Published in final edited form as:

Cancer. 2019 August 15; 125(16): 2877–2885. doi:10.1002/cncr.32167.

Body fat distribution on CT imaging and prostate cancer risk and mortality in the AGES-Reykjavik Study

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Abstract

Background: The World Cancer Research Fund classifies as "strong evidence" the link between obesity and risk of advanced prostate cancer. Given the different hormonal profiles associated with where adipose is stored, we investigated the role of objectively-measured body fat distribution and risk of clinically relevant prostate cancer.

Methods: We undertook a prospective study among 1,832 men in the AGES-Reykjavik Study. From 2002-2006, participants underwent baseline computed tomography (CT) imaging of fat

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Conflict of Interest: The authors declare no potential conflicts of interest.

deposition, bioelectric impedance analysis, and measurement of body mass index (BMI) and waist circumference. We followed men through linkage with nationwide cancer registries for incidence of total (n=172), high-grade (Gleason ≥8) (n=43), advanced (≥cT3b/N1/M1 at diagnosis or fatal prostate cancer over follow-up) (n=41), and fatal (n=31) prostate cancer through 2015. Cox regression was used to evaluate the association between adiposity measures and prostate cancer outcomes.

Results: Among all men, visceral fat (hazard ratio [HR] 1.31 per 1 SD increase, 95% confidence interval [CI]: 1.00-1.72) and thigh subcutaneous fat (HR 1.37 per 1 SD increase, 95% CI: 1.00-1.88) were associated with risk of advanced and fatal disease, respectively. Among leaner men based on BMI, visceral fat was associated with both advanced and fatal disease. BMI and waist circumference were associated with a higher risk of advanced and fatal disease. No adiposity measures were associated with total or high-grade disease.

Conclusion: Specific fat depots, as well as BMI and waist circumference, were associated with risk of aggressive prostate cancer, which may help elucidate underlying mechanisms and target intervention strategies.

Keywords

Adiposity; cohort; computed tomography; fat distribution; obesity; prostate cancer; visceral fat

INTRODUCTION

Obesity, as measured by body mass index (BMI) or waist circumference, has been consistently associated with a higher risk of advanced prostate cancer and poorer prognosis after diagnosis.[1] Emerging evidence suggests that the specific distribution of body fat may be an important prognostic factor for prostate cancer outcomes.[2-5] Body fat distribution is of interest because it may be a marker for different metabolic, hormonal, and inflammatory milieus that play a role in prostate carcinogenesis.[3,6-13] For example, visceral fat is inversely associated with bioavailable testosterone[7,8] and more strongly associated with insulin resistance and pro-inflammatory cytokines than subcutaneous fat.[6] Greater intermuscular thigh fat has been associated with poorer glucose tolerance,[9] while subcutaneous thigh fat has been associated with more favorable metabolic factors.[10,11] The identification of adiposity phenotypes at highest risk of aggressive prostate cancer may therefore help elucidate the mechanisms linking obesity with aggressive disease and target corresponding intervention strategies.

To date, few studies have investigated directly measured body fat distribution and prostate cancer risk. Cross-sectional and retrospective studies have reported associations between computed tomography (CT) measures of visceral fat and total[4] and high-grade[5] prostate cancer. However, these studies were limited by small samples and the potential that the disease or its treatment may have influenced adiposity.[4,5] Further, the association between other fat depots and prostate cancer outcomes remains unclear.

Here we undertook the first prospective study of CT-measured fat distribution and risk of prostate cancer and measures of aggressive disease.

MATERIALS AND METHODS

Study population

We leveraged data from the AGES-Reykjavik study, a longitudinal population-based study in Iceland described in detail elsewhere.[14] Briefly, AGES-Reykjavik originates from the Reykjavik Study, a cohort of 19,381 Reykjavik residents that was established in 1967 to prospectively investigate cardiovascular disease in Iceland. From 2002-2006, a random sample of 5,764 participants (42% men) were re-examined as part of the AGES-Reykjavik study and underwent a comprehensive baseline examination involving a medical history, physical examination, imaging studies, and questionnaires on health-related behaviors. At baseline, we excluded those with a history of cancer (n=453), missing CT data (n=136), or a BMI <18.5 kg/m^2 (n=17), leaving 1,832 men in our analysis. Men who were excluded were similar to those included with respect to all baseline characteristics in Table 1. The study was approved by the Icelandic Ethical Review Board and the Icelandic Data Protection Authority.

Adiposity measures and covariates

Adiposity was assessed at baseline. Participants underwent CT imaging for assessment of fat area in the abdomen (visceral and subcutaneous) and thigh (intermuscular and subcutaneous). CT imaging is the gold standard for measuring fat distribution,[15] and the internal reliability of this measure was excellent (CV <5% for all fat depot measures). CT imaging was performed with a 4-row detector system (Sensation; Siemens Medical Systems, Erlangen, Germany). Abdominal visceral and subcutaneous fat areas (cm^2) were measured from a single 10-mm trans-axial section at the L4/L5 vertebrae. Visceral fat was distinguished from subcutaneous fat by tracing along the fascial plane defining the internal abdominal wall. Thigh intermuscular and subcutaneous fat area (cm^2) was measured from a single 10-mm trans-axial section using a 120-kV peak at the femoral midpoint by manually drawing a line along the deep fascial plane surrounding the thigh muscles.[16] Analysis of the CT images was performed using specialized software developed at the University of California, San Francisco. Total body fat was assessed by bioelectrical impedance. Height, weight, and waist circumference were measured by trained technicians. BMI was calculated as weight (kg)/height (m)^2. We obtained information on lifestyle and clinical covariates from the baseline questionnaire.

Outcome ascertainment

Record linkage to the nationwide Icelandic Cancer Registry through unique identification numbers was used to identify prostate cancer diagnosed from study entry through December 31, 2015. Cancer registration is mandatory and estimated completeness is very high (99.2%).[17] Over 98% of prostate cancer diagnoses were morphologically verified.[17] Incident prostate cancer was categorized as total, high-grade (Gleason grade ≥8), advanced (≥cT3b or N1 or M1 at diagnosis, or fatal prostate cancer over follow-up), and fatal (which was also included in the advanced category). We were missing data on stage and grade for 13 (7.6%) cases. Linkage to the Cause of Death Registry held by the Directorate of Health was used to identify all-cause and prostate cancer-specific deaths over the study period. Cause of death (ICD-10) was coded from death certificates by a trained physician. The reported validity of

death certificates for identifying prostate cancer as the underlying cause of death is high (96%).[18]

Statistical analysis

We estimated the correlation between adiposity measures by calculating Spearman correlation coefficients. We also conducted partial correlation analysis adjusting for age.

We used Cox regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for total, high-grade, advanced, and fatal prostate cancer. To verify that the proportional hazards assumption was not violated, we included product terms between each adiposity measure and time and tested whether the coefficients for those terms were statistically significantly different from zero (Wald test, χ^2 with 1 df). Time since study entry was the underlying time scale. We followed men from the date of the baseline examination until the incident prostate cancer outcome of interest, death, or administrative end of follow-up (December 31, 2015), whichever happened first. We adjusted for the baseline covariates: age, family history of prostate cancer, smoking status, education, frequency of moderate/vigorous physical activity during youth and midlife, and presence of a physician visit over the past year. Our primary analyses did not adjust for alcohol consumption because of inconsistent findings for a link with prostate cancer; however, estimates were qualitatively similar with adjustment for alcohol (data not shown). Models for fat depots and waist circumference were additionally adjusted for height (continuous). In sensitivity analyses for the fat depot models, we additionally adjusted for BMI and mutually adjusted for all fat depots. Men missing data on covariates and men with complete data on all covariates (93%) were similar with respect to their baseline characteristics. Missing data for categorical covariates were assigned to the most populous group (smoking status, n=2; education, n=19, physical activity, n=111; physician visit, n=9); estimates were similar in analyses restricted to men with complete data on all covariates.[19]

We further conducted pre-specified stratified analyses to evaluate whether the association between fat distribution and prostate cancer varied by BMI (dichotomized at the median; <27 vs. ≥ 27 kg/m^2). This cut-off was selected to optimize case distribution and power for analyses in each stratum. Tests for heterogeneity were performed using likelihood ratio tests comparing models with and without a product term between the exposure of interest and BMI. Finally, we conducted sensitivity analyses (1) excluding men older than 80 years at study entry and (2) excluding the first five years of follow-up to address potential reverse causation.

Analyses were conducted using SAS 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Among 1,832 men, there were 172 prostate cancer diagnoses, including 31 prostate cancer-specific deaths, over the study period. Only one man was diagnosed with prostate cancer at the time of fatal prostate cancer. Of the incident prostate cancer diagnoses, 41 were advanced and 43 were high-grade tumors. Median follow-up time was 10.1 years (range:

0.1-13.3) until prostate cancer diagnosis and 10.4 years (range: 0.1-13.3) until prostate cancer death.

Table 1 shows baseline characteristics of the men by fat depot measures dichotomized at the median. Those with higher visceral fat had a higher BMI and waist circumference, lower physical activity during youth and midlife, and were less likely to be current smokers. Similar associations were seen for higher levels of other fat depots.

Supplemental Table 1 shows the distribution of adiposity measures. At baseline, the median BMI was 27 kg/m^2 and median waist circumference was 102 cm. Table 2 shows the Spearman correlation coefficients between adiposity measures. BMI was highly correlated with waist circumference (r_s=0.87) and total body fat (r_s=0.84). Of the fat depots, abdominal subcutaneous fat was highly correlated with BMI and waist circumference (r_s=0.82 and r_s=0.83, respectively); visceral fat was correlated with BMI and waist circumference to a lesser extent (r_s=0.69 and r_s=0.73, respectively). Estimates were similar after adjusting for age (data not shown).

Visceral fat was associated with risk of advanced prostate cancer (HR 1.31 per 1 standard deviation [SD] increase, 95% CI: 1.00-1.72) (Table 3). Thigh subcutaneous fat was associated with risk of fatal prostate cancer (HR 1.37 per 1 SD increase, 95% CI: 1.00-1.88) (Table 3). Mutual adjustment for all fat depots did not qualitatively change these results (HR for advanced disease 1.31 per 1 SD increase in visceral adiposity, 95% CI: 0.96-1.80; HR for fatal disease 1.42 per 1 SD increase in thigh subcutaneous adiposity, 95% CI: 0.90-2.25). Additional adjustment for BMI attenuated the estimates, particularly for the other fat depots (Supplemental Table 2). Results for total fat mass and percent fat were similar; a 1 SD increase in either was associated with a non-statistically significant higher risk of advanced and fatal disease (Table 3). The association between visceral fat and advanced and fatal disease was stronger and statistically significant among men with a BMI <27 kg/m^2 and weaker and not significant among men with BMI ≥27 kg/m^2; however, confidence intervals were wide and tests for heterogeneity by BMI were not significant (Table 4).

Each 5 kg/m^2 increase in BMI was associated with a 50% higher risk of advanced (HR 1.52, 95% CI: 1.02-2.27) and fatal (HR 1.56, 95% CI: 0.97-2.53) prostate cancer (Table 3). Those who were obese (BMI ≥30 kg/m^2) had a higher risk of advanced (HR 2.54, 95% CI: 1.08-6.00) and fatal (HR 2.59, 95% CI: 0.90-7.45) disease compared with those with a healthy BMI (Table 3). Each 1 SD (10.3 cm) increase in waist circumference was associated with a 40% higher risk of advanced (HR 1.40, 95% CI: 1.04-1.89) and fatal (HR 1.45, 95% CI: 1.01-2.07) disease (Table 3).

No adiposity measures were associated with risk of total or high-grade prostate cancer (Table 3). Results for all adiposity measures were qualitatively similar in sensitivity analyses excluding men older than 80 years at study entry and excluding the first five years of follow-up (data not shown).

DISCUSSION

In this prospective cohort of Icelandic men with objective measures of adiposity, visceral and thigh subcutaneous fat were associated with risk of advanced and fatal prostate cancer, respectively. Among men with a lower BMI, visceral fat was associated with both advanced and fatal disease. BMI and waist circumference were also associated with a higher risk of advanced and fatal disease. No adiposity measures were associated with total or high-grade disease.

To our knowledge, this is the first prospective study of directly measured fat distribution and risk of advanced prostate cancer. Previous retrospective and cross-sectional studies incorporating CT measures of adiposity have reported mixed findings.[4,5,20] A case-control study (63 prostate cancer cases) reported a positive association between visceral fat and total prostate cancer.[4] In contrast, we found an association between prospectively measured visceral fat and risk of advanced and fatal disease, but not total prostate cancer. In cross-sectional studies of men undergoing radiotherapy for prostate cancer (sample sizes ranging from 276-308 men), higher visceral and abdominal subcutaneous fat were associated with higher National Comprehensive Cancer Network prostate cancer risk group,[20] and abdominal subcutaneous adiposity was also associated with high-grade prostate cancer.[5] One of these studies found that visceral fat and high-grade (Gleason grade ≥7) disease were positively associated among black men but not associated among non-black men, similar to our results in a population of white men.[5] These previous studies differed in design, size, participant characteristics (*e.g.* age, race, adiposity measures), modeling of adiposity measures, and analytic approach.

BMI has been associated with a higher risk of advanced and fatal, but not total, prostate cancer,[3] which is in agreement with our findings. A meta-analysis showed an 8% higher risk of advanced prostate cancer (RR 1.08, 95% CI: 1.04-1.12; 23 studies) and 11% higher risk of prostate cancer-specific mortality (RR 1.11, 95% CI: 1.06-1.17; 12 studies) per 5 kg/m^2 increase in BMI.[3] In the present study, we found that each 5 kg/m^2 increase in BMI was associated with a 50% higher risk of advanced and fatal disease. Different estimates across studies may be related to the timing of BMI measurement, length of follow-up, and patient characteristics. For example, studies suggest that the association between BMI and prostate cancer risk may differ according to age[21,22] and race.[23] Because age and race are key determinants of fat distribution,[24] the heterogeneity of findings for BMI may be partly explained by variation in fat distribution patterns differentially associated with prostate cancer.

Findings for waist circumference, a surrogate of central adiposity, and prostate cancer have been mixed. Some studies have found higher waist circumference to be associated with a higher risk of advanced and high-grade disease,[2,3] while other studies have been null.[25] This is in line with our findings for a positive association between waist circumference and advanced disease, but null results for high-grade disease. Waist circumference is limited by the inability to differentiate visceral from subcutaneous adipose, which may partly explain heterogeneous findings.

Percent body fat, assessed using bioelectric impedance, has been associated with high-grade prostate cancer in case-control studies.[26,27] In contrast, we found no association between prospectively measured percent body fat and high-grade disease. A prospective analysis of 10,564 initially cancer-free men in the Malmö Diet and Cancer cohort similarly found no association between percent body fat and risk of aggressive prostate cancer (≥cT3 or N1 or M1, or Gleason grade ≥8, or pre-treatment PSA ≥50 ng/mL).[25]

A prospective study among 129,502 men in the European Prospective Investigation into Cancer and Nutrition (EPIC) reported that central adiposity, assessed by waist circumference, was associated with a higher risk of advanced and high-grade prostate cancer, particularly among men with a healthy BMI.[2] We similarly found that the association between visceral fat and advanced disease was stronger among men with a lower versus higher BMI, though confidence intervals were wide. Further exploration of metabolically unhealthy, normal weight phenotypes with respect to prostate cancer outcomes is needed.

Fat distribution may be an important prognostic factor for prostate cancer outcomes by serving as a marker for metabolic, hormonal, and inflammatory milieus that play a role in prostate carcinogenesis.[3,6-13] For example, visceral fat is inversely associated with bioavailable testosterone[7,8] and adiponectin,[4] and more strongly associated with insulin resistance and pro-inflammatory cytokines than subcutaneous fat[6] – factors that may influence prostate cancer progression.[12,13,28,29]

Further studies are needed to investigate whether the fat depots themselves exert systemic or local effects in ways that promote aggressive disease, or whether they are markers for a physical activity pattern or underlying hormonal milieu that influences both fat distribution and aggressive disease.[30] For example, fat may be preferentially deposited in the visceral depot among leaner men in the presence of a particular hormonal milieu. If this hormonal milieu is also a prognostic factor for advanced prostate cancer, this could partially explain the results of our analyses stratified by BMI.

These findings should be considered in light of potential limitations and strengths. Exposures were measured once at cohort entry, so we were unable to assess changes in fat depots over time. However, given the follow-up time, we were able to assess adiposity in a reasonable etiologic time window of exposure.[31,32] It has been hypothesized that obese men may experience delayed detection (due to lower PSA values and biopsy accuracy) and therefore more advanced disease at diagnosis than leaner men, which might partially explain our findings of a higher risk of aggressive disease for men with higher overall obesity.[33,34] However, we found that higher visceral fat was associated with a higher risk of aggressive disease even among leaner men based on BMI. We did not have data on PSA testing and cannot rule out the possibility that our findings might be partially explained by this factor. However, our population was not subject to routine PSA testing and we adjusted for a measure of recent healthcare utilization to account for varying degrees of diagnosis opportunity. The number of advanced and fatal cancers was small and thus power was reduced. Lastly, our study population consisted of older white men, so results may not be generalizable to younger, more diverse groups of men.

The major strength of this study is that it is the first prospective analysis of CT-quantified fat depots and prostate cancer risk. Our prospective design minimizes the likelihood of reverse causation, whereby the disease or its treatment influences fat distribution. Further, the use of gold-standard measures of fat distribution enabled us to examine the obesity-prostate cancer link with higher resolution than studies of BMI and waist circumference. This provides more insight into potential underlying mechanisms. The misclassification of fat distribution is a risk in studies relying on surrogate measures and may contribute to the variability in epidemiologic findings on obesity and prostate cancer. Precise measures of fat distribution are particularly important among older individuals, because BMI becomes a less reliable measure of adiposity with age due to the loss of lean body mass and redistribution of adipose toward the visceral compartment.[35] Additional strengths of this study include its population-based sample, long duration of follow-up, complete and reliable outcome data obtained through registry linkage, and the availability of comprehensive questionnaire data.

In summary, we found that specific fat depots, as well as BMI and waist circumference, were associated with risk of advanced and fatal prostate cancer. Studies of BMI or waist circumference alone may not capture important sub-phenotypes, which may explain the heterogeneity of previous findings for obesity and prostate cancer. Further studies are needed to prospectively investigate fat distribution and prostate cancer outcomes, with attention to changes in fat depots over time, biological pathways, and potential heterogeneity by BMI. The identification of the adiposity phenotypes at highest risk of clinically relevant prostate cancer may help elucidate the mechanisms linking obesity with aggressive disease and target intervention strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was supported by funding from the National Cancer Institute at the National Institutes of Health (T32 CA 009001 to B.A.D. and P50 CA 090381-15 to S.C.M. and L.A.M.), an ASISA Fellowship (to B.A.D.), and the Prostate Cancer Foundation (to L.A.M. and K.M.W.). The AGES-Reykjavik is supported by Contract N01 AG 12100 from the National Institutes on Aging Intramural Research Program; Hjartavernd (the Icelandic Heart Association); and the Althingi (the Icelandic Parliament). In addition, this study was supported by funding from the Harvard Catalyst Award and the Icelandic Cancer Society.

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Key Message: In the first prospective analysis of computed tomography–quantified body fat distribution and prostate cancer risk, evidence shows that specific fat depots are associated with the risk of advanced and fatal disease. Because of the different hormonal profiles associated with where fat is stored, these findings may help to elucidate underlying mechanisms of obesity and clinically significant prostate cancer.

Table 1

Age-standardized characteristics of 1,832 men at entry into the AGES-Reykjavik Study by fat depot measures[1], 2002

	Abdominal visceral		Abdominal subcutaneous		Thigh intermuscular		Thigh subcutaneous	
	<M N = 908	≥M N = 924	<M N = 907	≥M N = 925	<M N = 887	≥M N = 945	<M N = 901	≥M N = 931
Follow-up time[2,3] (years)	8.6(3.8)	8.8(3.5)	8.6(3.8)	8.8(3.5)	8.9(3.7)	8.5(3.6)	8.7(3.7)	8.6(3.6)
Age at entry[3] (years)	76.7(5.4)	75.9(5.2)	76.9(5.5)	75.6(5.1)	76.0(5.4)	76.5(5.3)	76.6(5.4)	76.0(5.3)
Height (cm)	175.0(6.0)	176.0(6.2)	175.0(6.0)	176.0(6.2)	175.1(6.0)	175.9(6.3)	175.2(6.0)	175.8(6.3)
Body mass index (kg/m^2)	24.9(2.8)	28.9(3.4)	24.5(2.4)	29.3(3.1)	25.2(3.1)	28.6(3.6)	25.2(2.9)	28.7(3.6)
Waist circumference (cm)	96.6(7.7)	108.3(9.2)	95.6(6.8)	109.2(8.5)	98.0(8.9)	106.7(9.9)	97.5(8.0)	107.3(9.9)
Total fat mass (kg)	14.8(4.9)	22.3(6.2)	14.3(4.2)	22.9(5.9)	15.6(5.6)	21.7(6.7)	15.4(5.2)	21.8(6.6)
Percent body fat	19.1(4.7)	24.7(4.2)	18.8(4.3)	25.1(4.1)	19.7(4.9)	24.2(4.8)	19.5(4.7)	24.3(4.7)
Highest education								
Primary, %	16.9	14.9	16.2	15.6	16.3	15.7	15.4	16.6
Secondary, %	53.4	53.3	54.0	52.7	53.0	53.2	53.5	52.7
College, %	12.1	12.1	12.5	11.6	12.0	12.2	12.7	11.5
University, %	16.8	18.4	16.6	18.6	17.7	17.8	17.6	17.9
Smoking status								
Never, %	32.0	27.0	29.9	28.9	30.0	28.3	31.9	26.9
Former[4], %	54.0	64.2	56.5	61.9	56.2	62.6	55.5	63.2
Current, %	13.9	8.7	13.5	9.2	13.7	9.0	12.6	9.7
Frequency of moderate/vigorous physical activity, ≥4 hours/week, %	38.9	34.7	39.0	34.6	39.5	33.7	37.7	35.7
Family history of prostate cancer, %	9.6	9.3	10.0	8.6	8.7	9.9	10.1	8.9
Physician visit over past 12 months, %	78.2	83.5	79.5	82.3	77.0	84.3	79.9	82.0
Type 2 diabetes[5], %	12.0	20.0	13.1	19.1	13.5	18.6	16.6	15.8

Values are means (SD) or percentages and are standardized to the age distribution of the study population.

[1] Adiposity measures dichotomized at median: 195 cm^2 for abdominal visceral, 193 cm^2 for abdominal subcutaneous, 33 cm^2 for thigh intermuscular, 71 cm^2 for thigh subcutaneous.

[2] Time from enrollment to prostate cancer diagnosis, death, or end of follow-up.

[3] Value is not age adjusted.

[4] Regularly smoked at least 100 cigarettes or 20 cigars in lifetime.

[5] Type 2 diabetes by self-report or fasting glucose ≥7 mmol/L.

Table 2

Spearman correlation between adiposity measures at baseline for men in the AGES-Reykjavik Study, 2002

	BMI	Waist circumference	Total body fat	Percent body fat	Abdominal visceral	Abdominal subcutaneous	Thigh intermuscular	Thigh subcutaneous
BMI	1.00							
Waist circumference	0.87	1.00						
Total body fat	0.84	0.87	1.00					
Percent body fat	0.71	0.77	0.95	1.00				
Abdominal visceral	0.69	0.73	0.70	0.65	1.00			
Abdominal subcutaneous	0.82	0.83	0.81	0.75	0.55	1.00		
Thigh intermuscular	0.57	0.55	0.57	0.53	0.38	0.53	1.00	
Thigh subcutaneous	0.60	0.58	0.59	0.56	0.36	0.69	0.34	1.00

Table 3

Association between adiposity measures and risk of prostate cancer among men in the AGES-Reykjavik Study, 2002-2015

	Total prostate cancer			High-grade prostate cancer			Advanced prostate cancer			Fatal prostate cancer		
	Events/ Total	Age-adjusted HR (95% CI)[1]	Fully-adjusted HR (95% CI)[2]	Events/ Total	Age-adjusted HR (95% CI)[1]	Fully-adjusted HR (95% CI)[2]	Events/ Total	Age-adjusted HR (95% CI)[1]	Fully-adjusted HR (95% CI)[2]	Events/ Total	Age-adjusted HR (95% CI)[1]	Fully-adjusted HR (95% CI)[2]
CT imaging of fat depots												
Abdominal visceral, per 1 SD increase	172/1832	1.02 (0.88, 1.19)	1.02 (0.88, 1.19)	43/1832	1.01 (0.75, 1.37)	0.98 (0.72, 1.33)	41/1832	1.31 (0.99, 1.74)	1.31 (1.00, 1.72)	31/1832	1.21 (0.86, 1.71)	1.24 (0.89, 1.73)
Abdominal subcutaneous, per 1 SD increase	172/1832	0.96 (0.82, 1.12)	0.97 (0.83, 1.13)	43/1832	1.02 (0.76, 1.38)	1.02 (0.76, 1.38)	41/1832	1.17 (0.87, 1.57)	1.22 (0.91, 1.63)	31/1832	1.18 (0.84, 1.66)	1.26 (0.89, 1.78)
Thigh intermuscular, per 1 SD increase	172/1832	0.91 (0.78, 1.07)	0.91 (0.78, 1.08)	43/1832	0.92 (0.67, 1.27)	0.92 (0.66, 1.27)	41/1832	1.00 (0.73, 1.36)	1.02 (0.75, 1.40)	31/1832	1.22 (0.88, 1.70)	1.27 (0.91, 1.78)
Thigh subcutaneous, per 1 SD increase	172/1832	1.01 (0.87, 1.18)	1.02 (0.88, 1.19)	43/1832	1.14 (0.87, 1.50)	1.14 (0.86, 1.50)	41/1832	1.21 (0.92, 1.59)	1.25 (0.95, 1.64)	31/1832	1.29 (0.94, 1.77)	1.37 (1.00, 1.88)
Bioelectric impedance analysis												
Total fat mass, per 1 SD increase	132/1425	1.00 (0.84, 1.19)	0.98 (0.83, 1.18)	35/1425	1.01 (0.72, 1.41)	0.98 (0.69, 1.40)	32/1425	1.17 (0.83, 1.65)	1.17 (0.83, 1.67)	25/1425	1.15 (0.77, 1.72)	1.17 (0.78, 1.75)
Percent fat, per 1 SD increase	132/1425	1.00 (0.84, 1.19)	0.99 (0.83, 1.18)	35/1425	1.05 (0.75, 1.49)	1.03 (0.73, 1.46)	32/1425	1.20 (0.84, 1.71)	1.19 (0.83, 1.69)	25/1425	1.20 (0.79, 1.81)	1.20 (0.80, 1.81)
Anthropometric measurements												
BMI, per 5 kg/m^2 increase	172/1832	1.01 (0.82, 1.24)	1.01 (0.82, 1.24)	43/1832	1.05 (0.71, 1.58)	1.02 (0.67, 1.53)	41/1832	1.45 (0.98, 2.16)	1.52 (1.02, 2.27)	31/1832	1.46 (0.91, 2.34)	1.56 (0.97, 2.53)
BMI <25 kg/m^2	56/579	1	1	12/579	1	1	10/579	1	1	7/579	1	1
25≤BMI<30 kg/m^2	81/899	0.86 (0.61, 1.21)	0.84 (0.59, 1.19)	22/899	1.05 (0.52, 2.12)	0.96 (0.47, 1.96)	18/899	1.14 (0.53, 2.48)	1.19 (0.54, 2.61)	16/899	1.53 (0.63, 3.73)	1.68 (0.68, 4.14)
BMI ≥30 kg/m^2	35/354	0.94 (0.61, 1.44)	0.95 (0.62, 1.46)	9/354	1.06 (0.44, 2.53)	1.00 (0.42, 2.43)	13/354	2.18 (0.95, 5.03)	2.54 (1.08, 6.00)	8/354	2.11 (0.76, 5.87)	2.59 (0.90, 7.45)
WC, per 1 SD increase	172/1832	1.01 (0.87, 1.17)	1.02 (0.87, 1.19)	43/1832	0.97 (0.72, 1.32)	0.95 (0.69, 1.31)	41/1832	1.32 (0.98, 1.77)	1.40 (1.04, 1.89)	31/1832	1.31 (0.92, 1.86)	1.45 (1.01, 2.07)

HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; WC: Waist circumference.

Unless otherwise noted, continuous adiposity measures were modeled per 1 standard deviation (SD) increase. The adiposity measures and corresponding 1 SD increments are: abdominal visceral fat (85.7 cm^2), abdominal subcutaneous fat (85.6 cm^2), thigh intermuscular (16.0 cm^2), thigh subcutaneous (39.2 cm^2), total fat mass (6.8 kg), percent fat (5.3%), waist circumference (10.3 cm)

[1]Adjusted for age at study entry (continuous).

[2] Additionally adjusted for the following variables, measured at study entry: family history of prostate cancer (yes, no), smoking status (never, former, current), education (primary/secondary, college/university), physical activity (≤3 hours/week, ≥4 hours/week), and physician visit over past 12 months (yes, no). Models for fat depots and waist circumference were additionally adjusted for height (continuous).

Table 4

Association between fat depots and risk of prostate cancer among 1,832 men in the AGES-Reykjavik Study, 2002-2015: By BMI

	Total prostate cancer		High-grade prostate cancer		Advanced prostate cancer		Fatal prostate cancer	
	Events/ Total	**Fully-adjusted HR (95% CI)[1]**	**Events/ Total**	**Fully-adjusted HR (95% CI)[1]**	**Events/ Total**	**Fully-adjusted HR (95% CI)[1]**	**Events/ Total**	**Fully-adjusted HR (95% CI)[1]**
Abdominal visceral, per 1 SD (85.7 cm^2) increase								
BMI <27 kg/m^2	99/981	1.20 (0.91, 1.57)	26/981	1.31 (0.76, 2.24)	20/981	1.95 (1.07, 3.54)	15/981	2.13 (1.12, 4.05)
BMI ≥27 kg/m^2	73/851	1.05 (0.83, 1.34)	17/851	0.97 (0.59, 1.61)	21/851	1.11 (0.73, 1.68)	16/851	0.83 (0.47, 1.48)
P-value[2]		0.82		0.92		0.67		0.41
Abdominal subcutaneous, per 1 SD (85.6 cm^2) increase								
BMI <27 kg/m^2	99/981	0.97 (0.69, 1.37)	26/981	1.60 (0.82, 3.11)	20/981	1.02 (0.48, 2.16)	15/981	1.34 (0.56, 3.21)
BMI ≥27 kg/m^2	73/851	1.12 (0.88, 1.42)	17/851	1.14 (0.70, 1.85)	21/851	1.33 (0.87, 2.04)	16/851	1.27 (0.75, 2.17)
P-value[2]		0.51		0.67		0.31		0.72
Thigh intermuscular, per 1 SD (16.0 cm^2) increase								
BMI <27 kg/m^2	99/981	0.90 (0.65, 1.22)	26/981	0.86 (0.46, 1.63)	20/981	0.59 (0.28, 1.25)	15/981	0.65 (0.28, 1.52)
BMI ≥27 kg/m^2	73/851	0.99 (0.79, 1.24)	17/851	1.11 (0.70, 1.74)	21/851	1.11 (0.73, 1.69)	16/851	1.56 (0.96, 2.53)
P-value[2]		0.78		0.63		0.67		0.08
Thigh subcutaneous, per 1 SD (39.2 cm^2) increase								
BMI <27 kg/m^2	99/981	1.12 (0.84, 1.51)	26/981	1.66 (0.99, 2.79)	20/981	1.07 (0.55, 2.08)	15/981	1.16 (0.55, 2.44)
BMI ≥27 kg/m^2	73/851	1.08 (0.88, 1.33)	17/851	1.19 (0.80, 1.78)	21/851	1.34 (0.95, 1.90)	16/851	1.50 (0.96, 2.33)
P-value[2]		0.59		0.45		0.17		0.14

HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index.

[1]Adjusted for the following variables, measured at study entry: age (continuous), height (continuous), family history of prostate cancer (yes, no), smoking status (never, former, current), education (primary/ secondary, college/university), physical activity (≤3 hours/week, ≥4 hours/week), and physician visit over past 12 months (yes, no).

[2]Likelihood ratio test for heterogeneity of the HRs from the two strata.