasing evidence suggested that higher BMI is associated with poorer outcomes, that is, higher risk of prostate cancer–specific mortality among both obese healthy adults (4, 6–8) and prostate cancer patients (9–13) and higher rates of biochemical recurrence among diagnosed patients (14–16); however, no systematic review data are available about the impact of obesity and overweight on prostate cancer progression.

It is crucial to review and evaluate the magnitude that obesity affects mortality and recurrence of prostate cancer, as proper management of this modifiable lifestyle factor may help improve prostate cancer outcomes. We therefore conducted a meta-analysis to quantitatively summarize the association between BMI and risk of dying of prostate cancer in initially cancer-free men, prostate cancer–specific mortality among the diagnosed, and biochemical recurrence in the treated.

Material and Methods

Search strategy

This systematic review was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (17). We searched MEDLINE and EMBASE to identify relevant articles on human subjects that were written in English from the inception of each database to January 5, 2010, using the key words related to obesity ("obesity," "overweight," "body weight," "body mass index," "BMI," "weight," "body size," "adiposity") combined with specific terms on prostate cancer mortality or biochemical recurrence ("prostate cancer" and "mortality," "survival," "death," "prognosis," "progression" or "recurrence'). Bibliographies of retrieved articles were also searched.

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Eligibility criteria

The eligibility of each study was assessed independently by 2 investigators (Y.C., J.M.). We included only cohort studies of mid/late life BMI and prostate cancer–specific mortality (prostate cancer as the underlying cause of death) and clinical studies of BMI and biochemical recurrence after treatment. We excluded reviews, editorials, meta-analysis, animal studies or *in vitro* studies, and non-English written studies. Among the 40 studies we carried out a full-text review on, we excluded studies conducted among patients with metastatic prostate cancer (18, 19), using a broader definition of progression rather than biochemical recurrence (20) and in which BMI was not used to measure obesity (21, 22). For studies previously published on the same database (23–25), we included only the most recent findings (16, 26).

We included studies that reported standardized forms of relative risk (RR), risk ratio, hazard ratio, or odds ratio, with estimates on confidence interval (CI), and used RRs to represent various effect estimates. We excluded studies failing to report these estimates (27–30) or presenting only univariate estimates (31, 32).

Data extraction

Data extraction was conducted independently by 2 investigators (Y.C., J.M.), using a standardized data extraction form. For each included article, we extracted information on the title, authors, journal and publication year, study design, study population and setting, duration of follow-up, BMI categories, definition of biochemical recurrence, number of outcomes, the most adjusted effect estimates, and covariates controlled in multivariable analysis. For studies that presented findings from more than 1 database, we extracted only the most recent update from each of the databases (8, 33).

Statistical analysis

We analyzed BMI as a continuous variable by first transforming all the RR estimates to the corresponding RRs for every 5 kg/m^2 increase in BMI, with the assumption that the risk increment is constant, and also allowed for a fair comparison among studies using different BMI categories.

Whenever RR per kg/m^2 increase in BMI and its 95% CI were available, we used them to estimate the RR and 95% CI for every 5 kg/m^2 increase in BMI. Category-specific RRs were converted into RRs associated with every 5 kg/m^2 increase in BMI by the use of either generalized least-squares for trend estimation whenever person-time data were available or weighted least-squares method when only counts of death were available (34, 35). The value assigned to each BMI category was the midpoint for closed categories and was adjusted for half range of the neighborhood categories when categories were open ended. In 3 studies for which BMI was only divided into 2 open-ended categories, we assumed that the RR and CI estimate for the higher BMI category was similar to estimates for a 5 kg/m^2 increase in BMI (15, 36, 37). We validated such methods in studies which presented RRs for both continuous and categorical BMI and found that the RR per kg/m^2 increase obtained by conversion was similar to the RR for continuous BMI shown in the article (11).

We pooled all the RRs for a 5 kg/m^2 increase in BMI by DerSimonian–Laired random-effect meta-analysis (38) and assessed the heterogeneity between studies by Q and I^2 statistics. Sensitivity analysis was conducted by omitting one study at a time, generating the pooled estimates and comparing with the original estimates. Stratified meta-analysis was carried out by country of study, BMI measurement, definition of biochemical recurrence, and specific treatment type among patients treated with radiation therapy. Funnel plots and both Begg's and Egger's tests were used to evaluate publication bias. We also calculated population attributable risk percent (PAR%) among diagnosed prostate cancer patients by using available category specific RRs, based on prevalence of overweight and obesity of U.S. males 60 years and older from the National Health and Nutrition Examination Survey (NHANES) 2007–2008 (39).

All analyses were done using STATA version 10.0 statistical software (Stata). All statistical comparisons were 2-sided, and a value $P < 0.05$ was considered statistically significant.

Results

Data extracted and quality

Twenty-six studies met the inclusion criteria. Of these studies, 12 evaluated BMI and prostate cancer–specific mortality (1, 4, 6–13, 40, 41) and 16 assessed biochemical recurrence after primary treatment (Fig. 1; refs. 12–16, 26, 33, 36, 37, 42–48). Two (12, 13) studies presented findings on both outcomes and therefore were included in both the meta-analyses of mortality and biochemical recurrence.

Six of the 12 studies of prostate cancer–specific mortality were population-based cohort studies conducted among volunteers in the United States and Europe (1, 4, 6–8, 40). A total of 1,263,483 initially cancer-free men were prospectively followed up for an average of more than 10 years, except one with 5.5 years (4), and 6,817 men died of prostate cancer (Table 1). BMI was self-reported, measured, or retrieved from medical records at study enrollment. All the studies had controlled for smoking status.

The other 6 studies (9–13, 41) followed the survival of 18,203 diagnosed prostate cancer patients in the United States and the Netherlands; 932 prostate cancer deaths were found. Prostate cancer patients were identified from population-based case–control or cohort studies (10, 11) or various clinical settings (9, 12, 13, 41). Four studies had an average follow-up of more than 7 years, but the 2 largest studies had only 4 years of follow-up (13, 41). The 2 population-based studies assessed BMI by self-report either 1 year before diagnosis (10) or at the study entrance years before diagnosis (11). Three clinical studies measured BMI at the time of first treatment (9, 12, 13), and 1 study retrieved postdiagnostic BMI from urologists at the time of entering the CaPSURE database (41). The 2

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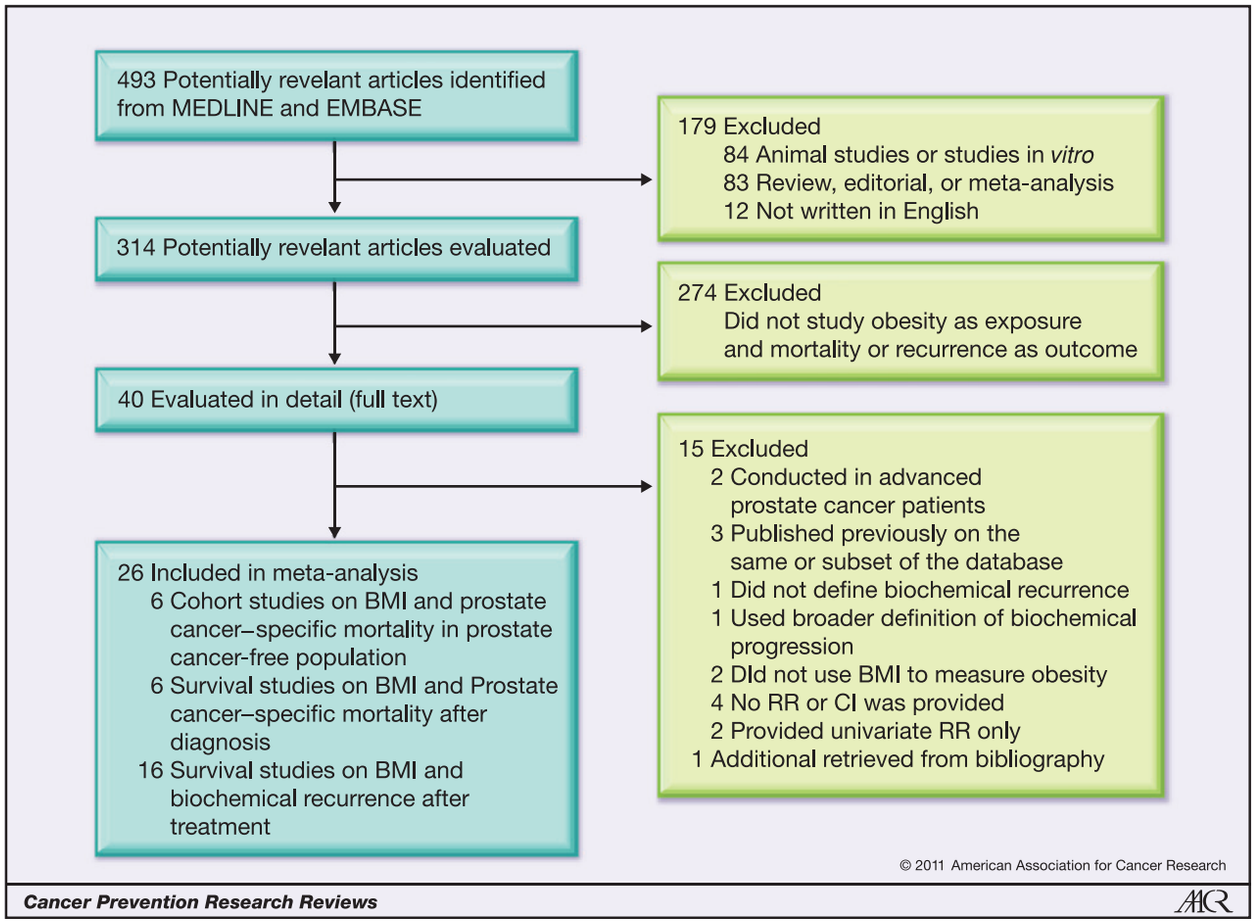

Figure 1. Selection of studies for meta-analysis.

population-based studies controlled for smoking status, but none of the 4 clinical studies did so. All the studies controlled for clinical risk, mostly through Gleason score.

The 16 studies on BMI and biochemical recurrence (12–16, 26, 33, 36, 37, 42–48) followed 26,479 prostate cancer patients after primary treatment for 2 to 10 years (Table 2). Majority of the studies were conducted in the United States, 2 in the Netherlands, 1 in Japan, and mostly in a single clinic or medical center. In most studies, BMI was measured or self-reported at study enrollment, either at diagnosis or immediately before surgery, whereas some did not indicate the timing for BMI measurement. Most studies controlled for preoperative clinical and/or pathologic characteristics (i.e., preoperative prostate-specific antigen (PSA) level, Gleason score, and surgical margin status), but none of the studies controlled for smoking status.

Main findings

The pooled estimates for the 6 cohort studies showed a significant 15% (RR: 1.15, 95% CI: 1.06–1.25, $P < 0.01$) higher risk of prostate cancer mortality associated with each 5 kg/m^2 increase in BMI (Fig. 2A). The P value for heterogeneity from the Cochran Q test ($Q = 12.23$) was 0.03 and I^2 was 59%, suggesting a moderate heterogeneity between studies.

Pooling the 6 postdiagnosis survival studies showed a 20% higher risk of prostate cancer–specific mortality (RR: 1.20, 95% CI: 0.99–1.46, $P = 0.06$) associated with each 5 kg/m^2 increase in BMI (Fig. 2A). The P value for heterogeneity from Cochran Q test ($Q = 19.18$) was less than 0.01 and I^2 was 74%, indicating high heterogeneity among studies. The high heterogeneity explains the borderline nonsignificance of the overall estimation and was mainly driven by nonsignificant inverse association reported from the CaPSURE study (41), which counted for more than a third of the pooled population.

A 5 kg/m^2 increase in BMI was associated with a 21% increased risk of biochemical recurrence (RR: 1.21, 95% CI: 1.11–1.31, $P < 0.01$; Fig. 2B). The P value for heterogeneity was less than 0.01 ($Q = 63.15$) and I^2 was 75%, suggesting a high degree of heterogeneity among studies.

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Table 1. Characteristics of identified studies on BMI and prostate cancer–specific mortality ($N = 12$)

Source	Study characteristics	BMI measurement	No. of subjects	No. of PCa deaths	BMI categories and RR (95% CI)		RR per 5 kg/m^2 increase in BMI (95% CI) and *P* value	Confounders adjusted
Population-based cohort study ($n = 6$)								
Andersson (ref. 6; J Natl Cancer Inst, 1997)	Period: 1971–1991 Setting: construction workers, Sweden Total person-years: 2,377,960	Measured BMI retrieved from medical record	135,006	708	<22.1 22.1–24.1 24.2–26.2 >26.2	1.00 1.36 (1.03–1.79) 1.33 (1.02–1.74) 1.40 (1.09–1.81)	1.25 (1.03–1.51) $P = 0.03$	Age, smoking status, marital status
Rodriguez (ref. 8; Cancer Epidemiol Biomarkers Prev, 2001)	Period: 1959–1972 Setting: CPS I, USA Total person-years: 4,120,363	Self-reported at baseline	381,638	1,590	<25 25–30 ≥30	1.00 1.02 (0.92–1.14) 1.27 (1.04–1.56)	1.08 (0.99–1.17) $P = 0.09$	Age, race, height, education, exercise, smoking status, and family history of prostate cancer
Calle (ref. 1; New Engl J Med, 2003)	Period: 1982–1998 Setting: CPS II, USA Total person-years: not shown	Self-reported at baseline	404,576	4,004	18.5–24.9 25–29.9 30–34.9 ≥35	1.00 1.08 (1.01–1.15) 1.20 (1.06–1.36) 1.34 (0.98–1.83)	1.08 (1.04–1.12) $P < 0.001$	Age, education, smoking status, number of cigarettes smoked, physical activity, alcohol use, marital status, race, aspirin use, fat consumption, and vegetable consumption
Eichholzer (ref. 40; Swiss Med Wkly, 2005)	Period: 1971–1990 Setting: employees from chemical/pharmaceutical companies, Switzerland Total person-years: not shown	Examination at study entry	2,974	30	Continuous	0.95 (0.93–1.18)	0.77 (0.70–2.29) $P = 0.42$	Age, smoking
Wright (ref. 4; Cancer, 2007)	Period: 1995–2000 Setting: NIII-AARP Diet and Health Study, USA Total person-years: 1,578,732	Self-reported at baseline	287,760	173	<25 25–29.9 30–34.9 ≥35	1.0 1.25 (0.87–1.80) 1.46 (0.92–2.33) 2.12 (1.08–4.15)	1.25 (1.04–1.50) $P = 0.02$	Age, race, smoking status, education, personal history of diabetes, and family history of prostate cancer
Giovannucci (ref. 7; Int J Cancer, 2007)	Period: 1986–2002 Setting: Health Professionals Follow-up Study, USA Total person-years: not shown	Self-reported at baseline	51,529	312	<23 23–24.9 25–27.4 27.5–29.9 ≥30	1.00 1.44 (1.01–2.05) 1.30 (0.91–1.87) 1.43 (0.93–2.22) 1.80 (1.10–2.93)	1.38 (1.16–1.66) $P < 0.001$	Age, time period, cigarette pack years, physical activity, family history of prostate cancer, BMI at 21, history of diabetes, race, intake of total calories, processed meat fish, α-linolenic acid, tomato sauce, vitamin E supplement

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Table 1. Characteristics of identified studies on BMI and prostate cancer–specific mortality ($N = 12$) (cont).

Source	Study characteristics	BMI measurement	No. of subjects	No. of PCa deaths (%)	No. of Other Deaths (%)	BMI categories and RR (95% CI)		RR per 5 kg/m^2 increase in BMI (95% CI) and *P* value	Confounders adjusted
Postdiagnosis survival study ($n = 6$)									
Siddiqui (ref. 12; Cancer, 2006)	Period: 1990–1999 Setting: 1 center, USA Treatment: RP Median follow-up: 10.1 y	Measured at surgery	5,313	151 (3%)	967 (18%)	Continuous	1.02 (0.97–1.07) $P = 0.372$	1.10 (0.86–1.40) $P = 0.37$	Gleason score, preoperative serum PSA, surgical margin status, seminal vesicle invasion, adjuvant treatment
Efstathiou (ref. 9; Cancer, 2007)	Period: 1987–1992 Setting: multicenter trial, USA Treatment: (i) RT and immediate ADT; (ii) RT and ADT at recurrence Median follow-up: 8.1 y	Measured at trial enrollment	788	169 (21%)	307 (39%)	<25 25–29.9 ≥30	1.00 1.52 (1.02–2.28) 1.64 (1.01–2.66)	1.34 (1.09–1.65) $P = 0.01$	Age, race, treatment arm, history of prostatectomy, nodal involvement, Gleason score, stage
Gong (ref. 10; Cancer, 2007)	Period: 1993–2004 Setting: participants for a population-based case–control study, USA Treatment: all types Median follow-up: 9.5 y	Self-reported BMI 1 y prior to prostate cancer diagnosis	752	50 (7%)	64 (9%)	<25 25–30 ≥30	1.00> 1.11 (0.55–2.25) 2.64 (1.18–5.92)	1.63 (1.09–2.44) $P = 0.02$	Age, race, smoking status, Gleason score, stage, primary treatment
Ma (ref. 11; Lancet Oncol, 2008)	Period: 1982–2007 Setting: Physicians' Health Study, USA Treatment: all types Median follow-up: 7 y	Self-reported at baseline	2,546	281 (11%)	485 (19%)	Continuous <25 25–29.9 ≥30	1.07 (1.02–1.12) 1.00 1.26 (0.98–1.62) 1.95 (1.17–3.23)	1.40 (1.10–1.76) $P < 0.001$	Age, baseline smoking status (1982), time interval from BMI measurement to prostate cancer diagnosis, stage, Gleason grade
van Roermund (ref. 13; BJU Int, 2009)	Period: 1991–2008 Setting: 1 center, the Netherlands Treatment: Brachytherapy Median follow-up: 3.9 y	At surgery (anesthesia record)	1,530	61 (4%)	132 (9%)	<25 25–30 ≥30	1.00 1.07 (0.60–1.88) 1.46 (0.50–4.28)	1.14 (0.77–1.69) $P = 0.51$	Age, risk group (stage, grade, and preoperative PSA), preoperative PLND, treatment period, number of seeds
Davies (ref. 41; J Urol, 2009)	Period: 1995–2007 Setting: CaPSURE, USA Treatment: all types Average follow-up: 4.3 y	After diagnosis, available information From CaPSURE	7,274	220 (3%)	824 (11.3%)	<25 25–29.9 30–34.9 ≥35	1.0 0.9 (0.7–1.2) 0.9 (0.6–1.3) 0.5 (0.2–1.2)	0.90 (0.78–1.03) $P = 0.14$	Age, clinical risk, diabetes, treatment

Abbreviation: RP, radical prostatectomy; RT, radiation therapy.

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Table 2. Characteristics of identified studies on BMI and biochemical recurrence after prostate cancer treatment ($N = 16$)

Source	Study characteristics	BMI measurement	Definition of recurrence	No. of subjects	No. of recurrence (%)	BMI categories and RR (95% CI)	RR per 5 kg/m^2 increase in BMI (95% CI) and P value	Confounders adjusted
Primary treatment: RP ($n = 11$)								
Bassett (ref. 42; Urology,2005)	Period: 1989–2002 Setting: 31 cites, USA Treatment: RP Median follow-up: 1.9 y	Not indicated	First PSA $\geq$ 0.2 ng/mL or if a second treatment after RP was needed	2,131	251 (12%)	Continuous 1.20 (1.02–1.41)	2.46 (1.10–5.48) $P = 0.03$	Stage, PSA, biopsy Gleason score, age, ethnicity, comorbidities (hypertension, diabetes, heart disease)
Strom (ref. 43; Clin Cancer Res, 2005)	Period: 1991–2001 Setting: 1 center, USA Treatment: RP Average follow-up: 4.5 y	Self-reported at diagnosis	PSA $\geq$ 0.1 ng/mL	526	97 (18%)	Continuous At diagnosis: 1.07 (1.02–1.13) < 30 1.00 $\geq$ 30 1.41 (0.91–2.18) At age 25 (univariate): < 30 1.00 $\geq$ 30 2.31 (1.01–5.30) At age 40 (univariate): < 30 1.00 $\geq$ 30 2.35 (1.43–3.86)	1.40 (1.10–1.84) $P = 0.01$	Preoperative PSA, Gleason score, pathologic stage, extraprostatic extension, seminal vesicle invasions, surgical margins, lymph node metastasis
Freedland (ref. 36; Clin Cancer Res, 2005)	Period: 1985–2004 Setting: 1 surgeon at 1 center, USA Treatment: RP Median follow-up: 5 y	Preoperative, retrieved from medical records	PSA $\geq$ 0.2 ng/mL	2,832	374 (14%)	< 30 1.00 $\geq$ 30 1.36 (0.98–1.89)	1.36 (0.98–1.89) $P = 0.07$	Age, race, height, year of surgery, clinical stage, biopsy Gleason sum, preoperative PSA; prostate weight, pathologic Gleason sum, positive surgical margins, extraprostatic extension, seminal vesicle invasion, and lymph node metastasis

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Table 2. Characteristics of identified studies on BMI and biochemical recurrence after prostate cancer treatment (N = 16) (Cont'd)

Source	Study characteristics	BMI measurement	Definition of recurrence	No. of subjects	No. of recurrence (%)	BMI categories and RR (95% CI)	RR per 5 kg/m^2 increase in BMI (95% CI) and *P* value	Confounders adjusted
Siddiqui (ref. 12; Cancer, 2006)	Period: 1990–1999 Setting: 1 center, USA Treatment: RP Median follow-up: 10.1 y	Measured at surgery	PSA ≥ 0.4 ng/mL	5,313	1,687 (32%)	Continuous 1.00 (0.99–1.01)	1.00 (0.95–1.05) *P* = 0.86	Gleason score, preoperative serum PSA, surgical margin status, seminal vesicle invasion, adjuvant treatment
Spangler (ref. 37; J Urol, 2007)	Period: 1995–2004 Setting: 1 center, USA Treatment: RP Median follow-up: 3 y	Self-reported at baseline	PSA ≥ 0.2 ng/dL	924	153 (17%)	Overall: <30 1.00 ≥30 1.76 (1.26–2.47)	1.76 (1.26–2.47)	Age, race, stage, pathology, Gleason grade, and seminal vesicle invasion
				140	29 (21%)	African American: <30 1.00 ≥30 5.49 (2.16–13.9)		
				784	124 (16%)	European American: <30 1.00 ≥30 1.41 (0.96–2.08)		
Hisasue (ref. 15; Jpn J Clin Oncol, 2008)	Period: 1998–2006 Setting: 1 center, Japan Treatment: RP Median follow-up: 1.4 y	Preoperative data	PSA elevation ≥ 0.2 ng/mL	126	30 (23%)	<26.4 1.00 ≥26.4 3.53 (1.29–9.68)	3.53 (1.29–9.68) *P* = 0.01	Age, surgical period, total testosterone, PSA, T1c stage, Gleason sum, surgical margin
Freedland (ref. 33; BJU Int, 2008)	Period: 1988–2006 Setting: 1 center (DPC), USA Treatment: RP Mean follow-up: 4.5 y	Not indicated	Single PSA > 0.2 ng/mL, 2 values of 0.2 ng/mL, or secondary treatment for a high PSA level after RP	2,014	483 (24%)	<25 1.00 25–29.9 1.16 (0.92–1.46) 30–34.9 1.43 (1.08–1.88) ≥35 1.29 (0.87–1.92)	1.14 (1.05–1.25) *P* < 0.01	Age, race, biopsy Gleason sum, clinical stage, preoperative PSA, year at surgery

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Table 2. Characteristics of identified studies on BMI and biochemical recurrence after prostate cancer treatment (N = 16) (Cont'd)

Source	Study characteristics	BMI measurement	Definition of recurrence	No. of subjects	No. of recurrence (%)	BMI categories and RR (95% CI)		RR per 5 kg/m^2 increase in BMI (95% CI) and *P* value	Confounders adjusted
Magheli (ref. 26; Urology, 2008)	Period: 1984–2006 Setting: 1 center, USA Treatment: RP Mean follow-up: 4.5 y	Not indicated	PSA ≥ 0.2 ng/mL	5,631	Not indicated	<25 25–30 ≥30	1.00 1.15 (0.89–1.49) 1.53 (1.20–1.96)	1.22 (1.09–1.36) *P* < 0.001	Age, race, Gleason score, preoperative PSA, clinical stage, year of surgery
van Roermund (ref. 48; BJU Int, 2009)	Period: 1992–2005 and 1998–2007 Setting: 2 centers, the Netherlands Treatment: RP Median follow-up: 4.9 y	Preoperative, from anesthesia records	Two subsequent PSA > 0.1 ng/mL or if a second treatment after RP was needed	1,302	297 (22.8%)	<25 25–30 ≥30	1.00 0.98 (0.74–1.29) 0.72 (0.40–1.30)	0.92 (0.75–1.12) *P* = 0.4	Not clearly indicated, Gleason score, pathologic stage
King (ref. 47; Int J Radiat Oncol Biol Phys, 2009)	Period: 1984–2004 Setting: USA Treatment: RP + salvage RT Median follow-up: 3.7 y	Clinical information, retrieved at the time of salvage RT	PSA ≥ 0.2 ng/mL with repeated measures	90	40 (36%)	Continuous	1.2 (1.04–1.4)	2.49 (1.22–5.38) *P* = 0.01	Preoperative PSA, Gleason, seminal vesicle, extracapsular extension, surgical margin, dose, pre-RT PSA, whole pelvic RT
Jayachandran (ref. 16; Cancer, 2009)	Period: Not indicated Setting: multicenters, USA Treatment: RP Median follow-up: 3.3 y	At surgery	Single PSA > 0.2 ng/mL, or 2 PSA at 0.2 ng/mL, or if a second treatment after RP was needed	Total: 1,415 Black: 662 White: 753	Total: 452 (31.9%) Black: 222 (33.5%) White: 230 (30.5%)	Continuous	Black: 1.04 (1.01–1.07) White: 1.06 (1.03–1.10)	Black: 1.22 (1.05–1.40) *P* = 0.01 White: 1.34 (1.16–1.61) *P* < 0.001	Age, pathologic Gleason score, prostate weight, extracapsular extension, positive surgical margins, seminal vesicle invasion, lymph node involvement, preoperative PSA, year of surgery, and center

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Table 2. Characteristics of identified studies on BMI and biochemical recurrence after prostate cancer treatment ($N = 16$)

Source	Study characteristics	BMI measurement	Definition of recurrence	No. of subjects	No. of recurrence (%)	BMI categories and RR (95% CI)	RR per 5 kg/m^2 increase in BMI (95% CI) and *P* value	Confounders adjusted	Source
Primary treatment: RT ($n = 5$)									
Strom (ref. 44; Cancer, 2006)	Period: 1988–2001 Setting: 1 center, USA Treatment: EBRT Average follow-up: 8 y	Retrieved from medical record at initial examination of EBRT	ASTRO, 3 consecutive increases in posttreatment PSA after achievement of a nadir	873	168 (19%)	Continuous	1.04 (1.02–1.07)	1.22 (1.10–1.40) $P < 0.01$	Clinical stage, Gleason score, PSA, dose, year of diagnosis
Efstathiou (ref. 14; Cancer, 2007)	Period: 1995–2001 Setting: multicenter trial, USA Treatment: RT + ADT Median follow-up: 6.9 y	Available at baseline	PSA ≥1.0 ng/mL and increased by more than 0.2 ng/mL on 2 consecutive measurements	99	25 Y(25%)	Continuous	1.10 (1.01–1.19)	1.61 (1.05–2.39) $P = 0.03$	PSA, age, Gleason, stage
Stroup (ref. 45; Cancer, 2007)	Period: 1989–2003 Setting: multicenter database, USA Treatment: EBRT Median follow-up: 3.6 y	Retrieved from medical record	PSA nadir + ≥2 ng/mL	1,320	554 (42%)	Continuous	1.03 (1.01–1.05) $P < 0.01$	1.13 (1.03–1.25) $P < 0.01$	PSA, dose, ethnicity, stage, Gleason score, neoadjuvant ADT, PSA nadir after EBRT, year of diagnosis
Efstathiou (ref. 46; Int J Radiat Oncol Biol Phys, 2008)	Period: 1996–2001 Setting: 2 centers, USA Treatment: Brachytherapy Median follow-up: 6 y	Available at baseline	PSA nadir + ≥2 ng/mL	353	76 (21%)	<25 25–30 ≥30	1.00 0.76 (0.45–1.29) 0.56 (0.29–1.10)	0.75 (0.43–1.32) $P = 0.32$	Age, race, preimplantation PSA, Gleason score, T stage, percent of prescription dose to 90% of the prostate, use of supplemental EBRT and ADT
van Roermund (ref. 13; BJU Int, 2009)	Period: 1991–2008 Setting: 1 center, the Netherlands Treatment: Brachytherapy Median follow-up: 3.9 y	Preoperative, from anesthesia records	PSA nadir + ≥2 ng/mL	1,530	249 (16.3%)	<25 25–30 ≥30	1.00 1.00 (0.77–1.31) 1.15 (0.72–1.85)	1.04 (0.87–1.24) $P = 0.7$	Age, risk group (stage, grade and preoperative PSA), preoperative PLND, treatment period, number of seeds

Abbreviations: RP, radical prostatectomy; RT, radiation therapy; EBRT, external beam radiation therapy.

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We also evaluated the association by types of treatment because severe obesity might prohibit patients from receiving surgical treatment and thus bias the overall estimate. Among the 11 (12 data points) studies of radical prostatectomy (RP), 10 (11 data points) showed positive associations and 9 were statistically significant. The pooled estimate showed that a 5 kg/m^2 increase in BMI was associated with a significant 25% higher risk of biochemical recurrence (RR: 1.25, 95% CI: 1.12–1.40, $P < 0.01$; $Q = 54.63$, $I^2 = 79\%$). Among patients treated with radiation therapy with or without androgen deprivation therapy (ADT), 4 of the 5 studies showed positive associations and 3 were statistically significant. The pooled estimate showed that a 5 kg/m^2 increase BMI was associated with a significant 15% higher risk of biochemical recurrence (RR: 1.15, 95% CI: 1.03–1.28, $P = 0.01$; $Q = 7.09$, $I^2 = 44\%$).

Sensitivity analysis

We conducted sensitivity analysis by omitting one study at a time, generating the pooled estimates and comparing with the original estimates. Omitting any 1 of 6 population-based cohort studies had no dramatic influence on the original pooled RRs, with newly pooled RR ranging from 1.11 (95% CI: 1.04–1.18) to 1.20 (95% CI: 1.05–1.35). In the 6 postdiagnosis survival studies, omitting the study of Davies and colleagues generated a significant RR of 1.30 (95% CI: 1.15–1.47) whereas none of the other had a huge influence on the original estimates, with RRs ranging from 1.17 (95% CI: 0.95–1.39) to 1.26 (95% CI: 0.99–1.54). Of the 16 studies on BMI and biochemical recurrence, none of the studies altered significance of the original estimate with newly pooled RRs from 1.24 (95% CI: 1.14–1.34) to 1.30 (95% CI: 1.19–1.41).

Subsequent sensitivity analysis by stratification suggested greater RR in studies conducted in the United States than in Europe, self-reported BMI compared with measured BMI in population-based cohort study, postdiagnosis survival study, and study of biochemical recurrence among patients treated with RP (Table 3). RR was slighter lower and nonsignificant (RR: 1.24; 95% CI: 0.98–1.58) in studies (12, 37, 42, 43, 48) that used definition of biochemical recurrence other than single PSA level of 0.2 ng/mL or more (15, 26, 36, 47) or single PSA level of more than 0.2 ng/mL, 2 values of 0.2 ng/mL, or secondary treatment of a high PSA level after RP (16, 33). Among patients treated with radiation therapy, no association between BMI and biochemical recurrence was detected in patients receiving brachytherapy (RR: 0.99, 95% CI: 0.78–1.25; refs. 13, 46).

Publication bias

Publication bias was not observed among the 6 population-based cohort studies and the 6 postdiagnosis survival studies on BMI and prostate cancer–specific mortality. Significant publication bias as indicated by an asymmetric funnel plot among the 16 studies on BMI and biochemical recurrence revealed the possibility of selective publication of positive findings.

Population attributable risk percent in diagnosed patients

In total, 20% of the prostate cancer deaths were attributable to overweight (10.9%) and obesity (9.1%), without the study by Davies and colleagues. With this study, the PAR% was 11.7% in total, 6.1% from overweight and 5.6% from obesity.

Discussion

We found that higher BMI in initially cancer-free population was significantly associated with higher risk of future prostate cancer mortality. Among diagnosed patients, higher BMI was associated with a significantly higher risk of biochemical recurrence after primary treatment and a borderline nonsignificantly elevated risk of prostate cancer–specific mortality. To our knowledge, this is the first meta-analysis that comprehensively summarized and quantitatively analyzed the current findings on obesity and outcomes of prostate cancer.

Previously, 2 meta-analyses on BMI and risk of prostate cancer were published but each addressed different hypothesis compared with our study. Robinson and colleagues summarized findings on the association of childhood and young adulthood BMI and risk of developing advanced prostate cancer and fatal prostate cancer (only 1 study on fatal outcome), and the RR was close to the null (RR: 1.01, 95% CI: 0.89–1.14) for each 5-unit increase in BMI (49), indicating little impact of young adulthood BMI on risk of advanced prostate cancer. MacInnis and colleagues meta-analyzed both cohort and case–control studies on BMI and risk of developing advanced prostate cancer and found that BMI was associated with 12% higher risk of advanced prostate cancer (RR: 1.12, 95% CI: 1.01–1.23) for each 5-unit increase in BMI (2). However, the association of BMI and fatal prostate cancer was not addressed in that study. In the present study, we assessed end points of disease progression such as prostate cancer mortality and biochemical recurrence among healthy population and among the diagnosed patients to specifically evaluate the role of adiposity on prostate cancer progression.

Overall, we found that the magnitude of the pooled effect estimates were quite similar to 15% to 21% increased risk for each 5 kg/m^2 increase in BMI, despite different study designs (cohort or survival studies), study settings (cohort from healthy group or clinical studies), outcome assessments (prostate cancer–specific mortality or recurrence), or from multiple countries with different social economic or racial (Caucasians, African Americans, and Asian men) backgrounds. The similar pooled estimates across different types of clinical treatments further suggest the robust association between obesity and prostate cancer progression.

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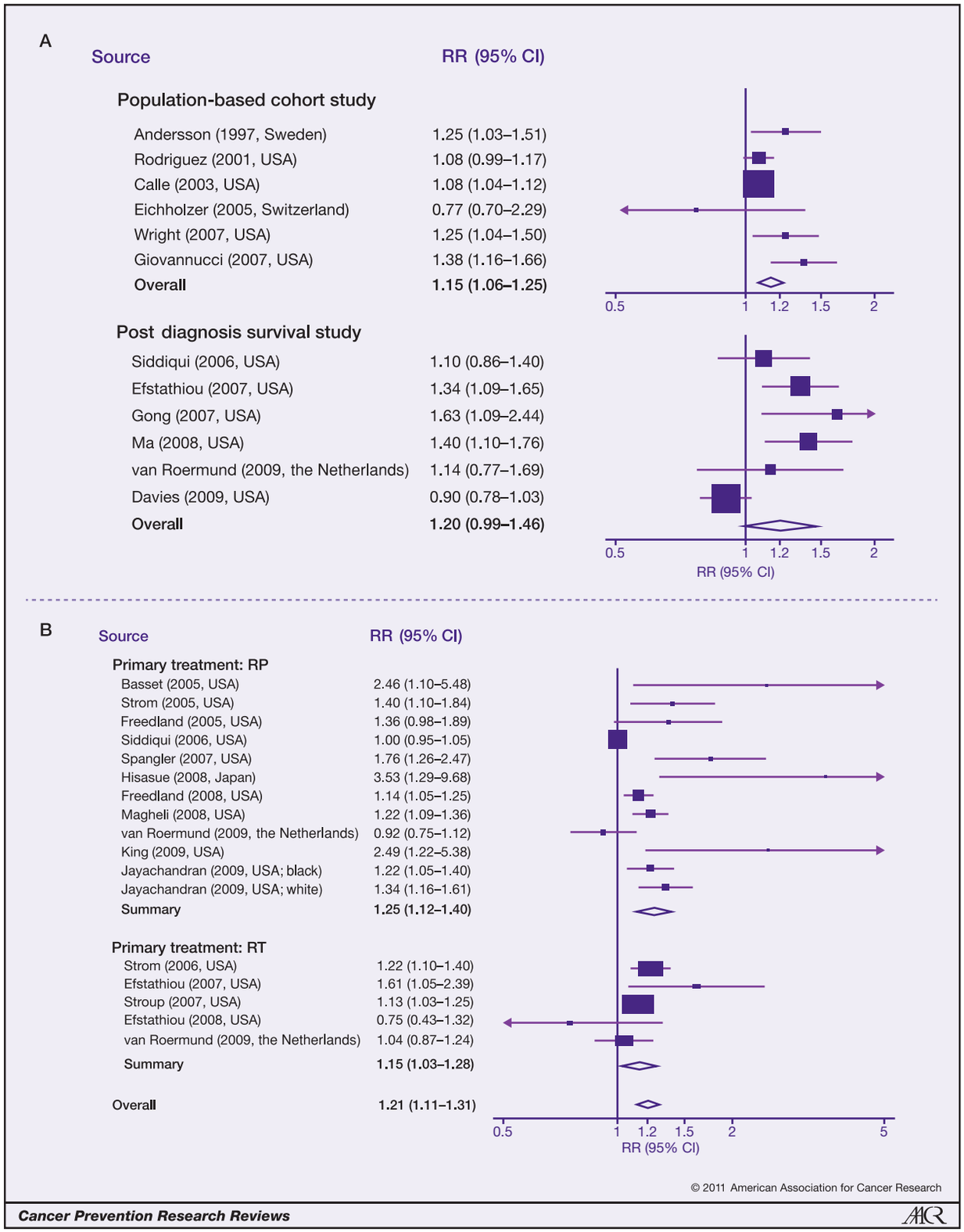

Figure 2. A, RRs per 5 kg/m^2 increase in BMI and prostate cancer–specific mortality. B, RRs per 5 kg/m^2 increase in BMI and biochemical recurrence after treatment. RP, radical prostatectomy; RT, radiation therapy, including brachytherapy, external beam radiation therapy, and radiation therapy with androgen suppression therapy.

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Table 3. Stratified meta-analysis of the association of BMI and prostate cancer-specific mortality and biochemical recurrence

Study type	No. of studies	RR per 5 kg/m^2 increase in BMI (95% CI)
BMI and prostate cancer–specific mortality		
Population-based cohort study		
Country (BMI measurement)		
USA (self-reported BMI)	4	1.15 (1.05–1.25)
Europe (measured BMI)	2	1.07 (0.68–1.67)
Postdiagnosis survival study		
Country		
USA	5	1.21 (0.97–1.51)
Europe	1	1.14 (0.77–1.69)
BMI measurement		
Self-reported	2	1.46 (1.19–1.78)
Measured	4	1.10 (0.89–1.35)
BMI and biochemical recurrence after treatment		
Primary treatment: RP		
Country		
USA	9	1.27 (1.13–1.43)
Europe	1	0.92 (0.75–1.12)
Asia	1	3.53 (1.29–9.68)
BMI measurement		
Self-reported at/around diagnosis	2	1.53 (1.23–1.90)
Measured preoperative BMI	7	1.21 (1.02–1.44)
Definition of biochemical recurrence		
PSA $\geq$ 0.2 ng/mL	4	1.32 (1.13–1.52)
Single PSA >0.2 ng/mL, 2 values of 0.2 ng/mL, or secondary treatment for a high PSA level after RP	2	1.22 (1.04–1.42)
Others	5	1.24 (0.98–1.58)
Primary treatment: RT		
Treatment		
EBRT	2	1.16 (1.08–1.26)
Brachytherapy	2	0.99 (0.78–1.25)

Abbreviations: RP, radical prostatectomy; RT, radiation therapy; EBRT, external beam radiation therapy.

Several possible explanations have been proposed. First, such association could be due to delayed diagnosis and more advanced stage at diagnosis in obese men. It has been suggested that obesity makes early detection of prostate cancer more difficult due to less PSA screening, lower accuracy of digital rectal examination in obese men, and lower PSA values caused by obesity-related hemodilution (33, 50). Obese individual has higher chance to be missed, as the cancer detected by PSA screening is so small and larger prostate gland (51) makes the detection of existent cancer less likely (52). Although the existence of such detection bias could not be fully ruled out, studies by Wright and colleagues and Ma and colleagues suggested that elevated BMI was significantly associated with higher risk of prostate cancer–specific mortality in those without PSA screening (4) and in both pre- and PSA screening era (11). Alternatively, difficulties in treatment, such as increased risk of positive surgical margins (12, 23, 31), and the greater day-to-day variation in prostate location that leads to lower dose and less effective radiation (53) could also contribute to the poorer outcome observed in diagnosed patients. However, the association with recurrence is still strong and significant after adjusting for margin status in many of the studies included in our analysis (Table 2).

Potential biological mechanisms of adiposity and prostate cancer progression have been proposed and are under investigation. Hormonal and metabolic changes in obese men are the primary concern. One hypothesis is that certain obesity-related metabolic dysregulation such as hyperinsulinemia and/or hypoadiponectinemia favors aggressive neoplastic behavior (11, 54). It was also found that lower levels of testosterone in obese men might be linked to poorly differentiated and hormone-insensitive tumors (55, 56). Obesity is also associated with increased levels of free insu-

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lin-like growth factor-I, which is found to stimulate growth of prostate cell lines *in vitro* and be more closely related to advanced stage prostate cancer in human (57).

High heterogeneity was detected among the studies reviewed in the present analysis. The stratified meta-analyses suggested strong and consistent association between BMI and higher prostate cancer mortality and biochemical recurrence in studies conducted in the United States. Smaller RRs in the few available studies from Europe could be attributable to large variability in the linear transformed RRs under a lower prevalence of obesity in European countries. We also found that studies using self-reported BMI presented stronger association than studies utilizing measured BMI, and different magnitudes of association between BMI and biochemical recurrence among patients on different radiation therapies were also observed. These evidences reflected the need for investigations in different countries and among different subgroup of patients.

In further reviewing the heterogeneity between cohort studies and clinical studies, several issues are worth noting. First, missing data of BMI and shorter period of follow-up in clinical studies could bias the estimate and limit the findings. For example, in the study by Siddiqui and colleagues, 23% of the patients had missing BMI, and in Davies and colleagues, only 53% of the patients in the CaPSURE database were included. Both studies and the study by van Roermund and colleagues reported lower prostate cancer–specific mortality (3%–4%) than other studies either due to short follow-up of 3 to 4 years or selection of much healthier individuals. Second, clinical studies have detailed treatment information but many of these studies lack data for major confounding factors such as cigarette smoking. The J-shape association of BMI with total mortality confounded by cigarette smoking (58, 59) may apply similarly to BMI and prostate cancer mortality, as current smokers may have increased risk of dying of prostate cancer (60, 61). However, none of the clinical studies included in our analysis controlled for smoking. In contrast, although large prospective cohort studies tend to have a more valid measurement of exposure and covariates, as well as complete follow-up, these studies usually lack detailed clinical treatment information. Therefore, the totality of the evidence obtained from different population, study settings, and outcome assessments in our meta-analysis provides a more objective conclusion.

Over the past 2 decades, widespread PSA screening significantly increased the number of prostate cancers detected at very early stage whereas cancer-specific mortality remains relatively constant over time (62). Many men with localized tumors, especially obese or overweight men, are likely to have diabetes and cardiovascular disease and are more likely to die of diseases other than prostate cancer. Because the majority of the studies reviewed in this meta-analysis did not control for competing causes of death, the pooled RR could be an attenuated estimate.

Timing of the BMI assessment is important to evaluate the possibility of reverse causation, that is, weight change influenced by disease severity or treatments (e.g., ADT causes weight gain even after a short period of treatment; ref. 63), and is crucial to the design of intervention. In our study, all of the 6 cohort studies and study by Ma and colleagues assessed BMI years in midlife and found stronger association, suggesting that adiposity precede cancer progression. Although whether weight control will help improve outcomes among overweight and obese patient remains uncertain, our findings from BMI measured at diagnosis or before surgery suggest additional clinical benefit to improve outcome from prostate cancer. In a recent study among patients underwent prostatectomy, Joshu and colleagues found that, those whose weight increased >2.2 kg from 5 years before to 1 year after surgery had twice the recurrence risk (HR = 1.94, 95% CI 1.14–3.32) compared with those who had stable weights (64), further supported the detrimental effect of adiposity and prostate cancer progression. Together, these data provide encouraging evidence for using weight management to prevent disease progression and prostate cancer-specific mortality. Interventions may include increasing self-awareness, more early detection efforts by health care professionals, more counseling on healthy lifestyle (i.e., exercise) after diagnosis, and appropriate individualized treatment of overweight or obese patients.

The strengths of our study include the use of generalized least-squares methods for RR transformations associated with a standard per 5 kg/m^2 increase in BMI to allow for comparisons among different studies using different BMI categories, the use of the random-effect model to incorporate heterogeneity, separated analysis on BMI and fatal prostate cancer by different study design and different outcomes, sensitivity analysis, and estimation of population attributable risk.

Meta-analysis of observational studies cannot avoid undetected biases and confounding factors inherent in the original studies. Analyzing BMI as a continuous variable by first transforming all the RR estimates to the corresponding RRs for every 5 kg/m^2 increase in BMI was a way to allow for comparisons among studies, but it also assumed the risk increment was constant. We validated such methods in studies that presented RRs for both continuous and categorical BMI and found that the RR per kg/m^2 increase obtained by conversion was similar to the RR for continuous BMI shown in the article (11).

We did not include 4 studies (27–30) on biochemical recurrence that did not present RR estimates or CIs. Among these 4 studies, 2 studies in Canada showed that elevated BMI was predictive of reduced biochemical disease-free survival among patients treated with radiation therapy (27) or RP (30). Another 2 consecutive studies by Merrick and colleague showed null association between BMI and biochemical recurrence-free survival in patients treated with brachytherapy, which were consistent with studies included in our meta-analysis (Table 3). We also excluded 2 studies that presented only univariate RR estimates because the association of BMI and prostate cancer outcome is potentially confounded by confounding factors such as

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age. Among these 2 studies, Motamedinia and colleagues found no difference in the actual observed biochemical failure rate of obese and nonobese patients, whereas Amling and colleagues showed that obesity alone predicted biochemical recurrence with RR of 1.20 (95% CI: 1.02–1.42) for obese versus nonobese patients. The association was not significant in the multivariate model after adjusting for pathologic variables, but the study unfortunately did not present the data. They also found that increased BMI was associated with worse pathologic outcomes, that is, BMI was an independent predictor of higher Gleason cancer grade, thus suggested that the association between obesity and poor biochemical recurrence could be mediated by pathologic factors. If true, our pooled RR would be a conservative estimate of the association between BMI and biochemical recurrence, as majority of the studies included in our meta-analysis had adjusted for pathologic variables.

In conclusion, this meta-analysis provides the first quantitative assessment of the evidence accumulated up to date from 26 studies of a pooled population of 1,302,246 from different countries and various study designs, and majority were published within the past 5 years. It showed a consistent 15% to 21% increased risk of fatal prostate cancer or biochemical recurrence and an estimated 12% to 20% of prostate cancer deaths could be attributable to overweight and obesity. Further investigations are needed to evaluate the role of BMI measured at different stages of life, before, at, or after prostate cancer diagnosis, and the impact of weight control on prostate cancer–specific and all-cause mortality. Studies of biomarkers and genetic markers related to adiposity and energy metabolism will provide biological plausibility for a causal role and can guide the development of effective and targeted cancer prevention and therapeutic strategies. Randomized weight control interventions in clinical setting or community-based program could provide a more definitive answer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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