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**Metabolic syndrome in the development and progression of prostate cancer**

Strine AC *et al*. Metabolic syndrome and prostate cancer

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**Abstract**

Prostate cancer (PCa) is the most common noncutaneous malignancy and second leading cause of cancer-specific mortality for men in the United States. There is a wide spectrum of aggressiveness ranging from biologically significant to indolent disease, which has led to an interest in the identification of risk factors for its development and progression. Emerging evidence has suggested an association between metabolic syndrome (MetS) and PCa. MetS represents a cluster of metabolic derangements that confer an increased risk of cardiovascular disease and type 2 diabetes mellitus. Its individual components include obesity, dyslipidemias, high blood pressure, and high fasting glucose levels. MetS has become pervasive and is currently associated with a high socioeconomic cost in both industrialized and developing countries throughout the world. The relationship between MetS and PCa is complex and yet to be fully defined. A better understanding of this relationship will facilitate the development of novel therapeutic targets for the prevention of PCa and improvement of outcomes among diagnosed men in the future. In this review, we evaluate the current evidence on the role of MetS in the development and progression of PCa. We also discuss the clinical implications on the management of PCa and consider the future direction of this subject.

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**Key words:** Diabetes mellitus; Dyslipidemias; Humans; Hyperglycemia; Hypertension; Insulin resistance; Male; Metabolic syndrome X; Obesity; Prostatic neoplasms

**Core tip:** The current literature is conflicted on the association between metabolic syndrome (MetS) and prostate cancer (PCa), although several studies have demonstrated that men with MetS or its individual components may have an increased risk of more aggressive disease and mortality as well as a poorer outcome after their treatment for PCa. These men may benefit from weight loss, physical activity, and the addition of medications like statins for preventing PCa and improving their outcomes after treatment. A majority of the existing evidence is retrospective or observational in nature, which underscores the need for more randomized controlled trials in the future.

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**INTRODUCTION**

Prostate cancer (PCa) has been the most common noncutaneous malignancy diagnosed in men since 1984 and currently accounts for almost 30% of new cancer cases in the United States. Concurrent with the introduction of prostate-specific antigen (PSA)-based screening and development of effective treatments for PCa, a steady decline in its mortality rate has been observed since 1991. Currently, only 16% of men diagnosed with PCa succumb to their disease[1]. This marked disparity between the incidence and mortality rates of PCa reflects a wide spectrum of aggressiveness. Differentiating between biologically significant and indolent disease, however, has proven to be difficult and led to an interest in the identification of risk factors for its development and progression.

Although the pathogenesis of PCa remains largely unknown, both genetic and environmental factors are thought to contribute to its development and progression. Significant geographic variations in the incidence and mortality rates of PCa indicate a possible role for dietary, lifestyle-related, and other environmental factors. Epidemiologic studies, for instance, have reported a 10- to 15-fold increased incidence of PCa in western compared to Asian countries and a rapidly rising incidence in Asian countries with the adoption of a more westernized lifestyle[2-4]. Migrant studies have also revealed that Asian men living in the United States. have an increased risk of PCa compared to their counterparts living in their native countries[2,5]. However, it is unclear whether this increased incidence is related to the routine use of PSA-based screening in the United States..

The influence of westernization on the risk of PCa may be related to the pervasiveness of obesity and a sedentary lifestyle. A growing body of evidence has specifically identified an association between metabolic syndrome (MetS) and PCa. Their relationship is complex and yet to be fully defined. Developing a better understanding of this relationship may provide an opportunity for the prevention of PCa and improvement of outcomes among diagnosed men in the future. In this review, we evaluate the current evidence on the role of MetS in the development and progression of PCa. We also discuss the clinical implications on the management of PCa and consider the future direction of this subject.

**REVIEW OF LITERATURE**

A PubMed search was performed for relevant articles between 1966 and 2014. Terms for the search included metabolic syndrome, obesity, dyslipidemias, hypertension, diabetes mellitus, hyperglycemia, and insulin resistance combined with prostate cancer. Only articles published in the English language and limited to humans were considered. All titles and abstracts were reviewed for their relevance, after which the full texts of selected articles were reviewed. The full texts of additional articles were also reviewed based on the references of selected articles.

**DEFINING THE METABOLIC SYNDROME**

MetS represents a cluster of metabolic derangements that confer an increased risk of cardiovascular disease and type 2 diabetes mellitus (DM). Its individual components include obesity, dyslipidemias, high blood pressure (BP), and high fasting glucose levels. There often is an associated proinflammatory state and insulin resistance, both of which have been implicated in the pathophysiology of MetS.

Since the introduction of syndrome X by Gerald Reavan in 1988, a considerable amount of disagreement has emerged over the terminology and diagnostic criteria related to MetS. Various definitions have been proposed by multiple groups and international organizations over the past 15 years, beginning with the original definition by the World Health Organization in 1998[6-9]. The most recent recommendations by the International Diabetes Federation and AHA/NHLBI still differed on the importance of abdominal obesity and its definition being based upon waist circumference[8,9]. However, an attempt has currently been made to reconcile these differences and agree upon common criteria for the clinical diagnosis of MetS (Table 1)[10].

MetS has become a global epidemic and public health-related issue with a high socioeconomic cost. Based on the National Health and Nutrition Examination Survey from 2003 to 2006, approximately 34% of adults in the United States met the National Cholesterol Education Program ATP III criteria for MetS. The prevalence of MetS increased with an advancing age and obesity as measured by body mass index (BMI) in this population. It also varied by race, ethnicity, and gender[11]. Similarly, MetS is prevalent in other industrialized and developing countries throughout the world. Based on a meta-analysis, the prevalence of MetS varied from 10% (France) to 36.4% (India) for men in various populations aged from 20 to 25 years and older, as defined by ATP III criteria[12].

**THE METABOLIC SYNDROME AND RISK OF PROSTATE CANCER**

It is well-established that the development and progression of prostate cancer is potentiated through the dysregulated stimulation of androgen receptor-mediated pathways in prostatic cells. Due to the identification of common putative pathways involving androgen synthesis and MetS, an increasing number of authors have investigated the association between MetS and development of PCa, but their findings have been equivocal and difficult to compare (Table 2). In 2004, Hammarsten *et al*[13] retrospectively analyzed 299 men diagnosed with PCa in Sweden and demonstrated that men with higher clinical stage and grade disease were more likely to have various components of MetS than men with lower clinical stage and grade disease. These findings were later supported by 3 cohort studies from Scandinavia, in which men with MetS or various components had an increased risk of developing PCa[14-16]. It should be noted that a majority of men did not participate in PSA-based screening in these studies.

Conversely, a large cohort study of a more diverse population from the US observed an inverse association between MetS and development of PCa. Its authors reported a decreased risk of 23% (95%CI: 0.6-0.98) in men with ≥ 3 components of MetS, which remained significant after excluding diabetic men (RR, 0.71; 95%CI: 0.54-0.94). Interestingly, non-diabetic men with 2 components had an increased risk of 37% (95%CI: 1.01-1.87), suggesting that the extent and duration of MetS as well as the presence of DM may affect the risk of PCa[17].

Other large cohort studies have also failed to demonstrate an association between MetS and development of PCa. In a cohort of 29364 men from Norway, Martin *et al*[18] observed that MetS and its individual components were not associated with the development of incident or fatal PCa, except for an increased risk of 8% (95%CI: 1-17%) for each 12 mmHg increase in diastolic BP[18]. Another study followed 2445 men between 40 and 79 years of age participating in the Olmsted County Study over a period of 15 years and reported that multiple components of MetS each had a distinct association with the risk of developing PCa when considered individually and in various combinations[19]. Similarly, Häggström *et al*[20] demonstrated that MetS and its individual components were differently associated with the development of incident PCa in a cohort of 289866 men from Austria, Norway, and Sweden. These authors, however, observed an increased risk of PCa-specific mortality for men in the top quintile for BMI (RR, 1.36; 95%CI: 1.08-1.71) and systolic BP (RR, 1.62; 95%CI: 1.07-2.45) as well as for each 1-unit increase in the composite z score of all metabolic factors (RR, 1.13; 95%CI: 1.03-1.25)[20]. These are the only studies to consider the effect of MetS and its individual components on the risk of PCa. The individual components of MetS were differently associated with PCa in each study, emphasizing the importance of considering their separate and combined effects.

Given other evidence suggesting an association between vitamin D levels and PCa as well as the identification of common putative pathways involving vitamin D and lipid metaboism, Tuohimaa *et al*[21] investigated the combined influence of MetS and vitamin D levels on the development of PCa in a cohort of 588 men between 40 and 58 years of age participating in Helsinki Heart Study. Vitamin D levels were defined as low if <40 nmol/L, normal if 40-59 nmol/L, and high if ≥ 60 nmol/L. These authors demonstrated an increased risk for men in the highest quartile for BMI (OR, 2.28; 95%CI: 1.22-4.25), systolic BP (OR, 3.33; 95%CI: 1.72-6.44), and diastolic BP (OR, 2.47; 95%CI: 1.3-4.69) only when they had low vitamin D levels as well. An increased risk of PCa was also observed when low vitamin D levels were simultaneously present with a high BMI and systolic BP (OR, 3.85; 95%CI: 1.57-9.41) as well as a high BMI, systolic BP, and low high-density lipoprotein (HDL) cholesterol levels (OR, 8.03; 95%CI: 1.89-34.09) but not when considered with normal or high vitamin D levels[21].

Several studies have been conducted outside of the US or Scandinavian countries with conflicting results. In a case-control study of 2,745 men less than 75 years of age from Italy, Pelucchi *et al*[22] reported an increased risk of PCa in those with MetS (OR, 1.66; 95%CI: 1.26-1.89). There was a dose-response relationship, with men having an increased risk of 12% (95%CI: 0.89-1.42) for any 2 components of MetS, 65% (95%CI: 1.15-2.36) for any 3 components, and 299% for any 4 components (95%CI: 1.03-15.4)[22]. Conversely, Russo *et al*[23] failed to demonstrate an increased incidence of PCa in a cohort of 16677 men greater than 40 years of age simultaneously prescribed with medications for hypertension, dyslipidemias, and DM in Italy[23]. Two large cohort studies from Japan have also failed to observe an association between MetS and development of PCa[24,25].

With the exception of the study by Tande *et al*[17], all of the previously discussed studies have primarily included Caucasian men. Due to the known increased risk of MetS and PCa in African-American men, Beebe-Dimmer *et al*[26] investigated the association between MetS and development of PCa in 498 African-American men between 40 and 79 years of age participating in the Flint Men’s Health Study. These authors reported an increased risk of PCa in men with hypertension (OR, 2.4; 95%CI: 1.5-3.7) and a waist circumference > 102 cm (OR, 1.8; 95%CI: 1.2-2.9) individually. There was also an increased risk of PCa in men with any 2 components of MetS (OR, 1.76; 95%CI: 1.1-2.83)[26]. A subsequent study followed a diverse population of 881 men less than 75 years of age participating in the Genes Environment and Prostate Cancer Study and sought to determine any racial differences in the association between MetS and development of PCa. Its authors demonstrated a marginal association between MetS and development of PCa among African-American men (OR, 1.71; 95%CI: 0.97-3.01) but not among Caucasian men (OR, 1.02; 95%CI: 0.64-1.62). MetS was further associated with organ-confined disease (OR, 1.82; 95%CI: 1.02-3.23) but not advanced disease (OR, 0.93; 95%CI: 0.31-2.77) among African-American men. Interestingly, obese Caucasian men had a decreased risk of PCa (OR, 0.51; 95%CI: 0.33-0.8) and high-grade disease (OR, 0.30; 95%CI: 0.15-0.59), neither of which was observed among obese African-American men[27]. Whether this increased incidence is related to more aggressive screening practices in African-American men in the United States is unclear.

Several studies have investigated the association between MetS and development of PCa in a population at risk rather than the general population. In a cohort of 195 men with a median age of 69 years undergoing transrectal ultrasound-guided biopsies for PSA ≥ 4 or an abnormal DRE, De Nuncio *et al*[28] reported an increased risk of high-grade disease in those with MetS (OR, 3.82; 95%CI: 1.33-10.9)[28]. A similar association between MetS and high-grade disease was demonstrated in another study of 2,408 men with a median age of 68 years undergoing biopsies (OR, 1.75; 95%CI: 1.26-2.41)[29]. Conversely, Jeon *et al*[30] observed a decreased risk of Gleason grade ≥ 7 (OR, 0.101; 95%CI: 0.022-0.473) as well as a lower Gleason grade of 6.63 ± 1.92 in men with MetS compared to 7.54 ± 1.71 in men without MetS[30]. Antonio *et al*[31] also reported that men with MetS and widespread high-grade prostatic intraepithelial neoplasia in ≥ 4 cores had an increased risk of PCa on repeat biopsy in 6 mo (57.4% *vs* 23.5%). However, there is a potential for selection bias in these studies, as primary care providers and urologists are more likely to have a higher threshold for referral and biopsy, respectively, in men with multiple medical comorbidities.

A recent pooled analysis of studies between 2004 and 2007 demonstrated a 54% increased risk (95%CI: 1.23-1.94) of developing PCa in men with any 3 components of MetS[32]. A meta-analysis of 19 studies, though, did not confirm an association between MetS and overall risk of PCa (RR, 0.96; 95%CI: 0.85-1.09) but observed an increased risk of high-grade (RR, 1.44; 95%CI: 1.2-1.72) and advanced (RR, 1.37; 95%CI: 1.12-1.68) disease[33]. However, the findings of these studies are difficult to compare due to their different designs, particularly concerning the dissimilar populations with different rates of PCa, variable screening practices, use of various and modified criteria for MetS, and exclusion of certain risk factors or diabetic men. All of these studies are also retrospective or observational with inconsistent consideration of certain confounding variables. Lastly, only a few studies consider both MetS and its individual components, which appear to be differently associated with PCa. It is therefore difficult to conclude an association between MetS and development of PCa with any certainty.

**COMPONENTS OF THE METABOLIC SYNDROME AND RISK OF PROSTATE CANCER**

Several authors have suggested that it may not be adequate to consider MetS as an individual entity but rather as a product of the separate and combined effects of its components[19].

***Obesity***

Several studies have reported an increased risk of PCa in obese men, while others have demonstrated either a null or even an inverse association between obesity and development of PCa. Due to these equivocal findings, MacInnis and English performed a meta-analysis of 31 cohort and 25 case-control studies and observed an increased risk of 5% (95%CI: 1.01-1.08) for each 5 kg/m2 increase in BMI. A sub-group analysis of only studies reporting the stage of disease demonstrated a stronger association for advanced disease (RR, 1.12 per 5 kg/m2 increment; 95%CI: 1.01-1.23) compared to localized disease (RR, 0.96 per 5 kg/m2 increment; 95%CI: 0.89-1.03)[34]. Several large cohort studies and a more recent meta-analysis have subsequently confirmed these findings by observing an increased risk of high-grade and advanced disease as well as a decreased risk of low-grade and localized disease in obese men[35-38].

Various theories have been proposed for the differential influence of obesity on the risk of PCa. Some authors have suggested an inherent difference in the aggressiveness of PCa due to lower testosterone levels in obese men[39]. Others have argued that a bias against the detection of PCa leads to its delayed diagnosis due to difficulty with DRE, lower serum PSA levels, and a larger prostatic size in obese men. Despite the anecdotal reports of difficulty with DRE in obese men, Price *et al*[40] failed to demonstrate any association between BMI and findings on DRE in men being screened for PCa. Alternatively, a number of studies have observed an inverse relationship between BMI and PSA, which may lead to delayed biopsies due to lower serum PSA levels in obese men[39]. This relationship is thought to be related to lower testosterone levels and/or a hemodilutional effect on serum PSA concentrations from greater plasma volumes in obese men[41,42]. Two studies have also reported a larger prostatic size in obese men, which may decrease the likelihood of detection due to sampling error[43,44].

***Dyslipidemias***

Many studies have investigated the association between dyslipidemias and PCa since the initial finding that a cholesterol-lowering diet may increase the risk of various cancers and cancer-specific mortality in 1971[45]. The findings of earlier studies have largely been equivocal and unable to differentiate whether low cholesterol levels are the cause or effect of PCa. More recent evidence seems to favor an increased risk of PCa in men with various derangements of lipid metabolism[46].

In a nested case-control study of 698 men between 40 and 75 years of age participating in the Health Professionals Follow-up Study, Platz *et al*[47] demonstrated a decreased risk of high-grade PCa for men in the bottom quartile for TC level (OR, 0.61; 95%CI: 0.39-0.98). Several large cohort studies have subsequently confirmed these findings and further observed an increased risk of high-grade disease, advanced disease, and cancer-specific mortality in men with high TC levels[48-52]. Conversely, Van Hemelrijck *et al*[53] failed to report an association between TC levels and development of PCa in a cohort of 200660 men participating in the Swedish Apolipoprotein Mortality Risk Study. These authors noted that the associations between various components of MetS and PCa may be altered by non-cancer-related mortality due to the competing risk of premature cardiovascular death before the development of PCa. They suggested that the association between high glucose levels and decreased incidence of PCa may be overestimated, while the increased incidence of PCa in diabetic men with high triglyceride (TG) levels may be underestimated under a competing risk analysis[53].

Few studies have investigated the separate influence of HDL and low-density lipoprotein (LDL) cholesterol levels on the development of PCa. Van Hemelrijck *et al*[54] conducted a follow-up of their initial study and investigated the association between the individual components of the lipid profile and development of PCa. These authors demonstrated an increased risk for men in the lower quartile for HDL cholesterol and apolipoprotein A-I levels but no association between LDL cholesterol or apolipoprotein B levels and development of PCa[54]. In a cohort of 29,093 men between 50 and 69 years of age participating in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Mondul *et al*[51] observed a similar trend toward a decreased risk of PCa in men with higher HDL cholesterol levels, which persisted across all grades and stages[51]. A cohort study of 2842 Dutch men also reported an association between higher HDL cholesterol levels and non-aggressive PCa (HR, 4.28; 95%CI: 1.17-15.67) as well as an increased risk of PCa in men with higher LDL cholesterol levels (HR, 1.42; 95%CI: 1-2.02)[55]. Conversely, Jacobs *et al*[56] failed to demonstrate an association between HDL or LDL cholesterol levels and risk of aggressive PCa in a cohort of 14241 men between 50 and 79 years of age within the Cancer Prevention Study II Nutrition Cohort. Only 6% of these men, however, met the ATPIII criteria for high LDL cholesterol levels. This proportion of men with high LDL cholesterol levels was much lower than in other studies, which may account for its conflicting results[56].

As previously discussed, Van Hemelrijck *et al*[53] reported that high TG levels were associated with an increased risk of PCa, but only in men with high glucose levels. Hayashi *et al*[57] also demonstrated an association between TG levels and development of PCa in a cohort of 905 men undergoing biopsies. This association was strengthened in men between 60-69 years of age (OR, 2.1; 95%CI: 1.31-3.37) and ≥ 70 years of age (OR, 1.91, 95%CI: 1.03-3.53), both of whom also had an increased risk of high-grade disease[57]. Several studies have supported these findings, while others have observed either a null or even an inverse association between TG levels and development of PCa but generally included a younger population of men ≤ 60 years of age[15,17,18,58-60]. In addition to age, the frequent co-occurrence of high TG levels and DM is thought to be a confounding factor that accounts for these conflicting results[17,32].

***High blood pressure***

The association between hypertension and development of PCa has not been as thoroughly investigated as other components of MetS but is thought to be related to the effect of sympathetic nervous activity on the androgen-mediated growth of prostatic tissue[61]. As previously discussed, several cohort studies have reported an increased risk of PCa in men with hypertension, including the 2nd Nord Trøndelag Health, Olmsted County, and Flint Men’s Health Studies[18,19,26]. The latter 2 studies actually demonstrated that hypertension was the only component of MetS associated with an increased risk[18,19]. However, the remaining evidence is limited and warrants further investigation.

***High fasting glucose***

There is a large body of evidence supporting an inverse association between DM and development of PCa. Several meta-analyses have observed a decreased risk of PCa in diabetic men with pooled RRs of 0.91 (95%CI: 0.86-0.96), 0.84 (95%CI: 0.76-0.93), and 0.86 (95%CI: 0.8-0.92)[62-64]. A more recent meta-analysis of 25 cohort and 12 case-control studies reported a similar association through a subgroup analysis of population-based studies (RR, 0.72; 95%CI: 0.64-0.81), cohort studies from the United States (RR, 0.79; 95%CI: 0.73-0.86), and studies with follow-up of greater than 5 years. Diabetic men on insulin were also noted to have a decreased risk of PCa in all studies included in this meta-analysis[65]. These findings suggest that the inverse relationship between DM and development of PCa is strengthened over time. There is a corresponding natural history for DM that begins with a rise in glucose and insulin levels followed by the development of insulin resistance and decline in insulin levels due to damaged pancreatic beta cells.

Various theories have been proposed for the inverse association between DM and development of PCa. Some authors have suggested a causal effect from the decreasing levels of hormones and other cancer-related mitogens such as insulin-like growth factor-1. Others have argued for a bias against the detection of PCa due to less health-care seeking behavior, lower serum PSA levels, and a larger prostatic size in diabetic men[66]. As previously discussed, a delayed diagnosis of PCa may lead to an increased risk of more aggressive disease in obese men. Several studies have indeed demonstrated an increased risk of high-grade and advanced disease in diabetic men undergoing biopsies and RP[67-73]. Interestingly, the association between DM and high-grade disease was only observed in obese Caucasian men in one of these studies and was strengthened in this population in another study[67,69].

**THE METABOLIC SYNDROME AND PATTERNS OF TREATMENT FOR PROSTATE CANCER**

Men with MetS are often perceived as poor surgical candidates due to a concern for an increased risk of perioperative complications, increased technical difficulty with surgery, and poorer outcomes. These concerns may affect the counseling of these men and their resulting treatment, regardless of whether they are well-founded. There is only limited evidence on the influence of obesity on the patterns of treatment for PCa. When investigating the choice of treatment in men newly diagnosed with PCa, Davies *et al*[74] reported that obese men were more likely to receive a non-surgical therapy, such as AS, external-beam radiation therapy (EBRT), brachytherapy, or androgen deprivation therapy (ADT). Men with BMI ≥ 35 k/m2, in particular, were more likely to receive brachytherapy (OR, 1.59; 95%CI: 1.01-2.52) or ADT (OR, 1.77; 95%CI: 1.12-2.81) alone[74].

**THE METABOLIC SYNDROME AND ONCOLOGIC OUTCOMES FOR PROSTATE CANCER**

Emerging evidence has suggested that men with MetS or its individual components may have a poorer oncologic outcome after their treatment for PCa.

***Radical prostatectomy***

In a study of over 4000 men with a median age of 61 years undergoing robot-assisted laparoscopic radical prostatectomy (RALP), Kheterpal *et al*[75] demonstrated a higher pathologic Gleason grade and stage as well as a greater upgrading of Gleason grade 6 disease in men with MetS compared to best-matched controls. However, the prostatic volumes were not included in this study, and a larger prostatic size in obese men may account for these findings due to an increased sampling error at biopsy[75]. Another study of 261 men with a mean age of 64.5 years undergoing RP observed an increased tumor volume in those with MetS (6.6 ± 5.5 mL *vs* 5 ± 4.5 mL) but no differences in any other histopathologic features[76]. Castillejos-Molina *et al*[77] further reported that MetS was associated with an increased risk of biochemical recurrence (BCR) in men with a median age of 64.8 years undergoing RP. MetS was the strongest predictor of BCR on multivariate analysis (OR, 2.73; 95%CI: 1.65-4.5), although men with MetS had a significantly higher proportion with Gleason grade > 7 on biopsy and pathologic stage T3a-b. Therefore, the increased risk of BCR in men with MetS may have been due to selection bias with only those with high-risk disease undergoing RP. When confining their analysis to men with organ-confined disease, the 5- and 10-year BCR-free survival was 55% and 48% for those with MetS compared to 80% and 73% for those without MetS, respectively. There was still a strong association between MetS and BCR in this subgroup (OR, 3.42; 95%CI: 1.68-7.01)[77]. Post *et al*[78] also demonstrated a 50% increase in the rate of BCR after RP in men with MetS. This finding was primarily influenced by the effect of hypertension, which conferred an approximately 2-fold increased risk of BCR and was the only consistent association among all components of MetS[78]. A similar association for hypertension was observed in another study of 1428 men with a mean age of 59.1 years undergoing RP[79]. Most recently, Kwon *et al*[80] failed to report any differences in the operative parameters, histopathologic features, or functional outcomes of men with MetS undergoing RALP, except for an increased blood loss (OR, 1.592; 95%CI: 1.15-2.21)[80].

The oncologic outcomes after RP have been most thoroughly investigated in obese men. Several studies have demonstrated an increased risk of BCR after RP independent of adverse clinicopathologic features in obese men. Two recent meta-analyses confirmed these findings by observing a 25% (95%CI: 1.12-1.4) and 16% (95%CI: 1.08-1.24) increased risk of BCR for each 5 kg/m2 increase in BMI[81,82]. Additional studies have also suggested an increased technical difficulty for all techniques of RP in obese men with increased operative times, estimated blood loss, complications, and positive surgical margins; while others have reported no differences in these operative parameters and demonstrated an increased risk of BCR independent of surgical margin status and in men with organ-confined disease. It therefore remains unclear whether the increased risk of BCR after RP is related to an increased technical difficulty, inherently more aggressive disease, or both in obese men[39].

The oncologic outcomes after RP have also been investigated in diabetic men. Two studies have failed to observe an association between DM and risk of BCR after RP[67,83]. Interestingly, the latter study reported an increased risk of BCR after RP (HR, 2.52; 95%CI: 1.4-4.54) only in obese, Caucasian men with DM[67]. This group subsequently performed a study of 2083 United States veterans with a median age of 61 years and again demonstrated that DM was only associated with the development of metastatic disease after RP (HR, 2.8; 95%CI: ) in obese men, despite receiving a more aggressive secondary treatment[84].

***Radiation therapy***

As with RP, a number of studies have observed that BMI is an independent predictor of BCR after EBRT and associated with a decreased PCa-specific survival. These findings are thought to be related to the greater daily variation in the location of the prostate and resulting loss of precision in the designated field of radiation in obese men[85-87]. One study also reported an increased risk of BCR in obese men with a median age of 61 years undergoing salvage EBRT therapy after RP[88]. In the absence of surgical pathology to confirm the grade and stage of disease, it is unclear whether a more aggressive disease accounts for these poorer outcomes in obese men undergoing EBRT. Furthermore, the demonstrated hemodilution of PSA in obese men may create the potential for these men being under risk-stratified and undergoing a less aggressive primary treatment with a shorter or absent regimen of ADT.

Conversely, brachytherapy appears to be feasible and effective in obese and diabetic men based on limited evidence. Several studies have failed to observe an association between BMI or DM and risk of BCR after brachytherapy[89-92].

***Androgen deprivation therapy***

While the development and exacerbation of MetS in men on ADT has been thoroughly investigated, the association between MetS and oncologic outcomes on ADT has not. Two studies have reported that obesity is an independent predictor of BCR and PCa-specific mortality after combined EBRT and ADT, while Keto *et al*[93] demonstrated an increased risk of metastatic disease as well as a trend toward an increased risk of progression to castration-resistant disease and decreased cancer-specific survival in men undergoing ADT after RP[93-95]. Only 1 study has investigated the oncologic outcomes of men on primary ADT alone. Flanagan *et al*[96] observed a shorter time to PSA progression in men with MetS, who were treated with luteinizing hormone-releasing hormone agonists for BCR after a definitive local therapy or newly diagnosed metastatic PCa (16 *vs* 36 mo). These authors also reported a shorter time to PSA progression for each component of MetS except for TG levels as well as a decreased overall survival in men with hypertension[96]. These studies suggest that men with MetS may have a poorer response to ADT. The mechanism behind this relationship has not been elucidated but may be related to an excess level of estrogens, particularly in obese men. Estrone, estradiol, and free estradiol levels have all demonstrated a direct relationship with BMI, while lower testosterone levels have been observed in obese men[97]. Men with MetS may therefore be androgen-deprived at baseline and have an increased risk of progression to castration-resistant disease. Whether the levels of these hormones affect the progression to castration-resistant disease is unclear.

**THE METABOLIC SYNDROME AND POST-TREATMENT QUALITY OF LIFE**

Men with various components of MetS may have a worse quality of life (QoL) after their treatment for PCa.

***The metabolic syndrome***

There is no evidence on the association between MetS and post-treatment QoL for men with PCa. However, 2 recent studies have investigated the combined influence of vascular risk factors on recovery of erectile function after RP, EBRT, and brachytherapy. In a study of 984 men with a mean age of 59.6 years undergoing RP, Teloken *et al*[98] investigated the effect of vascular risk factors (hypertension, hypercholesterolemia, DM, coronary artery disease, and history of smoking) on recovery of erectile function after RP. These authors reported a worse recovery in men with ≥ 3 compared to 1 or 2 vascular risk factors at 24 mo postoperatively (*P* = 0.02) independent of age, erectile function before RP, and nerve-sparing status[98]. Wang *et al*[99] conducted a study of 732 men with a mean age of 65.3 years undergoing EBRT and/or brachytherapy with or without ADT over 4 years and similarly demonstrated an increasing incidence of ED with an increasing number of vascular comorbidities (hypertension, DM, hyperlipidemia)[99]. Although men with MetS have many of the same risk factors, it is unclear whether the findings of these studies may be extrapolated to this population.

***Obesity***

The current evidence on the QoL for obese men after their treatment for PCa is equivocal. Two studies have observed a delayed return of bowel function and increased bother after RP as well as a worse hormonal function after RP and radiation therapy in obese men[100,101]. Others have failed to report a consistent difference between obese and non-obese men in any domains of QoL after RP[102,103]. Several recent studies have specifically addressed the recovery of urinary incontinence and erectile function after RP in obese men. Their conflicting results have been difficult to compare due to the different designs of these studies and use of variable surgical approaches. There was also an inconsistent use of validated questionnaires and lack of consideration for certain confounding variables[104-117]. These studies collectively suggest that obese men may have a slightly worse perioperative QoL. However, the major predictor of post-treatment QoL remains their QoL prior to the initiation of therapy. The current evidence is insufficient to recommend any particular treatment in obese men based on their post-treatment QoL.

***High fasting glucose***

The current evidence on the QoL for diabetic men after their treatment for PCa is much more robust. Latini *et al*[118] demonstrated a worse urinary function after RP in both diabetic and obese men. These authors further observed that the combined influence of DM and obesity may be greater than either alone[118]. Thong *et al*[119] also reported a worse urinary and sexual function as well as a worse general health-related QoL after all types of treatment in men with pre-existing DM compared to those with incident DM diagnosed after PCa and without DM[119]. Additional studies have demonstrated an association between DM and the development of ED after both EBRT and brachytherapy[120-122]. Most importantly, a growing body of evidence has established DM as a risk factor for the development of complications after radiation therapy. Several studies have observed an increased risk of ≥ grade 2 late gastrointestinal and genitourinary complications after EBRT in diabetic men based on the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scale[123-127]. As with obesity, the current evidence is insufficient to recommend any particular treatment in diabetic men based on their post-treatment QoL. However, it is recommended that diabetic men be counseled about a potentially increased risk of complications after radiation therapy and be considered for the modification of its planning and delivery.

**THE METABOLIC SYNDROME AND PROSTATE CANCER-SPECIFIC MORTALITY**

Emerging evidence has suggested an association between MetS and PCa-specific mortality. A recent meta-analysis pooled the findings of 3 cohort studies and reported an increased risk of PCa-specific mortality in men with MetS (RR, 1.12; 95%CI: 1.02-1.23)[33].

The risk of PCa-specific mortality has been most thoroughly investigated in obese men. Several studies have demonstrated that BMI is an independent predictor of PCa-specific mortality among obese men in a population-based cohort and those diagnosed with PCa. A recent meta-analysis of 12 studies confirmed these findings by observing a 16% increased risk of PCa-specific mortality in cohort studies (95%CI: 1.06-1.25) and a 20% increased risk in studies investigating the post-diagnosis survival (95%CI: 0.99-1.46) for each 5 kg/m2 increase in BMI[81]. Although a bias against the detection of PCa may account for the increased risk of PCa-specific mortality in obese men, 2 studies reported a similar association before the introduction of PSA-based screening[128,129].

There is only limited evidence that men with other components of MetS have an increased risk of PCa-specific mortality. In a cohort of 17934 men between 40 and 69 years of age participating in the Whitehall study, Batty *et al*[50] demonstrated an increased risk of PCa-specific mortality for men in the upper tertile for TC levels over a period of 4 decades (HR, 1.35; 95%CI: 1.11-1.65)[50]. Only 1 study has similarly observed an increased risk of PCa-specific mortality in men with hypertension[20]. A recent meta-analysis also identified 4 studies investigating the association between DM and PCa-specific mortality, only 1 of which reported an increased risk. There was insufficient evidence to perform a formal meta-analysis of these studies. However, the authors identified 7 additional studies investigating the non-PCa or long-term, overall mortality and conducted a preliminary meta-analysis from 4 of these studies, which demonstrated an increased risk of overall mortality in diabetic men (HR, 1.57; 95%CI: 1.12-2.2)[130].

**THE METABOLIC SYNDROME AND PREVENTION OF PROSTATE CANCER**

With the growing body of evidence on the association between MetS and PCa, the management of MetS has become a potential target for the prevention of PCa and improvement of outcomes among diagnosed men. Based on recommendations from the AHA and NHLBI, the primary emphasis on the management of MetS is to mitigate the modifiable risk factors of obesity and physical inactivity through dietary and lifestyle-related changes. The addition of pharmacologic treatment is a secondary consideration for patient at particularly high risk of cardiovascular disease and DM[9].

***Weight loss***

A majority of the evidence on the effect of weight loss and other dietary interventions on the risk of PCa is derived from animal studies. Several studies have observed a decreased risk in the development and progression of PCa in animals on a caloric restricted diet that is low in fats or carbohydrates[131].

Several studies have investigated the influence of weight change on the development and progression of PCa in humans, only a few of which focused on weight loss. The most intriguing of these studies is the Prostate Cancer Lifestyle Trial, which is a RCT of men with PCa on AS. These men had a Gleason grade < 7 on biopsy, PSA between 4 and 10 ng/mL, and clinical stage T1-2 disease. They were randomly assigned to either a program that included a vegan diet, several nutritional supplements, moderate aerobic exercise (30 min of walking on 6 d per week), and various techniques for stress management or no intervention. Those in the experimental group reduced their weight by 4.5 kg and had a 4% decrease in serum PSA levels compared to a 6% increase in the control group (*P* = 0.016) after 1 year. The growth of LNCaP cells was also inhibited by serum from the experimental group by almost 8-fold more than the control group[132]. At 2 years, a significantly fewer number of men pursued a conventional treatment for PCa in the experimental compared to the control groups (5% *vs* 27%)[133].

Several other trials have investigated the effect of various dietary and lifestyle-related interventions on a variety of biomarkers associated with PCa and its prevention. Freedland *et al*[131] recently published an excellent review on this subject. These trials generally reported that a low-fat and/or carbohydrate diet accompanied by weight loss may alter the tumor biology of PCa[131]. Larger studies with longer follow-up and assessment of clinical outcomes are necessary to determine the significance of these findings.

***Physical activity***

Physical activity has been increasingly recognized as a modifiable risk factor that may play a role in the prevention of many cancer, including PCa[134]. The mechanism behind this relationship remains unknown but is thought to be related to enhancing the immune system and altering the levels of various endogenous hormones associated with PCa, including androgens, insulin, insulin-like growth factors, and testosterone. Physical activity also assists in weight control and prevention of MetS, which may be associated with an increased risk of PCa. The findings of studies investigating the influence of physical activity on the risk of PCa have been equivocal. A recent meta-analysis of 19 cohort and 24 case-control studies demonstrated that total physical activity was associated with a small but significantly decreased risk of PCa (pooled RR, 0.9; 95%CI: 0.84-0.95). A sub-group analysis based on the type of physical activity observed a decreased risk of 19% (95%CI: 0.89-0.97) for occupational and 5% (95%CI: 0.89-1) for recreational physical activity. The risk reduction for total physical activity was reported in men between 20 and 45 years of age (pooled RR, 0.93; 95%CI: 0.89-0.97) as well as between 45 and 65 years of age (pooled RR, 0.91; 95%CI 0.86-0.97)[135]. The use of various methods to quantify the level of physical activity in these studies precluded the identification of a dose-response relationship or threshold of physical activity required for preventing PCa. There was also not any available data on the levels of various endogenous hormones associated with PCa.

***Chemoprevention***

The most thoroughly investigated and promising medication has been 3-hydroxyl-3-methylglutaryl-Coenzyme A reductase inhibitors (also known as statins). Our group recently published a review on this subject[136]. While there does not appear to be an association with the overall risk of PCa, several cohort studies and a meta-analysis have demonstrated a decreased risk of advanced disease in men taking statins[137-140]. Additional studies have investigated the oncologic outcomes of men taking statins after their treatment for PCa with conflicting results. Several recent meta-analyses have failed to observe an association between the use of statins and risk of BCR after RP with pooled RRs of 1.02 (95%CI: 0.8-1.29), 1 (95%CI: 0.8-1.19), and 1.05 (95%CI: 0.9-1.240)[141-143]. Studies of men undergoing EBRT were also included in the latter 2 meta-analyses. Scosyrev *et al*[142] failed to report an association with BCR after EBRT or any definitive local therapy, while Park *et al*[143] demonstrated an improved recurrence-free survival in their sub-group analysis of men undergoing EBRT (pooled HR, 0.68; 95%CI: 0.49-0.93). These findings may support the radiosensitizing effect of statins that has been observed in both *in vitro* and *in vivo* models[142,143].

Many other medications and dietary supplements targeting various components of MetS have been investigated. One particularly noteworthy medication is metformin, an oral biguanide medication used as a first-line treatment for type 2 DM. It is inexpensive, widely available, and thought to have an antineoplastic effect for various cancers. However, the current evidence on its association with the development and progression of PCa is equivocal. Several studies have reported a decreased risk of PCa and high-grade disease in diabetic men taking metformin as well as a decreased risk of progression, overall mortality, and PCa-specific mortality in those diagnosed with PCa[144-147]. In a study of 2901 men with a median age of 69 years undergoing EBRT, Spratt *et al*[148] also demonstrated a decreased risk of developing castration-resistant disease as well as an improved overall, BCR-free, distant metastases-free, and PCa-specific survival in diabetic men taking metformin[148]. Other studies have failed to observe an association between the use of metformin and development of PCa or BCR after RP in diabetic men[149-154]. Most recently, Rothermundt *et al*[155] performed a prospective clinical trial of 44 men with metastatic castration-resistant PCa on metformin and reported a stabilization of disease in 36% of men at 12 wk and 9.1% at 24 wk. These authors also demonstrated a prolongation of PSA doubling time in 52.3% of men after starting metformin[155].

***Recommendations***

The current evidence on the benefits of weight loss, physical activity, and medications like statins and metformin is encouraging but preliminary and requires further investigation before providing an specific recommendations. Nevertheless, it is important to recommend maintaining a desirable weight, engaging in regular exercise, and consuming a cardiovascular healthy diet to all patients. These interventions will improve their overall health and reduce their risk of cardiovascular disease, which is the primary cause of mortality among men in the US[156].

**CONCLUSION**

Emerging evidence has suggested an association between MetS and PCa. Many studies have observed that men with MetS or its individual components have an increased risk of more aggressive disease and mortality as well as a poorer outcome after their treatment for PCa, while others have not. These men may benefit from weight loss, physical activity, and the addition of medications like statins for preventing PCa as well as improving their oncologic outcomes and QoL after treatment. There is a paucity of RCTs with a majority of the existing evidence being retrospective or observational in nature. Potential biases such as screening practices, serum PSA level, or choice of treatment may therefore account for the findings of these studies. Lastly, only a few studies consider both MetS and its individual components. MetS is a complex disease with a poorly understood interplay among its individual components, which appear to be differently associated with PCa.

The association between MetS and PCa is a particularly attractive and fruitful area of research, given the increasingly aging population and epidemic proportions of both diseases. There is also a need for the identification of risk factors for the development and progression of PCa. Further research is necessary to corroborate the findings of earlier studies and to better define the separate and combined influence of the individual components of MetS on PCa. A majority of the existing evidence is retrospective or observational, which is subject to bias. More RCTs are needed to investigate the effect of dietary and lifestyle-related changes as well as chemopreventitive medications on the risk of PCa and oncologic outcomes after treatment. Further research should also focus on the molecular pathways involved in MetS as well as the development and progression of PCa. A better understanding of these pathways will facilitate the development of novel therapeutic targets for the prevention and treatment of PCa.

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**Table 1 Joint criteria for clinical diagnosis of the metabolic syndrome1**

|  |  |
| --- | --- |
| **Component** | **Threshold** |
| Abdominal obesity | Sex- and population-specific waist circumference based on definitions established by IDF and AHA/NHLBI [8,9] |
| Dyslipidemias (or pharmacologic treatment)  High triglycerides  and/or  Low high-density lipoprotein  cholesterol | ≥ 150 mg/dL  < 40 mg/dL in males  < 50 mg/dL in females |
| High blood pressure (or pharmacologic treatment) | Systolic ≥ 130 mm Hg  and/or  Diastolic ≥ 85 mm Hg |
| High fasting glucose (or pharmacologic treatment) | ≥100 mg/dL |

1Must have 3 of the following 5 components.IDF: International Diabetes Federation; AHA/NHLBI: American Heart Association/National Heart, Lung, and Blood Institute.

**Table 2 Summary of studies on the association between the metabolic syndrome and prostate cancer**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Association** | Positive | Positive | Positive | Inverse | Positive | Positive | Null | Null |
| **Findings** | Increased risk of clinical stage T3 and high-grade disease with various components | Increased risk (RR, 1.9; 95%CI: 1.1-3.5) | Increased risk (RR, 1.56; 95%CI: 1.21-2.0) | Decreased risk (RR, 0.77; 95%CI: 0.6-0.98) | Increased risk with high BMI, SBP, low HDL-C, vitamin D (OR, 8.03; 95%CI: 1.89-34.09) | Increased risk in AA men with 2 components (OR, 1.76; 95%CI: 1.1-2.83) | No association (RR, 0.93; 95%CI: 0.75-1.14) | No association (HR, 0.76; 95%CI: 0.47-1.22) |
| **Criteria for MetS** | N/A | Modified WHO | Modified ATP III | ATP III | N/A | Modified ATP III | Treated for MetS | Modified IDF |
| **Number of PCa cases** | 299 | 56 | 507 | 385 | 132 | 139 | 94 | 119 |
| **Size of cohort** | 299 | 1880 | 15933 | 6429 | 588 | 498 | 16677 | 9548 |
| **Time period** | 1995-2002 | 1984-2001 | 1972-1998 | 1987-2000 | 1981-1997 | 1996-2002 | 1999-2005 | 1993-2004 |
| **Population** | Referrals with PCa | Kuopio communities | Oslo Study | ARIC Study | Helsinki Heart Study | Flint Men’s Health Study | Men treated for MetS | Japan Public Health Center-based Prospective Study |
| **Country** | Sweden | Finland | Norway | USA | Finland | USA | Italy | Japan |
| **Design** | Cross-sectional | Longitudinal Population-based cohort | Longitudinal Population-based cohort | Longitudinal Population-based cohort | Longitudinal nested case-control | Longitudinal case-control | Longitudinal Population-based cohort | Longitudinal Population-based cohort |
| **Authors, year** | Hammarsten *et al*[13], 2004 | Laukkanen *et al*[14], 2004 | Lund Håheim *et al*[15], 2006 | Tande *et al*[17], 2006 | Tuohimaa *et al*[21], 2007 | Beebe-Dimmer *et al*[26], 2007 | Russo *et al*[23], 2008 | Inoue *et al*[24], 2009 |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Association** | Positive | Null | Positive | Positive | Null | Positive | Null | Positive |
| **Findings** | Increased risk of organ-confined disease in AA men (OR, 1.82; 95%CI: 1.02-3.23) | No association (HR, 0.91; 95%CI: 0.77–1.09) | Increased risk only under competing risk analysis | Increased risk of high-grade disease (OR, 3.82; 95%CI: 1.33-10.9) | No association (HR, 0.81; 95%CI: 0.2-3.3) | Increased risk (OR, 1.66; 95%CI: 1.22-2.28) | No association based on any criteria | Increased risk of high-grade disease (OR, 0.101; 95%CI: 0.022-0.473) |
| **Criteria for MetS** | Modified ATP III | Modified ATP III | ATP III, modified IDF | ATP III | Modified WHO | Joint criteria | Modified WHO, ATP III, IDF | ATP III |
| **Number of PCa cases** | 637 | 687 | 237 | 83 | 206 | 6,673 | 152 | 90 |
| **Size of cohort** | 881 | 29364 | 2,322 | 195 | 2445 | 289866 | 8239 | 354 |
| **Time period** | 2001-2004 | 1995-2005 | 1970-2003 | 2009-2010 | 1990-2005 | 1991-2002 | 1992-2007 | 2003-2011 |
| **Population** | GECAP Study | 2nd Nord Trøndelag Health Study | Uppsala Longitudinal Study of Adult Men | Men with PSA ≥ 4 or abnormal DRE | Olmsted County Study | Men admitted to participating hospitals | General health examinees in Tottori Prefecture | Men with PSA ≥ 4 or abnormal DRE |
| **Country** | United States | Norway | Sweden | Italy | United States | Italy | Japan | South Korea |
| **Design** | Longitudinal case-control | Longitudinal Population-based cohort | Longitudinal Population-based cohort | Cross-sectional | Cross-sectional | Longitudinal case-control | Longitudinal Population-based cohort | Cross-sectional |
| **Ref.** | Beebe-Dimmer *et al*[27], 2009 | Martin *et al*[18], 2009 | Grundmark *et al*[16], 2010 | De Nunzio *et al*[28], 2011 | Wallner *et al*[19], 2011 | Pelucchi *et al*[22], 2011 | Osaki *et al*[25], 2012 | Jeon *et al*[30], 2012 |

|  |  |  |  |
| --- | --- | --- | --- |
| **Association** | Positive | Positive | Positive |
| **Findings** | Increased risk of PCa-specific mortality with increased composite metabolic factors (RR 1.13; 95% CI, 1.03-1.25) | Increased risk of high-grade disease (OR, 1.75; 95%CI: 1.26-2.41) | Increased risk with widespread HGPIN (57.4% *vs* 23.5%) |
| **Criteria for MetS** | Modified ATP III | ATP III | ATP III |
| **Number of PCa cases** | 6673 | 848 | 42 |
| **Size of cohort** | 289866 | 2408 | 161 |
| **Time period** | 1972-2006 | 2006-2010 | 2004-2011 |
| **Population** | Metabolic syndrome and Cancer project | Men with PSA ≥ 4 or abnormal DRE | Men with HGPIN |
| **Country** | Norway, Sweden, Austria | Spain | Italy |
| **Design** | Longitudinal Population-based cohort | Cross-sectional | Cross-sectional |
| **Ref.** | Häggström *et al*[20], 2012 | Morote *et al*[29], 2013 | Cicione *et al*[31], 2014 |

PCa: Prostate cancer; MetS: Metabolic syndrome; N/A: Not applicable; WHO: World Health Organization; RR: Risk ratio; CI: Confidence intervals; ATP: Adult treatment panel; ARIC: Atherosclerosis risk in communities; OR: Odds ratio; AA: African-American; GECAP: Genes environment and prostate cancer; IDF: International diabetes federation; PSA: Prostate-specific antigen; HR: Hazard ratio; HGPIN: High-grade prostatic intraepithelial neoplasia.