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Original Contribution

Obesity and Prostate Cancer Risk According to Tumor *TMPRSS2:ERG* Gene Fusion Status

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The *T2E* gene fusion, formed by fusion of the transmembrane protease, serine 2, gene (*TMPRSS2*) with the erythroblast transformation-specific (ETS)-related gene (*ERG*), is found in approximately 50% of prostate cancers and may characterize distinct molecular subtypes of prostate cancer with different etiologies. We investigated the relationship between body mass index (BMI; weight (kg)/height $(m)^2$) and prostate cancer risk by *T2E* status. Study participants were residents of King County, Washington, recruited for 2 population-based case-control studies conducted in 1993–1996 and 2002–2005. Tumor *T2E* status was determined for 563 prostate cancer patients who underwent radical prostatectomy. Information on weight, height, and covariables was obtained through in-person interviews. We performed polytomous logistic regression to calculate odds ratios and 95% confidence intervals for *T2E*-positive and -negative prostate cancer. Comparing the highest BMI quartile with the lowest, inverse associations were observed between recent (≥29.7 vs. <24.5: odds ratio = 0.66, 95% confidence interval: 0.45, 0.97) and maximum (≥31.8 vs. <25.9: odds ratio = 0.69, 95% confidence interval: 0.47, 1.02) BMI and the risk of *T2E*-positive prostate cancer. No significant associations were seen for men with *T2E*-negative tumors. This study provides evidence that obesity is specifically associated with reduced risk of developing androgen-responsive *T2E* fusion–positive tumors. The altered steroid hormone profile in obese men may contribute to this inverse association.

body mass index; obesity; prostate cancer; *TMPRSS2:ERG* gene fusion

Abbreviations: BMI, body mass index; CI, confidence interval; *ERG*, ETS-related gene; ETS, erythroblast transformation-specific; OR, odds ratio; PSA, prostate-specific antigen; *T2E*, *TMPRSS2:ERG* gene fusion; *TMPRSS2*, transmembrane protease, serine 2, gene.

Fusion of the transmembrane protease, serine 2, gene (*TMPRSS2*) and the erythroblast transformation-specific (ETS)-related gene (*ERG*), creating the *TMPRSS2:ERG* (*T2E*) gene fusion, is found in approximately 50% of prostate cancers (1–5). *TMPRSS2* encodes for a transmembrane serine protease and harbors androgen-responsive elements in the promoter region. *ERG* encodes for a nuclear protein that binds to DNA and acts as a transcription factor (6). When fused with *TMPRSS2*, the activity of the *ERG* gene increases and becomes regulated by androgens. Recent evidence suggests that *T2E* fusion status may characterize distinct molecular subtypes of prostate cancer that have different etiologies (2, 7–10). For example, 1 study found an association between obesity and lethal prostate cancer that was modified by *T2E* status (10). Few studies to date, however, have considered the possibility that environmental or lifestyle factors such as obesity may have differing associations with risk of prostate cancer when tumors are stratified by molecular profile.

Obesity is associated with changes in levels of several circulating proteins, including steroid hormones, and has therefore been hypothesized to play a role in the development of prostate cancer (11). The evidence for an association between body mass index (BMI) and prostate cancer risk has not been consistent across studies, possibly due to the etiological and molecular heterogeneity of the disease (12, 13). We hypothesized that molecular profiling of prostate tumors by *T2E*

status might allow for more specific assessment of the role of obesity in relation to prostate cancer.

To further evaluate the potential contribution of BMI to the risk of developing specific molecular subtypes of prostate cancer, we stratified cases by tumor *T2E* status. We hoped that this analysis might also provide new insights into the influence of the hormonal environment associated with obesity on prostate carcinogenesis.

METHODS

Study population

Study participants were white and black residents of King County, Washington, who were identified for 2 prior population-based case-control studies (14, 15). Incident cases were men who were diagnosed with histologically confirmed prostate cancer and were identified via the Seattle-Puget Sound Surveillance, Epidemiology, and End Results (SEER) cancer registry. Cases from the first study were 40- to 64-year-old men diagnosed between 1993 and 1996. Cases from the second study were 35- to 74-year-old men diagnosed between 2002 and 2005. In total 1,754 prostate cancer patients were interviewed, of whom 984 underwent radical prostatectomy as primary treatment.

Cases who underwent radical prostatectomy were less likely to be classified in the highest BMI quartile (≥29.7) than patients treated with other therapies (19.5% vs. 26.1%; $P = 0.001$). Radical prostatectomy patients were also less likely to have a diagnostic prostate-specific antigen (PSA) level ≥20 ng/mL (6.4% vs. 14.8%; $P < 0.0001$) and to have a tumor with Gleason score ≥7 (4 + 3) (13.9% vs. 18.5%; $P = 0.01$) (16). Of the 984 radical prostatectomy cases, 563 had tumor tissue available, were eligible for the current study, and had *T2E* fusion status determined. Cases with determined fusion status had a higher frequency of high-grade tumors (Gleason score ≥7 (4 + 3)) than cases who had not had their fusion status determined (15.8% vs. 11.4%; $P = 0.05$). There were no statistically significant differences in age, race, BMI, pathological stage of disease, history of PSA screening, or diagnostic PSA levels between these 2 groups.

Population-based controls without a history of prostate cancer ($n = 1{,}645$) were identified using random digit telephone dialing, recruited evenly throughout the ascertainment periods for cases, and frequency-matched to cases by 5-year age group. All participants gave signed informed consent for participation, and the studies were approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Data collection

Trained staff conducted in-person interviews using a structured questionnaire about demographic and lifestyle factors, personal and family medical history, and prostate cancer screening history. Information on dietary intake was collected with a validated food frequency questionnaire, which was completed by 89.2% of the cases and 90.7% of the controls. The study questionnaire contained questions about weight 1 year before diagnosis (cases) or the reference date (controls), maximum weight, weight during ages 18 and 29 years, and maximum adult height. The question about weight at ages 18–29 years differed slightly between the 2 case-control studies; the first study inquired about usual weight when participants were in their 20s, while the second study included a question about usual weight at age 18 years. BMI was calculated as weight (kg) divided by maximum adult height (m) squared. Participants with extreme BMI values (<16.5 or >65) were excluded from the analyses.

Determination of *T2E* status

Formalin-fixed and paraffin-embedded tumor tissue blocks from radical prostatectomy specimens were collected and used to make hematoxylin-and-eosin slides. These slides were reviewed by a prostate pathologist, who marked areas containing ≥75% tumor tissue. From these areas, two 1-mm tumor cores were taken and embedded in recipient paraffin blocks for the creation of tumor tissue microarrays.

For identification of the *T2E* gene fusion, fluorescence in situ hybridization "break-apart" assays were performed as previously described (17). A 2-color fluorescence in situ hybridization technique was used, and the green fluorescein isothiocyanate signals were amplified with goat anti-fluorescein isothiocyanate Fluorescein/Oregon Green Antibody, Alexa Fluor 488 conjugate (Life Technologies, Carlsbad, California) antibodies. Pictures were made with a Zeiss Axioplan 2 imaging system (Carl Zeiss AG, Oberkochen, Germany) using Metafer (MetaSystems, Altlussheim, Germany) imaging software. A 4′,6-diamidino-2-phenylindole prescan (10× magnification) of the whole tumor tissue microarray slide was used to identify the core positions. Core identification numbers were assigned using a tumor tissue microarray tool implemented in Metafer. Each core was scanned at 40× magnification, in a 6 × 9 grid of 54 fields. Each field was photographed in at least 3 different focus planes with filters for fluorescein isothiocyanate and cyanine 3. Referring layer and filter captures were then merged into 1 final 3-colored image per field. Each core was evaluated by 2 separate individuals to determine whether the specimen was *T2E*-positive or *T2E*-negative. If there was disagreement, the specimen was reviewed until consensus was reached. There were 48 (7.9%) cases excluded because cores could not be evaluated. Cores were considered positive if multiple cells contained the *T2E* rearrangement. Of the 270 cases with a *T2E*-positive tumor who had 2 cores evaluated, there were 37 (13.7%) for whom only 1 of those cores was positive for the fusion. For 38 (6.7%) cases, *T2E* status had been determined using fluorescence in situ hybridization for a prior analysis (18), and those data were included.

Statistical analyses

Quartiles of BMI were computed based on the distribution of BMI values in the controls. Secondly, we categorized BMI according to World Health Organization definitions: <25, 25–<30, 30–<35, and ≥35 (19). BMI was also modeled as a continuous variable using 5-unit increments. Polytomous logistic regression was performed to calculate odds ratios and 95% confidence intervals for developing a *T2E*-positive

Table 1. Medical and Demographic Characteristics of Prostate Cancer Cases Who Underwent Radical Prostatectomy and Population-Based Controls, by Tumor *TMPRSS2:ERG* Gene Fusion Status, King County, Washington, 1993–1996 and 2002–2005

Factor	Controls ($n = 1,645$)		Cases			
			T2E-Negative ($n = 268$)		*T2E*-Positive ($n = 295$)	
	No.[a]	%	No.	%	No.	%
Age at reference date, years[b]	59.2 (7.2)		59.3 (6.9)		56.9 (6.6)	
Race						
White	1,529	92.9	238	88.8	280	94.9
Black	116	7.1	30	11.2	15	5.1
Positive family history of prostate cancer[c]	178	10.8	64	23.9	63	21.4
Smoking status						
Never smoker	695	42.3	112	41.8	128	43.4
Former smoker	716	43.6	133	49.6	135	45.8
Current smoker	233	14.2	23	8.6	32	10.9
Positive history of diabetes	148	9.0	11	4.1	12	4.1
Educational level						
High school or less	314	19.1	47	17.5	46	15.6
Some college or vocational school	401	24.4	71	26.5	67	22.7
Bachelor's degree	453	27.6	84	31.3	93	31.5
Graduate degree	476	29.0	66	24.6	89	30.2
Annual household income						
<$50,000	570	34.7	74	27.6	64	21.7
$50,000–$99,999	672	40.9	103	38.4	119	40.3
≥$100,000	369	22.4	85	31.7	104	35.3
Unknown	34	2.1	6	2.2	8	2.7
Frequency of strenuous physical activity, times/week						
0	353	21.5	48	17.9	68	23.1
1	354	21.5	49	18.3	65	22.1
2–3	517	31.5	105	39.2	89	30.3
≥4	420	25.6	66	24.6	72	24.5

Table continues

or -negative tumor in comparison with controls. Recent BMI was used for all models to assess potential confounding. All models were adjusted for age (5-year categories) and race (white, black). Further adjustment for possible confounders, including frequency of strenuous exercise per week (0, 1, 2–3, or ≥4 times/week), annual household income (<$50,000, $50,000–$99,999, ≥$100,000, or unknown), first-degree family history of prostate cancer (no, yes), smoking status (never, former, or current), number of PSA tests within the past 5 years (none, 1–2, 3–4, ≥5, or unknown), and history of diabetes (no, yes), was performed to assess whether such factors changed the odds ratios comparing the highest BMI quartile with the lowest by more than 5%. Adjustment for dietary factors, including intakes of cruciferous vegetables, lycopene, red meat, calcium, dairy products, eicosapentaenoic acid, docosahexaenoic acid, and fried foods and percentage of calories derived from fat, was also performed for the subset of participants with food frequency questionnaire data. Categorization of the dietary variables was based on quartiles derived from the distributions among the controls. All *P* values were 2-sided, and they were considered statistically significant at the <0.05 level. All analyses were performed using SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Table 1 shows the distribution of descriptive variables for controls and cases according to *T2E* fusion status. *T2E* fusion status was positive in 295 (52%) of the 563 cases. As expected, cases were more likely to have a positive family history of prostate cancer than controls. A lower proportion of cases than of controls were current smokers, had a history of diabetes, or reported a low income. In case-case comparisons, *T2E*-positive cases were younger at diagnosis, were more likely to be white, and were more likely to have tumors with a Gleason score ≤7 (3 + 4) than *T2E*-negative cases.

Table 1. Continued

Factor	Controls ($n = 1,645$)		Cases			
			T2E-Negative ($n = 268$)		*T2E*-Positive ($n = 295$)	
	No.[a]	%	No.	%	No.	%
No. of PSA screening tests within past 5 years						
0	596	36.2	49	18.3	70	23.7
1–2	303	18.4	62	23.1	71	24.1
3–4	188	11.4	53	19.8	63	21.4
≥5	290	17.6	91	34.0	78	26.4
Unknown	268	16.3	13	4.9	13	4.4
PSA level, ng/mL[d]						
<4.0	1,259	76.5	33	12.3	54	18.3
4.0–9.9	81	4.9	156	58.2	176	59.7
≥10.0	18	1.1	62	23.1	48	16.3
Unknown/no PSA test	287	17.5	17	6.3	17	5.8
Gleason score[e]						
≤6			117	43.7	161	54.6
7 (3 + 4)			96	35.8	100	33.9
7 (4 + 3)			32	11.9	15	5.1
8–10			23	8.6	19	6.4
Tumor pathological stage						
Local (T2)			186	69.4	200	67.8
Regional (T3)			82	30.6	95	32.2

Abbreviations: *ERG*, ETS-related gene; ETS, erythroblast transformation-specific; PSA, prostate-specific antigen; *T2E*, *TMPRSS2:ERG* gene fusion; *TMPRSS2*, transmembrane protease, serine 2, gene.

[a] Numbers in some sections of the table do not add up to the totals because of missing data.

[b] Value is presented as mean (standard deviation). Age ranges (in years) were 40–74 for controls, 42–74 for *T2E*-negative cases, and 35–72 for *T2E*-positive cases.

[c] History of prostate cancer in a first-degree relative.

[d] PSA level was measured at diagnosis for cases and at interview for controls.

[e] Gleason grade describes 5 distinct patterns of glandular differentiation and growth of tumor cells based on microscopic appearance. The most common (primary) tumor pattern and the second most common (secondary) tumor pattern are each given a grade of 1–5. The primary and secondary grades are then combined to create a Gleason score or sum, which ranges from 2 (well differentiated) to 10 (poorly differentiated, anaplastic) (16).

Table 2 shows the distribution of controls and cases by *T2E* status and the corresponding odds ratios according to BMI. The final model adjusted for age, race, and history of diabetes. Two cases and 5 controls with a BMI lower than 16.5 at ages 18–29 years were omitted from analyses of BMI in young adulthood. No statistically significant association between BMI at ages 18–29 years and *T2E* status was observed, when comparing the highest BMI quartile (≥24.5) with the lowest quartile (<21.1). However, when BMI was analyzed as a continuous variable, every 5-unit increase in young adult BMI was associated with a 17% reduction in the odds ratio (odds ratio (OR) = 0.83, 95% confidence interval (CI): 0.68, 1.03) for a *T2E*-positive tumor.

Overall, 24.8% of the controls had a recent BMI greater than or equal to 29.7 (the highest quartile for recent BMI), compared with 20.5% of the *T2E*-negative cases and 17.0% of *T2E*-positive cases. The odds ratio for having *T2E*-negative prostate cancer was 0.87 (95% CI: 0.59, 1.27) when the highest BMI quartile (≥29.7) was compared with the lowest (<24.5), while the corresponding odds ratio for having a *T2E*-positive tumor was 0.66 (95% CI: 0.45, 0.97). The aforementioned odds ratios comparing the highest BMI quartile with the lowest were not significantly different between *T2E*-negative and *T2E*-positive prostate cancer (*P* for heterogeneity = 0.23). With every 5-unit increase in recent BMI, the odds ratio for a *T2E*-positive tumor declined by 14% (OR = 0.86, 95% CI: 0.73, 1.00). Analyses limited to the subset of participants who had food frequency questionnaire data revealed that adjustment for percentage of calories from fat slightly attenuated the results.

A case-only analysis was undertaken to assess whether adjustment for Gleason score altered the BMI-*T2E* association. When comparing the highest recent BMI quartile with the lowest, the odds ratio for developing *T2E*-positive prostate cancer versus *T2E*-negative prostate cancer was 0.72 (95% CI: 0.43, 1.19) in a model adjusted for age, race, and diabetes. Further adjustment for Gleason score did not substantially attenuate the results (OR = 0.68, 95% CI: 0.41, 1.14).

Table 2. Odds Ratios for *T2E*-Negative and *T2E*-Positive Prostate Cancer According to Body Mass Index,[a] King County, Washington, 1993–1996 and 2002–2005

BMI Variable	Controls, % (*n* = 1,645)	Cases					
		T2E-Negative (*n* = 268)			*T2E* -Positive (*n* = 295)		
		%	OR[b]	95% CI	%	OR[b]	95% CI
BMI at ages 18–29 years[c,d]							
<21.1	25.8	23.6	1.00		21.8	1.00	
21.1–22.9	25.3	31.8	1.41	0.99, 2.02	31.0	1.40	0.99, 1.99
23.0–24.4	26.6	24.3	1.01	0.69, 1.46	29.3	1.23	0.87, 1.76
≥24.5	22.4	20.2	1.04	0.70, 1.54	18.0	0.92	0.62, 1.36
P for trend				0.70			0.59
Continuous (per 5-unit increment)			0.96	0.78, 1.19		0.83	0.68, 1.03
Recent BMI							
<24.5	27.5	27.6	1.00		30.9	1.00	
24.5–26.6	23.6	27.2	1.15	0.81, 1.64	27.1	1.06	0.76, 1,48
26.7–29.6	24.1	24.6	1.03	0.72, 1.48	25.1	0.98	0.70, 1.37
≥29.7	24.8	20.5	0.87	0.59, 1.27	17.0	0.66	0.45, 0.97
P for trend				0.42			0.05
Continuous (per 5-unit increment)			0.93	0.80, 1.09		0.86	0.73, 1.00
Maximum BMI							
<25.9	27.0	27.2	1.00		28.1	1.00	
25.9–28.2	23.2	24.6	1.05	0.73, 1.50	26.1	1.10	0.78, 1.56
28.3–31.7	25.4	28.4	1.14	0.81, 1.62	29.8	1.16	0.83, 1.62
≥31.8	24.4	19.8	0.86	0.58, 1.26	15.9	0.69	0.47, 1.02
P for trend				0.65			0.18
Continuous (per 5-unit increment)			0.95	0.82, 1.10		0.87	0.75, 1.01

Abbreviations: BMI, body mass index; CI, confidence interval; *ERG*, ETS-related gene; ETS, erythroblast transformation-specific; OR, odds ratio; *T2E*, *TMPRSS2:ERG* gene fusion; *TMPRSS2*, transmembrane protease, serine 2, gene.

[a] Weight (kg)/height (m)^2.

[b] Adjusted for age, race, and history of diabetes. One control had missing data for history of diabetes.

[c] Two controls had missing data for BMI at ages 18–29 years.

[d] Five controls, 1 *T2E*-positive case, and 1 *T2E*-negative case with BMIs less than 16.5 at ages 18–29 years were excluded from these analyses.

For maximum adulthood BMI, a BMI of ≥31.8 was associated with a borderline-significant reduction in risk of a *T2E*-positive tumor (OR = 0.69, 95% CI: 0.47, 1.02) as compared with a BMI of <25.9. Every 5-unit increase in maximum adult BMI was associated with a 13% reduction in the odds ratio for *T2E*-positive prostate cancer (OR = 0.87, 95% CI: 0.75, 1.01). The odds ratios for *T2E*-negative prostate cancer were in the same direction but were not statistically significant.

To allow for comparison of our results with those of other studies, we also performed analyses with BMI categorized according to World Health Organization definitions (see Appendix Table 1). When focusing specifically on Class I obesity (BMI 30–34.9), there was a 43% lower odds ratio for a *T2E*-positive tumor (OR = 0.57, 95% CI: 0.37, 0.87), but no association was seen for *T2E*-negative prostate cancer. Class II and III obesity (BMI ≥35) combined was not significantly associated with risk of either molecular subtype of prostate cancer, but there were limited numbers of men in these extreme categories.

DISCUSSION

Our population-based case-control study provides some evidence for a differential association between obesity and the risk of developing *T2E* fusion–positive versus *T2E* fusion–negative prostate cancer. When comparing the highest BMI quartile with the lowest, we found inverse associations between recent and maximum BMI and risk of *T2E*-positive prostate cancer, while no associations with BMI were seen among men with *T2E*-negative tumors. For BMI at ages 18–29 years, we also observed a slightly lower odds ratio for *T2E*-positive tumors among men in the highest BMI quartile, although the result was not statistically significant.

The association between obesity and prostate cancer incidence is complex, and inconsistent findings have been reported (20). However, recent evidence suggests that obesity is associated with a modest reduction in the risk of clinically localized, lower-grade prostate cancer but an increased risk of more aggressive or fatal disease (21). In the current study, we

observed no significant association between obesity and Gleason score or pathological stage in either *T2E*-negative or *T2E*-positive cases. Early-life exposures may have a lasting and important impact on the development of prostate cancer. As is the case with adulthood BMI, studies assessing the association between BMI in early adulthood and prostate cancer risk have demonstrated mixed results. Two studies found inverse relationships between young adulthood obesity and risk of advanced and metastatic prostate cancer (22, 23), and a third study found an inverse relationship limited to localized prostate cancer (24). However, a positive relationship between early adulthood BMI and prostate cancer risk has been reported in 2 studies (25, 26), while several others have demonstrated null results (27–30). These previous studies did not consider the molecular subtyping of tumors by *T2E* status. Only 1 earlier study considered *T2E* stratification when evaluating prostate cancer risk and obesity (31). In that study, a higher BMI was associated with a reduction in risk for developing *T2E*-positive prostate cancer but was unrelated to risk of *T2E*-negative disease, similar to our results.

Studies of obesity are complicated by challenges related to detection of prostate cancer in overweight men. Obesity has been associated with reduced PSA levels, possibly due to increased blood volume in obese men leading to PSA hemodilution (32). In our control group, PSA values in obese men were lower than those in normal-weight men. Obese men may therefore be less likely to undergo prostate biopsy than normal-weight men. Furthermore, obesity is associated with a larger prostate volume (32, 33). For this reason, biopsy detection of small focal tumors is more difficult in obese men (34). Both lower PSA concentrations and prostatic enlargement could hamper detection of prostate cancer among obese men, which may have contributed to the previously reported inverse association between BMI and prostate cancer risk observed in some populations. However, the influence of BMI on prostate cancer detection would not be expected to differ according to *T2E* status. If detection bias was a problem, we would expect to observe an inverse association of BMI with risk of both *T2E*-negative and *T2E*-positive tumors.

Obesity influences the synthesis and bioavailability of steroid hormones through different mechanisms. Obese men have higher levels of circulating estrogen than normal-weight men due to conversion of testosterone into estradiol by aromatase in adipocytes (35). Insulin-like growth factor 1 levels are elevated in obese men, which is associated with reduced levels of sex hormone–binding globulin. Consequently, total and free testosterone levels are decreased in obese men (36).

The *T2E* gene fusion is an early driver of prostate carcinogenesis. Overexpression of the *ERG* gene is associated with alterations in the Wnt pathway, epigenetic reprogramming, and deregulation of cell death pathways (37, 38). Since *ERG* expression is regulated by androgens and possibly estrogens in *T2E* fusion–positive tumors, the changes in hormone levels associated with obesity described above may have different relationships with tumor development in *T2E*-positive and *T2E*-negative prostate cancers. Recently, androgens have also been implicated in the induction of *TMPRSS2:ERG* fusion events (39–42). Androgen exposure can induce the proximity of the transcription units of *TMPRSS2* and its fusion partners (40). Androgen receptor signaling also induces double-strand breaks, mediated by DNA topoisomerase 2-β, at *TMPRSS2:ERG* rearrangement junction sites (41). Although serum androgen levels may not correlate with intraprostatic androgen levels (43), these studies support the hypothesis that obesity, with its associated lower level of androgen exposure, may reduce the risk for development of androgen-regulated *T2E*-positive prostate cancer.

Strengths of this study include its population-based design and the relatively large number of incident cases with *T2E* status determined by fluorescent in situ hybridization. One potential concern is that data on height and weight were recalled and self-reported; however, any misclassification would likely have been nondifferential, biasing the odds ratios toward the null. Selection bias could also have influenced our results. First, the response level of the 2 case-control studies combined was 67% for controls and 78% for cases. We acquired information on recent BMI for a small proportion of nonresponding cases and controls, which indicated that mean BMI did not differ among nonrespondents and participants in either group. Furthermore, it seems unlikely that case participation would be related to *T2E* status, as the presence of the gene fusion has not been consistently shown to influence cancer progression or mortality among men treated with radical prostatectomy (44).

Second, our study included only men who underwent radical prostatectomy. In our data set, men who underwent radical prostatectomy were less likely to be classified in the highest BMI quartile (≥29.7) at diagnosis than men who were treated with androgen deprivation therapy or radiotherapy or who opted for active surveillance. This selection of patients could have biased our results. Further, fusion status was confirmed for 563 of the 984 (57.2%) cases who underwent radical prostatectomy. The subset of cases with *T2E* data had a slightly higher frequency of tumors with a Gleason score ≥7 (4 + 3) compared with cases for whom fusion status could not be determined (15.8% vs. 11.4%; $P = 0.05$). However, the BMI distribution did not differ among cases with and without tumor tissue available.

In conclusion, we found that recent and maximum BMI are inversely associated with the odds of developing *T2E*-positive prostate cancer, but no associations were observed for *T2E*-negative prostate cancer. The altered steroid hormone profile in obese men (e.g., lower circulating levels of androgens) may contribute, at least partially, to the reduction in risk of developing androgen-responsive *T2E*-positive prostate cancer observed in obese men. Additional studies are needed to confirm these results and to determine the mechanisms by which obesity may differentially affect the development of these molecularly distinct subtypes of prostate tumors.

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Appendix Table 1. Odds Ratios for *T2E*-Negative and *T2E*-Positive Prostate Cancer According to World Health Organization Body Mass Index Category,[a] King County, Washington, 1993–1996 and 2002–2005

BMI Variable	Controls, % ($n = 1,645$)	Cases					
		T2E-Negative ($n = 268$)			*T2E*-Positive ($n = 295$)		
		%	OR[b]	95% CI	%	OR[b]	95% CI
BMI at ages 18–29 years[c,d]							
<25.0	78.1	79.8	1.00		82.3	1.00	
25.0–29.9	20.5	19.9	0.99	0.71, 1.37	17.0	0.78	0.56, 1.09
≥30.0	1.4	0.4	0.28	0.04, 2.07	0.7	0.44	0.10, 1.90
P for trend				0.52			0.07
Recent BMI							
<25.0	29.7	29.5	1.00		33.6	1.00	
25.0–29.9	47.4	51.5	1.11	0.82, 1.50	51.2	0.99	0.75, 1.31
30.0–34.9	18.4	16.8	0.95	0.64, 1.42	11.2	0.57	0.37, 0.87
≥35	4.6	2.2	0.54	0.23, 1.31	4.1	0.91	0.47, 1.76
P for trend				0.41			0.06
Maximum BMI							
<25.0	16.2	15.3	1.00		19.3	1.00	
25.0–29.9	48.0	50.8	1.14	0.78, 1.66	51.5	0.96	0.68, 1.34
30.0–34.9	26.1	27.6	1.17	0.77, 1.77	23.1	0.80	0.54, 1.19
≥35	9.8	6.3	0.79	0.43, 1.47	6.1	0.63	0.35, 1.13
P for trend				0.79			0.07

Abbreviations: BMI, body mass index; CI, confidence interval; *ERG*, ETS-related gene; ETS, erythroblast transformation-specific; OR, odds ratio; *T2E*, *TMPRSS2:ERG* gene fusion; *TMPRSS2*, transmembrane protease, serine 2, gene.

[a] Weight (kg)/height (m)^2.

[b] Adjusted for age, race, and history of diabetes. One control had missing data for history of diabetes.

[c] Two controls had missing data for BMI at ages 18–29 years.

[d] Five controls, 1 *T2E*-positive case, and 1 *T2E*-negative case with BMIs less than 16.5 at ages 18–29 years were excluded from these analyses.