REVIEW

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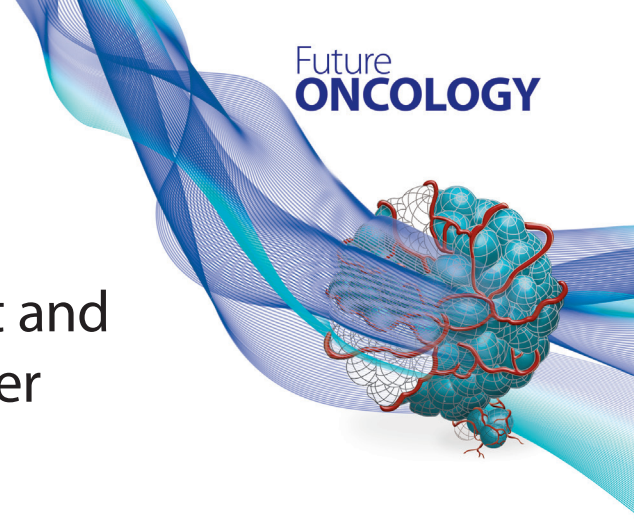

The emerging role of obesity, diet and lipid metabolism in prostate cancer

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Obesity is associated with an increased risk of a number of serious medical conditions, including cancer. As far as prostate cancer is concerned, obesity is associated with an increased risk of high-grade tumors, which is possibly related to lower androgen levels. Diet may also affect prostate cancer risk since countries with a higher dietary fat intake also present higher prostate cancer mortality rates. Interestingly, prostate cancer is associated with a number of metabolic alterations that may provide valuable diagnostic and therapeutic targets. This review explores the available clinical as well as biological evidence supporting the relationship between obesity, diet, alteration in metabolic pathways and prostate cancer.

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KEYWORDS
• diet • obesity
• urologic/prostate

Overweight and obesity are respectively defined as a BMI of 25–29 kg/m^2, and of greater than 30 kg/m^2, and are characterized by an abnormal/excessive fat deposits in the body [1]. As a result of their increasing prevalence, which rose by 47% in children and by 28% in adults since 1980–2013, currently an estimated 2.1 billion people are either overweight or obese worldwide and, by the year 2030, 58% of the world's adult population is expected to be overweight or obese [1]. Not only is obesity associated with an increased risk of a variety of chronic medical conditions including hypertension, coronary artery disease, diabetes, musculoskeletal disorders (especially osteoarthritis), gastroesophageal reflux disease and obstructive sleep apnea syndrome, but it also increases the risk of cancer [2–4]. In particular, obese individuals are more frequently diagnosed with cancer [5], and also have a worse cancer-specific survival with respect to nonobese controls. The complex biological

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mechanisms underlying the association between cancer and obesity include a number of different factors, such as the increased secretion of steroid hormones, chronic high insulin levels, insulin resistance and a persistent inflammatory state [6,7]. Prostate cancer is a highly prevalent tumor, accounting for approximately 25% of all malignancies diagnosed in men in the USA [8]. Treatment for localized as well as advanced disease is rapidly evolving [9,10]. Early detection of prostate cancer can be achieved in older asymptomatic men by the use of prostate-specific antigen (PSA)-based screening, which is associated with a substantial risk of overdiagnosis and overtreatment. The low diagnostic accuracy of PSA may be improved by the incorporation of clinical risk factors, biological markers and radiological assessment into screening procedures [11–17]. Obesity is an established risk factor of prostate cancer, since it is associated with an increased incidence of high-risk or aggressive prostate cancer [18] and an increased incidence of disease relapse [19]. A higher BMI has also been associated with increased risk of upstaging and upgrading in male candidates for active surveillance [20]. Intake of dietary fats, which is related to obesity [21], may be an independent risk factor [22]. In addition to being a risk factor in prostate cancer patients, obesity may also be a consequence of the androgen deprivation therapy administered to patients with locally advanced or metastatic prostate cancer [23]. Changes in body composition can affect the quality of life in patients with prostate cancer and increase the risk of cardiovascular diseases [24]. The interplay between obesity and prostate cancer has profound consequences from an epidemiologic, social or clinical point of view. We here review the clinical as well as preclinical evidence regarding the association between obesity and prostate cancer, with a focus on the potential role of dietary factors.

Obesity & prostate cancer

• Clinical evidence

A large body of evidence suggests that the BMI does not only influence PSA levels in healthy individuals, but it also affects the risk of being diagnosed with high-grade tumors, which has important prognostic implications. In a large prospective cohort [25] of 15,827 men without prostate cancer assessed for both serum PSA levels and BMI at baseline during the years 2010–2012 and followed up until 2015, 735 men were diagnosed with prostate cancer and 282 patients (38.4%) presented high-grade cancers. An inverse relationship between BMI and serum PSA levels was reported, with PSA levels decreasing by 1.6% (95% CI: -2.1 to -1.1) for each one unit increase in BMI. With respect to the reference (BMI: 18.5 to <25 kg/m^2), men having a BMI of 25 to <30, 30 to <35 and ≥35 kg/m^2, respectively, showed decreases of 3.7, 11.7 and 32.3% of PSA levels. A decreased risk of low-grade prostate cancer in men with a BMI of 30 to <35 kg/m^2 or >35 kg/m^2 along with an increased risk of high-grade prostate cancer among men with a BMI of 30 to <35 kg/m^2 was also reported [25]. These findings are consistent with the results obtained in a meta-analysis of 12 studies including 19,130 cases of localized prostate cancer in a sample of 1,033,009 men and of 13 studies including 7067 cases of advanced prostate cancer in a sample of 1,080,790 men. A higher BMI was associated with a decreased risk of localized prostate cancer (relative risk [RR]: 0.94 [95% CI: 0.91–0.97] for every 5 kg/m^2 increase) and with an increased risk of advanced prostate cancer (RR: 1.09 [95% CI: 1.02–1.16] for every 5 kg/m^2 increase) [18]. Several additional cohort studies indicated that prostate cancer was associated with a higher BMI [26–28]. Although other studies failed to do so [29–31], one meta-analysis [23] including 55,521 cases reported among 2,818,767 men enrolled in 31 studies, and 13,232 cases and 16,317 controls enrolled in 25 case–control studies showed an overall RR of prostate cancer of 1.05 (95% CI: 1.01–1.08) per 5 kg/m^2 BMI increment, with a significant RR of 1.12 per 5 kg/m^2 increment (95% CI: 1.01–1.23) for advanced disease compared with a nonsignificant RR of 0.96 per 5 kg/m^2 increment (95% CI: 0.89–1.03) for localized disease. Other studies have highlighted the positive and inverse relationship of BMI with high- and low-grade tumors, respectively [24–26]. Of note, in the Prostate Cancer Prevention trial [25], obese men (BMI: ≥30 kg/m^2) presented an 18% lower risk of low-grade prostate cancer, but also a 78% increased risk of high-grade tumors compared with men who had a BMI of <25 kg/m^2. In men who have been diagnosed with prostate cancer, a higher BMI has a detrimental prognostic effect, as shown in a retrospective study including 3161 prostate cancer patients followed up for 11 years [32]. In this patient cohort, a BMI of ≥27.5 kg/m^2 and also a BMI of <22.5 kg/m^2 were associated with an increased risk of dying

of prostate cancer (hazard ratio [HR]: 1.44; 95% CI: 1.09–1.90 and HR: 1.33; 95% CI: 1.02–1.74, respectively) compared with the reference group (BMI: 22.5 to <25 kg/m^2). Nevertheless, if patients dying within the first 2 years of follow-up were not included in the analyses, the excess of risk of dying of prostate cancer remained statistically significant in men with a BMI of ≥27.5 kg/m^2, but not in men with a BMI of <22.5 kg/m^2. In this regard, it is noteworthy that lower serum testosterone levels are both associated with a higher BMI [33] and with a detrimental prognostic effect in patients with advanced disease [34]. In a retrospective analysis of patients with advanced prostate cancer enrolled in the COU-AA-301 trial testing abiraterone plus prednisone versus prednisone alone, patients with higher baseline androgen levels showed a more favorable outcome, with median survival significantly increasing with each quartile increase in testosterone level in both treatment arms [34]. Nevertheless, the detrimental effects of obesity may be only partially dependent on its effect on androgen levels, as prostate cancer incidence does not appear to be related to endogenous testosterone levels [35]. In fact, apart from the fact that lower androgen levels in obese men may contribute to select more aggressive androgen-independent clones [32,36], obesity may also make early diagnosis more difficult due to its association with lower PSA levels and larger prostates. The mechanisms underlying the relationship of obesity with prostate cancer are yet to be fully elucidated.

• Biological mechanisms

Systemic inflammation, alterations in the insulin and IGF-1 axis, and variations in sex hormone levels and adipokines are among the underlying mechanisms of the relationship between obesity and prostate cancer. In particular, hyperinsulinemia was reported to accelerate tumor growth in different prostate cancer xenograft models [37,38] and primary human prostate cancer commonly expresses the insulin receptor [39], suggesting that insulin may stimulate human prostate cancer growth. Population studies have also suggested an association between the blood levels of IGF-1 and IGFBPs, and the risk of prostate cancer [40]. As mentioned before, obesity is also associated with decreased androgen levels [41], which may cause the conditions for the selection of neoplastic clones less dependent on androgens, with a shorter duration of the castration sensitivity state and worse prognosis [42]. Furthermore, obesity itself is associated with a chronic inflammatory condition that results in alteration of serum levels of leptin and adipokines. Although leptin exerts a predominantly protumor effect in human androgen-independent PC-3 and DU145 prostate cancer cell lines, with increased proliferation, decreased apoptosis [43–45] and increased migration [46], adiponectin exerts a potent antitumor effect. Although serum leptin levels are elevated in obese individuals, adiponectin levels were found to be reduced significantly in metastatic prostate cancer patients versus those with organ-confined disease [47]. Cytokines, such as IL-6, TNF-α and VEGF, may also play a role, since their serum levels are reported to be increased in prostate cancer versus controls and in patients with advanced versus localized prostate cancer [48–50]. Obesity may also mediate a more aggressive phenotype in certain cancers via a paracrine effect. Adipocytes are recognized to be part of the tumor microenvironment in a variety of cancers. The term 'cancer-associated adipocytes' has been used to describe the abnormal adipocytes adjacent to cancer cells. These adipocytes show lower lipid content, decreased levels of markers (e.g., hormone-sensitive lipase, adiponectin and resistin) of adipocyte differentiation and overexpression of several inflammatory cytokines (e.g., IL-6 and IL-1β). Peritumoral adipocytes and tumor cells present intersecting signaling pathways. In one study assessing prostate cancer specimens, the infiltration of adipocytes was associated with cancer grade, and 90 versus 20% of high- versus low-grade specimens showed infiltrative fat [51]. Cancer-associated adipocytes may also act as an energy source for tumor cells [52]. Obesity increases the odds that the tumor invades the periprostatic adipose tissue (PPAT) surrounding the prostate gland, and extraprostatic extension is a widely acknowledged adverse factor in prostate cancer [53]. The prostate gland is surrounded by PPAT, which represents an active endocrine organ and an energy source. The existing correlation between the abundance of PPAT and tumor aggressiveness suggests a paracrine role during tumorigenesis [54]. Mature adipocytes are able to support prostate cancer cell malignant phenotype. Recently, Laurent *et al.* suggested that the chemokine CCL7 released by adipocyte of PPAT increased migration of prostate

cancer cells [55]. Interestingly, Ribeiro *et al.* found that prostate cancer-released factors can regulate the expression of protumorigenic adipokines (osteopontin, TNF-α, IL-6 and adiponectin), matrix metalloproteinase activity and mitochondrial DNA in PPAT [56]. A role for diet-induced obesity in promoting prostate tumor growth has also been documented in the transgenic adenocarcinoma of the prostate mouse model [57].

The evidence reviewed shows that multiple biological mechanisms underlie the association of obesity with prostate cancer (see **Figure 1**), which supports epidemiological and clinical findings.

Diet & prostate cancer

• Clinical evidence

Dietary factors that may be associated with an increased risk of both obesity and prostate cancer include positive energy balance, processed and unprocessed meat, saturated fat, trans fatty acid intake and total dietary fat intake [22,58–59]. Conversely, n-3 fatty acids may have a potentially protective effect against prostate cancer [60]. A pooled analysis of 45 observational studies showed no evidence of an association between dairy (RR: 1.06; 95% CI: 0.92–1.22), milk (RR: 1.06; 95% CI: 0.91–1.23), calcium (RR: 1.04; 95% CI: 0.90–1.15) and vitamin D (RR: 1.16; 95% CI: 0.98–1.38) intake and prostate cancer risk [61]. Of note, higher serum vitamin D levels have been associated not only with increased incidence of prostate cancer, but also with a decreased mortality in prostate cancer patients [62]. Evidence supporting the role of nutritional habits as a risk factor for prostate cancer includes the observation that countries with a higher dietary fat intake also present higher prostate cancer mortality rates [63]. In this regard, it is noteworthy that men migrating from Japan and China have an increased risk of prostate cancer, with second- and third-generation Chinese and Japanese Americans showing a similar risk to white American men [63]. Although migration studies suggest a positive correlation between changes in diet and prostate cancer risk, they also present a number of limitations, including the lack of quantification of dietary fat and the lack of appropriate controls for confounders. Prospective cohort studies do not suffer from such limitations. In one recently published meta-analysis of 19 different prospective cohort studies [59], no association of prostate cancer with total red meat consumption, fresh red meat consumption and measures of exposure to heterocyclic amine and heme iron was identified. Conversely, the standardized RR estimate for total prostate cancer and processed meat consumption was 1.05 (95% CI: 1.01–1.10). In another report including 52,683 prostate cancer patients with 4924 cases of advanced disease diagnosed in a cohort of 842,149 men, no significant association between seafood, total red meat, unprocessed red meat and processed meat was identified for all prostate cancer outcomes, although men in the highest red meat and processed meat intake subgroups presented a 17–19% increased risk of being diagnosed at an advanced stage than those in the lowest category [58]. Of note, an inverse association was identified for poultry intake, with a pooled RR for advanced and fatal cancers of men consuming ≥45 versus <5 g/day of 0.83 (95% CI: 0.70–0.99) and 0.69 (95% CI: 0.59–0.82), respectively. Furthermore, men who ate ≥25 versus <5 g/day of eggs presented a significant 14% increased risk of fatal and advanced cancers. It is also noteworthy that in this international cohort, positive associations of advanced and fatal cancers with egg and unprocessed red meat consumption, and inverse associations with poultry intake were limited to North American studies only. The relationship of dietary fat intake with prostate

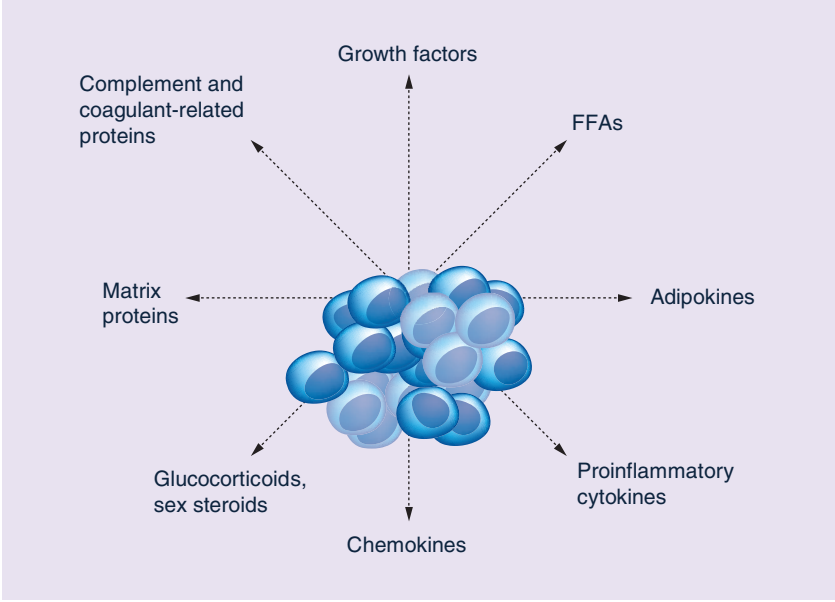

Figure 1. Adipocyte secreted factors with a role in prostate cancer development.
FFA: Free fatty acid.

cancer mortality was explored in a prospective study [64] examining trans, animal, saturated, monounsaturated, polyunsaturated and vegetable intake in 4577 nonmetastatic prostate cancer patients enrolled in the Health Professionals Follow-up Study during the years 1986–2010. Crude rates per 1000 person-years for lethal prostate cancer in men in the lowest versus highest quartile of fat intake: 7.3 versus 7.6 for saturated fat; 6.4 versus 7.2 for monounsaturated fat; 5.8 versus 8.2 for polyunsaturated fat; 8.7 versus 6.1 for trans fat; 8.3 versus 5.7 for animal fat; and 4.7 versus 8.7 for vegetable fat. Of note, this study showed that using vegetable fat in order to replace 10% of energy intake from carbohydrate lowered the risk of lethal prostate cancer (HR: 0.71; 95% CI: 0.51–0.98; p = 0.04) and all-cause mortality (HR: 0.74; 95% CI: 0.61–0.88; p = 0.001). In another a prospective study [65] including 926 patients with nonmetastatic prostate cancer who were followed up for a median of 10 years after the completion of a dietary questionnaire, it was found that men who derived >5 and <5% of their daily caloric intake from saturated fat and from carbohydrate, respectively, presented a 1.8-fold increased risk of all-cause mortality (HR: 1.81; 95% CI: 1.20–2.74; p = 0.005) and a 2.8-fold increased risk of prostate cancer-specific mortality (HR: 2.78; 95% CI: 1.01–7.64; p = 0.05). In conclusion, although no strong association of a particular food or food class with prostate cancer has been reported, the reviewed studies indicate that saturated fat may increase the risk of prostate cancer-related death, while vegetable fat may exert a protective effect after a diagnosis of nonmetastatic prostate cancer.

• Biological mechanisms

The increased local and/or systemic flux of fatty acids derived from dietary intake may affect prostate cancer cell malignant phenotype. Fatty acids provide both energy and signaling molecules implicated in a number of pathologic and physiologic cellular processes. Several G-protein-coupled receptors (GPRs) have been identified as fatty acid sensors with nutrient-sensing capabilities by endocrine cells [66,67]. Moreover, free fatty acids bind to nuclear PPAR-γ regulating the expression of genes involved in glucose and lipids metabolism [68]. In cancer cells, fatty acids are essential to support cell growth, proliferation, differentiation and motility [69–72]. Hardy *et al.* [73] reported that oleate is able to promote breast cancer cells growth by activating Ca^{2+} signaling, Src proteins and PI3K/Akt via interaction with GPR40. Furthermore, Liu *et al.* [74] reported that oleate-mediated GPR40/ILK/Akt pathway activation is associated with the development of renal cell carcinoma. Prostate cancer is also highly dependent on fatty acid metabolism [69,75]. In fact, prostate cancer is a slowly proliferating tumor and the rates of glucose uptake and glycolysis are relatively low. This is due, at least in part, to the low expression of the primary glucose transporter GLUT1 [76]. Hagen *et al.* [77] showed different responses to fatty acid treatment in different prostate cancer cell lines. Yue *et al.* [78] revealed an accumulation of cholesterol ester-rich lipid droplets (LDs) in high-grade and metastatic prostate cancers. Interestingly, cholesterol esters accumulation correlated with androgen-independence and phosphate and tensin homolog loss. Moreover, the presence of cholesterol ester-rich lipid droplets seems to support the migratory and invasive capacities of prostate cancer cells and potentiates PI3K-dependent SREBP activity, which may enhance cancer aggressiveness.

Lipid metabolism in prostate cancer

During neoplastic progression, prostate cancer cells undergo adaptive metabolic changes in order to sustain their growth and proliferation [79]. The increased lipid biosynthesis required for cellular proliferation, membrane formation and cell signaling represents a critical event in metabolic reprogramming. An increased expression and activity of choline kinase, an enzyme involved in cell membrane phospholipids biosynthesis, has also been reported in prostate cancer, along with high levels of phosphatidylcholine, phosphatidylethanolamine and glycerophosphocholine. These findings are consistent with active membrane remodeling and cellular proliferation processes.

In addition, metabolic intermediates of *de novo* lipogenesis, including diacylglycerol, sphingosine 1-phosphate, phosphatidic acid and lysophosphatidic acid, act as second messengers in different signaling pathways regulating cell-to-cell communication, migration and invasion. *De novo* lipogenesis and cholesterogenesis are associated with the lipogenic phenotype of prostate cancer and are sustained by the conversion in the cytosol of citrate (derived from Krebs cycle in the mitochondria) to acetyl-CoA

and oxaloacetate by ATP citrate lyase (ACLY). Acetyl-CoA is then transformed in malonyl-CoA by the enzyme acetyl-CoA carboxylase (ACC), and oxaloacetate is converted into pyruvate, which can re-enter the mitochondria for further utilization. Along with the NADPH generated in the pentose phosphate pathway, the NADPH synthesized by this pathway is able to provide the reducing equivalents required for reductive synthesis of fatty acids. Saturated fatty acids may then undergo other molecular modifications such as insertion of double bounds or elongation of the carbon chain, and can be used for energy, membrane integrity and cell signaling. In normal conditions, human cells preferentially use exogenous lipids for their metabolic requirements, whereas *de novo* synthesis is usually maintained at low levels. Instead, in cancer cells *de novo* lipogenesis and cholesterogenesis are highly activated, and in accordance with these findings, it has been demonstrated an increased expression of ACLY, ACC and fatty acid synthase (FAS) in prostate cancer cells [80,81]. In this context, it has been reported that SREBP-1 – a critical transcription factor for lipogenesis – is involved in the transcriptional regulation of androgen receptor and formation of fatty acids through an altered expression of ACLY, ACC and FAS. In addition, Huang *et al.* showed that SREBP-1-induced prostate cancer cell proliferation, migration and invasion by activating lipogenesis and through an increased expression of NADPH oxidase 5 [46]. Lipid metabolism is regulated in cancer cells by oncogenic signals. The LKB1–AMPK pathway acts as a cellular energy status sensor that protects cells from stresses caused by ATP depletion, thus deactivating ATP-consuming biosynthetic pathways. In fact, the activation of LKB1–AMPK axis blocks lipid metabolism via inhibition of ACC, FAS, ACLY and SREBP-1. In this scenario, it has recently been shown that loss of LKB1 expression is an early event in prostate cancer carcinogenesis and that an inverse correlation exists between the activity of the LKB1–AMPK pathway and the p38 MAPK cascade [82]. Moreover, the pivotal role of the LKB1–AMPK axis in controlling oncogenic pathways and cell metabolism is also due to its crosstalk with the PI3K–Akt, mTOR and MAPK pathways [83]. In particular, PI3K–Akt–mTORC1 pathway, which is activated in around 40% of primary and over 70% of metastatic prostate cancer, stimulates glucose uptake and promote glycolysis, providing more precursors for lipogenesis [84].

Consistently with such epidemiologic associations, cholesterol has been reported to stimulate prostate cancer growth both *in vitro* and *in vivo* [85]. Furthermore, reduced serum cholesterol levels were associated with lower intratumoral androgen levels and impaired tumor growth in xenograft mouse models of human prostate cancer [86], which underlines the role of steroid biosynthesis as an important biological mechanism linking cholesterol and prostate cancer.

Conclusion

In this review article, we aimed to explore currently available data about the relationship of prostate cancer incidence/biological aggressiveness with obesity, dietary factors and alteration in tumor lipid metabolism. Although the role of dietary factors remains uncertain, the preponderance of the evidence reviewed suggests that obesity does affect the risk of high-grade prostate cancer and has a detrimental effect on prostate cancer-specific mortality.

Future perspective

Interventions to tackle the obesity pandemic may be beneficial for primary prevention of prostate cancer. Increased attention toward proper diet and lifestyle should be given to patients undergoing androgen ablation treatment, due to the adverse metabolic effects of androgen deprivation. Diet modifications including increased consumption of vegetable fats should be considered in men undergoing radical treatment for localized prostate cancer, as such a simple and innocuous intervention may decrease the risk of disease recurrence. Finally, the rapidly expanding knowledge of the metabolic alterations involving lipid metabolism in prostate cancer cells has the potential to provide novel biological targets for prevention and treatment of prostate cancer.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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EXECUTIVE SUMMARY

- Evidence obtained in large case–control studies suggests that obesity is associated with an increased risk of being diagnosed with high-grade prostate cancer and dying of the disease.
- The increased risk of high-grade prostate cancer in obese men has a strong biological rationale, which includes systemic effects, such as the increased levels of IGF-1 and decreased levels of testosterone, as well as increased levels of inflammation and cytokines, and also local effects, such as larger prostates and periprostatic fat accumulation.
- As far as dietary habits are concerned, saturated fat may increase the risk of prostate cancer-related death, while vegetable fat may exert a protective effect after a diagnosis of nonmetastatic prostate cancer.
- Unlike other malignancies, prostate cancer is highly dependent on lipid metabolism, with free fatty acids being able to support cell growth, proliferation, differentiation and motility via binding to several biological targets, such as the nuclear PPAR-γ.
- Prostate cancer cells present both intratumoral lipogenesis and steroidogenesis, which can provide druggable targets for prevention and treatment purposes.

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