Appetite-regulating hormones—leptin, adiponectin and ghrelin— and the development of prostate cancer: a systematic review and exploratory meta-analysis

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ABSTRACT

Background Obesity has been proposed as a risk factor for prostate cancer (PCa). In obesity, serum levels of the appetite- regulating hormones—leptin, adiponectin, and ghrelin—become deregulated. Objective To explore whether serum levels of appetite-regulating hormones associate with the incidence of PCa, the incidence of advanced disease, or PCa-specific mortality.

Methods PRISMA guidelines were followed. A systematic search for relevant articles published until March 2019 was performed using the databases PubMed, EMBASE, and Web of Science. Observational studies with data on serum levels of leptin, adiponectin, or ghrelin and PCa outcome were included. Meta-analysis was used to combine risk estimates. Meta- relative risks (mRRs) were calculated using random effects models. When available, raw data was pooled. Publication bias was assessed by funnel plot and Begg's test.

Results Thirty-five studies were eligible for inclusion. The qualitative analysis indicated that leptin was not consistently associated with any PCa outcome, although several cohorts reported decreased adiponectin levels in men who later developed advanced PCa. Based on the meta-analysis, there was no significant effect of leptin on PCa incidence (mRR = 0.93 (95% CI 0.75–1.16), p = 0.52) or advanced PCa (mRR = 0.90 (95% CI 0.74–1.10), p = 0.30). There were insufficient studies to estimate the mRR of PCa incidence for men with the highest levels of adiponectin. The combined risk of advanced PCa for men with the highest levels of adiponectin was reduced but did not reach significance (mRR = 0.81 (95% CI 0.61–1.08), p = 0.15).

Conclusions The current evidence does not suggest an association between leptin and PCa outcome. However, there may be an inverse association between adiponectin and the incidence of advanced PCa that should be investigated by further studies. Serum ghrelin has not been largely investigated.

INTRODUCTION

Obesity affects numerous signalling networks that can influence carcinogenesis, including: insulin signalling, sex hormone signalling, and appetite-regulating hormones [1]. Therefore, obesity was proposed a risk factor for cancer, including prostate cancer (PCa), although the underlying mechanisms remain obscure in this context [2]. The Inter- national Agency for Research on Cancer (IARC) concluded that there was “limited evidence” for a positive association between body mass index (BMI) and risk of fatal cancer of the prostate, but no consistent association between BMI and incidence of total, non-aggressive (non-advanced), or aggressive (advanced) cancer of the prostate, from a review of about 50 prospective studies and more than 40 case-control studies [3]. However, the European Associa- tion of Urology (EAU) guidelines of 2018 cited the REDUCE study which indicated an increased risk of high- grade PCa associated with obesity [4]. Furthermore, the Continuous Update Project review conducted by the World Cancer Research Fund (WCRF) indicated that there was “strong evidence” that being overweight/obese increases the risk of "advanced" PCa [5]. To investigate these putative associations further, this review assessed the association between serum levels of appetite-regulating hormones and PCa, with a focus on advanced and fatal forms of the disease.

Leptin and adiponectin are mainly produced and secreted by adipose cells, and are often referred to as "adipokines". Both act on the hypothalamus in the brain; leptin inhibits the sensation of hunger while adiponectin increases hunger. Ghrelin is mainly secreted by the stomach and gastro- intestinal tract and induces hunger. Adipokines regulate appetite, metabolism, and tissue expansion [6, 7]. Serum leptin levels increase with higher body fatness, while adi- ponectin and ghrelin levels may be reduced [8, 9]. In vitro studies indicated that leptin increased the proliferation of PCa cells by activating JAK/STAT, ERK, and PI3K/AKT/ mTOR pathways (Fig. 1) [7, 10]. Moreover, epidemiolo- gical studies suggested abnormally high serum leptin levels in patients with colon cancer, ovarian cancer, PCa, and breast cancer [6, 7]. Ghrelin similarly activates PI3K/AKT/ mTOR signalling, although its effect on PCa cells is unclear and seems to depend on the concentration administered to the cells [11]. One study found that ghrelin levels were lower in PCa patients [9], but the effect of this on PCa development is unclear, considering its interaction with growth-promoting signalling in vitro. Adiponectin may have growth-suppressing effects in vitro: it activated AMPK and PKC with pro-apoptotic effects, and antagonised ERK signalling [7, 12]. Patients with liver cancer, breast cancer, and ovarian cancer had reduced adiponectin levels [6]. Furthermore, a meta-analysis concluded that the risk of PCa in men was associated with genetic polymorphisms in both the leptin and adiponectin receptors, suggesting that pros- tate cells are responsive to these hormones [13]. Therefore, adipokines may link obesity and PCa

promotion. An association between serum levels and the incidence of PCa or of advanced PCa would support recommendations for men to maintain a healthy body weight to reduce their risk of PCa or to reduce its severity. Furthermore, it would suggest that these appetite-regulating hormones may have clinical value as biomarkers of PCa. However, the association between serum levels of these appetite-regulating hormones has not been investigated by meta-analysis. Here, we performed a systematic review and meta-analysis of observational stu- dies with data on serum levels of leptin, adiponectin, and ghrelin. The outcomes analysed were: the incidence of PCa, the incidence of an advanced form of the disease, and PCa- specific mortality.

SUBJECTS AND METHODS

The review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta- Analyses (PRISMA) [14]. Prospero registration number: CRD42018105863.

Data sources and search strategy

PubMed/MEDLINE, EMBASE, Web of Science and The Cochrane Library (Central Trials) were searched, including MeSH terms (Supplementary appendix 1). The final search was conducted on 14 March 2019.

Inclusion criteria

Inclusion criteria: (1) The study design was defined as case-control or nested case-control. (2) Cases were diagnosed by histological examination (biopsy or radical prostatectomy). (3) The cases had not received therapeutic intervention such as chemotherapy or radiotherapy for their PCa at the time of hormone measurement. (4) Results included comparison of serum leptin, adiponectin or ghrelin levels in cases and controls, or comparison of advanced and non-advanced cases. (5) The article was published as a full peer-reviewed report. Two reviewers performed screening independently at both stages.

Evidence acquisition

Data was extracted including the mean/median leptin levels (ng/μL) and adiponectin levels (μg/μL) with the standard deviation/standard error, odds ratios (OR) of the outcome with 95% confidence intervals (CI), and details of any covariates adjusted for. Information about the study and cohort was extracted, including the population, study design, year, and country of recruitment. The outcomes investigated were: the incidence of PCa (all cases of PCa versus non-cancer controls), the incidence of advanced forms of the disease (advanced versus non-advanced cases), and PCa-specific mortality. The classification system used to measure tumour advancement was recorded, such as by Tumour-Node-Metastasis (TNM) clinical or pathological staging, or solely Gleason grading. An advanced clinical or pathological stage, and advanced Gleason grade tumour are hereafter referred to as “high-stage” and “high-grade” respectively. The authors’ definition of a “high-stage” or “high-grade” tumour was recorded. Details of control group were recorded, including number and type (i.e., healthy, benign prostatic hyperplasia (BPH), low-grade/low-stage cancer). The mean ages of the case and control

groups, and race distribution were also recorded (Table 1, for full ver- sion see Supplementary Tables 1–7). In one study there was a typographical error (confirmed by the author): adiponectin levels were presented in ng/μL rather than μg/μL [15]. In another, leptin level was presented as pg/μL rather than ng/ μL (assumed an error but contact author did not reply) [16]. In another, adiponectin levels were presented in ng/μL rather than μg/μL but the author did not reply [17].

Evidence synthesis and statistical analysis

Random effects models (Dersimonian and Laird method) were used to calculate summary risk estimates and 95% CIs [18]. Only ORs with age- and BMI-adjustment were included in the meta-analysis since age is a confirmed risk factor for the disease [19] and BMI was considered a con- founding variable. In case-control studies, the mean/median differences in hormone levels between case and control group was analysed. In nested case-control studies, participants were considered as having "high" hormone levels, if they were in a top subset (tertile/quartile/quintile) and the OR of PCa for the top subsets from each cohort were combined to produce meta relative risk (mRR). The risk of high-stage and high-grade forms of the disease were assessed by comparing high-stage and high-grade cases compared to the low-stage and low-grade cases. Addition- ally, high-stage and high-grade cancers were combined to assess the risk of "advanced" cancers, as has been previously reported in the IARC handbook of Cancer Prevention volume 16 [3]. Inconsistencies between the studies was assessed using the I2 statistic. An I2 value ranging from 0 to 25% was considered to represent low heterogeneity, from 26 to 50% moderate, and above 50% substantial het- erogeneity [20]. Publication bias was assessed by funnel plots using fixed effects models and Begg's tests [21]. Analyses were conducted in Review Manager 5.3 [22].

RESULTS

Study characteristics

Six hundred twenty four studies were obtained through literature review; 39 studies were included after the screening process (Fig. 2). Study characteristics are listed in brief in Table 1, with a full version in Supplementary Tables 1–7. There were 13 nested case-control studies (10 of which analysed leptin, 7 analysed adiponectin) and 26 case-control studies (17 of which analysed leptin, 11 ana- lysed adiponectin and 2 analysed ghrelin). From all the studies combined, there were 7071 PCa patients in total. The nested case-control studies combined contained 4668 men who developed PCa, of which 2867 with low-stage and 1425 with high-stage tumours, and 2058 with low-grade and 1502 with high-grade tumours. The case-control studies combined contained 2403 men with PCa, of which 613 had a low-stage and 245 had a high-stage tumour, and 463 had a low-grade and 274 had a high-grade tumour.

Systematic (qualitative) review

Nested case-control and case-control studies were analysed separately. The results of studies with a case-control design, in which hormone levels in PCa cases versus controls were compared at the time of diagnosis, were considered a measure of "diagnostic" hormone levels. The results of nested case-control studies, in which hormone levels in PCa cases versus controls were measured at the baseline of the cohort study and prior to the diagnosis of cancer, were considered as a measure of "pre-diagnostic" hormone levels.

Leptin

Six out of eight nested case-control studies reported no association between leptin and the onset of PCa [16, 23– 27], nor high-stage [24, 25, 28], nor high-grade PCa [16, 24, 25, 28]. Conversely, ten out of fourteen case-control studies reported an association with PCa incidence [29–37], two out of six with PCa stage [33, 35], and seven out of eight found an association with PCa grade [29, 33, 35, 38, 39]. However, many had not adjusted for BMI [29–33, 35, 36]. Since leptin and adiponectin are derived from fat cells it is necessary to adjust for an anthropometric measurement such as BMI or waist-to-hip ratio, to analyse the effect independently of fat mass. Overall, despite a few exceptions there was no consistent association between leptin levels and PCa.

Adiponectin

All four nested case-control studies that compared adiponectin level and the incidence of PCa found no association [16, 25, 27, 40] although results of a large cohort reported that participants that later developed PCa had lower levels of high-molecular weight (HMW) adiponectin [40] which is the most biologically active form [41]. One nested case-control study reported no association with tumour stage [28] and three reported no association with grade [16, 28, 42]. One group combined the stage and grade score to classify tumours as "high-risk" and found no association [43]. The largest nested case-control analysis of high-stage PCa observed increased adiponectin levels inversely associated with incidence of advanced disease, in the over- weight and obese group (high-grade cases n = 311, low- grade controls n = 413, OR = 0.62 (95% CI, 0.42–0.90)) [28]. Another small analysis indicated an inverse association with high-grade PCa when diagnosed at radical prostatectomy (RP) (high-grade cases n = 9, low-grade controls n = 98; bottom quartile OR = 1.87, (95% CI, 0.82–4.23) [44]. However, another analysis at the time of RP reported that adiponectin was positively associated with high-stage but not high-grade PCa (high-stage OR = 1.14 (95% CI, 1.02–1.29)) in non-overweight men, whereas in overweight and obese men it was inversely associated with high-grade but not high-stage disease (high-grade OR = 0.94 (95% CI, 0.87–1.01) [45]. An analysis of a 25-year cohort (the Physicians' Health Study) reported that increased pre-diagnostic adiponectin was strongly associated with decreased incidence of high-grade and lethal cancer (high-grade n = 121, low-grade n = 121; metastases or PCa-specific death n = 118; risk of high-grade RR = 0.49, (95% CI, 0.20–1.22); risk of lethal RR = 0.25, (95% CI, 0.07–0.87)) [25]. This was the only study identified to have analysed mortality and had a large number of advanced cases.

As with leptin, case-control studies were more likely to report an association between adiponectin levels and PCa incidence than nested case-control studies. Most case-control studies reported lower adiponectin levels in total PCa patients than controls [15, 29, 32, 35, 46–50] with the exception of two [38, 39]. Similarly, most found reduced adiponectin levels in high-stage cases [29, 35, 46, 48] except for two [49, 51]. Three out of six found reduced adiponectin levels in high-grade cases [29, 35, 46] and three did not find them significantly different [38, 39, 48]. This difference between case-control and nested case-control results indicated that while pre-diagnostic adiponectin did not always predict PCa, it was frequently deregulated at the time of diagnosis. How- ever, since some of the case-control studies who reported an association had not matched case and control groups' by BMI [29–31, 33, 35], it cannot be confirmed that the association is valid.

Ghrelin

Two small case-control studies had analysed serum levels of ghrelin; one reported higher mean levels in PCa patients [52], another reported that native ghrelin was unaltered in PCa patients, but the In1 splice variant (a pathological splice variant) was increased in PCa at both the tissue and serum level [53].

Quantitative analysis

A small number of nested case-control studies provided data suitable for inclusion in an exploratory meta-analysis of the published ORs, to assess the effect of pre-diagnostic hormone levels. There were too few case-control studies with published ORs to assess the effect of diagnostic hormone levels by meta-analysis.

Leptin

Men in the top subsets of leptin levels did not have a significantly different risk of total PCa relative to those in the bottom subsets (Fig. 3a). Furthermore, the mRR of advanced PCa in men with high leptin was not significantly different from non-advanced cases (Fig. 3b). This reflected the conclusion of the literature review of nested case-control studies, in which the majority of studies reported no significant difference between the pre-diagnostic levels of leptin in PCa cases and controls, or advanced PCa cases compared to non-advanced.

Adiponectin

There were insufficient studies that had provided BMI- adjusted ORs of the incidence of PCa, or of high-stage PCa, to calculate a mRR for either outcome. When the ORs of high-grade and high-stage PCa were combined to estimate the risk of advanced PCa in men with the highest subsets of adiponectin, the estimate for adiponectin levels in association with advanced PCa was mRR = 0.81 (0.61–1.08), p = 0.15, I2 = 0% (Fig. 3d). Therefore, despite not reaching statistically significant levels, this may suggest an inverse association between adiponectin levels and advanced PCa. The analysis of the Physicians' Health Study [25] which reported a significant inverse association between adiponectin and high-grade and lethal PCa, was excluded from the meta-analysis since they calculated Relative Risk (RR) rather than OR. We performed sensitivity analysis including and excluding this study, which did not affect the significance of the mRR (mRR of advanced PCa in men with highest subset of adiponectin, including Li et al. [25], mRR = 0.75 (0.54–1.06), p = 0.10, I2 = 27%).

Ghrelin

Meta-analysis was not possible due to insufficient studies.

Analysis of standardised mean differences (SMD) and subgrouping

For both leptin, pooling the SMD and subgrouping studies by mean age and BMI of participants (over and under 60 years, and over and under BMI of 25) did not affect mRR of PCa incidence (not shown).

Publication bias

There was no indication of publication bias in the studies utilised in the meta-analyses as indicated by funnel plot and Begg's test (Supplementary Fig. 1).

DISCUSSION

Summary of evidence

Overall, the evidence was very mixed, and due to study heterogeneity, only a small exploratory meta-analysis could be performed. However, it seemed that while neither leptin nor adiponectin consistently associated with PCa incidence, and leptin did not consistently associate with advanced PCa, there was some suggestive evidence of an inverse association between adiponectin and advanced PCa. The mRR of advanced PCa was reduced for men with the highest pre- diagnostic levels of adiponectin, although this was not statistically significant, and based on a small number of studies. This reflected the results of our qualitative review, which revealed nested case-control studies which had reported reduced adiponectin in men who were later diagnosed with advanced forms of PCa. Moreover, some case-control studies reported reduced adiponectin levels in advanced PCa cases. Overall, there was some limited evidence of an inverse association between adiponectin and advanced PCa incidence, which could be investigated by further research. Interestingly, only one study had analysed PCa-specific mortality, reporting that pre-diagnostic adiponectin levels were predictive. Although stand alone, this cohort was large and further studies should investigate fatal PCa. Overall, these findings may implicate adiponectin as a hormone with anti-cancer effects. To ascertain causation, in vitro and in vivo work

could further explore the effect of low adiponectin levels on PCa. Only two studies had analysed serum ghrelin levels, with opposing results, high- lighting a gap in the research.

The IARC and WCRF came to differing conclusions regarding the association between obesity and advanced PCa, with the WCRF reporting a strong link between obesity and advanced PCa [3, 5]. This could be due to different inclusion criteria or qualitative scoring methods used by the different research groups when reviewing the evidence. Additionally, the WCRF evaluation focused on epidemiologic data whereas the IARC review also included mechanistic data from in vitro and in vivo studies and hence the overall evidence base was larger. Here we observed a lack of association between leptin and advanced PCa, and some limited evidence for an association between adiponectin and advanced PCa. However, it is important to note that a relationship between obesity and advanced PCa may hinge on other factors. Obesity affects many other circulating factors that in turn could affect PCa. For example, obesity is associated with increased fasting plasma triglycerides and LDL cholesterol, with lower HDL cholesterol, and with increased blood glucose, insulin and insulin-like growth factor 1 levels, as well as increased levels of free testosterone and estradiol [54, 55]. Moreover, obesity is considered a state of chronic, subclinical inflammation and is associated with increased systemic pro-inflammatory cytokines. Furthermore, men with obesity may have accompanying diabetes or high cholesterol, and may thus receive medications such as metformin or statins, which have been shown to affect PCa development [56, 57]. Thus the relationship between obesity and cancer risk and progression is highly complex and other factors beyond the scope of this review may play a role in PCa.

Additionally, cancer cells may upregulate the appetite- regulating hormones' pathways independently of circulating levels of the ligand (e.g. by overexpression or mutation of the receptor). In line with this hypothesis, genetic variants of the leptin receptor were shown to significantly correlate with PCa risk [13]. Moreover, prostate tumours develop within a fatty tissue called periprostatic adipose tissue (PPAT), and increased PPAT has been correlated with PCa aggressiveness [58]. Potentially, the variant of leptin receptor or the concentration of local leptin levels are more important than systemic levels. Similarly, high molecular weight adiponectin may be more relevant than total levels. Hormaechea-Agulla et al. reported that the In1-ghrelin variant was upregulated in PCa patients, as was observed in breast and endocrine tumours [59–61]. Furthermore, other studies have reported that the ghrelin receptor and ghrelin-O-acetyltransferase (which converts ghrelin to its active form) were overexpressed in PCa cells and the serum of PCa patients [62, 63]. Therefore, downstream pathways may become dysregulated regardless of serum levels or the degree of adiposity. Nevertheless, this review suggests that neither leptin nor adiponectin would be sufficiently robust to act as markers of PCa incidence or

prognosis.

Study heterogeneity and limitations

Several methodological discrepancies were observed. Authors had adjusted for various covariates including age, BMI, insulin signalling (i.e. c-peptide), smoking and testosterone. We suggest that future studies should adjust for body fat (e.g. BMI), and the confirmed risk factors for PCa: age [19], race/ethnicity [64] and family history [65]. Furthermore, differences in the researchers' tumour classification systems (clinical staging, pathological staging at RP, or Gleason grading alone) produced heterogeneity. Reporting of tumour Gleason grade classification was inconsistent, some studies classed Gleason grade 7 as high-grade whereas others classed it as intermediate-grade. One would also expect variation in the apparent distribution of grade scores over time, due to revisions to the Gleason score system in 2005 and 2013 [66, 67]. Future approaches should use Grade Grouping; in which Gleason score 7 is split into its constituents (3 + 4 and 4 + 3) to characterise better the tumours with the most aggressive potential [68]. The TNM prognostic staging system has likewise been updated during the time in which the included studies were carried out. Although TNM stage ≥T3, locally advanced, or Stage III are typically considered "advanced/high-stage", some cohorts had a different definition of high stage, such as ≥T2 and some included patients with metastatic PCa. This was a limitation of the review of advanced PCa, as studies designed with different definitions were compared. The small number of cohorts that were eligible for meta- analysis and had provided raw data was a limitation although heterogeneity was low. Another limitation was that, presumably, studies had utilised a single blood sample for the hormone measurement, as adipokines can be affected by time of day or even season. Furthermore, the use of a fasted blood sample was not always stated. Different sensitivities between the hormone-measuring assays that each study had used may have biased the pooling of the mean differences in hormone levels, although the results of pooled raw data reflected the mRR. In nested case-control studies, the participants had a hormone measurement taken at the study baseline but the length of time between baseline and diagnosis in each study was varied, which may have affected the mRR based on pre-diagnostic hormone levels. The review has several strengths; this is the first meta-analysis of studies examining the effect of serum levels of

leptin and adiponectin on PCa, advanced PCa, and lethal PCa. This review addressed whether they associate and therefore may have a contributory role PCa incidence or progression, and to evaluate their usefulness as a potential biomarker of disease. The search covered a particularly high number of publications, with no limits on geographical location or time-period. We concluded that leptin was not

a robust predictor of PCa incidence nor advanced disease, although there may be an inverse association between adiponectin and advanced PCa that requires further attention. We considered that adjusting for BMI was essential since it is related to both the exposure (hormone) and outcome (PCa) and is thus a confounder. There were surprisingly few studies with data that were appropriate for combining by meta-analysis, namely studies with BMI-matched groups and risk estimates of PCa by subset of hormone level. We believe this indicates the need for further research, with a particular focus on adiponectin and advanced PCa. We highlight the in vitro evidence for a potential role of ghrelin in PCa development and the lack of data on serum levels in PCa patients. We came to different conclusions than previous reviews that concluded that leptin levels were likely associated with high-grade PCa [10, 69]; we do not consider the evidence for this to be substantial.

CONCLUSIONS

The results suggested that serum levels of leptin were not associated with PCa nor advanced disease. However, the few studies that analysed adiponectin levels in PCa at the time of radical prostatectomy and PCa-specific mortality reported inverse associations, and our exploratory meta- analysis similarly suggested an inverse association. This implicates adiponectin as a potentially important hormone in mediating the relationship between obesity and PCa advancement. The effect of obesity on ghrelin levels and its relationship with prostate tumours has not been thoroughly investigated and may be important considering its emerging role in PCa signalling as shown by in vitro studies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

REFERENCES

1. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemio- logical evidence and proposed mechanisms. Nat Rev Cancer. 2004;4:579–91.
2. Freedland SJ, Platz EA. Obesity and prostate cancer: making sense out of apparently conflicting data. Epidemiol Rev. 2007;29:88–97.
3. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body Fatness and Cancer — Viewpoint of the IARC Working Group. N Engl J Med. 2016;375:794–8.
4. Mottet, N. et al. 'EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent', Eur Urol, 2017;71:618–29. https://doi.org/10. 1016/j.eururo.2016.08.003.
5. World Cancer Research Fund International. Prostate cancer | How diet, nutrition and physical activity affect prostate cancer. 2014 [cited 2019 Mar 19]. https://www.wcrf.org/dietandcancer/prosta te-cancer
6. Park J, Morley TS, Kim M, Clegg DJ, Scherer PE. Obesity and cancer--mechanisms underlying tumour progression and recur- rence. Nat Rev Endocrinol. 2014;10:455–65.
7. Vansaun MN. Molecular pathways: adiponectin and leptin sig- naling in cancer. Clin Cancer Res. 2013;19:1926–32.
8. Kubota N, Yano W, Kubota T, Yamauchi T, Itoh S, Kumagai H, et al. Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. Cell Metab. 2007;6:55–68.
9. Tschöp M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E, Heiman ML. Circulating ghrelin levels are decreased in human obesity. Diabetes. 2001;50:707–9.
10. Alshaker H, Sacco K, Alfraidi A, Muhammad A, Winkler M, Pchejetski D. Leptin signalling, obesity and prostate cancer: Molecular and clinical perspective on the old dilemma. Onco- target. 2015;6:35556–63.
11. Lin T-C, Hsiao M. Ghrelin and cancer progression. Biochim Biophys Acta - Rev Cancer. 2017;1868:51–7.
12. Muppala S, Konduru SKP, Merchant N, Ramsoondar J, Ram- persad CK, Rajitha B, et al. Adiponectin: Its role in obesity- associated colon and prostate cancers. Crit Rev Oncol Hematol. 2017;116:125–33.
13. Hu M-B, Xu H, Hu J-M, Zhu W-H, Yang T, Jiang H-W, et al. Genetic polymorphisms in leptin, adiponectin and their receptors affect risk and aggressiveness of prostate cancer: evidence from a meta-analysis and pooled-review. Oncotarget. 2016;7:81049–61.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.
15. Michalakis K, Williams CJ, Mitsiades N, Blakeman J, Balafouta- Tselenis S, Giannopoulos A, et al. Serum adiponectin concentra- tions and tissue expression of adiponectin receptors are reduced in patients with prostate cancer: a case control study. Cancer Epi- demiol Biomark Prev. 2007;16:308–13.
16. Baillargeon J, Platz EA, Rose DP, Pollock BH, Ankerst DP, Haffner S, et al. Obesity, adipokines, and prostate cancer in a prospective population-based study. Cancer Epidemiol Biomark Prev. 2006;15:1331–5.
17. Serretta V, Abrate A, Siracusano S, Gesolfo CS, Vella M, Di Maida F, et al. Clinical and biochemical markers of visceral adi- pose tissue activity: body mass index, visceral adiposity index, leptin, adiponectin, and matrix metalloproteinase-3. Correlation with Gleason patterns 4 and 5 at prostate biopsy. Urol Ann. 2018;10:280–6.
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88.
19. Glass AS, Cary KC, Cooperberg MR. Risk-based prostate cancer screening: who and how? Curr Urol Rep. 2013;14:192–8.

20. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta- analysis. Stat Med. 2002;21:1539–58.
21. Begg CB, Mazumdar M. Operating characteristics of a rank cor- relation test for publication bias. Biometrics. 1994;50:1088–101.
22. Copenhagen: The Nordic Cochrane Centre TCC. Review Manager (RevMan) [Computer program]. Version 5.3. 2014.
23. Hsing AW, Chua S, Gao YT, Gentzschein E, Chang L, Deng J, et al. Prostate cancer risk and serum levels of insulin and leptin: a population-based study. J Natl Cancer Inst. 2001;93:783–9.
24. Lai GY, Giovannucci EL, Pollak MN, Peskoe SB, Stampfer MJ, Willett WC, et al. Association of C-peptide and leptin with prostate cancer incidence in the Health Professionals Follow-up Study. Cancer Causes Control. 2014;25:625–32.
25. Li HJ, Stampfer MJ, Mucci L, Rifai N, Qiu WL, Kurth T, et al. A 25-year prospective study of plasma adiponectin and leptin con- centrations and prostate cancer risk and survival. Clin Chem. 2010;56:34–43.
26. Stattin P, Kaaks R, Johansson R, Gislefoss R, Söderberg S, Alfthan H, et al. Plasma leptin is not associated with prostate cancer risk. Cancer Epidemiol Biomark Prev. 2003;12:474–5.
27. Touvier M, Fezeu L, Ahluwalia N, Julia C, Charnaux N, Sutton A, et al. Association between pre-diagnostic biomarkers of inflam- mation and endothelial function and cancer risk: a nested case-control study. Am J Epidemiol. 2013;177:3–13.
28. Burton A, Martin RM, Holly J, Lane JA, Donovan JL, Hamdy FC, et al. Associations of adiponectin and leptin with stage and grade of PSA-detected prostate cancer: The ProtecT study. Cancer Causes Control. 2013;24:323–34.
29. Arisan ED, Arisan S, Atis G, Palavan-Unsal N, Ergenekon E. Serum adipocytokine levels in prostate cancer patients. Urol Int. 2009;82:203–8.
30. Gade-Andavolu R, Cone LA, Shu S, Morrow A, Kowshik B, Andavolu MVS. Molecular interactions of leptin and prostate cancer. Cancer J. 2006;12:201–6.
31. Grosman H, Fabre B, Lopez M, Scorticati C, Lopez Silva M, Mesch V, et al. Complex relationship between sex hormones, insulin resistance and leptin in men with and without prostatic disease. Aging Male. 2016;19:40–5.
32. Nishimura K, Soda T, Nakazawa S, Yamanaka K, Hirai T, Kishikawa H, et al. Serum adiponectin and leptin levels are useful markers for prostate cancer screening after adjustments for age, obesity-related factors, and prostate volume. Minerva Urol e Nefrol. 2012;64:199–208.
33. Sağlam K, Aydur E, Yilmaz MI, Göktaş S. Leptin influences cellular differentiation and progression in prostate cancer. J Urol. 2003;169:1308–11.
34. Singh SK, Grifson JJ, Mavuduru RS, Agarwal MM, Mandal AK, Jha V. Serum leptin: a marker of prostate cancer irrespective of obesity. Cancer Biomark. 2010;7:11–5.
35. Tewari R, Rajender S, Natu SM, Goel A, Dalela D, Goel MM, et al. Significance of obesity markers and adipocytokines in high grade and high stage prostate cancer in North Indian men - A cross-sectional study. Cytokine. 2013;63:130–4.
36. Duarte, M. F. et al. 'Clinical and metabolic implications of obesity in prostate cancer: is testosterone a missing link?', The Aging Male, EPub ahead of print, 2018, p. 1–13. https://doi.org/10.1080/ 13685538.2018.1519695.
37. Fryczkowski M, Buldak RJ, Hejmo T, Kukla M, Zwirska- Korczala K. Circulating levels of omentin, leptin, VEGF, and HGF and their clinical relevance with PSA marker in prostate cancer. Dis Markers. 2018;2018:3852401.
38. Fontana CML, Maselli ME, Elizalde RFP, Monaco NAD, Recupero ALU, Laur JDL. Leptin increases prostate cancer aggressiveness. J Physiol Biochem. 2011;67:531–8.
39. Sieminska L, Borowski A, Marek B, Nowak M, Kajdaniuk D, Warakomski J, et al. Serum concentrations of adipokines in men with prostate cancer and benign prostate hyperplasia.

Endokrynol Pol. 2018;69:120–7.
40. Medina EA, Shi XY, Grayson MH, Ankerst DP, Livi CB, Medina MV, et al. The Diagnostic value of Adiponectin multimers in healthy men undergoing screening for prostate cancer. Cancer Epidemiol Biomark Prev. 2014;23:309–15.
41. Wang Y, Lam KSL, Chan L, Chan KW, Lam JBB, Lam MC, et al. Post-translational modifications of the four conserved lysine residues within the collagenous domain of Adiponectin are required for the formation of its high molecular weight oligomeric complex. J Biol Chem. 2006;281:16391–400.
42. Fowke JH, Motley S, Dai Q, Concepcion R, Barocas DA. Asso- ciation between biomarkers of obesity and risk of high-grade prostatic intraepithelial neoplasia and prostate cancer - Evidence of effect modification by prostate size. Cancer Lett. 2013;328:345–52.
43. Stevens VL, Jacobs EJ, Sun JZ, Gapstur SM. No association of plasma levels of Adiponectin and c-peptide with risk of aggressive prostate cancer in the cancer prevention study II nutrition cohort. Cancer Epidemiol Biomark Prev. 2014;23:890–2.
44. Sher DJ, Oh WK, Jacobus S, Regan MM, Lee GS, Mantzoros C. Relationship between serum adiponectin and prostate cancer grade. Prostate . 2008;68:1592–8.
45. Freedland SJ, Sokoll LJ, Platz EA, Mangold LA, Bruzek DJ, Mohr P, et al. Association between serum adiponectin, and pathological stage and grade in men undergoing radical prosta- tectomy. J Urol. 2005;174(4 Pt 1):1266–70.
46. Goktas S, Mahmut IY, Caglar K, Sonmez A, Kilic S, Bedir S. Prostate cancer and adiponectin. Urology. 2005;65:1168–72.
47. Grosman H, Fabre B, Mesch V, Lopez MA, Schreier L, Mazza O, et al. Lipoproteins, sex hormones and inflammatory markers in association with prostate cancer. Aging Male. 2010;13:87–92.
48. Housa D, Vernerová Z, Heráček J, Procházka B, Čechák P, Kuncová J, et al. Adiponectin as a potential marker of prostate cancer progression: Studies in organ-confined and locally advanced prostate cancer. Physiol Res. 2008;57:451–8.
49. Ikeda A, Nakagawa T, Kawai K, Onozawa M, Hayashi T, Mat- sushita Y, et al. Serum adiponectin concentration in 2,939 Japa- nese men undergoing screening for prostate cancer. Prostate Int. 2015;3:87–92.
50. Michalakis K, Venihaki M, Mantzoros C, Vazaiou A, Ilias I, Gryparis A, et al. In prostate cancer, low adiponectin levels are not associated with insulin resistance. Eur J Clin Invest. 2015;45:572–8.
51. Kang M, Byun SS, Lee SE, Hong SK. Clinical significance of serum adipokines according to body mass index in patients with clinically localized prostate cancer undergoing radical prosta- tectomy. World J Mens Health. 2018;36:57–65.
52. Malendowicz W, Ziolkowska A, Szyszka M, Kwias Z. Elevated blood active ghrelin and unaltered total ghrelin and obestatin concentrations in prostate carcinoma. Urol Int. 2009;83:471–5.
53. Hormaechea-Agulla D, Gahete MD, Jiménez-Vacas JM, Gómez- Gómez E, Ibáñez-Costa A, L-López F, et al. The oncogenic role of the In1-ghrelin splicing variant in prostate cancer aggressiveness. Mol Cancer. 2017;16:146.
54. Buschemeyer WC, Freedland SJ. Obesity and prostate cancer: epidemiology and clinical implications. Eur Urol. 2007;52:331–43.
55. Allott EH, Hursting SD. Obesity and cancer: mechanistic insights from transdisciplinary studies. Endocr Relat Cancer. 2015;22: R365–86.
56. Alfaqih MA, Allott EH, Hamilton RJ, Freeman MR, Freedland SJ. The current evidence on statin use and prostate cancer prevention: are we there yet? Nat Rev Urol. 2017;14:107–19.
57. Raval AD, Thakker D, Vyas A, Salkini M, Madhavan S, Sam- bamoorthi U. Impact of metformin on clinical outcomes among men with prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2015;18:110–21.

58. van Roermund JGH, Hinnen KA, Tolman CJ, Bol GH, Witjes JA. Bosch JLHR, et al. Periprostatic fat correlates with tumour aggressiveness in prostate cancer patients. BJU Int. 2011;107:1775–9.
59. Luque RM, Sampedro-Nuñez M, Gahete MD, Ramos-Levi A, Ibáñez-Costa A, Rivero-Cortés E, et al. In1-ghrelin, a splice variant of ghrelin gene, is associated with the evolution and aggressiveness of human neuroendocrine tumors: evidence from clinical, cellular and molecular parameters. Oncotarget. 2015;6: 19619–33.
60. Ibáñez-Costa A, Gahete MD, Rivero-Cortés E, Rincón-Fernández D, Nelson R, Beltrán M, et al. In1-ghrelin splicing variant is overexpressed in pituitary adenomas and increases their aggres- sive features. Sci Rep. 2015;5:8714.
61. Gahete MD, Córdoba-Chacón J, Hergueta-Redondo M, Martínez- Fuentes AJ, Kineman RD, Moreno-Bueno G, et al. A Novel Human Ghrelin Variant (In1-Ghrelin) and Ghrelin-O-Acyltransferase Are Overexpressed in Breast Cancer: Potential Pathophysiological Relevance. Ulasov I, editor. PLoS ONE. 2011;6:e23302.
62. Seim I, Jeffery PL, de Amorim L, Walpole CM, Fung J, Whiteside EJ, et al. Ghrelin O-acyltransferase (GOAT) is expressed in prostate cancer tissues and cell lines and expression is differentially regulated in vitro by ghrelin. Reprod Biol Endocrinol. 2013;11:70.
63. Gómez-Gómez, E et al. 'Plasma ghrelin O-acyltransferase (GOAT) enzyme levels: A novel non-invasive diagnosis tool for patients with significant prostate cancer'. J Cell Mol Med. John Wiley & Sons, Ltd (10.1111), 2018;22, p. 5688–97. https://doi. org/10.1111/jcmm.13845.
64. Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS, et al. Assessing prostate cancer risk: results from the prostate cancer prevention trial. J Natl Cancer Inst. 2006;98:529–34.
65. Brawley, OW 'Prostate cancer epidemiology in the United States', World J Urol 2012;30:195–200. https://doi.org/10.1007/s00345- 012-0824-2.
66. Helpap B, Egevad L. Modified Gleason grading. An updated review. Histol Histopathol. 2009;24:661–6.
67. Gordetsky J, Epstein J. Grading of prostatic adenocarcinoma: current state and prognostic implications.
68. Kryvenko ON, Epstein JI. Prostate Cancer Grading A Decade After the 2005 Modified Gleason Grading System.
69. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. Eur Urol. 2013;63:800–9.
70. Capoun O, Soukup V, Kalousová M, Sobotka R, Pešl M, Zima T, et al. Diagnostic Importance of Selected Protein Serum Markers in the Primary Diagnostics of Prostate Cancer. Urol Int. 2015;95:429–35.
71. Medina EA, Shi X, Grayson MH, Ankerst DP, Livi CB, Medina MV, et al. The Diagnostic Value of Adiponectin Multimers in Healthy Men Undergoing Screening for Prostate Cancer. Can- cer Epidemiol Prev. 2014;23:309–15.
72. Stattin P, Söderberg S, Hallmans G, Bylund A, Kaaks R, Stenman U-H, et al. Leptin Is Associated with Increased Prostate Cancer Risk: A Nested Case-Referent Study. J Clin Endocrinol Metab. 2001;86:1341–5.
73. Chang S, Hursting SD, Contois JH, Strom SS, Yamamura Y, Babaian RJ, et al. Leptin and prostate cancer. Prostate. 2001;46:62–67.
74. Housa D, et al. 'Adiponectin as a potential marker of prostate cancer progression: Studies in organ-confined and locally advanced prostate cancer'. Physiol Res. 2008;57:451–8.
75. Lagiou P, Signorello LB, Trichopoulos D, Tzonou A, Tri- chopoulou A, Mantzoros CS. Leptin in relation to prostate cancer and benign prostatic hyperplasia. Int J Cancer. 1998;76: 25–28.
76. Sieminska L, et al. 'Serum concentrations of adipokines in men with prostate cancer and benign prostate hyperplasia'. Endokrynol Pol. 2018;69:120–7.
77. Touvier M, Fezeu L, Ahluwalia N, Julia C, Charnaux N, Sutton A, et al. Association Between

Prediagnostic Biomarkers of Inflam- mation and Endothelial Function and Cancer Risk: A Nested Case-Control Study. Am J Epidemiol. 2012;177:3–13.

78. Stocks T, Lukanova A, Rinaldi S, Biessy C, Dossus L, Lindahl B, et al. Insulin resistance is inversely related to prostate cancer: A pro- spective study in Northern Sweden. Int J Cancer. 2007;120:2678–86.

Table 1. Study characteristics of the articles in the systematic review.

Study	Study design (cohort, and duration)	Hormone analysed	PCa outcome analysed (and classification of Gleason grade 7)	Gleason 7 classed as intermediate grade or high-grade	Country	Detection Method	Fasted blood	Cases *N*	Cancer free controls *N* (or otherwise)
Arisan et al 2009	Case-control	Leptin, adiponectin	Incidence, risk of high-stage, risk of high-grade	Intermediate	Turkey	ELISA	Yes	50 (of which 18 advanced stage, and either 8 (Table 1 data) or 24 or 8 (Table 2 data) high-grade)	50 (and 32 organ-confined, and either 10 (Table 1 data) or 11 (Table 2 data) low-grade tumours)
Baillargeon et al 2006	Nested case-control (San Antonio Center for Biomarkers of Risk of Prostate Cancer (SABOR) cohort, March 2001 - Aug 2005)	Leptin, adiponectin	Incidence, risk of high-grade	High	USA	LabMAP	Not stated	125 (of which 40 high-grade)	125 (and 85 low-grade tumours)
Burton et al 2013	Nested case-control (ProtecT cohort, 2001-2009)	Leptin, adiponectin	Risk of high-stage, risk of high-grade	High	UK	ELISA	No	307 (of which 311 locally advanced, 307 high-grade)	416 (and 413 low-stage and 416 low-grade tumours)
Capoun et al 2015	Case-control	Leptin	Incidence	High	Czech Republic	ELISA	Yes	167 (of which 10 high-grade)	206 (and 119 low-grade tumours)
Chang et al 2001	Case-control	Leptin	Risk of high-volume localised tumour	Measured tumour volume	USA	RIA	Not stated	151 (all high-volume)	48 (all low-volume)
Duarte et al 2018	Case-control	Leptin	Incidence	Not stated	Portugal	ECLIA	Not stated	103	78
Fontana et al 2011	Case-control	Leptin, adiponectin	Incidence, risk of high-grade	Intermediate	Argentina	ELISA	Not stated	35 (of which 9 high-grade)	35 (and 12 low-grade and 14 intermediate-grade tumours)
Fowke et al 2013	Nested case-control (Nashville Men's Health Study, 2003-Dec 2008)	Leptin, adiponectin	Risk of high-grade	High	USA	RIA	Not stated	100 (high-grade)	100 (all low-grade)
Freedland et al 2005	Case-control	Leptin	Risk of stage pT3 and high-grade at RP	High	USA	ELISA	Not stated	1 (pT3a), 78 (high-grade)	224 (non-pT3a), 158 (low-grade)
Freedland et al 2005	Case-control	Adiponectin	Risk of stage pT3 and high-grade at RP	High	USA	ELISA	Not stated	1 (pT3a), 78 (high-grade)	224 (non-pT3a), 158 (low-grade)
Fryczkowski et al 2018	Case-control	Leptin	Incidence	Not stated	Poland	ELISA	Not stated	40 (all Gleason grade 6-7)	40 BPH
Gade-Andavolu et al 2006	Case-control	Leptin	Incidence	Not stated	USA	RIA	Not stated	69	137
Goktas et al 2005	Case-control	Adiponectin	Risk of high-stage, risk of high-grade	Intermediate	Turkey	RIA	Yes	30 (of which 16 (advanced stage ≥T3N0M0, 9 high-grade)	36 (and 8 low-grade and 13 intermediate-grade tumours)

Grosman et al 2010	Case-control	Adiponectin	Incidence	High	Argentina	RIA	Yes	25 (of which 10 high-grade)	25
Grosman et al 2016	Case-control	Leptin	Incidence	High	Argentina	RIA	Yes	70 (of which 12 poorly differentiated)	70 (58 moderately differentiated tumours)
Hormaeche a-Agulla et al 2017	Case-control	Ghrelin	Incidence	Gleason -7 and Gleason >7	Spain	ELISA (total ghrelin), RIA (In1 ghrelin)	Not stated	20 (of which 8 Gleason 6, 9 Gleason 7, 7 Gleason 8, 6 Gleason 9)	30
Housa et al 2007	Case-control	Adiponectin	Incidence, risk of high-stage	High	Czech Republic	ELISA	Yes	43 (of which 26 pT3 locally advanced, not metastasised, 7 high-grade)	25 BPH (17 pT2 and 19 low-grade tumours)
Hsing et al 2001	Nested case-control (Shanghai Cancer Institute and 28 collaborating hospitals, 1993-1995)	Leptin	Incidence	"Advanced" and "poorly differentiated"	China	RIA	Yes	128 (of which approximately 66% high-stage, >60% moderately or poorly differentiated)	306 (approximately 33% low-stage, and <40% low-grade tumours)
Ikeda et al 2015	Case-control	Adiponectin	Incidence, risk of high-stage	Measured Clinical T stage and D'Amico	Japan	Latex particle-enhanced turbidimetric immunoassay	Not stated	24 (of which 4 T2c (1 T2a, 1 T2b, 2 T2c), 8 D'Amico high-risk)	2,817 (20 T1c and 16 low or medium D'Amico risk tumours)
Kang et al 2018	Case-control	Leptin, adiponectin	Risk of high-grade at RP in healthy versus obese men	Intermediate	South Korea	RIA (for leptin), ELISA (for adiponectin)	Not stated	62 (of which 1 high-stage (≥pT3))	24 low-stage (≤T2)
Lagiou et al 1998	Case-control	Leptin	Incidence	Not stated	Greece	RIA	Not stated	43 (of which 5 metastatic at time of diagnosis)	48
Lai et al 2014	Nested case-control (Health Professionals Follow-up Study, 1993-2004)	Leptin	Incidence	High	USA	ELISA	No	1314 (of which 156 high-stage, 477 high-grade)	1314 (1064 low-stage, 736 low-grade tumours)
Li et al 2010	Nested case-control (Physician's Health Study, 1982-2000 +10 year follow up on cases)	Adiponectin, leptin	Incidence, risk of high-stage, risk of high-grade	Intermediate	USA	RIA	Not stated	654 (of which 121 high-stage and 124 high-grade used in analysis)	644 (121 low-stage and 124 low-grade tumours)
Malendowicz et al 2009	Case-control	Ghrelin	Incidence	Measured Localised and metastasised	Poland	RIA	Yes	18 (of which 13 low-stage, 5 metastasised)	16
Medina et al 2013	Nested case-control (SABOR cohort, 2001 - 2013)	Adiponectin	Incidence, risk of high-grade	High	USA	ELISA	Not stated	228 (of which 72 high-grade	239 (and 140 low grade tumours)
Michalakis et al 2007	Case-control	Adiponectin	Incidence	Intermediate	Greece	RIA	Yes	75 (of which 13 stage III and 5 stage IV, and 19 high-grade)	150 (and 8 stage I, 45 stage II, and 5 low-grade and 48 intermediate grade tumours)

Michalakis et al 2015	Case-control	Adiponectin	Incidence	Measured localised and metastasised	Greece	RIA	Yes	75 (of which 5 metastasised)	150
Nishimura et al 2012	Case-control	Leptin, adiponectin	Incidence	Not stated	Japan	ELISA	Not stated	54	70 BPH
Sağlam et al 2003	Case-control	Leptin	Incidence, risk of high-stage, risk of high-grade	Intermediate	Turkey	RIA	Yes	21 (of which 10 locally advanced and T3N0M0, 7 high-grade)	50 (and 11 organ-confined, 5 low-grade and 9 intermediate grade tumours)
Serretta et al 2018	Case-control	Leptin, adipopnectin	Risk of Gleason score 4 or 5	High	Not stated	ELISA	Not stated	146 (of which 68 Gleason score 4 or 5)	81 Gleason score 3
Sher et al 2008	Nested case-control (Dana Farber Cancer Institute, Nov 2001 - Dec 2005)	Adiponectin	Risk of high-grade	Intermediate	USA	ELISA	Not stated	539 (of which 199 high-stage (1 pTx, 176 pT2, 19 pT3) and 9 high-grade)	98 low-stage (67 cTx, 355 cT1, 105 cT2, 5 cT3) 98 low-grade and 92 low-grade)
Siemińska et al 2018	Case-control	Leptin, adiponectin	Incidence, risk of high-grade	Intermediate	Poland	ELISA	Yes	74 (of which 22 high-grade)	66 BPH (and 24 low-grade tumours)
Singh et al 2010	Case-control	Leptin	Incidence	High	India	ELISA	Not stated	30 (of which 12 locally advanced, 14 metastasised to bone, 7 high-grade)	30 (and 4 localised, 23 low-grade tumours)
Stattin et al 2000	Nested case-control (WHO Monica 1986-1994, Vasterbotten Intervention Program (VIP) Jan 1985 - March 1999)	Leptin	Incidence	"highly, intermediatel y, or poorly differentiated "	Sweden	RIA	Yes	149 (of which 16 locally advanced, 20 metastasis (6 to lymph node, 14 to bone)	298 (and 113 low-stage and 130 low-grade tumours)
Stattin et al 2003	Nested case-control (Janus project 1973-1997)	Leptin	Incidence	Not stated	Norway	RIA	Not stated	200	397
Stevens et al 2014	Nested case-control (CPS II Nutrition cohort, 1992-2014)	Adiponectin	Risk of high-stage	Aggressive defined as Gleason ≥7, High-risk defined as Gleason ≥8	USA	ELISA	Not stated	69 (of which 44 stage T3, 25 stage T4, 108 Gleason 7, 73 Gleason 8, 46 Gleason 9-10).	194 (and 194 organ confined, 27 Gleason 6 or 7 tumours)
Stocks et al 2007	Nested case-control (Vasterbotten Intervention Project 1985-2004)	Leptin	Incidence, risk of high-stage, risk of high-grade	Intermediate	Sweden	RIA	Yes	392 (of which 12 stage N1 lymph node metastasis, 232 stage Nx no lymph node extirpation; 37 with bone metastasis; 84 Mx no bone scan, 51 high-grade)	392 (and 20 stage T1a,b; 167 stage T1c; 146 stage localised T2; 55 stage non-localised T3, T4, 146 low-grade, 195 intermediate-grade)
Tewari et al 2013	Case-control	Leptin, adiponectin	Incidence, risk of high-stage, risk of high-grade	Not stated	India	Not stated	Not stated	95 (of which 31 Stage IV, 62 high-grade)	95 BPH (and 64 Stage III, 33 low-grade)
Touvier et al 2012	Nested case-control (Supplémentati	Leptin, adiponectin	Incidence	Not stated	France	ELISA	Yes	156	312

	on en Vitamines et Minéraux AntioXydants (SU. VI. MAX), 1994-2007)								

ELISA: enzyme-linked immunoassay, RIA: radio-immunoassay, LabMAP: Luminex LabMAP^{TM} system, BPH: benign prostatic hyperplasia, n/a: non-applicable, ECLIA: electrochemiluminescent assay.

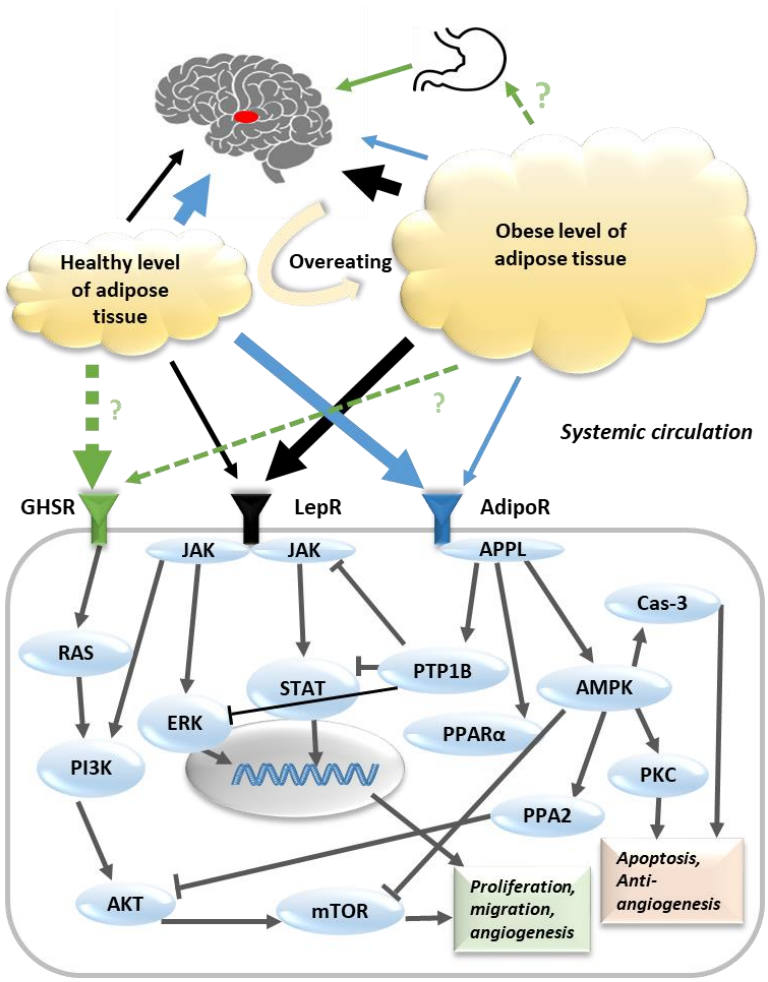
FIGURE LEGENDS

Fig. 1 Schematic overview of the interaction between appetite- regulating hormones and the prostatic epithelial cell (see also ref. [1]). Arrows indicate direction of regulation, barred lines indicate inhibition. Arrows' thickness indicates serum concentration (thick = high, thin = low). Dotted lines = indirect action, solid lines = direct action. Black arrows = leptin, blue arrows = adiponectin, green arrows = ghrelin. Leptin is secreted proportionally by adipocytes and adiponectin inverse proportionally, so that when adipose tissue increases, circulating leptin is increased and circulating adiponectin decreased. Ghrelin is secreted by the stomach. The hormones act on the hypothalamus (red spot) to modulate appetite, which can in turn affect appetite. The effect of obesity on the level of ghrelin remains poorly understood. In prostate cells, receptors responsive to acetylated ghrelin (growth hormone secretagogue receptor (GHSR)), adiponectin receptor (AdipoR), and leptin receptor (LepR) are expressed. These activate pathways that are involved in regulation of proliferation, migration, angiogenesis (e.g. growth promoting JAK/STAT/ERK or PI3K/AKT/mTOR or growth-inhibiting AMPK/PPA2) and apoptosis (AMPK/PKC and Caspase-3). The pathways are interlinked and the hormones regulate one another [7]

Fig. 2 Flow chart depicting the systematic screening process. Adapted From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org.

Fig. 3 Meta-analysis of BMI-adjusted models from nested case- controls. a The mRR of PCa incidence in men with highest subset of leptin. Baillargeon et al: 125 PCa cases, 125 healthy controls, Hsing et al: 128 PCa cases, 306 healthy controls; Lai et al: 1,314 PCa cases, 1,314 healthy controls; Stattin et al: 146 PCa cases, 298 healthy controls; Touvier et al: 156 PCa cases, 312 healthy controls. Total: 1,872 PCa cases, 2,355 healthy controls. b The mRR of advanced PCa in men with highest subset of leptin. Baillargeon et al (grade): 40 high- grade cases, 85 low-grade cases; Burton et al (grade): 307 high-grade cases, 416 low-grade cases; Burton et al (stage) 311 high-stage cases, 413 low-stage cases; Lai et al. (grade): 477 high-grade cases, 736 low- grade cases; Lai et al. (stage): 156 high-stage cases, 1,064 low-stage cases. Total: 1,291 advanced cases, 2,714 non-advanced cases. c The mRR of high-grade PCa in men with highest subset of adiponectin. Baillargeon et al: 40 high-grade cases, 85 low-grade cases; Burton et al.: 307 high-grade cases, 416 low-grade cases; Sher et al: 9 high- grade cases, 92 low-grade cases. Total: 356 high-grade cases, 593 low- grade cases. d The mRR of advanced PCa in men with highest subset of adiponectin. Baillargeon et al. (grade): 40 high-grade cases, 85 low- grade cases;

Burton et al (stage): 311 high-stage cases, 413 low-stage cases; Burton et al. (grade): 307 high-stage cases, 416 low-stage cases; Sher et al. (grade): 9 high-grade cases, 92 low-grade cases; Stevens et al. (stage): 69 high-stage cases, 194 low-stage cases. Total:736 advanced cases, 1,200 non-advanced cases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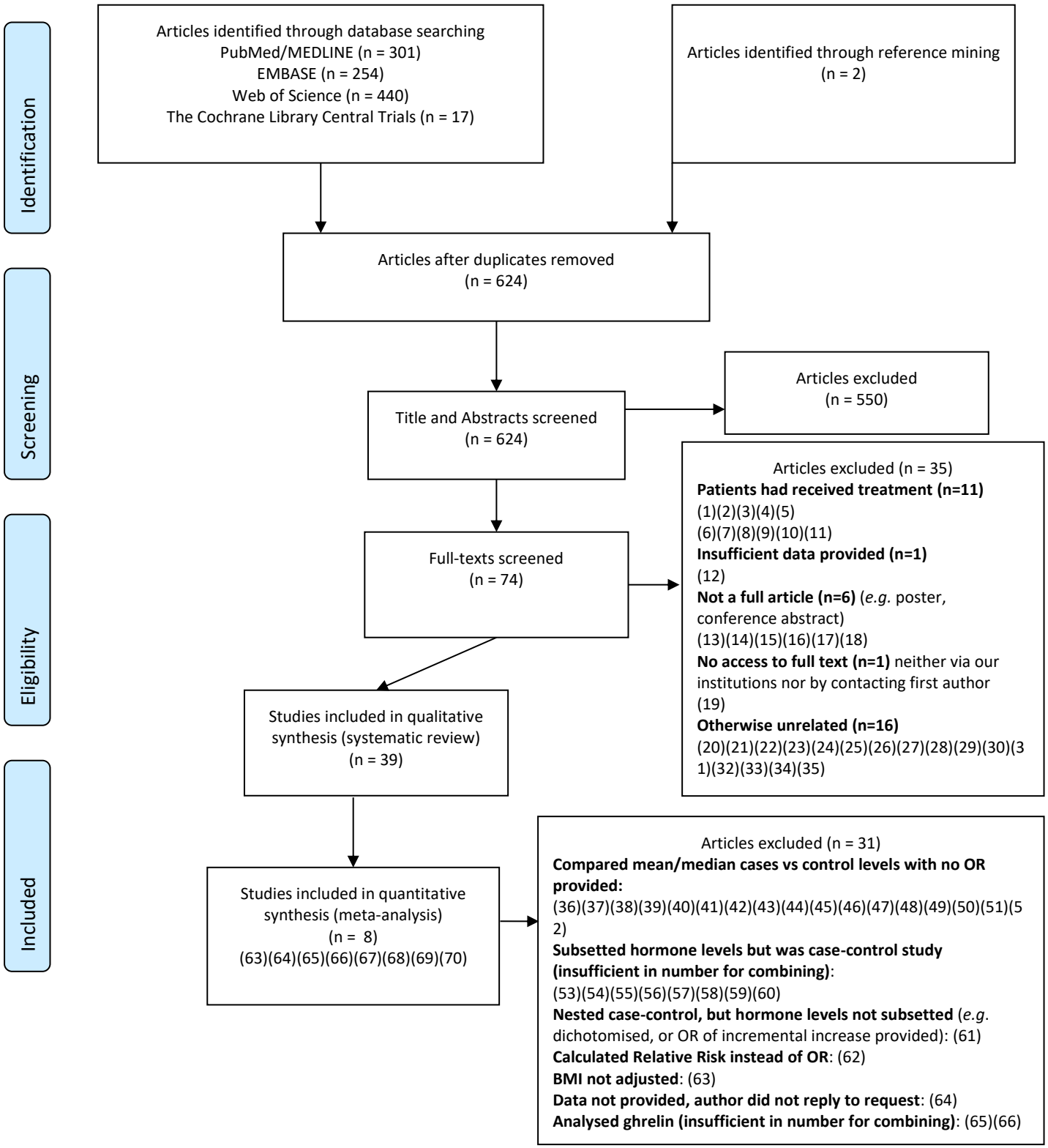
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EMBASE (n = 254)
Web of Science (n = 440)
The Cochrane Library Central Trials (n = 17)
Articles identified through reference mining
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Articles after duplicates removed
(n = 624)
Title and Abstracts screened
(n = 624)
Articles excluded
(n = 550)
Full-texts screened
(n = 74)
Articles excluded (n = 35)
Patients had received treatment (n=11)
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Insufficient data provided (n=1)
(12)
Not a full article (n=6) (e.g. poster, conference abstract)
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No access to full text (n=1) neither via our institutions nor by contacting first author
(19)
Otherwise unrelated (n=16)
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Studies included in qualitative synthesis (systematic review)
(n = 39)
Studies included in quantitative synthesis (meta-analysis)
(n = 8)
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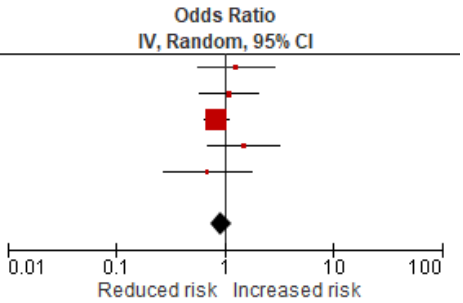
Articles excluded (n = 31)
Compared mean/median cases vs control levels with no OR provided:
(36)(37)(38)(39)(40)(41)(42)(43)(44)(45)(46)(47)(48)(49)(50)(51)(52)
Subsetted hormone levels but was case-control study (insufficient in number for combining):
(53)(54)(55)(56)(57)(58)(59)(60)
Nested case-control, but hormone levels not subsetted (e.g. dichotomised, or OR of incremental increase provided): (61)
Calculated Relative Risk instead of OR: (62)
BMI not adjusted: (63)
Data not provided, author did not reply to request: (64)
Analysed ghrelin (insufficient in number for combining): (65)(66)

A) The mRR of PCa incidence in men with highest subset of leptin

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Baillargeon 2006	0.24686	0.413242	7.4%	1.28 [0.57, 2.88]
Hsing 2001	0.09531	0.320199	12.3%	1.10 [0.59, 2.06]
Lai 2014	-0.17435	0.138163	66.3%	0.84 [0.64, 1.10]
Stattin 2000	0.405465	0.387711	8.4%	1.50 [0.70, 3.21]
Touvier 2012	-0.37106	0.476773	5.6%	0.69 [0.27, 1.76]
Total (95% CI)			**100.0%**	**0.93 [0.75, 1.16]**

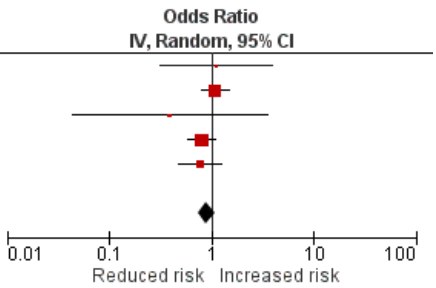
Heterogeneity: Tau² = 0.00; Chi² = 3.33, df = 4 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.52)



B) The mRR of advanced PCa in men with highest subset of leptin

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Baillargeon (grade) 2006	0.11332868	0.64795918	2.4%	1.12 [0.31, 3.99]
Burton (grade) 2013	0.07696104	0.16071429	39.2%	1.08 [0.79, 1.48]
Burton (stage) 2013	-0.94160854	1.125	0.8%	0.39 [0.04, 3.54]
Lai (grade) 2014	-0.21072103	0.15816326	40.4%	0.81 [0.59, 1.10]
Lai (stage) 2014	-0.26136476	0.24234694	17.2%	0.77 [0.48, 1.24]
Total (95% CI)			**100.0%**	**0.90 [0.74, 1.10]**

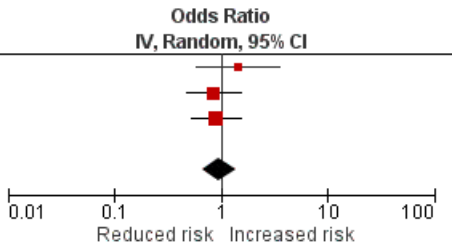
Heterogeneity: Tau² = 0.00; Chi² = 2.81, df = 4 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)



C) The mRR of high-grade PCa in men with highest subset of adiponectin

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Baillargeon 2006	0.371564	0.4586229	16.2%	1.45 [0.59, 3.56]
Burton 2013	-0.15082	0.29903676	38.2%	0.86 [0.48, 1.55]
Sher 2008	-0.10536	0.27375847	45.6%	0.90 [0.53, 1.54]
Total (95% CI)			**100.0%**	**0.96 [0.67, 1.37]**

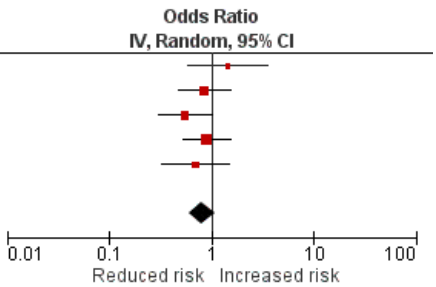
Heterogeneity: Tau² = 0.00; Chi² = 1.00, df = 2 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.81)



D) The mRR of advanced PCa in men with highest subset of adiponectin

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Baillargeon (grade) 2006	0.37156356	0.4586229	10.3%	1.45 [0.59, 3.56]
Burton (grade) 2013	-0.15082289	0.29903676	24.2%	0.86 [0.48, 1.55]
Burton (stage) 2013	-0.597837	0.312188	22.2%	0.55 [0.30, 1.01]
Sher (grade) 2008	-0.10536052	0.27375847	28.8%	0.90 [0.53, 1.54]
Stevens (stage) 2014	-0.35667494	0.3845507	14.6%	0.70 [0.33, 1.49]
Total (95% CI)			**100.0%**	**0.81 [0.61, 1.08]**

Heterogeneity: Tau² = 0.00; Chi² = 3.48, df = 4 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.45 (P = 0.15)



SUPPLEMENTARY FIGURES AND TABLES

LEGENDS

Supplementary Figure 1. Publication bias assessment of the studies included in the meta-analyses of BMI-adjusted models from nested case-controls. A) ORs of the PCa incidence in men with highest subset leptin. B) ORs of advanced PCa in men with highest subset leptin. C) ORs of high-grade PCa in men with highest subset adiponectin. D) ORs of advanced PCa in men with highest subset adiponectin.

Supplementary Table 1. **Extracted data from studies analysing serum leptin levels and the incidence of PCa**. C-C: cases vs. controls; SD: standard deviation; SEM: standard error of the mean; OR: Odds ratio; RR: risk ratio; BMI: body mass index; T: tertile; Q: quartile or quintile; PSA: prostate specific antigen; BPH: Benign prostate hyperplasia; WHR: waist-to-hip ratio, IGF-1: insulin-like growth factor-1; SHGB: sex hormone-binding globulin; SU.VI.MAX: The Supplementation en Vitamines et Mineraux Antioxydants study.

Supplementary Table 2. Extracted data from studies analysing serum leptin levels and the incidence of high-stage PCa. C-C: cases vs. controls; SD: standard deviation; SEM: standard error of the mean; OR: Odds ratio; RR: risk ratio; BMI: body mass index; T: tertile; Q: quartile or quintile; PSA: prostate specific antigen. *In the methods section it states that fasting was stratified and adjusted for although the stratified table is not provided in the results.

Supplementary Table 3. **Extracted data from studies analysing serum leptin levels and the incidence of high-grade PCa.** C-C: cases vs. controls; SD: standard deviation; SEM: standard error of the mean; OR: Odds ratio; RR: risk ratio; BMI: body mass index; T: tertile; Q: quartile or quintile; PSA: prostate specific antigen. *As presented in tables 1 and 2, respectively. *In the methods section it states that fasting was stratified and adjusted for although the stratified table is not provided in the results.

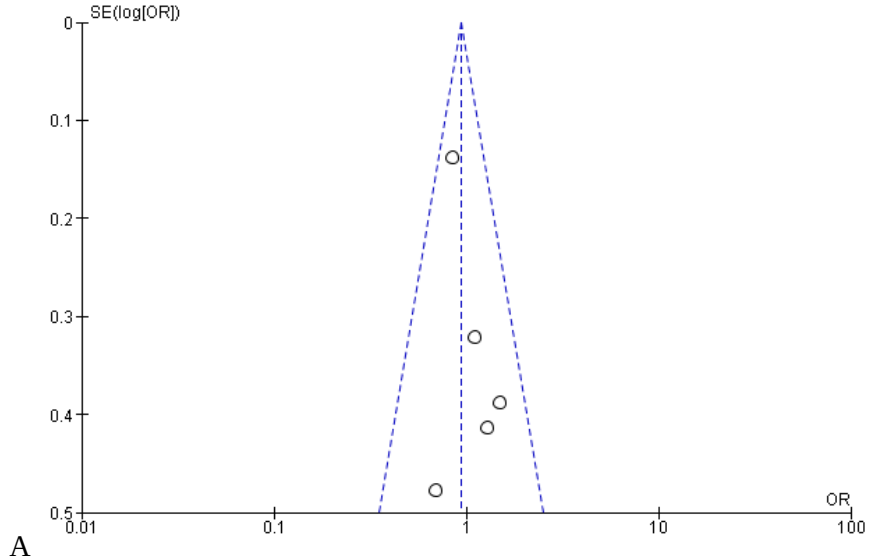
Supplementary Table 4. **Extracted data from studies analysing serum adiponectin levels and the incidence of PCa**. C-C: cases vs. controls; SD: standard deviation; SEM: standard error of the mean; OR: Odds ratio; RR: risk ratio; BMI: body mass index; T: tertile; Q: quartile or quintile; PSA: prostate specific antigen; BPH: Benign prostate hyperplasia; WHR: waist-to-hip ratio, IGF-1: insulin-like growth factor-1; SHGB: sex hormone-binding globulin; SU.VI.MAX: The Supplementation en Vitamines et Mineraux Antioxydants study. *Human adiponectin latex kit; Otsuka Pharmaceutical Co., Tokyo, Japan.

Supplementary Table 5. **Extracted data from studies analysing serum adiponectin levels and the incidence of high-stage PCa**. C-C: cases vs. controls; SD: standard deviation; SEM: standard error of the mean; OR: Odds ratio; BMI: body mass index; RR: risk ratio; HR: Hazard ratio; CDR: cancer detection rate; T: tertile; Q: quartile or quintile.

Supplementary Table 6. Extracted data from studies analysing serum adiponectin levels and the incidence of high-grade PCa. C-C: cases vs. controls; SD: standard deviation; SEM: standard error of the mean; OR: Odds ratio; BMI: body mass index; RR: risk ratio; T: tertile; Q: quartile or quintile; RP: radical prostatectomy. *As presented in tables 1 and 2, respectively.

Supplementary Table 7. Extracted data from studies analysing serum ghrelin levels and the incidence PCa. C-C: cases vs. controls; SEM: standard error of the mean, In1 ghrelin: oncogenic ghrelin splice variant with retention of intron 1, IQR: interquartile range.

Supplementary Figure 1.



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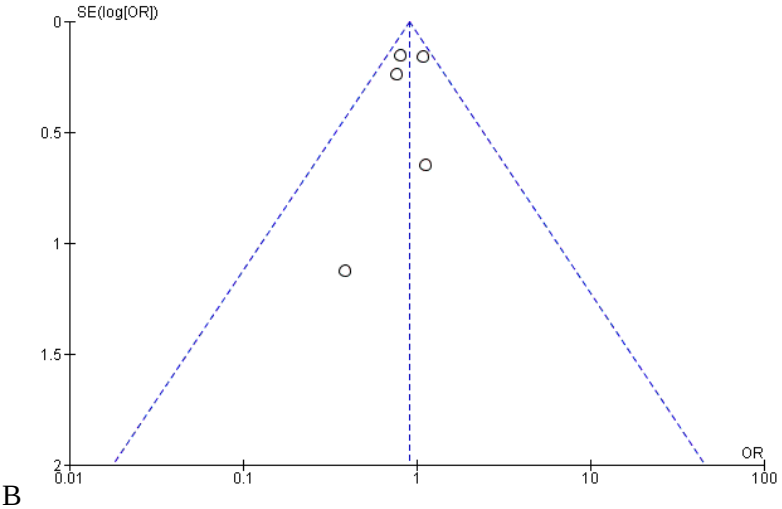

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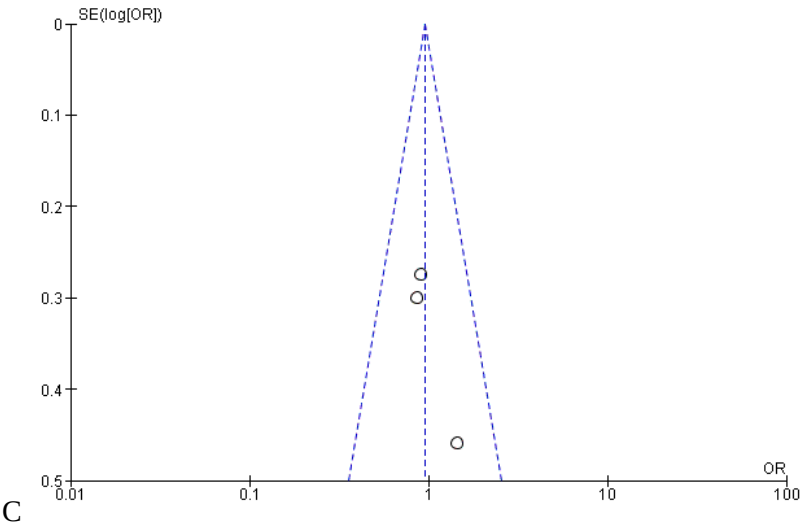
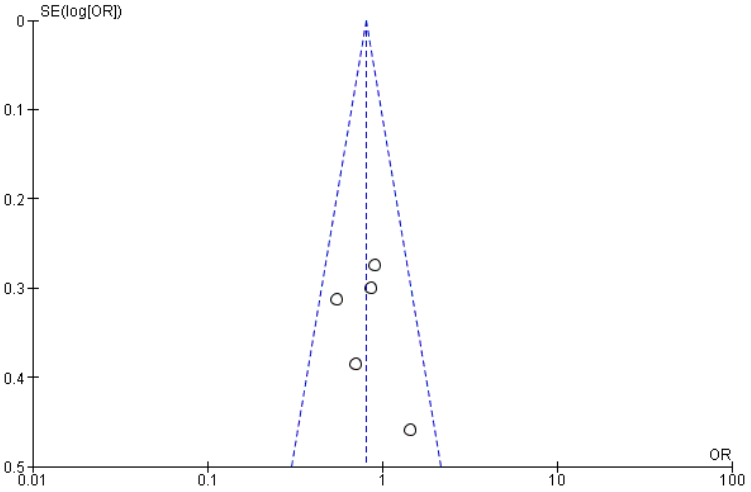


C



D

Study	Country	Study design	Exposure category	Detection Method	Exposure metric (ng/ml)	Risk estimate	*PInteraction*/*PTrend*	Matched factors/ Covariates	Fasted blood	Cases *N*	Cancer-free controls *N*
Arisan et al 2009(1)	Turkey	Case-control	Comparison of C-C mean levels	ELISA	Controls 12.98[no SD/SEM], Cases not provided. P-value not provided.	Not provided		Age, BMI	Yes	50	50
Baillargeon et al 2006(2)	USA	Nested case-control	Tertiles	LabMAP	T1: range not provided	*Reference*			Not stated	125	125
			Tertiles		T2: range not provided	OR=0.50(0.26-0.97)		Age, Race/ethnicity			
			Tertiles		T3: range not provided	OR=0.77(0.43-1.37)	P=0.57	Age, Race/ethnicity			
			Tertiles		T2: range not provided	OR=0.51(0.19-1.27)		Age, Race/ethnicity, BMI			
			Tertiles		T3: range not provided	OR=1.28(0.57-2.88)	P=0.35	Age, Race/ethnicity, BMI			
			Tertiles		Highest *vs.* lowest tertile (range not provided)	OR=0.77(0.28-1.37)	P=0.57	Age, Race/ethnicity			
			Tertiles		Highest *vs.* lowest tertile (range not provided)	OR=1.28(0.57-2.88)	P=0.35	Age, Race/ethnicity, BMI			
			Comparison of C-C mean levels		Controls mean 11.1pg/ml (SD± 11.7pg/ml) . Cases mean 8.62pg/ml (SD± 7.4pg/ml) (p=0.09, (McNemar's test/ paired t test, α=0.05))						
Capoun et al 2015(3)	Czech Republic	Case-control	Comparison of C-C mean levels	ELISA	Controls: Mean 7.64 (SD±6.44). Cases: Mean 7.84 (SD±7.35). P=0.9001	Not provided		Age, BMI	Yes	167	206
Duarte et al 2018 (4)	Portugal	Case-control	Comparison of C-C mean levels		Controls: Mean 11.93 (± 19.45). Cases: Mean 15.26 (± 23.60). P value not provided.	Not provided		None	Not stated	103	78
Fontana et al 2011(5)	Argentina	Case-control	Comparison of C-C mean levels	ELISA	Controls: Mean 5.96 (SEM not provided). Cases: Mean 4.89 (SEM not provided). P-value not provided	Not provided		Age, BMI	Not stated	35	35
Fryczkowski et al 2018 (6)	Poland	Case-control	Comparison of C-C mean levels	ELSIA	Controls: Mean 11.2(6.0–16.0), Cases: Mean 15.7 (8.2–26.8), p=0.02	OR=1.053(1.009-1.098)	p=0.04	Age, BMI	Not stated	40	40 BPH
Gade-Andavolu et al 2006(7)	USA	Case-control	Comparison of C-C mean levels	RIA	Controls: Mean 7.88 (SEM± 1.08). Cases:	Not provided		Age	Not stated	69	137

					Mean 14.7 (SEM± 1.38). P-value not provided.						
Grosman et al 2016(8)	Argentina	Case-control	Comparison of C-C median levels	RIA	Controls: Median 4.8(Range 1.1–12.3). Cases: Median 6.5(Range 1.3–28.0). p<0.01	Not provided		Age, BMI	Yes	70	70
Hsing et al 2001(9)	China	Nested case-control	Per tertile	RIA	T1: <2.30	*Reference*			Yes	128	306
			Per tertile		T2: 2.31–4.04	OR=0.97(0.56-1.69)		Age			
			Per tertile		T3: >4.04	OR=1.78(1.07-2.95)	P=0.02	Age			
			Per tertile		T2: 2.31–4.04	OR=0.67(0.36-1.27)		Age, Education, BMI, WHR			
			Per tertile		T3: >4.04	OR=1.10(0.59-2.07)	P=0.66	Age, Education, BMI, WHR			
			Per tertile		T2: 2.31–4.04	OR=0.60(0.38-1.15)		Age, Education, BMI, WHR, Insulin, IGF-1			
			Per tertile		T3: >4.04	OR=0.80(0.52-1.90)	P=0.95	Age, Education, BMI, WHR, Insulin, IGF-1			
Lagiou et al 1998(10)	Greece	Case-control	Incremental OR	RIA	Per 4ng/ml increase	OR=1.02		Age	Not stated	43	48
			Incremental OR		Per 4ng/ml increase	OR=0.97.		Age, height, Years of Schooling			
			Incremental OR		Per 4ng/ml increase	OR=1.02		Age, height, Years of Schooling, BMI			
Lai et al 2014(11)	USA	Nested case-control	Incremental	ELISA	Per quartile increase	OR=0.94(0.88–1.01)		Age, PSA, Year, Time of day, Season	No		1314
			Incremental		Per quartile increase	OR=0.93(0.86–1.02)		Age, PSA, Year, Time of day, Season, BMI, history of diabetes			
			Per quartile		Q1: cut-off not provided						
			Per quartile		Q2: cut-off s of 4 batches 8.72, 8.63, 8.39, 4.42	OR=0.97(0.78–1.20)		Age, PSA, Year, Time of day, Season			
			Per quartile		Q3: cut-off s of 4 batches 15.34, 14.45, 13.95, 6.83	OR=0.85(0.68–1.06)		Age, PSA, Year, Time of day, Season			
			Per quartile		Q4: cut-off s of 4 batches 24.05, 25.24, 21.82, 11.41	OR=0.86(0.69–1.06)	Not provided	Age, PSA, Year, Time of day, Season			
			Per quartile		Q2: cut-off s of 4 batches 8.72, 8.63, 8.39, 4.42	OR=0.96(0.78–1.20)		Age, PSA, Year, Time of day, Season, BMI, history of diabetes			
			Per quartile		Q3: cut-off s of 4 batches 15.34, 14.45, 13.95, 6.83	OR=0.84(0.67–1.06)		Age, PSA, Year, Time of day, Season, BMI, history of diabetes			

			Per quartile		Q4: cut-off s of 4 batches 24.05, 25.24, 21.82, 11.41	OR=0.84(0.64–1.10)	Not provided	Age, PSA, Year, Time of day, Season, BMI, history of diabetes			
Li et al 2010(12)	USA	Nested case-control	Per quintile	RIA	Q1: 2.3(0.8–3.2)	*Reference*			Not stated	654	644
			Per quintile		Q2: 3.9(3.3–4.6)	RR=1.06(0.74–1.52)		Age			
			Per quintile		Q3: 5.5(4.7–6.5)	RR=1.07(0.75–1.54),		Age			
			Per quintile		Q4: 8.0(6.6–10.0)	RR=1.09(0.76–1.56)		Age			
			Per quintile		Q5: 14.1(10.1–50.6)	RR=1.05(0.73–1.51)	p=0.9	Age			
			Per quintile		Q2: 3.9(3.3–4.6)	RR=1.00(0.67–1.49)		Age, BMI, c-peptide			
			Per quintile		Q3: 5.5(4.7–6.5)	RR=1.07(0.70–1.64)		Age, BMI, c-peptide			
			Per quintile		Q4: 8.0(6.6–10.0)	RR=1.10(0.71–1.71)		Age, BMI, c-peptide			
			Per quintile		Q5: 14.1(10.1–50.6)	RR=1.06(0.65–1.72)	p=0.8	Age, BMI, c-peptide			
Nishimura et al 2012(13)	Japan	Case-control	Per quartile	ELISA	Q1: range not provided	*Reference*			Not stated	54	70 BPH
			Per quartile		Q2: range not provided	OR=1.00(0.36-2.77)		Age			
			Per quartile		Q3: range not provided	OR=1.15(0.40-3.30)		Age			
			Per quartile		Q4: range not provided	OR=2.83(1.00-8.43)	Wald p=0.17.	Age			
			Highest *vs.* lowest		Q1-4 *vs.* 4	OR=2.72(1.14-6.81)	Wald p=0.027	Age			
			Per quartile		Q2: range not provided	OR=0.87(0.31-2.45)		BMI			
			Per quartile		Q3: range not provided	OR=1.07(0.38-3.00)		BMI			
			Per quartile		Q4: range not provided	OR=0.48(0.16-1.39)	Wald p=0.46.	BMI			
Sağlam et al 2003(14)	Turkey	Case-control	Comparison of C-C mean levels	RIA	Controls: Mean 17.55(SE±7.20). Cases: Mean 27.33 (SE±12.50). p<0.001	Not provided		None	Yes	21	50
Siemińska et al 2018 (15)	Poland	Case-control	Comparison of C-C mean levels	ELISA	BPH controls: Mean 9.03 (SE± 7.26). Cases: Mean 9.79 (SE± 8.27), p>0.05.	Not provided		BMI	Yes	74	66
Singh et al 2010(16)	India	Case-control	Comparison of C-C mean levels	ELISA	Controls: Mean 5.15ng/ml (SD±10.11). Cases: Mean	Not provided		Age	Not stated	30	30

					19.51ng/ml (SD±20.2). p=0.001						
Stattin et al 2000(17)	Sweden	Nested case-control	Per quartile	RIA	Q2: range not provided	OR=1.0(0.6–1.6)		Age	Yes	200	397
			Per quartile		Q3: range not provided	OR=0.7(0.4–1.1)		Age			
			Per quartile		Q4: range not provided	OR=0.9(0.6–1.6)	Not provided	Age			
			Per quartile		Q2: range not provided	OR=1.0(0.6–1.7)		Age, Testosterone, Estradiol, SHBG			
			Per quartile		Q3: range not provided	OR=0.7(0.4–1.1)		Age, Testosterone, Estradiol, SHBG			
			Per quartile		Q4: range not provided	OR=0.9(0.6–1.6)	Not provided	Age, Testosterone, Estradiol, SHBG			
Stattin et al 2003(18)	Norway	Nested case-control	Per quintile (grouped as tertiles)	RIA	Q1: ≤2.6	*Reference*			Not stated	149	298
			Per quintile (grouped as tertiles)		Q2:-3 2.6	RR=2.4(1.3-4.2)		Age			
			Per quintile (grouped as tertiles)		Q4-5: >5.5	RR=1.5(0.8-2.7)	Not provided	Age			
			Per quintile (grouped as tertiles)		Q2-3: 2.6	RR=2.4(1.3-4.5)		Age, BMI, insulin			
			Per quintile (grouped as tertiles)		Q4-5: >5.5	RR=1.5(0.7-3.2)	Not provided	Age, BMI, insulin			
Stocks et al 2007(19)	Sweden	Nested case-control	Incremental	RIA	Per one unit increase	OR=0.93(0.89-0.97)	p=0.002	Age	Yes	392	392
			Per quartile		Q1: <3.0	*Reference*					
			Per quartile		Q2: 3.0-4.5	OR=0.81(0.5-1.21)		Age			
			Per quartile		Q3: 4.5-6.9	OR=0.73(0.49-1.09)		Age			
			Per quartile		Q4: >6.9	OR=0.55(0.36-0.84)	p=0.006	Age			
Tewari et al 2013(20)	India	Case-control	Comparison of C-C mean levels	Not stated	BPH controls' Mean 37.51 (SD±25.60). Cases: Mean 55.48 (SD±40.26). p<0.0001. Units not provided.	Not provided		None	Not stated	95	95 BPH
Touvier et al 2012(21)	France	Nested case-control		ELISA	Q1: range not provided	*Reference*			Yes	156	312
			Per quartile		Q2: 2.4	OR=0.54(0.30-0.96)		Age			

Per quartile	Q3: 4.1	OR=1.02(0.59-1.76)		Age	
Per quartile	Q4: 6.6	OR=1.19(0.64-2.22)	P trend 0.3	Age	
Per quartile	Q2: 2.4	OR=0.47(0.22-0.97)		Age, BMI, height, SU.VI.MAX intervention group	
Per quartile	Q3: 4.1	OR=0.89(0.44-1.77)		Age, BMI, height, SU.VI.MAX intervention group	
Per quartile	Q4: 6.6	OR=0.69(0.27-1.75)	P=0.9	Age, BMI, height, SU.VI.MAX intervention group	

Table 1. **Extracted data from studies analysing serum leptin levels and the incidence of PCa**. C-C: cases vs. controls; SD: standard deviation; SEM: standard error of the mean; OR: Odd's ratio; RR: risk ratio; BMI: body mass index; T: tertile; Q: quartile or quintile; PSA: prostate specific antigen; BPH: Benign prostate hyperplasia; WHR: waist-to-hip ratio, IGF-1: insulin-like growth factor-1; SHGB: sex hormone-binding globulin; SU.VI.MAX: The Supplementation en Vitamines et Mineraux Antioxydants study.

Study	**Country**	**Study design**	**Exposure category**	**Detection assay**	**Exposure metric (ng/ml)**	**Risk Estimate**	***P*Interaction/ *P***	**Matched factors/ Covariates**	**Fasted blood**	**High-stage cases *N***	**Low-stage controls *N***
Arisan et al 2009(1)	Turkey	Case-control	Comparison of Mean C-C levels	ELISA	Low-stage: Mean 14.78 [no SD provided], High-stage: Mean 15.24, p=0.027	Not provided	Not provided	Age, BMI	Yes	18	32
Burton et al 2013(22)	UK	Nested case-control	Risk of high-stage per quartile	ELISA	Q1: 0.3–2.8	*Reference*			No		
			Risk of high-stage per quartile		Q2: 2.8–4.5	OR=0.50(0.32–0.78)		Age		311	413
			Risk of high-stage per quartile		Q3: 4.5–7.3	OR=0.83(0.54–1.28)		Age			
			Risk of high-stage per quartile		Q4: 7.3–54.4	OR=0.96(0.62–1.49)	Differences across groups p=0.009	Age			

Chang et al 2001(23)	USA	Case-control	Risk of high-volume localised tumour	RIA	With high leptin (>7.12)	OR=2.41(1.16-5.01)		Age	Not stated	151	48
			Risk of high-volume localised tumour		With high leptin (>7.12)	OR=2.06(0.93-4.58)		Age, BMI			
			Risk of high-volume localised tumour		With high leptin (>7.12)	OR=2.35(1.01-5.44).		Age, BMI, testosterone			
			Risk of high-volume localised tumour		With high leptin (>7.12) and high testosterone >1.32 ng/ml	OR=9.73(2.05-46.24)		Age, BMI			
Freedland et al 2005(24)	USA	Case-control	Risk of stage pT3 at RP, BMI ≤25	ELISA	Logistic regression	OR=1.14(0.76–1.71)		Age	Not stated	1	224
			Risk of stage pT3 at RP, BMI 25-30		Logistic regression	OR=1.21 (0.63–2.34)		Age, BMI			
			Risk of stage pT3 at RP, BMI ≥30		Logistic regression	OR=0.73 (0.28–1.87)		Age, BMI			
Kang et al 2018 (25)	South Korea	Case-control	Risk of stage ≤pT3	RIA	Multivariate logistic regression analysis used to identify independent predictors for advanced tumour stage (≥pT3)	OR=1.13(0.92-1.39), p=0.249		BMI	Not stated	1	24
Lai et al 2014(11)	USA	Nested case-control	Risk of Localised. Highest vs lowest quartile	ELISA	Q1: cutoff not provided, Q4 cutoffs of 4 batches: 24.05, 25.24, 21.82, 11.41	OR=0.85(0.67–1.06)	P=0.09	Age, PSA test before blood draw, Year, Time of day, season of blood draw	Not presented *	156	1064
			Risk of Localised. Highest vs lowest quartile		Q1: cutoff not provided, Q4 cutoffs of 4 batches: 24.05, 25.24, 21.82, 11.41	OR=0.88(0.66–1.17)	P=0.24	Age, PSA test before blood draw, Year, Time of day, season of blood draw, BMI, diabetes			
			Risk of Advanced. Highest vs lowest quartile		Q1: cutoff not provided, Q4 cutoffs of 4 batches: 24.05, 25.24, 21.82, 11.41	OR=0.94(0.58–1.50)	P=0.78	Age, PSA test before blood draw, Year, Time of day, season of blood draw		156	1064
			Risk of Advanced. Highest vs lowest quartile		Q1: cutoff not provided, Q4 cutoffs of 4 batches: 24.05, 25.24, 21.82, 11.41	OR=0.77(0.43–1.38)	P=0.37	Age, PSA test before blood draw, Year, Time of day, season of blood draw, BMI, diabetes			
Li et al 2010(12)	USA	Nested case-control	Risk of high-stage per quintile	RIA	Q1: 2.3(0.8–3.2)	*Reference*			Not stated	121	121
			Risk of high-stage per quintile		Q2: 3.9(3.3–4.6)	RR=0.96(0.43–2.14)		Age			
			Risk of high-stage per quintile		Q3: 5.5(4.7–6.5)	RR=1.22 (0.54–2.77)		Age			

Risk of high-stage per quintile	Q4: 8.0(6.6–10.0)	RR=0.99 (0.44–2.26)		Age		
Risk of high-stage per quintile	Q5: 14.1(10.1–50.6)	RR=1.69 (0.67–4.23)	P=0.24	Age		
Risk of high-stage per quintile	Q2: 3.9(3.3–4.6)	RR=0.66(0.25–1.74)		Age, BMI, c-peptide		
Risk of high-stage per quintile	Q3: 5.5(4.7–6.5)	RR=0.58(0.19–1.79)		Age, BMI, c-peptide		
Risk of high-stage per quintile	Q4: 8.0(6.6–10.0)	RR=0.41(0.12–1.45)		Age, BMI, c-peptide		
Risk of high-stage per quintile	Q5: 14.1(10.1–50.6)	RR=0.94 (0.25–3.51)	P=0.81	Age, BMI, c-peptide		
Risk of PCa-specific mortality	Q2: 3.9(3.3–4.6)	HR=1.08 (0.58–2.03)		Age	94 deaths	461
Risk of PCa-specific mortality	Q3: 5.5(4.7–6.5)	HR=1.06 (0.56–2.02)		Age		
Risk of PCa-specific mortality	Q4: 8.0(6.6–10.0)	HR=0.73 (0.36–1.47)		Age		
Risk of PCa-specific mortality	Q5: 14.1(10.1–50.6)	HR=1.21 (0.65–2.24)	P=0.68	Age		
Risk of PCa-specific mortality	Q2: 3.9(3.3–4.6)	HR=1.03 (0.55–1.94)		Age, BMI		
Risk of PCa-specific mortality	Q3: 5.5(4.7–6.5)	HR=0.94 (0.49–1.80)		Age, BMI		
Risk of PCa-specific mortality	Q4: 8.0(6.6–10.0)	HR=0.59 (0.28–1.22)		Age, BMI		
Risk of PCa-specific mortality	Q5: 14.1(10.1–50.6)	HR=0.82 (0.40–1.68)	P=0.47	Age, BMI		
Risk of PCa-specific mortality	Q2: 3.9(3.3–4.6)	HR=0.97 (0.49–1.93)		Age, BMI, c-peptide		
Risk of PCa-specific mortality	Q3: 5.5(4.7–6.5)	HR=0.91 (0.46–1.82)		Age, BMI, c-peptide		

			Risk of PCa-specific mortality		Q4: 8.0(6.6–10.0)	HR=0.57 (0.26–1.24)		Age, BMI, c-peptide				
			Risk of PCa-specific mortality		Q5: 14.1(10.1–50.6)	HR=0.71 (0.32–1.58)	P=0.32	Age, BMI, c-peptide,				
			Risk of PCa-specific mortality		Q2: 3.9(3.3–4.6)	HR=1.10 (0.54–2.22)		Age, BMI, c-peptide, stage, grade				
			Risk of PCa-specific mortality		Q3: 5.5(4.7–6.5)	HR=0.90 (0.43–1.87)		Age, BMI, c-peptide, stage, grade				
			Risk of PCa-specific mortality		Q4: 8.0(6.6–10.0)	HR=0.46 (0.20–1.09)		Age, BMI, c-peptide, stage, grade				
			Risk of PCa-specific mortality		Q5: 14.1(10.1–50.6)	HR=0.66 (0.28–1.53)	P=0.24	Age, BMI, c-peptide, stage, grade				
Sağlam et al 2003(14)	Turkey	Case-control	Comparison of Mean C-C levels	RIA	Low-stage: Mean 19.01 (SE±2.72), High-stage: Mean 36.47 (SE±12.73), p<0.001	Not provided		None	Yes	10	11	
Tewari et al 2013(20)	India	Case-control	Risk of high-stage	Not stated	Low-stage: Mean 49.50 (SD±39.70), High-stage: Mean 67.83 (SD39.19) [unit not provided]	OR=1.01(1.00-1.02)		None	Not stated	31	64	

Table 2. **Extracted data from studies analysing serum leptin levels and the incidence of high-stage PCa.** C-C: cases vs. controls; SD: standard deviation; SEM: standard error of the mean; OR: Odd's ratio; RR: risk ratio; BMI: body mass index; T: tertile; Q: quartile or quintile; PSA: prostate specific antigen. *In the methods section it states that fasting was stratified and adjusted for although the stratified table is not provided in the results.

Study	**Country**	**Study design**	**Exposure category**	**Detection assay**	**Exposure metric (ng/ml)**	**Risk estimate**	***P*Interaction/*P***	**Covariates**	**Fasted blood**	**High-grade cases**	**Low grade controls**	**Classification of Gleason Score 7**
Arisan et al 2009(1)	Turkey	Case-control	Comparison of Mean C-C levels	ELISA	Low-grade: 13.90, High-grade: Mean 15.98 [no SDs provided], p=0.038	Not provided		Age, BMI	Yes	10 or 11*	8 or 24*	Intermediate-grade
Baillargeon et al 2006(2)	USA	Nested case-control	Risk of high-grade per tertile	LabMAP	T1: range not provided	*Reference*			Not stated	40	85	Intermediate-grade

			Risk of high-grade per tertile		T2: range not provided	OR=1.26(0.48-3.31)		Age, Race/ethnicity				
			Risk of high-grade per tertile		T3: range not provided	OR=1.20(0.48-3.01)	P=0.85	Age, Race/ethnicity				
			Risk of high-grade per tertile		T2: range not provided	OR=1.24(0.44-3.50)		Age, Race/ethnicity, BMI				
			Risk of high-grade per tertile		T3: range not provided	OR=1.12(0.43-2.97)	P=0.83	Age, Race/ethnicity, BMI				
			Comparison of Mean C-C levels		Low-grade controls: Mean 8.2pg/ml (SD±6.2pg/ml) . High-grade cases: Mean 9.6pg/ml (SD± 9.4pg/ml) (p=0.032 (Chi2/ t test, α=0.05)							
Burton et al 2013(22)	UK	Nested case-control	Risk of high-grade per quintile	ELISA	Q4: 8.0(6.6–10.0)	RR=0.99(0.44–2.26)		Age	No	307	416	Intermediate-grade
			Risk of high-grade per quintile		Q5: 14.1(10.1–50.6)	RR=1.69(0.67–4.23)	P=0.24	Age				
			Risk of high-grade per quintile		Q2: 3.9(3.3–4.6)	RR=0.76(0.30–1.89		Age, BMI, c-peptide				
			Risk of high-grade per quintile		Q3: 5.5(4.7–6.5)	RR=0.52(0.19–1.46		Age, BMI, c-peptide				
			Risk of high-grade per quintile		Q4: 8.0(6.6–10.0)	RR=1.04(0.36–3.02)		Age, BMI, c-peptide				
			Risk of high-grade per quintile		Q5: 14.1(10.1–50.6)	RR=1.29(0.44–3.80)	P=0.34	Age, BMI, c-peptide				
Duarte et al 2018 (4)	Portugal	Case-control	Chi-square (χ^2) of Gleason score (tumour aggressiveness) in relation	ECLIA	Not stated	χ^2 of Gleason score = 8.39	P=0.136	None	Not stated	Not stated	Not stated	Not stated

			to clinical and biochemical profiles.									
Fontana et al 2011(5)	Argentina	Case-control	Comparison of Mean C-C levels	ELISA	Low-grade: Mean 2.6 (SEM±0.41), High-grade Mean 12.1(SEM±3.01), p<0.0001	.Not provided		Age, BMI	Not stated	9	12	Intermediate-grade
Fowke et al 2013(26)	USA	Nested case-control	Risk of Low-grade	RIA	Dichotomised at Median, High >8.49 vs. Low ≤8.49	OR=1.88(1.05-3.37)	p=0.03	Age	Not stated	100	100	Intermediate-grade
			Risk of High-grade		Dichotomised at Median, High >8.49 vs. Low ≤8.49	OR=1.11(0.63-1.96)	p=0.71	Age				
Lai et al 2014(11)	USA	Nested case-control	Risk of low-grade. Highest vs lowest quartile	ELISA	Q1: cutoff not provided, Q4 cutoffs of 4 batches: 24.05, 25.24, 21.82, 11.41	OR=0.85(0.66–1.10)	P=0.13	Age, PSA, Year, Time of day, season of blood draw	Not presented*	477	736	Intermediate-grade
			Risk of low-grade. Highest vs lowest quartile		Q1: cutoff not provided, Q4 cutoffs of 4 batches: 24.05, 25.24, 21.82, 11.41	OR=0.92(0.67–1.26)	P=0.41	Age, PSA, Year, Time of day, season of blood draw, BMI, diabetes				
			Risk of high-grade. Highest vs lowest quartile		Q1: cutoff not provided, Q4 cutoffs of 4 batches: 24.05, 25.24, 21.82, 11.41	OR=0.85(0.63–1.14)	P=0.19	Age, PSA, Year, Time of day, season of blood draw				
			Risk of high-grade. Highest vs lowest quartile		Q1: cutoff not provided, Q4 cutoffs of 4 batches: 24.05, 25.24, 21.82, 11.41	OR=0.81(0.56–1.18)	P=0.18	Age, PSA, Year, Time of day, season of blood draw, BMI, diabetes				
Li et al 2010(12)	USA	Nested case-control	Risk of high-grade per quintile	RIA	Q1: 2.3(0.8–3.2)	*Reference*			Not stated	124	124	High-grade

			Risk of high-grade per quintile		Q2: 3.9(3.3–4.6)	RR=1.02(0.46–2.22)		Age				
			Risk of high-grade per quintile		Q3: 5.5(4.7–6.5)	RR=0.83(0.37–1.85)		Age				
			Risk of high-grade per quintile		Q4: 8.0(6.6–10.0)	RR=1.58(0.68–3.68)		Age				
			Risk of high-grade per quintile		Q5: 14.1(10.1–50.6)	RR=1.74(0.76–4.00)	P=0.12	Age				
			Risk of high-grade per quintile		Q2: 3.9(3.3–4.6)	RR=0.76(0.30–1.89)		Age, BMI, c-peptide				
			Risk of high-grade per quintile		Q3: 5.5(4.7–6.5)	RR=0.52(0.19–1.46)		Age, BMI, c-peptide				
			Risk of high-grade per quintile		Q4: 8.0(6.6–10.0)	RR=1.04(0.36–3.02)		Age, BMI, c-peptide				
			Risk of high-grade per quintile		Q5: 14.1(10.1–50.6)	RR=1.29(0.44–3.80)	P=0.34	Age, BMI, c-peptide				
Sağlam et al 2003(14)	Turkey	Case-control	Comparison of Mean C-C levels	RIA	Low-grade: Mean 19.52(SE±2.02), High-grade: Mean 33.15ng/ml (SE±6.36), p=0.003	Not provided		None	Yes	10	11	Intermediate-grade
Serretta et al 2018 (27)	Case-control	Not stated	Risk of Gleason score 4 and 5	ELISA	Median (25^{th}-75^{th} percentile): Low-grade 1.15(0.24-2.64), high-grade 0.88(0.11-3.9), p=0.18.	Not provided		BMI	Not stated	68	81	Not stated
Siemińska et al 2018 (15)	Poland	Case-control	Comparison of C-C mean levels	ELISA	Low-grade: Mean 7.73 (SD± 7.01), high-grade: 13.34 (SD± 11.20)	Not provided		Age, BMI	Yes	22	24	Intermediate-grade

Singh et al 2010(16)	India	Case-control	Comparison of Mean C-C levels	ELISA	Data not provided	Not provided	Age	Not stated	12	4	High-grade
Tewari et al 2013(20)	India	Case-control	Risk of high-grade	Not stated	Low-grade: Mean 9.84 (SD±5.68), High-grade: Mean 79.77 (SD±24.47) [unit not provided]	OR=1.31(1.10-1.56)	None	Not stated	62	33	not stated

Table 3. **Extracted data from studies analysing serum leptin levels and the incidence of high-grade PCa.** C-C: cases vs. controls; SD: standard deviation; SEM: standard error of the mean; OR: Odd's ratio; RR: risk ratio; BMI: body mass index; T: tertile; Q: quartile or quintile; PSA: prostate specific antigen, ECLIA: electrochemiluminescent assay. *As presented in tables 1 and 2, respectively. *In the methods section it states that fasting was stratified and adjusted for although the stratified table is not provided in the results.

Study	**Country**	**Study design**	**Exposure category**	**Detection assay**	**Exposure metric (µg/mL)**	**Risk estimate**	***P*Interaction/ *P***	**Covariates**	**Fasted blood**	**Cases**	**Cancer-free controls**
Arisan et al 2009(1)	Turkey	Case-control	Compared Mean C-C levels	ELISA	Controls: Mean 18.4 (SEM not provided). Cases Mean not provided.	Not provided		Age, BMI	Yes	50	50
Baillargeon et al 2006(2)	USA	Nested case-control	Per tertile	LabMAP	T1: range not provided	*Reference*			Not stated	228	239
			Per tertile		T2: range not provided	OR=0.83(0.43-1.58)		Age, Race/ethnicity			
			Per tertile		T3: range not provided	OR=0.87(0.46-1.65),	P=0.24.	Age, Race/ethnicity			
			Per tertile		T2: range not provided	OR=0.80(0.33-1.97)		Age, Race/ethnicity, BMI			
			Per tertile		T3: range not provided	OR=0.81(0.34-1.91)	P=0.44.	Age, Race/ethnicity, BMI			
			Highest vs lowest tertile		Tertiles not provided	OR=0.87(0.46-1.65)	P=0.24.	Age, Race/ethnicity			
			Highest vs lowest tertile		Tertiles not provided	OR=0.81(0.34-1.91)	P=0.44.	Age, Race/ethnicity, BMI			
Goktas et al 2005(28)	Turkey	Case-control	Compared Mean C-C levels	RIA	Controls: Mean 16.2(SD±4.1). Cases: Mean 5.3(SD±1.6). P<0.001	Not provided		None	Yes	30	36
Grosman et al 2010(29)	Argentina	Case-control	Compared Median C-C levels	RIA	Controls: Median 20.5(Range 4.6–48.5) Cases: Median	Not provided		Age, BMI	Yes	25	25

					10.3(Range 3.7–28.5), p=0.049					
Housa et al 2007(30)	Czech Republic	Case-control	Compared Mean C-C levels	ELISA	BPH controls: Mean 0.02047 (SD±0.01013), Cases: Mean 0.01868(SD± 0.00775) [converted from ng/ml], p=0.64	Not provided	None	Yes	43	25 BPH
Ikeda et al 2015(31)	Japan	Case-control	Compared Mean C-C levels	Latex particle-enhanced turbidimetric immunoassay*	Controls: Mean 7.63(No SD provided), Cases: Mean 9.86, p=0.0049	Not provided	None	Not stated	24	2816
Li et al 2010(12)	USA	Nested case-control	Per quintile	RIA	Q1: 2.8(0.3–3.8)	*Reference*		Not stated	654	644
			Per quintile		Q2: 4.7(3.9–5.5)	RR=0.86(0.59–1.26)	Age[matched]			
			Per quintile		Q3: 6.4(5.6–7.2)	RR=0.85(0.58–1.25)	Age[matched]			
			Per quintile		Q4: 8.6(7.3–10.4)	RR=1.04(0.73–1.49)	Age[matched]			
			Per quintile		Q5: 13.1(10.5–31.9)	RR=0.69(0.47–1.03) P=0.18	Age[matched]			
			Per quintile		Q2: 4.7(3.9–5.5)	RR=0.82(0.53–1.27)	Age, BMI, c-peptide			
			Per quintile		Q3: 6.4(5.6–7.2)	RR=1.00(0.66–1.53)	Age, BMI, c-peptide			
			Per quintile		Q4: 8.6(7.3–10.4)	RR=1.13(0.75–1.69)	Age, BMI, c-peptide			
			Per quintile		Q5: 13.1(10.5–31.9)	RR=0.73(0.46–1.14) P=0.39	Age, BMI, c-peptide			
Medina et al 2013(32)	USA	Nested case-control	Compared Median C-C levels	ELISA	Controls: Median 4.52(SD±3.25–6.15). Cases: Median 4.52(SD±3.03–6.59). No p-value provided (only shown when <0.05)	Not provided	None	Not stated	228	239
Michalakis et al 2007(33)	Greece	Case-control	Per quartile	RIA	Q1: (0.0009-0.0053) [converted from ng/ml]	*Reference*		Yes	75	150
			Per quartile		Q2: (0.0053-0.0087)	OR=0.74(0.28– 1.94)	Age			
			Per quartile		Q3: (0.0087–0.0137)	OR=0.27(0.11– 0.67)	Age			
			Per quartile		Q4: (0.0137–0.0432)	OR=0.31(0.13–0.77) p<0.01	Age			

			Per quartile		Q2: (0.0053-0.0087)	OR=0.70(0.27– 1.86)		Age, BMI		
			Per quartile		Q3: (0.0087–0.0137)	OR=0.27(0.11– 0.67)		Age, BMI		
			Per quartile		Q4: (0.0137–0.0432)	OR=0.29(0.12–0.73)	p=<0.01	Age, BMI		
Michalakis et al 2015(34)	Greece	Case-control	Incrememental	RIA	Effect of adiponectin on identifying PCa	OR=0.931(0.888-0.977)		None	Yes	75	150
			Incrememental		Effect of adiponectin on identifying PCa	OR=0.912(0.85-0.98)	p=0.016 (of multivariate OR)	Age, BMI, Smoking, Cholesterol			
Nishimura et al 2012(13)	Japan	Case-control	Per quartile	ELISA	Q1: range not provided	*Reference*			Not stated	54	70 BPH
			Per quartile		Q2: range not provided	OR=1.18(0.42-3.4)		Age			
			Per quartile		Q3: range not provided	OR=1.06(0.33-3.39)		Age			
			Per quartile		Q4: range not provided	OR=3.05(1.08-9.15)	Wald p=0.1	Age			
			Highest vs lowest		Q1-3 vs 4	OR=2.79(1.25-6.43)	Wald p=0.014	Age			
			Per quartile		Q2: range not provided	OR=2.44(0.86-7.24)		BMI			
			Per quartile		Q3: range not provided	OR=2.61(0.93-7.67)		BMI			
			Per quartile		Q4: range not provided	OR=1.77(0.62-5.19)	Wald p=0.27	BMI			
Tewari et al 2013(20)	India	Case-control	Compared Mean C-C levels	Not stated	BPH controls: Mean 114.87 (SD±13.22. Cases Mean 18.64 (SD±20.23), p<0.0001. Units not provided	Not provided		None	Not stated	95	95 BPH
Touvier et al 2012(21)	France	Nested case-control	Per quartile	ELISA	Q1: cutoff not provided	*Reference*			Yes	156	312
			Per quartile		Q2: 4.3	OR=0.92(0.54-1.58)		Age			
			Per quartile		Q3: 6.4	OR=0.99(0.57-1.71)		Age			
			Per quartile		Q4: 9.2	OR=1.10(0.64-1.90)	P=0.7	Age			
			Per quartile		Q2: 4.3	OR=0.90(0.45-1.80)		Age, BMI, Height, SU.VI.MAX intervention group			
			Per quartile		Q3: 6.4	OR=1.38(0.69-2.76)		Age, BMI, Height, SU.VI.MAX intervention group			

			Per quartile		Q4: 9.2	OR=1.34(0.68-2.61)	P=0.3	Age, BMI, Height, SU.VI.MAX intervention group			

Table 4. **Extracted data from studies analysing serum adiponectin levels and the incidence of PCa**. C-C: cases vs. controls; SD: standard deviation; SEM: standard error of the mean; OR: Odd's ratio; RR: risk ratio; BMI: body mass index; T: tertile; Q: quartile or quintile; PSA: prostate specific antigen; BPH: Benign prostate hyperplasia; WHR: waist-to-hip ratio, IGF-1: insulin-like growth factor-1; SHGB: sex hormone-binding globulin; SU.VI.MAX: The Supplementation en Vitamines et Mineraux Antioxydants study. *Human adiponectin latex kit; Otsuka Pharmaceutical Co., Tokyo, Japan.

Study	**Population**	**Study design**	**Exposure category**	**Detection assay**	**Exposure metric (µg/mL)**	**Risk Estimate**	***P*Interaction/ *P***	**Covariates**	**Fasted blood**	**High-stage cases**	**Low-stage controls**
Arisan et al 2009(1)	Turkey	Case-control	Compared Mean C-C levels	ELISA	Low-stage: Mean 8.9, High-stage: Mean 5.5 [no SD provided], p=0.044	Not provided		Age, BMI	Yes	18	32
Burton et al 2013(22)	UK	Nested case-control	Risk of high-stage per quartile	ELISA	Q1: 0.9-4.5	*Reference*		Age	No	311	413
			Risk of high-stage per quartile		Q2: 4.5-6.5	OR=0.81(0.53–1.25)		Age			
			Risk of high-stage per quartile		Q3: 6.5-9.7	OR=0.67(0.43–1.03)		Age			
			Risk of high-stage per quartile		Q4: 9.7-37.2	OR=0.81(0.52–1.25)	p=0.35	Age			
			Risk of high-stage per log (unit)			OR=0.86(0.66-1.11)		Age			
			Risk of high-stage per quartile, BMI < 25		Q1: 0.9-4.5	*Reference*		Age			
			Risk of high-stage per quartile, BMI < 25		Q2: 4.5-6.5	OR=2.10(0.55-8.06)		Age			
			Risk of high-stage per quartile, BMI < 25		Q3: 6.5-9.7	OR=1.03(0.32-3.38)		Age			
			Risk of high-stage per quartile, BMI < 25		Q4: 9.7-37.2	OR=1.77(0.58-5.45)	p=0.46	Age			
			Risk of high-stage per log (unit), BMI < 25			OR=1.48(0.77-2.82)		Age			

			Risk of high-stage per quartile, BMI ≥ 25		Q1: 0.9-4.5	*Reference*		Age			
			Risk of high-stage per quartile, BMI ≥ 25		Q2: 4.5-6.5	OR=0.61(0.34 -1.08)		Age			
			Risk of high-stage per quartile, BMI ≥ 25		Q3: 6.5-9.7	OR=0.52(0.28 -0.93)		Age			
			Risk of high-stage per quartile, BMI ≥ 25		Q4: 9.7-37.2	OR=0.55(0.30 -1.02)	p=0.1	Age			
			Risk of high-stage per log (unit), BMI ≥ 25			OR=0.62(0.42 -0.90)	p=0.006	Age			
Freedland et al 2005 (35)	USA	Case-control	Risk of ≥pT3 at RP per quartile	ELISA	Q1: range not provided	*Reference*		Age	Not stated	78	158
					Q2: range not provided	OR=0.59 (0.27–1.30)		Age			
					Q3: range not provided	OR=0.69 (0.32–1.51)		Age			
					Q4: range not provided	OR=1.03 (0.49–2.18)	p=0.75	Age			
					Q2-4: range not provided	OR=0.74 (0.39–1.39)	p=0.35	Age			
					Q2: range not provided	OR=0.58 (0.26–1.29)		Age, BMI			
					Q3: range not provided	OR=0.68 (0.31–1.49)		Age, BMI			
					Q4: range not provided	OR=1.01 (0.47–2.16)	p=0.77	Age, BMI			
					Q2-4: range not provided	OR=0.76 (0.41–1.40)	p=0.38	Age, BMI			
Goktas et al 2005(28)	Turkey	Case-control	Compared Mean C-C levels	RIA	Low-stage: Mean 6.0(SD±1.7), High-stage: Mean 4.7(SD±1.2), p=0.012	Not provided		None	Yes	16	14
Housa et al 2007(30)	Czech Republic	Case-control	Compared Mean C-C levels	ELISA	Low-stage: Mean 0.01451 (SD± 0.00492), High-stage: Mean 0.02141	Not provided		None	Yes	26	17

					(SD±0.00812), p=0.003						
Ikeda et al 2015(31)	Japan	Case-control	Risk of high-risk by adiponectin and BMI	Latex particle-enhanced turbidimetric immunoassay*	High adiponectin (≥6.7 median), High BMI (≥25)	CDR=1.670		Age, BMI	Not stated	4	20
			Risk of high-risk by adiponectin and BMI		High adiponectin (≥6.7 median), Low BMI (<25)	CDR=0.725		Age, BMI			
			Risk of high-risk by adiponectin and BMI		Low adiponectin (<6.7 median), High BMI (≥25)	CDR=0.577		Age, BMI			
			Risk of high-risk by adiponectin and BMI		Low adiponectin (<6.7 median), Low BMI (<25)	CDR=0.633		Age, BMI			
			CDR of risk by adiponectin		High adiponectin (≥6.7 median), Low/intermediate risk PCa	CDR=0.717.		Age			
			CDR of risk by adiponectin		High adipoenctin (≥6.7 median), High risk PCa	CDR0.254		Age			
			CDR of risk by adiponectin		Low adiponectin (<6.7 median). Low/intermediate-risk PCa	CDR=0.294		Age			
			CDR of risk by adiponectin		Low adiponectin (<6.7 median), High-risk PCa	CDR=0.323		Age			
Kang et al 2018 (25)	South Korea	Case-control		Risk of stage ≤pT3	ELISA	Multivariate logistic regression analysis used to identify independent predictors for advanced tumour stage (≥pT3)	OR=0.97(0.88-1.06), p=0.534	BMI	Not stated	1	24
Li et al 2010(12)	USA	Nested case-	Risk of lethal-stage per quintile	RIA	Q1: 2.8(0.3–3.8)	*Reference*			Not stated	121	121

control							
	Risk of lethal-stage per quintile	Q2: 4.7(3.9–5.5)	RR=0.69(0.27–1.76)		Age		
	Risk of lethal-stage per quintile	Q3: 6.4(5.6–7.2)	RR=0.70(0.24–2.03)		Age		
	Risk of lethal-stage per quintile	Q4: 8.6(7.3–10.4)	RR=0.53(0.21–1.32)		Age		
	Risk of lethal-stage per quintile	Q5: 13.1(10.5–31.9)	RR=0.25(0.07–0.87)	P=0.02	Age		
	Risk of lethal-stage per quintile	Q2: 4.7(3.9–5.5)	RR=0.77(0.26–2.26)		Age, BMI, c-peptide		
	Risk of lethal-stage per quintile	Q3: 6.4(5.6–7.2)	RR=0.97(0.26–3.53)		Age, BMI, c-peptide		
	Risk of lethal-stage per quintile	Q4: 8.6(7.3–10.4)	RR=0.69(0.24–1.98)		Age, BMI, c-peptide		
	Risk of lethal-stage per quintile	Q5: 13.1(10.5–31.9)	RR=0.61(0.12–2.99)	P=0.44	Age, BMI, c-peptide		
	Risk of PCa-specific mortality	Q2: 4.7(3.9–5.5)	HR=0.81(0.45–1.47)		Age	90 deaths	440
	Risk of PCa-specific mortality	Q3: 6.4(5.6–7.2)	HR=0.69(0.37–1.30)		Age		
	Risk of PCa-specific mortality	Q4: 8.6(7.3–10.4)	HR=0.69(0.39–1.23)		Age		
	Risk of PCa-specific mortality	Q5: 13.1(10.5–31.9)	HR=0.39(0.17–0.85)	P=0.02	Age		
	Risk of PCa-specific mortality	Q2: 4.7(3.9–5.5)	HR=0.83(0.46–1.49)		Age, BMI		
	Risk of PCa-specific mortality	Q3: 6.4(5.6–7.2)	HR=0.73(0.39–1.36)		Age, BMI		
	Risk of PCa-specific mortality	Q4: 8.6(7.3–10.4)	HR=0.76(0.42–1.37)		Age, BMI		
	Risk of PCa-specific mortality	Q5: 13.1(10.5–31.9)	HR=0.42(0.19–0.92)	P=0.03	Age, BMI		
	Risk of PCa-specific mortality	Q2: 4.7(3.9–5.5)	HR=0.87(0.45–1.65)		Age, BMI, c-peptide		
	Risk of PCa-specific mortality	Q3: 6.4(5.6–7.2)	HR=0.69(0.35–1.36)		Age, BMI, c-peptide		
	Risk of PCa-specific mortality	Q4: 8.6(7.3–10.4)	HR=0.87(0.46–1.62)		Age, BMI, c-peptide		
	Risk of PCa-specific mortality	Q5: 13.1(10.5–31.9)	HR=0.36(0.14–0.90)	P=0.04	Age, BMI, c-peptide,		
	Risk of PCa-specific mortality	Q2: 4.7(3.9–5.5)	HR=0.97(0.50–1.88)		Age, BMI, c-peptide, stage, grade		
	Risk of PCa-specific mortality	Q3: 6.4(5.6–7.2)	HR=0.58(0.28–1.17)		Age, BMI, c-peptide, stage, grade		
	Risk of PCa-specific mortality	Q4: 8.6(7.3–10.4)	HR=0.79(0.40–1.53)		Age, BMI, c-peptide, stage, grade		

			Risk of PCa-specific mortality		Q5: 13.1(10.5–31.9)	HR=0.35(0.14–0.89)	P=0.03	Age, BMI, c-peptide, stage, grade			
Stevens et al 2014(36)	USA	Nested case-control	Risk of aggressive per quartile	ELISA	Q1: <6.178	*Reference*			Not stated	69	194
			Risk of aggressive per quartile		Q2: 6.178-7.878	OR=1.05(0.62-1.78)		Age, family history of PCa, BMI, physical activity in metabolic equivalents, total calcium intake, and energy intake			
			Risk of aggressive per quartile		Q3: 7.879-11.108	OR=1.43(0.87-2.36)		Age, family history of PCa, BMI, physical activity in metabolic equivalents, total calcium intake, and energy intake			
			Risk of aggressive per quartile		Q4: ≥11.109	OR=1.11(0.64-1.93)	P=0.59	Age, family history of PCa, BMI, physical activity in metabolic equivalents, total calcium intake, and energy intake			
			Risk of aggressive per quartile		Q2: 6.178-7.878	OR=0.76(0.38-1.52)		Age, family history of PCa, BMI, physical activity in metabolic equivalents, total calcium intake, and energy intake			
			Risk of aggressive per quartile		Q3: 7.879-11.108	OR=1.10(0.58-2.11)		Age, family history of PCa, BMI, physical activity in metabolic equivalents, total calcium intake, and energy intake			
			Risk of aggressive per quartile		Q4: ≥11.109	OR=0.70(0.33-1.49)	P=0.56	Age, family history of PCa, BMI, physical activity in metabolic equivalents, total calcium intake, and energy intake			
Tewari et al 2013(20)	India	Case-control	Risk of high-stage	Not stated	Increased adiponectin (increment not specified)	OR =0.94(0.88-0.99)		None	Not stated	31	64

Table 5. **Extracted data from studies analysing serum adiponectin levels and the incidence of high-stage PCa**. C-C: cases vs. controls; SD: standard deviation; SEM: standard error of the mean; OR: Odd's ratio; BMI: body mass index; RR: risk ratio; HR: Hazard ratio; CDR: cancer detection rate; T: tertile; Q: quartile or quintile.

Study	Study design	Population	Exposure category	Detection assay	Exposure metric (µg /ml)	Risk estimate	PInteraction/ P	Covariates	Fasted blood	High-grade cases	Low grade controls	Classification of Gleason Score 7
Arisan et al 2009(1)	Case-control	Turkey	Compared Mean C-C levels	ELISA	Low-grade: Mean 9.2, High-grade: Mean 4.1 [no SDs provided], p=0.0021	Not provided		Age, BMI	Yes	10 or 11*	8 or 24*	Intermediate-grade
Baillargeon et al 2006(2)	Nested case-control	USA	Risk of high-grade per tertile	LabMAP	T1: range not provided	*Reference*			Not stated	40	85	High-grade
			Risk of high-grade per tertile		T2: range not provided	OR=1.48(0.57-3.82)		Age, Race/ethnicity				
			Risk of high-grade per tertile		T3: range not provided	OR=1.93(0.74-5.10)	p=0.3	Age, Race/ethnicity				
			Risk of high-grade per tertile		T2: range not provided	OR=1.17(0.41-3.33)		Age, Race/ethnicity, BMI				
			Risk of high-grade per tertile		T3: range not provided	OR=1.45(0.55-3.32	p=0.49	Age, Race/ethnicity, BMI				
Burton et al 2013(22)	Nested case-control	UK	Risk of high-grade per quartile	ELISA	Q1: 0.9-4.5	OR=1.00[*Reference*]		None	No	307	416	High-grade
			Risk of high-grade per quartile		Q2: 4.5-6.5	OR=0.84(0.55-1.30)		None				
			Risk of high-grade per quartile		Q3: 6.5-9.7	OR=0.81(0.53-1.24)		None				
			Risk of high-grade per quartile		Q4: 9.7-37.2	OR=0.89(0.58-1.36)	p=0.79	None				
			Risk of high-grade per log (unit)			OR=0.91(0.70-1.18)		None				
			Risk of high-grade per quartile, BMI < 25		Q1: 0.9-4.5	OR=1.00[*Reference*]		None				
			Risk of high-grade per		Q2: 4.5-6.5	OR=0.84(0.27-2.61)		None				

			quartile, BMI < 25									
			Risk of high-grade per quartile, BMI < 25		Q3: 6.5-9.7	OR=0.84(0.30-2.35)		None				
			Risk of high-grade per quartile, BMI < 25		Q4: 9.7-37.2	OR=0.93(0.35-2.49)	p=0.98	None				
			Risk of high-grade per log (unit), BMI < 25			0.88(0.49-1.57)		None				
			Risk of high-grade per quartile, BMI ≥ 25		Q1: 0.9-4.5	OR=1.00[*Reference*]		None				
			Risk of high-grade per quartile, BMI ≥ 25		Q2: 4.5-6.5	OR=0.75(0.44-1.30)		None				
			Risk of high-grade per quartile, BMI ≥ 25		Q3: 6.5-9.7	OR=0.89(0.51-1.55)		None				
			Risk of high-grade per quartile, BMI ≥ 25		Q4: 9.7-37.2	OR=0.86(0.48-1.55)	p=0.79	None				
			Risk of high-grade per log (unit), BMI ≥ 25			OR=0.90(0.63-1.28)		None				
Fowke et al 2013(26)	Nested case-control	USA	Risk of low grade	RIA	Dichotomised at Median, Low <0.02015 vs. High ≥0.02015	OR=1.46(0.80-2.65)	p=0.22	Age	Not stated	100	100	High-grade
			Risk of high-grade		Dichotomised at Median, Low <0.02015 vs. High ≥0.02015	OR=0.96(0.53-1.76)	p=0.90	Age				

Freedland et al 2005 (35)	Case-control		Risk of high-grade	ELISA	Q1: range not provided	*Reference*		Age	Not stated	65	171	High-grade
					Q2: range not provided	OR=0.77 (0.34–1.75)		Age				
					Q3: range not provided	OR=0.60 (0.27–1.37)		Age				
					Q4: range not provided	OR=0.68 (0.30–1.55)	p=0.33	Age				
					Q2-4: range not provided	OR=0.68 (0.35–1.32)	p=0.26	Age				
					Q2: range not provided	OR=0.77 (0.34–1.77)		Age, BMI				
					Q3: range not provided	OR=0.61 (0.26–1.40)		Age, BMI				
					Q4: range not provided	OR=0.67 (0.29–1.53)	p=0.35	Age, BMI				
					Q2-4: range not provided	OR=0.69 (0.35–1.34)	p=0.27	Age, BMI				
Goktas et al 2005(28)	Case-control	Turkey	Compared Mean C-C levels	RIA	Low-grade: Mean 6.7 (SD ± 1.8), High-grade: Mean 3.8 (SD±0.7), p<0.001	Not provided		None	Yes	9	8	Intermediate-grade
Housa et al 2007(30)	Case-control	Czech Republic	Compared Mean C-C levels	ELISA	Low-grade: Mean 0.0196 (SD±0.0883), High-grade: Mean 17.13 (SD±0.0538), p=0.32	Not provided		None	Yes	7	19	High-grade
Li et al 2010(12)	Nested case-control	USA	Risk of high-grade per quartile	RIA	Q1: 2.8(0.3–3.8)				Not stated	124	124	Intermediate-grade
			Risk of high-grade per quartile		Q2: 4.7(3.9–5.5)	RR=0.83(0.32–2.11)		Age				
			Risk of high-grade per quartile		Q3: 6.4(5.6–7.2)	RR=0.47(0.20–1.10)		Age				
			Risk of high-grade per quartile		Q4: 8.6(7.3–10.4)	RR=0.95(0.42–2.16)		Age				
			Risk of high-grade per quartile		Q5: 13.1(10.5–31.9)	RR=0.49(0.20–1.22)	p=0.25	Age				

			Risk of high-grade per quartile		Q2: 4.7(3.9–5.5)	RR=0.29(0.08–1.06)		Age, BMI, c-peptide				
			Risk of high-grade per quartile		Q3: 6.4(5.6–7.2)	RR=0.23(0.07–0.72)		Age, BMI, c-peptide				
			Risk of high-grade per quartile		Q4: 8.6(7.3–10.4)	RR=0.37(0.12–1.16)		Age, BMI, c-peptide				
			Risk of high-grade per quartile		Q5: 13.1(10.5–31.9)	RR=0.23(0.06–0.83)	p=0.08	Age, BMI, c-peptide				
Serretta et al 2018 (27)	Case-control	Not stated	Risk of Gleason score 4 and 5	ELISA	Median (25^{th}-75^{th} percentile): Low-grade 1.66(1.52-1.95), high-grade 1.73(1.55-2.04), p=0.68.	Not provided		BMI	Not stated	68	81	Not stated
Sher et al 2008(37)	Nested case-control	USA	Risk of high-grade at biopsy	ELISA	Dichotomised at Median, Low ≥12.3	OR=0.98(0.70-1.37)	Wald p=0.899	None	Not stated	9	98	Intermediate-grade
			Risk of high-grade at biopsy		Dichotomised at Median, Low ≥12.3	OR=0.90(0.62-1.31)	Wald p=0.581	BMI, prostate size				
			Risk of high-grade at RP		Dichotomised at Median, Low ≥12.3	OR=2.04(1.16-3.58)	Wald p=0.014	None				
			Risk of high-grade at RP		Dichotomised at Median, Low ≥12.3	OR= 2.14(1.13–4.07)	Wald p=0.020	BMI, prostate size				
			Risk of high-grade per quartile at biopsy		Q4: >18	*Reference*						
			Risk of high-grade per quartile at biopsy		Q3: 12.3 - 18.1	OR=1.25(0.77-2.02)		None				
			Risk of high-grade per quartile at biopsy		Q2: 7.4 - 12.3	OR=1.21(0.75-1.96)		None				
			Risk of high-grade per		Q1: ≤7.4	OR=0.98 (0.61-1.59)	Wald p=0.662	None				

			quartile at biopsy										
			Risk of high-grade per quartile at biopsy		Q3: 12.3 - 18.1	OR=1.35(0.80-2.27		BMI, prostate size					
			Risk of high-grade per quartile at biopsy		Q2: 7.4 - 12.3	OR=1.23(0.72-2.10)		BMI, prostate size					
			Risk of high-grade per quartile at biopsy		Q1: ≤7.4	OR=0.90(0.53-1.55)	Wald p=0.388	BMI, prostate size					
			Risk of high-grade per quartile at RP		Q3: 12.3 - 18.1	OR=1.15(0.52-2.54)		None					
			Risk of high-grade per quartile at RP		Q2: 7.4 - 12.3	OR=2.46(1.13-5.34)		None					
			Risk of high-grade per quartile at RP		Q1: ≤7.4	OR=1.87(0.82-4.23)	Wald p=0.085	None					
			Risk of high-grade per quartile at RP		Q3: 12.3 - 18.1	OR=1.04(0.42-2.54)		BMI, prostate size					
			Risk of high-grade per quartile at RP		Q2: 7.4 - 12.3	OR= 2.52(1.04-6.10)		BMI, prostate size					
			Risk of high-grade per quartile at RP		Q1: ≤7.4	OR=1.82(0.72-4.63)	Wald p=0.115	BMI, prostate size					
Tewari et al 2013(20)	Case-control	India	Risk of high-grade	Not stated	Increased adiponectin (increment not specified)	OR=0.86(0.80-0.92)		None	Not stated	62	33	Not stated	

Table 6. Extracted data from studies analysing serum adiponectin levels and the incidence of high-grade PCa. C-C: cases vs. controls; SD: standard deviation; SEM: standard error of the mean; OR: Odd's ratio; BMI: body mass index; RR: risk ratio; T: tertile; Q: quartile or quintile; RP: radical prostatectomy. *As presented in tables 1 and 2, respectively.

Study	Country	Study design	Exposure category	Detection assay	Exposure metric	Risk estimate	Matched factors/ covariates	Fasted blood	Cases *N*	Cancer-free controls *N*
Hormaechea-Agulla et al 2017(38)	Spain	Case-control	Comparison of C-C median levels	ELISA (total ghrelin), RIA (In1 ghrelin)	No significant difference in levels of native ghrelin. Significantly higher median In1	Not provided	BMI	Not stated	30	20

					ghrelin in PCa cases (controls median 0pg/mL (IQR 0–0), cases median 4.6pg/mL (IQR 0–18), p=0.003)					
Malendowicz et al 2009(39)	Poland	Case-control	Comparison of C-C mean levels	RIA	Controls mean 19pg/ml (SEM±5), Cases mean 40pg/ml(SEM±7). P-value not provided, described as "significantly higher" in text.	Not provided	Not provided	Yes	18	16

Table 7. Extracted data from studies analysing serum ghrelin levels and the incidence PCa. C-C: cases vs. controls; SEM: standard error of the mean, In1 ghrelin: oncogenic ghrelin splice variant with retention of intron 1, IQR: interquartile range.

Bibliography

1. Arisan ED, Arisan S, Atis G, Palavan-Unsal N, Ergenekon E. Serum adipocytokine levels in prostate cancer patients. Urol Int. 2009;82(2):203–8.
2. Baillargeon J, Platz EA, Rose DP, Pollock BH, Ankerst DP, Haffner S, et al. Obesity, adipokines, and prostate cancer in a prospective population-based study. Cancer Epidemiol Biomarkers Prev. 2006;15(7):1331–5.
3. Capoun O, Soukup V, Kalousova M, Sobotka R, Pesl M, Zima T, et al. Diagnostic Importance of Selected Protein Serum Markers in the Primary Diagnostics of Prostate Cancer. Urol Int. 2015;95(4):429–35.
4. Duarte MF, Luis C, Baylina P, Faria MI, Fernandes R, La Fuente JM. Clinical and metabolic implications of obesity in prostate cancer: is testosterone a missing link? aging male Off J Int Soc Study Aging Male. 2018 Oct;1–13.
5. Fontana CML, Maselli ME, Elizalde RFP, Monaco NAD, Recupero ALU, Laur JDL. Leptin increases prostate cancer aggressiveness. J Physiol Biochem. 2011;67(4):531–8.
6. Fryczkowski M, Buldak RJ, Hejmo T, Kukla M, Zwirska-Korczala K. Circulating Levels of Omentin, Leptin, VEGF, and HGF and Their Clinical Relevance with PSA Marker in Prostate Cancer. Dis Markers. 2018;2018:3852401.
7. Gade-Andavolu R, Cone LA, Shu S, Morrow A, Kowshik B, Andavolu MVS. Molecular interactions of leptin and prostate cancer. Cancer J. 2006;12(3):201–6.
8. Grosman H, Fabre B, Lopez M, Scorticati C, Lopez Silva M, Mesch V, et al. Complex relationship between sex hormones, insulin resistance and leptin in men with and without prostatic disease. Aging Male. 2016;19(1):40–5.
9. Hsing AW, Chua S, Gao YT, Gentzschein E, Chang L, Deng J, et al. Prostate cancer risk and serum levels of insulin and leptin: a population-based study. J Natl Cancer Inst. 2001;93(10):783–9.
10. Lagiou P, Signorello LB, Trichopoulos D, Tzonou A, Trichopoulou A, Mantzoros CS. Leptin in relation to prostate cancer and benign prostatic hyperplasia. Int J Cancer. 1998;76(1):25–8.
11. Lai GY, Giovannucci EL, Pollak MN, Peskoe SB, Stampfer MJ, Willett WC, et al. Association of C-peptide and leptin with prostate cancer incidence in the Health Professionals Follow-up Study. Cancer Causes Control. 2014;25(5):625–32.
12. Li HJ, Stampfer MJ, Mucci L, Rifai N, Qiu WL, Kurth T, et al. A 25-Year Prospective Study of Plasma Adiponectin and Leptin Concentrations and Prostate Cancer Risk and Survival. Clin Chem. 2010;56(1):34–43.
13. Nishimura K, Soda T, Nakazawa S, Yamanaka K, Hirai T, Kishikawa H, et al. Serum adiponectin and leptin levels are useful markers for prostate cancer screening after adjustments for age, obesity-related factors, and prostate volume. Minerva Urol e Nefrol. 2012;64(3):199–208.
14. Sağlam K, Aydur E, Yilmaz MI, Göktaş S. Leptin influences cellular differentiation and progression in prostate cancer. J Urol. 2003;169(4):1308–11.
15. Sieminska L, Borowski A, Marek B, Nowak M, Kajdaniuk D, Warakomski J, et al. Serum concentrations of adipokines in men with prostate cancer and benign prostate hyperplasia. Endokrynol Pol. 2018;69(2):120–7.
16. Singh SK, Grifson JJ, Mavuduru RS, Agarwal MM, Mandal AK, Jha V. Serum leptin: A marker of prostate cancer irrespective of obesity. Cancer Biomarkers. 2010;7(1):11–5.
17. Stattin P, Soderberg S, Hallmans G, Bylund A, Kaaks R, Stenman UH, et al. Leptin is associated with increased prostate cancer risk: a nested case-referent study. J Clin Endocrinol Metab.

2001/03/10. 2001;86(3):1341–5.
18. Stattin P, Kaaks R, Johansson R, Gislefoss R, Söderberg S, Alfthan H, et al. Plasma leptin is not associated with prostate cancer risk. Cancer Epidemiol Biomarkers Prev. 2003;12(5):474–5.
19. Stocks T, Lukanova A, Rinaldi S, Biessy C, Dossus L, Lindahl B, et al. Insulin resistance is inversely related to prostate cancer: A prospective study in Northern Sweden. Int J Cancer. 2007;120(12):2678–86.
20. Tewari R, Rajender S, Natu SM, Goel A, Dalela D, Goel MM, et al. Significance of obesity markers and adipocytokines in high grade and high stage prostate cancer in North Indian men - A cross-sectional study. Cytokine. 2013;63(2):130–4.
21. Touvier M, Fezeu L, Ahluwalia N, Julia C, Charnaux N, Sutton A, et al. Association between prediagnostic biomarkers of inflammation and endothelial function and cancer risk: A nested case-control study. Am J Epidemiol. 2013;177(1):3–13.
22. Burton A, Martin RM, Holly J, Lane JA, Donovan JL, Hamdy FC, et al. Associations of adiponectin and leptin with stage and grade of PSA-detected prostate cancer: The ProtecT study. Cancer Causes Control. 2013;24(2):323–34.
23. Chang S, Hursting SD, Contois JH, Strom SS, Yamamura Y, Babaian RJ, et al. Leptin and prostate cancer. Prostate. 2001/02/15. 2001;46(1):62–7.
24. Freedland SJ, Sokoll LJ, Mangold LA, Bruzek DJ, Mohr P, Yiu SK, et al. Serum leptin and pathological findings at the time of radical prostatectomy. J Urol. 2005/02/16. 2005;173(3):773–6.
25. Kang M, Byun SS, Lee SE, Hong SK. Clinical Significance of Serum Adipokines according to Body Mass Index in Patients with Clinically Localized Prostate Cancer Undergoing Radical Prostatectomy. World J Mens Health. 2018 Jan;36(1):57–65.
26. Fowke JH, Motley S, Dai Q, Concepcion R, Barocas DA. Association between biomarkers of obesity and risk of high-grade prostatic intraepithelial neoplasia and prostate cancer - Evidence of effect modification by prostate size. Cancer Lett. 2013;328(2):345–52.
27. Serretta V, Abrate A, Siracusano S, Gesolfo CS, Vella M, Di Maida F, et al. Clinical and biochemical markers of visceral adipose tissue activity: Body mass index, visceral adiposity index, leptin, adiponectin, and matrix metalloproteinase-3. Correlation with Gleason patterns 4 and 5 at prostate biopsy. Urol Ann. 2018;10(3):280–6.
28. Goktas S, Mahmut IY, Caglar K, Sonmez A, Kilic S, Bedir S. Prostate cancer and adiponectin. Urology. 2005;65(6):1168–72.
29. Grosman H, Fabre B, Mesch V, Lopez MA, Schreier L, Mazza O, et al. Lipoproteins, sex hormones and inflammatory markers in association with prostate cancer. Aging Male. 2010;13(2):87–92.
30. Housa D, Vernerová Z, Heráček J, Procházka B, Čechák P, Kuncová J, et al. Adiponectin as a potential marker of prostate cancer progression: Studies in organ-confined and locally advanced prostate cancer. Physiol Res. 2008;57(3):451–8.
31. Ikeda A, Nakagawa T, Kawai K, Onozawa M, Hayashi T, Matsushita Y, et al. Serum adiponectin concentration in 2,939 Japanese men undergoing screening for prostate cancer. Prostate Int. 2015;3(3):87–92.
32. Medina EA, Shi XY, Grayson MH, Ankerst DP, Livi CB, Medina M V, et al. The Diagnostic Value of Adiponectin Multimers in Healthy Men Undergoing Screening for Prostate Cancer. Cancer Epidemiol Biomarkers Prev. 2014;23(2):309–15.
33. Michalakis K, Williams CJ, Mitsiades N, Blakeman J, Balafouta-Tselenis S, Giannopoulos A, et al. Serum adiponectin concentrations and tissue expression of adiponectin receptors are reduced in patients with prostate cancer: A case control study. Cancer Epidemiol Biomarkers Prev. 2007;16(2):308–13.
34. Michalakis K, Venihaki M, Mantzoros C, Vazaiou A, Ilias I, Gryparis A, et al. In prostate cancer, low adiponectin levels are not associated with insulin resistance. Eur J Clin Invest. 2015;45(6):572–8.
35. Freedland SJ, Sokoll LJ, Platz EA, Mangold LA, Bruzek DJ, Mohr P, et al. Association between serum adiponectin, and pathological stage and grade in men undergoing radical prostatectomy. J Urol. 2005 Oct;174(4 Pt 1):1266–70.
36. Stevens VL, Jacobs EJ, Sun JZ, Gapstur SM. No Association of Plasma Levels of Adiponectin and c-peptide with Risk of Aggressive Prostate Cancer in the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev. 2014;23(5):890–2.
37. Sher DJ, Oh WK, Jacobus S, Regan MM, Lee GS, Mantzoros C. Relationship between serum adiponectin and prostate cancer grade. Prostate. 2008;68(14):1592–8.
38. Hormaechea-Agulla D, Gahete MD, Jiménez-Vacas JM, Gómez-Gómez E, Ibáñez-Costa A, L-López F, et al. The oncogenic role of the In1-ghrelin splicing variant in prostate cancer aggressiveness. Mol Cancer. 2017 Dec 29;16(1):146.
39. Malendowicz W, Ziolkowska A, Szyszka M, Kwias Z. Elevated blood active ghrelin and unaltered total ghrelin and obestatin concentrations in prostate carcinoma. Urol Int. 2009;83(4):471–5.

Supplementary appendix 1. Search strategies.
The “no reviews” limit was applied to all databases except PubMed, from which relevant reviews were collected to identify further studies from the reference lists. MeSH terms were included in the search strategy in PubMed, and exploded EMTREE terms included in the EMBASE search strategy. The “no reviews” limit was applied to all databases except PubMed, from which relevant reviews were collected to identify further studies from the reference lists.

Pubmed/MEDLINE:
((prostat* cancer) OR (prostat* neoplasm) OR (prostat* carcinoma) OR (prostat* tumo*)) AND (leptin OR adiponectin OR ghrelin)

EMBASE:

'prostate cancer'/exp OR 'prostate cancer' OR 'prostatic neoplasia'/exp OR 'prostatic neoplasia' OR 'prostatic neoplasms'/exp OR 'prostatic neoplasms' OR 'prostate carcinoma'/exp OR 'prostate carcinoma' OR 'prostatic carcinoma'/exp OR 'prostatic carcinoma' OR 'prostate tumor'/exp OR 'prostate tumor' AND ('leptin' OR 'leptin'/exp OR leptin OR 'adiponectin' OR 'adiponectin'/exp OR adiponectin OR 'ghrelin' OR 'ghrelin'/exp OR ghrelin) NOT ‘review’

Web of Science (no review filter):
((prostate cancer) OR (prostate tumor) OR (prostate carcinoma) OR (prostate neoplasm)) AND (ghrelin OR leptin OR adiponectin)

Cochrane Library Central Records (Trials) (Trials but not review filters):

("prostate cancer" OR "prostate neoplasm" OR "prostatic neoplasm" OR "prostate tumor" OR "prostate carcinoma") AND ("leptin" OR "ghrelin" OR "adiponectin")