Androgens, diabetes and prostate cancer

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Abstract

Metabolic disorders such as diabetes, obesity and the metabolic syndrome have been shown to modulate prostate cancer (PCa) risk and aggressiveness in population-based and experimental studies. While associations between these conditions are modest and complex, two consistent findings have emerged. First, there is observational evidence that obesity and associated insulin excess are linked to increased PCa aggressiveness and worse outcomes. Secondly and somewhat paradoxically, long-standing diabetes may be protective against PCa development. This apparent paradox may be due to the fact that long-standing diabetes is associated with insulin depletion and decreased IGF1 signalling. Men with obesity or diabetes have moderate reductions in their androgen levels. The interconnectedness of metabolic and androgen status complicates the dissection of the individual roles of these factors in PCa development and progression. Metabolic factors and androgens may promote prostate carcinogenesis via multiple mechanisms including inflammation, adipokine action, fatty acid metabolism and IGF signalling. Moreover, androgen deprivation, given to men with PCa, has adverse metabolic consequences that need to be taken into account when estimating the risk benefit ratio of this therapy. In this review, we will discuss the current epidemiological and mechanistic evidence regarding the interactions between metabolic conditions, sex steroids and PCa risk and management.

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Introduction

Diabetes and prostate cancer (PCa) are two major, growing health problems that affect millions of men worldwide. PCa is the most common solid organ cancer in men in the USA, Canada and Australia, and the second most common cancer in men globally. US men have a current estimated lifetime risk of one in six (Siegel *et al.* 2011) and PCa represents, after lung cancer, the second leading cause of cancer-related mortality (Jemal *et al.* 2010). Established risk factors of PCa are older age, African American Ethnicity and a history of the disease in a first-degree relative. PCa has one of the strongest relationships between age for any human cancer, and genetic factors are estimated to account for 42% of the risk (Lichtenstein *et al.* 2000). Genome-wide association studies (GWAS) in mostly Caucasian populations have, to date, found more than 30 single nucleotide polymorphisms (SNPs) that are consistently associated with PCa (Kim *et al.* 2010). However, the magnitude of risk elevation attributable to individual SNPs is low (odds ratio (OR) < 1.30), and

these SNPs in aggregate are estimated to account for only one-quarter of the total genetic variance of PCa risk (Kote-Jarai *et al.* 2011). Recently, there has been an increasing interest in the role of metabolic factors, such as disordered glucose metabolism, in the aetiology and pathogenesis of PCa. This is important not only because life expectancy is increasing globally, but also because of the global increase in the prevalence of diabetes, predicted to increase by 69% in developing countries and by 20% in developed countries over the next 20 years (Shaw *et al.* 2010).

While it has long been known that established PCa is an androgen-dependent malignancy (Huggins & Hodges 1941), the roles of androgens in initiation of prostate carcinogenesis are less well understood. This is in part because there is a complex relationship between metabolic disorders and circulating androgens in men (Atlantis *et al.* 2009, Mah & Wittert 2010, Araujo & Wittert 2011, Grossmann 2011), both of which may affect prostate biology in different ways. Moreover, the role of androgen deprivation therapy (ADT) for PCa

continues to evolve, with both efficacy and side effects of this treatment coming into sharper focus. ADT has been associated with an increased risk of diabetes in observational and experimental studies (Grossmann & Zajac 2011b). This is concerning given the overall good prognosis for most men with PCa, with a contemporary 5-year relative survival rate for all stages of PCa combined of 98.8%. Indeed, more than 30% of men with PCa die of cardiovascular disease, which constitutes one of the most common causes of death (Satariano *et al.* 1998) in this patient population.

In this review, we examine the observational evidence and the proposed mechanisms linking diabetes and androgens to PCa epidemiology and biology. We also discuss the effect of ADT on PCa, and provide recommendations for future research.

Evidence acquisition

The clinical and experimental studies discussed in this review were retrieved from the peer-reviewed journals indexed on the PubMed database from 1970 to February 2012. Multiple searches were performed, using the search terms PCa, testosterone, androgen, diabetes, insulin resistance, metabolic syndrome (MetS) and males. In addition, references listed in published meta-analyses were reviewed.

Metabolic risk factors for PCa: evidence from population-based studies

Obesity

Substantial geographic variations in PCa prevalence, not fully accounted for by ascertainment bias (e.g. volume of prostate specific antigen (PSA) testing), suggest that environmental and lifestyle factors may contribute to PCa aetiology and pathogenesis. For example, migrant studies have shown that Asian men living in the USA have much higher PCa rates than their counterparts living in native lands, and the incidence of PCa in previously low-risk Asian countries has increased in parallel to affluence. This suggested that westernization may represent an important risk factor for PCa (Hsing *et al.* 2007). However, multiple observational studies have given conflicting evidence regarding the relationship of obesity and PCa (Table 1). A meta-analysis of observational studies including more than 68 000 men with PCa found that increasing body mass index (BMI) was weakly associated with an increased risk of PCa, with an overall relative risk (RR) of 1.05 per 5 kg/m² increment (95% confidence interval (CI), 1.01–1.08) (MacInnis & English 2006). This risk increase was significant only for advanced disease (RR, 1.12 per 5 kg/m² increment; 95% CI, 1.01–1.23) but not for localised disease (RR, 0.96 per 5 kg/m² increment; 95% CI, 0.89–1.03) (MacInnis & English 2006).

Table 1 PCa and obesity: population-based studies

Author	Study design	Study population	Main study findings
MacInnis & English (2006)	Meta-analysis of observational studies	55 521 cases identified among 2 818 767 men from 31 cohort studies and 13 232 cases and 16 317 controls from 25 case-control studies	Overall RR for BMI: 1.05 per 5 kg/m ² increment, (95% CI, 1.01–1.08). RR stronger for advanced disease (RR 1.12 per 5 kg/m ² increment; 95% CI, 1.01–1.23) compared with localised disease (RR 0.96 per 5 kg/m ² increment; 95% CI, 0.89–1.03), <i>P</i> =0.02. Stronger associations were observed among cohort studies compared with case-control studies for BMI (<i>P</i> =0.006) and weight (<i>P</i> =0.02)
Rodriguez <i>et al.</i> (2007)	Prospective cohort study with 11-year follow-up	69 991 men with 5252 incident PCa cases	Inverse association of BMI with low-grade PCa (RR, 0.84; 95% CI, 0.66–1.06). Positive association of BMI with high-grade PCa (RR, 1.22; 95% CI, 0.96–1.55) and risk of metastatic or fatal PCa (RR, 1.54; 95% CI, 1.06–2.23). Compared with weight maintenance, men who lost > 11 pounds during follow-up were at a decreased risk of high-grade PCa (RR, 0.58; 95% CI, 0.42–0.79)
Su <i>et al.</i> (2011)	Population-based incident PCa study	1049 African American and 1083 Caucasian American men with newly diagnosed PCa	ORs for aggressive PCa among pre-diagnosis obese and severely obese were 1.48 (95% CI, 1.02–2.16) and 1.98 (95% CI, 1.31–2.97) respectively compared with normal weight subjects. Race-stratified results suggested the association was stronger among Caucasian American men. WHR > 0.98 among all research subjects adjusted for race was significantly associated with aggressive PCa (OR=1.42; 95% CI, 1.00–2.00) when compared with WHR <0.90

RR, relative risk; CI, confidence interval; BMI, body mass index; OR, odds ratio; WHR, waist hip ratio.

The positive association of obesity with increased PCa aggressiveness has since been confirmed in more recent observational studies (Rodriguez *et al.* 2007, Su *et al.* 2011). Thus, obesity may reduce the risk of non-aggressive PCa, while at the same time promote the risk of aggressive PCa. Part of this relationship may be explained by detection bias. Given that adiposity is associated with decreased PSA values, larger prostate gland size and more difficult digital rectal examination (Stewart & Freedland 2011), PCa may be under-diagnosed in obese men. In addition, obese men receiving treatment for PCa have worse surgical and radiation treatment outcomes that are related not only to technical challenges, but may also reflect inherent differences in tumour biology (Ma *et al.* 2008, Smith *et al.* 2008).

The MetS

The association of the MetS with PCa has been assessed in multiple observational studies, which have yielded conflicting results (Table 2). There have been three larger prospective cohort studies in the USA (Tande *et al.* 2006) and Norway (Lund Haheim *et al.* 2006, Martin *et al.* 2009) comprising 6500 (Tande *et al.* 2006), 16 000 (Lund Haheim *et al.* 2006) and 29 000 (Martin *et al.* 2009) men initially free of PCa who were followed up between 9 and 27 years. Incident PCa was diagnosed in 385 (Tande *et al.* 2006), 507 (Lund Haheim *et al.* 2006) and 687 (Martin *et al.* 2009)

men respectively. After exclusion of men with diabetes, baseline presence of the MetS, assessed by NCEP-ATP-III criteria, was associated either with a reduced risk of PCa (RR, 0.77; 95% CI, 0.60–0.98) (Tande *et al.* 2006), an increased risk of PCa (RR for three MetS components 1.56 *P*<0.01; Lund Haheim *et al.* 2006), or no significant risk of PCa (Martin *et al.* 2009). These divergent results are in part explained by differences in study populations, analytical methods, definitions used to define the MetS and length of follow-up. Conflicting results may also relate to differential or even opposing effects of individual components of the MetS on prostate carcinogenesis. For example, the dynamic association of insulin action with PCa, discussed further below, may confound the relationship of the MetS with PCa. In addition, non-cancer-related mortality may influence the observed associations of a given variable with cancer incidence. Men who die of other causes are no longer at risk for cancer, a concept that is known as competing risk. This concept is particularly relevant for cancers with a long natural history and strong age-dependence such as PCa. Conceivably, men with adverse metabolic risk factors may not live to an age where PCa is the highest, leading to an under-estimation of the association of the MetS with PCa. Indeed, in a prospective study of 2322 Swedish men followed up for 34 years, the increased risk of MetS for PCa became significant only after death from other causes was taken into account

Table 2 PCa and the MetS: population-based studies

Author	Study design	Study population	Main study findings
Tande <i>et al.</i> (2006)	Prospective cohort study with 13-year follow-up	6429 US American men (aged 45–64 at baseline) with 385 incident PCa cases	Men with the MetS (≥ 3 components according to the ATP III definition) were significantly less likely to develop PCa (RR = 0.77; 95% CI, 0.60–0.98) than men without the MetS
Lund Haheim <i>et al.</i> (2006)	Prospective cohort study with 27 year follow-up	15 933 Norwegian men (aged 40–49 at baseline) with 507 incident PCa cases	Combinations of any two (RR = 1.23; <i>P</i> = 0.04) or any three (RR = 1.56; <i>P</i> = 0.00) components of the MetS (according to the NCEP definition) using quartile values of risk factors were predictive of PCa
Martin <i>et al.</i> (2009)	Prospective cohort study with 9.3-year follow-up	29 364 Norwegian men (aged 44–62 at baseline) with 687 incident PCa cases, and 110 PCa deaths	No association of baseline BMI, WC, WHR, total or HDL-cholesterol, triglycerides, presence of the MetS, diabetes, anti-hypertensive use, or cardiovascular disease with incident or fatal PCa. Raised blood pressure was weakly associated with an increased risk: for each s.d. (12 mm) increase in diastolic blood pressure, there was an 8% (95% CI, 1–17%; <i>P</i> = 0.04) increased risk of incident PCa
Grundmark <i>et al.</i> (2010)	Prospective cohort study with 32-year follow-up	2322 Swedish men (aged 46–54 at baseline) with 237 incident PCa cases	Conditional probability of PCa considering death from other causes was significantly higher (7.3 percent-units (95% CI, 0.2–14.5%); OR of 1.64 (95% CI, 1.03–2.23; NCEP)) and non-significantly higher (5.0 percent-units (CI, –1.6% to 11.6%); OR of 1.43 (95% CI, 0.89–1.90; IDF)

ATP III, Adult Treatment Panel III; NCEP, National Cholesterol Education Program, IDF, International Diabetes Foundation; RR, relative risk; CI, confidence interval; BMI, body mass index; OR, odds ratio; WC, waist circumference; and WHR, waist hip ratio.

(Grundmark *et al.* 2010). In this study, the predominant components responsible for the increased PCa risk were abdominal obesity and a high serum triglyceride level (Grundmark *et al.* 2010). In contrast, in the HUNT 2 cohort, among individual components of the MetS, only hypertension was associated with increased PCa risk (Martin *et al.* 2009).

Diabetes

A meta-analysis of 19 population-based studies published between 1971 and 2005 showed that men with diabetes had a 16% reduction in their risk of PCa (Kasper & Giovannucci 2006) (Table 3). An early analysis from the Health Professionals Follow-Up study from 1986 to 1994 showed that this reduced risk only occurred from at least 5 years after the diagnosis of diabetes (Giovannucci *et al.* 1998). A subsequent report from the same cohort extending the follow-up to 2004 including a total of 4511 new PCa cases confirmed that PCa risk was not reduced in the first year after diabetes diagnosis (hazard ratio (HR): 1.30, CI: 0.97, 1.72), but was lower for men diagnosed for 1–6 years (HR: 0.82, CI: 0.66, 1.02), and even lower for men who had been diagnosed for 6–15 years (HR: 0.75, CI: 0.61, 0.93) or > 15 years (HR: 0.78, CI: 0.63, 0.96). This decreased risk of PCa in men with diabetes was irrespective of current or previous BMI, and interestingly, reduced PCa risk was stronger in men diagnosed before 1994 (pre-PSA era) vs after 1994 (Kasper *et al.* 2009). Similarly, an observational study of the prospective Cancer Prevention Study II Nutrition cohort confirmed that diabetes was associated with a reduced risk of PCa, but only 4 years after the diagnosis of diabetes (Rodriguez *et al.* 2005). A large population-based prospective multi-ethnic study among 86 303 men including 5941 PCa cases found that diabetes reduced the risk of PCa consistently among ethnic groups, with RRs ranging from 0.65 (95% CI, 0.50–0.84) among European Americans to 0.89 (95% CI, 0.77–1.03) among African Americans (Waters *et al.* 2009). Although both PSA levels and PSA testing frequencies were significantly lower in men with diabetes when compared with men without diabetes, the authors estimated that this explained only 20% of the inverse association of diabetes with PCa (Waters *et al.* 2009). The fact that this protective effect of diabetes on PCa is not simply a consequence of detection bias is supported by findings from a cohort of men from the Prostate Cancer Prevention Trial, who had prostate biopsies regardless of PSA (Gong *et al.* 2006). In this cohort, diabetes was not only associated with an overall decreased risk of PCa but also associated with 28%

(OR, 0.72; 95% CI, 0.55–0.94) reduced risk of high-grade PCa, which argues against detection bias from delayed diagnosis. Explanations proposed for the protective effect of diabetes have included the progressive development of β -cell exhaustion with insulin depletion, the association of diabetes with lower testosterone and lower insulin-like growth factor 1 (IGF1) levels or genetic effects operating in different directions (Elliott *et al.* 2010, Meyer *et al.* 2010, Stevens *et al.* 2010), the evidence for which we will discuss in subsequent sections. A recent analysis of the Swedish Apolipoprotein Mortality database including 200 660 men, 5112 of whom developed PCa, used competing risk analysis to show that conventional Cox proportional hazard models, employed in previous studies, may over-estimate the prospective effects of increased glucose levels on PCa risk (Van Hemelrijck *et al.* 2011). This over-estimation of risk occurred because high glucose levels increased the probability of early death, thus masking PCa risk (Van Hemelrijck *et al.* 2011).

Although long-standing diabetes may protect against PCa development, there is evidence that diabetic men with PCa may have a worse outcome. In a prospective study, among men who developed PCa, diabetes was associated with a higher risk of cancer case fatality and all-cause mortality (Yeh *et al.* 2012). However, an analysis of the RTOG 92-02 randomised controlled trial (RCT) comparing short-term vs long-term adjuvant goserelin for men with locally advanced PCa receiving radiation therapy concluded that while diabetes was associated with increased all-cause and non-PCa-related mortality, the association of diabetes with increased PCa mortality was driven by obesity (Smith *et al.* 2008).

Metabolic risk factors for PCa: possible mechanisms

The possible mechanisms mediating the effects of metabolic risk factors on prostate carcinogenesis are summarised in Fig. 1.

Genetics

Among the risk SNPs identified in GWAS of PCa, several PCa susceptibility loci such as *HNF1 β* (*TFC2*), *JAZF1* and *THADA* have also been shown to be associated with diabetes risk (Gudmundsson *et al.* 2007, Zeggini *et al.* 2008). Interestingly, *HNF1 β* mutations have been associated with maturity-onset diabetes of the young type 5 (MODY5), which presents with pancreatic atrophy and early insulin requirement.

Table 3 PCa and diabetes: population-based studies

Author	Study design	Study population	Main study findings
Kasper & Giovannucci (2006)	Meta-analysis of observational studies published between 1971 and 2005	13 275 cases identified among 1 040 064 men from 11 cohort studies and 7068 cases and 16 277 controls from eight case-control studies	Inverse association between diabetes mellitus and PCa (RR, 0.84; 95% CI, 0.76–0.93, $P=0.01$). Cohort studies alone: RR 0.81 (CI, 0.71–0.92, $P=0.01$). Case-control studies alone: RR 0.89 (95% CI, 0.72–1.11, $P=0.02$). For studies that adjusted for three or more potential confounders, the RR was 0.74 (95% CI, 0.65–0.85, P for heterogeneity = 0.06) and for studies that adjusted for less than three potential confounders, the RR was 0.93 (95% CI, 0.86–1.02, P for heterogeneity = 0.18)
Kasper <i>et al.</i> (2009)	Prospective cohort study with 18-year follow-up	51 529 US American men (aged 40–75 at baseline) with 4511 incident PCa cases	The HR of PCa comparing men with vs without diabetes was 0.83 (95% CI, 0.74–0.94). PCa risk was not reduced in the first year after diabetes diagnosis (HR: 1.30; 95% CI, 0.97–1.72), was lower for men diagnosed for 1–6 years (HR: 0.82; 95% CI, 0.66–1.02) and was even lower for men who had been diagnosed for 6–15 years (HR: 0.75; 95% CI, 0.61–0.93) or > 15 years (HR: 0.78; CI: 0.63, 0.96). Reduced PCa risk was stronger in men diagnosed before 1994 (pre-PSA era) vs after 1994 (0.96). Diabetes was associated with a lower incidence of PCa (RR) = 0.67; 95% CI, 0.60–0.75). This association differed significantly by time since diagnosis of diabetes ($P<0.0002$); risk of PCa was slightly increased during the first 3 years after diagnosis of diabetes (RR = 1.23; 95% CI, 0.92–1.65) but was reduced among men diagnosed 4 or more years before (RR = 0.63; 95% CI, 0.56–0.71)
Rodriguez <i>et al.</i> (2005)	Prospective cohort study with 9-year follow-up	72 529 US American men (aged 50–74 at baseline) with 5318 incident PCa cases	Men with diabetes had significantly lower risk of PCa than men without diabetes (RR = 0.81; 95% CI, 0.74–0.87; $P<0.001$, with RRs ranging from 0.65 (95% CI, 0.50–0.84; $P=0.001$) among European Americans to 0.89 (95% CI, 0.77–1.03; $P=0.13$) among African Americans. Mean PSA levels were significantly lower in men with diabetes than in men without diabetes (mean PSA levels, 1.07 and 1.28 respectively $P=0.003$) as were PSA screening frequencies (44.7 vs 48.6%; $P<0.001$); however, this difference could explain only 20% of the inverse association between these diseases
Waters <i>et al.</i> (2011)	Prospective cohort study with 12-year follow-up	86 303 US American men (aged 45–75 at baseline) with 5941 incident PCa cases	Diabetes was associated with a 47% (OR, 0.53; 95% CI, 0.34–0.83) reduced risk of low-grade PCa and a 28% (OR, 0.72; 95% CI, 0.55–0.94) reduced risk of high-grade PCa
Gong <i>et al.</i> (2006)	Randomised, placebo-controlled trial testing whether the 5 α -reductase inhibitor finasteride could reduce the 7-year period prevalence of PCa	10 258 US American men (mean age 64) with 1936 PCa cases	
Van Hemelrijck <i>et al.</i> (2011)	Cross-sectional study	200 660 Swedish Men (age <20 to > 80) with 5112 PCa cases	Age-stratified analyses for quartiles of glucose showed a negative association between glucose and PCa risk (HR, 0.93; 95% CI, 0.86–1.01), 0.93 (0.86–1.01), 0.87 (95% CI, 0.81–0.94) for the second, third and fourth quartiles compared with the first ($P=0.001$). Competing risk analysis showed that protective effects of glucose were over-estimated in conventional Cox proportional hazard models
Yeh <i>et al.</i> (2012)	Prospective cohort study with 17-year follow-up	599 Diabetic and 17 681 non-diabetic US American men with 116 cancer cases in men with and 2365 cases in men without diabetes	Diabetes was associated with a higher risk of incident cancer (HR 1.22 (95% CI, 0.98–1.53)) and cancer mortality (1.36 (95% CI, 1.02–1.81)), after multivariate adjustment. In individuals who developed cancer, adults with diabetes had a higher risk of cancer case fatality (1.34 (95% CI, 1.002–1.79)) and all-cause mortality (1.61 (95% CI, 1.29–2.01)). For PCa, the attributable fraction resulting from diabetes was larger for cancer fatality and mortality than cancer incidence
Smith <i>et al.</i> (2008)	Randomised trial of short-term vs long-term adjuvant goserelin in men receiving radiotherapy	1554 US American men with locally advanced PCa. There were a total of 765 deaths; 210 (27%) were attributed to PCa	Prevalent diabetes was significantly associated with greater all-cause mortality and non-PCa mortality (HR = 2.12; 95% CI, 1.69–2.66; $P<0.0001$) but not PCa mortality (HR = 0.80; 95% CI, 0.51–1.25; $P=0.34$)

RR, relative risk; CI, confidence interval; HR, hazard ratio; and OR, odds ratio.

Figure 1 Metabolic risk factors for prostate cancer: possible mechanisms.

While the MODY5 phenotype is consistent with the observational studies suggesting a protective effect of insulin depletion, a recent study concluded that the relationship between *HNF1 β* and *JAZF1* variants with decreased PCa was not mediated by diabetic status (Stevens *et al.* 2010). A further study testing 17 diabetes risk variants in a PCa case–control study of 2746 cases and 3317 controls from five racial/ethnic groups in the Multiethnic Cohort (MEC) study did not find any association of any of the diabetes loci with PCa risk (Waters *et al.* 2011). Given that the relationship of diabetes with PCa is likely a complex interplay between environmental factors and pleiotropic genetic effects that may vary in a diabetes- and PCa stage-dependent fashion, further study is required to evaluate the shared genetic components of diabetes and PCa.

Insulin and IGF1

Although the results from population-based studies discussed above are somewhat complex and the overall strengths of the associations are modest, two consistent findings have emerged. First, obesity appears to be associated with increased risk of high-grade PCa and with increased PCa mortality, and possibly, with reduced low-risk PCa. Secondly and somewhat paradoxically given its strong association with adiposity, long-standing diabetes appears to protect against both high- and low-grade PCa. This apparent paradox may be due to the fact that long-standing diabetes is associated with insulin resistance. Insulin is a potent mitogenic and anti-apoptotic factor, which has potent growth-stimulatory effects on the prostate, and DNA polymorphisms in the insulin gene may be associated with increased PCa risk (Hsing *et al.* 2007). Thus, progressive insulin resistance and β -cell failure with insulin depletion occurring with increasing

duration of diabetes may limit insulin actions and hence protect against PCa. Different degrees of insulin sensitivity may also in part explain the confusing observational data linking the MetS to PCa discussed above where combining multiple components of the syndrome – which individually may have opposing effects on PCa risk – could obscure these independent interactions of individual metabolic factors with PCa risk. This insulin–PCa association however remains speculative, as data supporting a direct causal role of insulin in prostate carcinogenesis remain limited. The relationship of insulin with PCa is further confounded by, among others, complex interactions with adiposity-associated inflammation and decreases in circulating androgens, which will be discussed further below.

Consistent with a role for insulin in promoting PCa are findings from a prospective case–cohort study in non-diabetic men suggesting that both elevated insulin concentrations and increased HOMA-IR values, but not glucose levels, predicted increased PCa risk (Albanes *et al.* 2009). Moreover, in the placebo arm of the finasteride PCa prevention trial, higher baseline C-peptide levels were associated with a nearly twofold increased risk of high-grade PCa (multivariate-adjusted OR 1.88; 95% CI, 1.19–2.97; Neuhauser *et al.* 2010). Similarly, a prospective analysis from the Physicians' Health Study showed that baseline high C-peptide concentrations predisposed men with a subsequent diagnosis of PCa to an increased risk of PCa death that was independent of and additive to baseline BMI (Ma *et al.* 2008). In an LNCaP xenograft model, mice fed a high fat diet showed significantly increased serum insulin levels and experienced accelerated PCa growth compared to mice receiving a low fat diet, and serum from mice receiving the high fat diet was more mitogenic for LNCaP cells *in vitro* (Venkateswaran *et al.* 2007).

Insulin stimulates IGF1 secretion, which has been shown to promote growth of primary prostate cell cultures and of human PCa cell lines *in vitro* (De Nunzio *et al.* 2011). Transgenic mice over-expressing human IGF1 in basal epithelial cells of the prostate develop prostate carcinoma at a high rate (50%) (DiGiovanni *et al.* 2000), and mice with global or liver-specific inactivation of IGF1 show reduced prostate size and reduced androgen-dependent prostate growth (Svensson *et al.* 2008). Indeed, a meta-analysis of 42 observational studies confirmed that raised circulating IGF1 levels were significantly associated with PCa risk (OR 1.21; 95% CI, 1.07–1.36), with weak evidence that this association was stronger for advanced PCa (Rowlands *et al.* 2009). Similarly, a pooled analysis of individual patient data from 12 prospective studies showed that greater serum IGF1 concentrations were associated with a greater subsequent risk of PCa (OR 1.38; 95% CI, 1.19–1.60), although in this study, the association was somewhat stronger for low-grade disease (Roddam *et al.* 2008b). Associations of other IGFs or their binding proteins with PCa were inconsistent (Roddam *et al.* 2008b, Rowlands *et al.* 2009). Limitations of individual studies analysed in both papers (Roddam *et al.* 2008b, Rowlands *et al.* 2009) included absence of information regarding PCa stage, PSA screening history and reliance on single serum samples.

Adipokines and inflammation

In addition to insulin and IGF1, visceral obesity may mediate effects on PCa via secretion of adipokines and proinflammatory cytokines. While leptin promotes PCa cell proliferation and inhibits apoptosis *in vitro* (Onuma *et al.* 2003), epidemiological evidence linking leptin levels to PCa in men has been inconsistent (Hsing *et al.* 2007, Li *et al.* 2010, Neuhauser *et al.* 2010). Adiponectin is an insulin sensitising adipokine which is inversely correlated with amount of visceral fat. Interestingly, in a prospective analysis from the Physicians' Health Study, men with higher adiponectin levels had a lower risk of developing high grade or lethal PCa, and this risk remained independent of BMI and C-peptide levels (HR 0.39; 95% CI, 0.17–0.85; Li *et al.* 2010). Further support that adiponectin may play a protective role – rather than simply serving as a surrogate of insulin sensitivity – stems from observations that adiponectin inhibits tumour-induced angiogenesis (Brakenhielm *et al.* 2004) and PCa cell growth (Bub *et al.* 2006) *in vitro*. In addition, adiponectin gene polymorphisms have recently been associated with PCa risk, serum adiponectin levels and

insulin receptor or IGF1 receptor expression in prostate tumour specimens, although there was no association by tumour grade or clinical stage (Dhillon *et al.* 2011).

The chronic proinflammatory state associated with obesity and the MetS may also contribute to PCa development and progression. Proinflammatory cytokines known to be elevated in the MetS such as tumour necrosis factor α (TNF α), interleukin (IL) 6 and IL8 have been associated with increased PCa risk and stage (Hsing *et al.* 2007). These cytokines stimulate the nuclear factor kappaB (NF- κ B) pathway, which in turn has been linked to prostate carcinogenesis. NF- κ B activation is constitutive in PCa cell lines, directly related to the extent of lymph node invasion in radical prostatectomy specimens, and may be involved in androgen-independent PCa progression (Jin *et al.* 2008, Gorbachinsky *et al.* 2010). Elegant experiments in mice with a targeted deletion of the NF- κ B stimulatory kinase IKK- α have revealed an essential requirement for NF- κ B activation in the emergence of castrate-resistant PCa (Ammirante *et al.* 2010). One upstream activator of the proinflammatory and anti-apoptotic NF- κ B pathway is the endoplasmic reticulum (ER) chaperone protein GRP78. The presence of GRP78 activating auto-antibodies in patient sera is associated with a poor PCa prognosis (Misra *et al.* 2010). Interestingly, treatment of PCa cell lines with an antibody that inhibits auto-antibody induced GRP78 activation inhibits NF- κ B activation *in vitro*, providing preliminary evidence for a strategy for anti-PCa therapy (Misra *et al.* 2010).

Nutrients and fatty acids

In population-based studies, a diet high in animal fat and low in vegetables has been associated with increased PCa risk, unfavourable prognosis and relapse after treatment for localised PCa (Chan *et al.* 2005). PCa cells express high levels of fatty acid synthase from which they derive fatty acids for membrane biosynthesis to sustain cell proliferation. In addition, there is evidence that PCa-associated lipogenesis may disturb cell surface cilium formation leading to impaired environmental sensing, aberrant signalling and disruption of cellular architecture (Willemarck *et al.* 2010). A genome-wide gene expression analysis has found the lipogenic gene *ELOVL7* to be over-expressed in PCa, and knockdown of *ELOVL7* in the PCa cell lines LNCaP and 22RV1 markedly reduced their growth and androgen synthesis *in vitro* (Tamura *et al.* 2009). The fatty acid arachidonic acid has also been shown to stimulate *de novo* androgen biosynthesis in steroid-starved PCa cells, which may in turn trigger

AR reactivation in castrate-resistant PCa (Locke *et al.* 2010). In addition, saturated fatty acids may promote prostate carcinogenesis by increasing IGF1 signalling, increasing ER stress and disturbing activation of the innate immune system (Lu & Archer 2010).

Some but not all epidemiological studies show that an increased intake of omega-3 (*n*-3) polyunsaturated fatty acids (PUFA) decreases, whereas increased consumption of *n*-6 PUFA increases PCa risk (Astorg 2004, Heinze & Actis 2012). In addition, there is experimental evidence that *n*-3 PUFA suppresses, whereas *n*-6 PUFA promotes prostate carcinogenesis. For example, increasing the dietary *n*-3/*n*-6 PUFA ratio also increased this ratio in tumour membranes and reduced vascular endothelial growth factor expression, cell proliferation and tumour volume (Kobayashi *et al.* 2006). Xenograft studies with androgen-dependent (CWR22) and androgen-independent (CWR22R)+ human PCa cells have suggested that dietary changes that increased tumour *n*-3 PUFA content enhanced the response to androgen-ablative therapy (McEntee *et al.* 2008). Treatment of PCa cell lines with the *n*-3 PUFA docosahexaenoic acid (DHA) reduced NF- κ B activation and cell survival in response to oxidative stress, suggesting that DHA sensitises PCa cells to growth arrest through attenuation of the NF- κ B survival pathway (Cavazos *et al.* 2011). Although there is to date no controlled evidence that dietary interventions modulate PCa risk and progression, clinical trials using DHA in the prevention and treatment of PCa are underway (<http://clinicaltrials.gov>).

Effects of sex steroids on PCa

Since Huggins Nobel-Prize winning observations (Huggins & Hodges 1941), it has been known that androgens are critical for normal prostate development and function, as well as for PCa growth and progression. For example, men with 5- α reductase deficiency (the enzyme that converts testosterone into dihydrotestosterone (DHT), the main intraprostatic androgen) are protected against the development of PCa (Imperato-McGinley *et al.* 1974). However, the role of 5- α reductase inhibitors in the prevention of PCa remains under debate. ADT further discussed below has long been the mainstay in the treatment of metastatic PCa. DNA sequences associated with PCa risk identified in GWAS are significantly enriched in androgen receptor (AR)-binding sites, as well as in FoxA1-binding sites, an AR co-activator required for AR binding to enhancers in multiple AR-target genes (Lu *et al.* 2011). While a recent meta-analysis has concluded that an increased number of AR CAG

repeats, which leads to a biologically less active AR, may be associated with protection against PCa in men older than 45 years (Gu *et al.* 2011), the association between AR CAG repeat length and PCa risk remains controversial. A germline mutation in the homeobox transcription factor *HOXB13* gene has recently been associated with a 20-fold increased risk of familial PCa, and *HOXB13* physically interacts with the AR (Ewing *et al.* 2012).

Although it is well accepted that PCa is an androgen-dependent malignancy, whether androgens are involved in the initiation of PCa remains controversial. The association of testosterone and other sex steroids with PCa risk has been analysed in multiple observational studies. The most definitive evidence comes from a collaborative analysis of 18 prospective studies including 3886 men with incident PCa and 6438 control subjects. In this study, no associations were found between the risk of PCa and serum concentrations of total testosterone, calculated free testosterone, DHT, oestradiol, DHEAS, or indeed any other sex steroid tested (Roddam *et al.* 2008a).

Consistent with these observational studies suggesting a lack of a role of circulating sex steroids in PCa initiation are findings from trials of testosterone therapy. While regular rectal examinations and PSA monitoring during testosterone therapy is recommended (Bhasin *et al.* 2010), several meta-analyses failed to show an increased risk of PCa with testosterone therapy (Calof *et al.* 2005, Fernandez-Balsells *et al.* 2010), despite an increased rate of prostate biopsies in one analysis (Calof *et al.* 2005). However, studies included in these meta-analyses have been limited by small numbers, low quality and short duration. Thus, in the absence of an adequately designed and powered RCT, the PCa risk of testosterone therapy remains unknown. It has been estimated that 6000 men would need to be randomised to testosterone or placebo for 5 years to determine if testosterone therapy increases the risk of PCa by 30% (Liverman & Blazer 2004). Current guidelines advise avoidance of testosterone therapy in patients with PCa, a palpable nodule or induration or a PSA of >4 ng/ml (>3 ng/ml in high-risk men) (Bhasin *et al.* 2010). Although some have suggested that testosterone therapy can be considered in selected hypogonadal men with previously treated PCa, the safety of this approach is currently based on anecdotal evidence, and remains a matter of debate (Landau *et al.* 2012).

It is well recognised that relating a serum testosterone level to a clinical phenotype is an oversimplification, given that circulating testosterone levels, whether free or total (Ly *et al.* 2010), are

unlikely to accurately reflect androgen action at the tissue level. Testosterone action is modulated by AR polymorphisms and transcriptional cofactors, and local androgen synthesis and inactivation may not be reflected in circulating testosterone levels. DHT, the principal prostatic androgen, has a tenfold higher activity at the AR compared to testosterone, and circulating DHT concentrations in serum are tenfold lower than testosterone, while the opposite is true for intraprostatic DHT concentrations (Marks *et al.* 2008). Whether variations in intraprostatic androgens which may have little correlation with circulating androgens affect prostate carcinogenesis is more difficult to study. In a small (44 men) short-term (6 months) RCT of testosterone therapy, there was no difference in intraprostatic androgen levels, prostate histology or gene expression in men given testosterone compared to placebo (Marks *et al.* 2006). In a 4-week RCT of DHT vs placebo in 31 men, despite robust increases in circulating DHT in the DHT-treated group, there was again no difference in intraprostatic DHT or testosterone concentrations, epithelial cell proliferation or AR-regulated gene expression (Page *et al.* 2011). In addition, a larger RCT of DHT therapy of 2 year duration in 114 healthy men showed no effect on prostate volume (measured by ultrasonography) or PSA levels (Idan *et al.* 2010).

The lack of correlation of circulating or intraprostatic androgens with PCa risk in preliminary studies, combined with the lack of evidence to date that testosterone therapy increases this risk, has led to the proposal of the so-called ‘saturation model’ of the AR (Morgentaler & Traish 2009). According to this model, there is a limited ability of the prostate to respond to increased androgens because of a finite capacity of the AR to bind androgens. Therefore, the androgenic response of the prostate is postulated to be sensitive to changes in circulating androgens only at low androgen concentrations. An increase of circulating androgens above a certain threshold will saturate the AR, so that the prostate will no longer respond to further increases in circulating levels of androgens above this saturation point. Conversely, below a certain lower androgen threshold, the ‘castrate’ level, the androgenic response will decrease, consistent with the therapeutic effect of ADT on established PCa (Morgentaler & Traish 2009, Goldenberg *et al.* 2011). While there is experimental evidence to support such a model reviewed elsewhere (Morgentaler & Traish 2009, Goldenberg *et al.* 2011), the saturation model is not yet proven and more research is needed.

Interestingly, some evidence suggests that low circulating testosterone levels may be a risk factor

for PCa aggressiveness. For example, several, but not all (Salonia *et al.* 2011) cross-sectional, studies have suggested that low testosterone levels at the time of PCa diagnosis is associated with more aggressive disease, for review see Goldenberg *et al.* (2011) and Morgentaler (2011). Low testosterone levels have also been linked to more advanced PCa stages, and more aggressive phenotypes in radical retropubic prostatectomy specimens (Goldenberg *et al.* 2011).

Relationship between sex steroids and diabetes

In part, the contradictory literature regarding the relationship between circulating androgens and PCa risk may relate to the fact that obesity and diabetes, which themselves may increase or decrease PCa risk or aggressiveness respectively, have complex interactions with circulating sex steroid levels (Grossmann *et al.* 2010). Several large studies have shown that 30–50% of ageing, obese men with type 2 diabetes have circulating testosterone levels below the reference range derived from healthy young men (Dhindsa *et al.* 2004, Kapoor *et al.* 2007, Grossmann *et al.* 2008). A meta-analysis of cross-sectional case–control studies showed that men with diabetes had significantly lower total testosterone compared to men without diabetes, even after adjustment for age and crude measures of body fat (mean pooled difference 1–0.61 nmol/l; 95% CI, –2.56 to –0.65 nmol/l) (Ding *et al.* 2006). In addition, in prospective studies, men with higher testosterone levels had a 42% lower risk of future diabetes (Ding *et al.* 2006), although the relationship between low testosterone and diabetes may be partially explained by several modifiable risk factors (Atlantis *et al.* 2009, 2011). Similar to diabetes, the presence of the MetS is also associated with a moderate, 2–3 nmol/l decrease in total testosterone in population-based studies, reviewed in Grossmann (2011). The lower testosterone levels in men with diabetes or the MetS is driven, at least in part, by increased visceral adiposity and insulin resistance, via a complex bi-directional relationship (Araujo & Wittert 2011). Visceral adiposity promotes a lowering of testosterone, and low testosterone predisposes to central weight gain, creating a viscous circle promoting insulin resistance (Fig. 2; Grossmann *et al.* 2010). Indeed, testosterone therapy promotes metabolically favourable changes in body composition (Wittert *et al.* 2003) associated with moderate decreases in insulin resistance (Grossmann 2011), whereas, conversely ADT given to men with PCa leads to visceral fat gain and increased insulin resistance (Hamilton *et al.* 2011). In addition, weight loss can lead to substantial increases in testosterone

Figure 2 Bi-directional relationship between visceral fat and testosterone. A self-perpetuating cycle promoting insulin resistance. HPG, hypothalamo–pituitary–gonadal axis. (Adapted from Grossmann *et al.* (2010)).

levels, especially in morbidly obese men (Khoo *et al.* 2010), and this increase in testosterone is proportional to the amount of weight lost (Grossmann 2011). Thus, testosterone has complex interactions not only with prostate biology, but also direct relationships with PCa metabolic risk factors such as diabetes, obesity and the MetS. This mutual interdependence further complicates the dissection of the relative roles of androgens and metabolic factors in prostate carcinogenesis.

Testosterone is not only a hormone, but also a pro-hormone and at least some of its actions in men occur as a consequence of its aromatisation to oestradiol. Characterisation of the role of oestradiol in prostate carcinogenesis is made difficult by its close association with adiposity and the challenges in accurately quantifying the very low circulating oestradiol levels in men. In addition, circulating oestradiol is positively associated with diabetes even after adjustment for fat mass and distribution (Vikan *et al.* 2010). In prostate epithelial cells, oestradiol activation of the oestrogen receptor (ER) α aberrantly stimulates cell proliferation and is pro-inflammatory, whereas oestradiol action through ER β is anti-proliferative and anti-inflammatory (Risbridger *et al.* 2010). There is evidence that oestradiol is involved, either by itself or in synergy with androgens, in PCa pathogenesis. For example, the

circulating oestradiol/testosterone ratio is higher in older men, and in African American men, who are at higher risk of PCa, but lower in less susceptible Japanese men (Ho *et al.* 2011). There is evidence that intraprostatic activation of aromatase increases during prostate carcinogenesis, and animal models support the suggestion that oestrogens, alone or in concert with androgens, are potent inducers of aberrant growth and neoplastic transformation in the prostate (Risbridger *et al.* 2010, Ho *et al.* 2011).

Metabolic side effects of ADT

ADT is the standard therapy for palliation of metastatic PCa and improves mortality as adjuvant therapy for locally advanced or high-risk localised tumours treated with radiotherapy (Shahinian 2011). Use of ADT doubled over the course of the 1990 and extended to settings where mortality benefit is unproven, such as primary treatment of asymptomatic disease or of biochemical (PSA) recurrence after prior prostatectomy or radiotherapy (Shahinian 2011). Given the overall favourable prognosis of PCa and the high prevalence of underlying cardiovascular disease and osteoporosis in older men, even a modest increase in ADT-associated cardiovascular or fracture risk may be

important, especially in settings where the benefit of ADT on PCa mortality has not been proven (Grossmann & Zajac 2011a). Given that cardiovascular events are among the most common causes of death in men with PCa (Satariano *et al.* 1998), it is of concern that several retrospective studies have associated ADT with increased risk of diabetes and possibly, cardiovascular events, for review, see Grossmann & Zajac (2011b). While retrospective studies are subject to bias and confounding factors, findings have, at least with respect to diabetes, been consistent. They are also biologically plausible, because prospective studies have shown that ADT leads to metabolically unfavourable changes in body composition with increased total and visceral fat, loss of muscle mass and associated increases in insulin resistance, itself an independent cardiovascular risk factor (Smith *et al.* 2001, Hamilton *et al.* 2011). This prompted the US Food and Drug Administration to issue a safety warning in October 2010, requiring labelling on GnRH agonists warning about and ‘increased risk of diabetes and certain cardiovascular diseases’. However, in a recent meta-analysis of RCTs in unfavourable-risk PCa, ADT was not associated with an increased risk of cardiovascular death, but was associated with a lower risk of PCa-specific and all-cause mortality (Nguyen *et al.* 2011). While further study is necessary to better define the risk benefit ratio of ADT, these findings provide reassurance regarding the use of ADT in appropriately selected PCa patients. In addition, evidence-based guidelines are available to monitor and manage metabolic health in patients with PCa receiving ADT in order to minimise ADT-related adverse outcomes (Grossmann *et al.* 2011).

Summary and conclusions

While the strength of the associations between metabolic conditions and PCa risk and disease progression in population-based studies is modest, there is a consistent picture of obesity being associated with aggressive PCa and worse cancer-specific outcome. Increased insulin and IGF1 signalling, inflammation and obesity-associated changes in sex steroid levels, and disturbances in fatty acid metabolism may all play a role in prostate carcinogenesis (Fig. 3). Indeed, testosterone and oestradiol have complex relationships not only with prostate biology, but also with metabolic disorders. In contrast, the protective effect of long-standing diabetes may be explained by associated β -cell exhaustion with insulin depletion. However, evidence to date is largely observational and therefore, the causality of such associations has not yet been proven. In addition, some of these associations may be overestimated because of competing risk, given the long latency of PCa. On the other hand, because of the interplay between sex steroids and metabolic conditions which individually may either promote or suppress prostate carcinogenesis, isolating their respective contributions to PCa development and promotion has proven difficult. In light of the high and increasing global prevalence of PCa and of metabolic conditions as life expectancy and affluence increases worldwide, this is clearly a high priority for further research. Future adequately powered prospective studies should incorporate accurate measures of sex steroids by HPLC/mass spectrometry, of regional (especially visceral) obesity, of glucose metabolism, and of PCa grade and stage. The available data are sufficiently mature to warrant controlled trials to test

Figure 3 Metabolic factors, sex steroids and prostate cancer.

the hypothesis that weight loss, either by diet or exercise, or medical therapies that reduce insulin excess may decrease PCa risk or disease progression. Institution of healthy lifestyle to promote weight loss is unlikely to have negative effects on prostate health and has multiple other health benefits, including moderate increases in endogenous testosterone levels. Since ADT may increase risk of diabetes and cardiovascular events, this therapy should only be used in settings of proven benefit. Men receiving ADT should be routinely monitored to minimise ADT-associated adverse events.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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