Metabolic syndrome in the development and progression of prostate cancer

Andrew C Strine, Kevin R Rice, Timothy A Masterson

Andrew C Strine, Kevin R Rice, Timothy A Masterson, Department of Urology, Indiana University School of Medicine, Indianapolis, IN 46202, United States
Author contributions: Strine AC, Rice KR and Masterson TA contributed to this work; Strine AC wrote this manuscript.
Correspondence to: Andrew C Strine, MD, Department of Urology, Indiana University School of Medicine, 535 N. Barnhill Drive, Suite 150, Indianapolis, IN 46202, United States. astrine@iupui.edu
Telephone: +1-317-9487560 Fax: +1-317-9440174
Received: March 9, 2014   Revised: June 12, 2014
Accepted: July 12, 2014
Published online: November 24, 2014

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.

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.

Strine AC, Rice KR, Masterson TA. Metabolic syndrome in the development and progression of prostate cancer. *World J Clin Urol* 2014; 3(3): 168-183 Available from: URL: http://www.wjgnet.com/2219-2816/full/v3/i3/168.htm DOI: http://dx.doi.org/10.5410/wjcu.v3.i3.168

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.

Table 1 Joint criteria for clinical diagnosis of the metabolic syndrome[1]

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	≥ 150 mg/dL
Low high-density lipoprotein cholesterol	< 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

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

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 MetS, obesity, dyslipidemias, hypertension, diabetes mellitus, hyperglycemia, and insulin resistance combined with PCa. 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 METS

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 American Heart Association/National Heart, Lung, and Blood Institute (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 adult treatment panel (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 METS AND RISK OF PCA

It is well-established that the development and progression of PCa 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 United States 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 $\geq$ 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 metabolism, 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 $\geq$ 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 United States or Scandinavian countries with conflicting results. In a case-control study of 2745 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 PCa 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

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

Ref.	Design	Country	Population	Time period	Size of cohort	Number of PCa cases	Criteria for MetS	Findings	Association
Hammarsten *et al*[13]	Cross-sectional	Sweden	Referrals with PCa	1995-2002	299	299	N/A	Increased risk of clinical stage T3 and high-grade disease with various components	Positive
Laukkanen *et al*[14]	Longitudinal population-based cohort	Finland	Kuopio communities	1984-2001	1880	56	Modified WHO	Increased risk (RR = 1.9; 95%CI: 1.1-3.5)	Positive
Lund Håheim *et al*[15]	Longitudinal population-based cohort	Norway	Oslo study	1972-1998	15933	507	Modified ATP III	Increased risk (RR = 1.56; 95%CI: 1.21-2.0)	Positive
Tande *et al*[17]	Longitudinal population-based cohort	United States	ARIC study	1987-2000	6429	385	ATP III	Decreased risk (RR = 0.77; 95%CI: 0.6-0.98)	Inverse
Tuohimaa *et al*[21]	Longitudinal nested case-control	Finland	Helsinki heart study	1981-1997	588	132	N/A	Increased risk with high BMI, SBP, low HDL-C, vitamin D (OR = 8.03; 95%CI: 1.89-34.09)	Positive
Beebe-Dimmer *et al*[26]	Longitudinal case-control	United States	Flint Men's Health Study	1996-2002	498	139	Modified ATP III	Increased risk in AA men with 2 components (OR = 1.76; 95%CI: 1.1-2.83)	Positive
Russo *et al*[23]	Longitudinal population-based cohort	Italy	Men treated for PCa	1999-2005	16677	94	Treated for MetS	No association (RR = 0.93; 95%CI: 0.75-1.14)	Null
Inoue *et al*[24]	Longitudinal population-based cohort	Japan	Japan Public Health Center-based Prospective Study	1993-2004	9548	119	Modified IDF	No association (HR = 0.76; 95%CI: 0.47-1.22)	Null
Beebe-Dimmer *et al*[27]	Longitudinal case-control	United States	GECAP study	2001-2004	881	637	Modified ATP III	Increased risk of organ-confined disease in AA men (OR = 1.82; 95%CI: 1.02-3.23)	Positive
Martin *et al*[18]	Longitudinal population-based cohort	Norway	2nd Nord Trøndelag Health Study	1995-2005	29364	687	Modified ATP III	No association (HR = 0.91; 95%CI: 0.77-1.09)	Null
Grundmark *et al*[16]	Longitudinal population-based cohort	Sweden	Uppsala Longitudinal Study of Adult Men	1970-2003	2322	237	ATP III, modified IDF	Increased risk only under competing risk analysis	Positive
De Nunzio *et al*[28]	Cross-sectional	Italy	Men with PSA ≥ 4 or abnormal DRE	2009-2010	195	83	ATP III	Increased risk of high-grade disease (OR = 3.82; 95%CI: 1.33-10.9)	Positive
Wallner *et al*[19]	Cross-sectional	United States	Olmsted county study	1990-2005	2445	206	Modified WHO	No association (HR = 0.81; 95%CI: 0.2-3.3)	Null
Pelucchi *et al*[22]	Longitudinal case-control	Italy	Men admitted to participating hospitals	1991-2002	289866	6673	Joint criteria	Increased risk (OR = 1.66; 95%CI: 1.22-2.28)	Positive
Osaki *et al*[25]	Longitudinal population-based cohort	Japan	General health examinees in Tottori Prefecture	1992-2007	8239	152	Modified WHO, ATP III, IDF	No association based on any criteria	Null
Jeon *et al*[30]	Cross-sectional	South Korea	Men with PSA ≥ 4 or abnormal DRE	2003-2011	354	90	ATP III	Increased risk of high-grade disease (OR = 0.101; 95%CI: 0.022-0.473)	Positive
Häggström *et al*[20]	Longitudinal population-based cohort	Norway, Sweden, Austria	Metabolic Syndrome and Cancer Project	1972-2006	289866	6673	Modified ATP III	Increased risk of PCa-specific mortality with increased composite metabolic factors (RR = 1.13; 95%CI: 1.03-1.25)	Positive

Ref		Country	Design	Study period			Population	Criteria	Findings	Association
Morote *et al*[29]		Spain	Cross-sectional	2006-2010	2408	848	Men with PSA ≥ 4 or abnormal DRE	ATP III	Increased risk of high-grade disease (OR = 1.75; 95%CI: 1.26-2.41)	Positive
Cicione *et al*[31]		Italy	Cross-sectional	2004-2011	161	42	Men with HGPIN	ATP III	Increased risk with widespread HG-PIN (57.4% *vs* 23.5%)	Positive

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

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 digital rectal exam (DRE), De Nunzio *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 2408 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]. Cicione *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 METS AND RISK OF PCA

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 hemodilution 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 total cholesterol (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 29093 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 ATP III 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 radical prostatectomy (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 METS AND PATTERNS OF TREATMENT FOR PCA

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 active surveillance (AS), external-beam radiation therapy (EBRT), brachytherapy, or androgen deprivation therapy (ADT). Men with BMI $\geqslant$ 35 k/m^2, 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 METS AND ONCOLOGIC OUTCOMES FOR PCA

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 $\pm$ 5.5 mL *vs* 5 $\pm$ 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/m^2 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: 1.29-6.09) 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 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 mo *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 METS 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 MetS

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 ap-

proaches. 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 METS AND PCA-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/m^2 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 METS AND PREVENTION OF PCA

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 PCa Lifestyle Trial, which is a randomized control trial (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 United States[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 chemo-preventive 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.

REFERENCES

1   **Siegel R**, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin* 2011; **61**: 212-236 [PMID: 21685461 DOI: 10.3322/caac.20121]

2   **Hsing AW**, Devesa SS. Trends and patterns of prostate cancer: what do they suggest? *Epidemiol Rev* 2001; **23**: 3-13 [PMID: 11588851 DOI: 10.1093/oxfordjournals.epirev.a000792]

3   **Hsing AW**, Devesa SS, Jin F, Gao YT. Rising incidence of prostate cancer in Shanghai, China. *Cancer Epidemiol Biomarkers Prev* 1998; **7**: 83-84 [PMID: 9456247]

4   **Park SK**, Sakoda LC, Kang D, Chokkalingam AP, Lee E, Shin HR, Ahn YO, Shin MH, Lee CW, Lee DH, Blair A, Devesa SS, Hsing AW. Rising prostate cancer rates in South Korea. *Prostate* 2006; **66**: 1285-1291 [PMID: 16741923 DOI: 10.1002/pros.20419]

5   **Hsing AW**, Chokkalingam AP. Prostate cancer epidemiology. *Front Biosci* 2006; **11**: 1388-1413 [PMID: 16368524 DOI: 10.2741/1891]

6   **Alberti KG**, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; **15**: 539-553 [PMID: 9686693 DOI: 10.1002/(SICI)1096-9136(199807)15:7<5 39::AID-DIA668>3.0.CO;2-S]

7   **National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)**. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; **106**: 3143-3421 [PMID: 12485966]

8   **Alberti KG**, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. *Lancet* 2005; **366**: 1059-1062 [PMID: 16182882 DOI: 10.1016/S0140-6736(05)67402-8]

9   **Grundy SM**, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; **112**: 2735-2752 [PMID: 16157765 DOI: 10.1161/CIRCULATIONAHA.105.169404]

10 **Alberti KG**, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; **120**: 1640-1645 [PMID: 19805654 DOI: 10.1161/CIRCULATIONAHA.109.192644]

11 **Ervin RB**. Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003-2006. *Natl Health Stat Report* 2009; (**13**): 1-7 [PMID: 19634296]

12 **Cameron AJ**, Shaw JE, Zimmet PZ. The metabolic syndrome: prevalence in worldwide populations. *Endocrinol Metab Clin North Am* 2004; **33**: 351-375, table of contents [PMID: 15158523 DOI: 10.1016/j.ecl.2004.03.005]

13 **Hammarsten J**, Högstedt B. Clinical, haemodynamic, anthropometric, metabolic and insulin profile of men with high-stage and high-grade clinical prostate cancer. *Blood Press* 2004; **13**: 47-55 [PMID: 15083641 DOI: 10.1080/08037050310025735]

14 **Laukkanen JA**, Laaksonen DE, Niskanen L, Pukkala E, Hakkarainen A, Salonen JT. Metabolic syndrome and the risk of prostate cancer in Finnish men: a population-based study. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 1646-1650 [PMID: 15466982]

15 **Lund Håheim L**, Wisløff TF, Holme I, Nafstad P. Metabolic syndrome predicts prostate cancer in a cohort of middle-aged Norwegian men followed for 27 years. *Am J Epidemiol* 2006; **164**: 769-774 [PMID: 16952929 DOI: 10.1093/aje/kwj284]

16 **Grundmark B**, Garmo H, Loda M, Busch C, Holmberg L, Zethelius B. The metabolic syndrome and the risk of prostate cancer under competing risks of death from other causes. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 2088-2096 [PMID: 20647401 DOI: 10.1158/1055-9965.EPI-10-0112]

17 **Tande AJ**, Platz EA, Folsom AR. The metabolic syndrome is associated with reduced risk of prostate cancer. *Am J Epidemiol* 2006; **164**: 1094-1102 [PMID: 16968859 DOI: 10.1093/aje/kwj320]

18 **Martin RM**, Vatten L, Gunnell D, Romundstad P, Nilsen TI. Components of the metabolic syndrome and risk of prostate cancer: the HUNT 2 cohort, Norway. *Cancer Causes Control* 2009; **20**: 1181-1192 [PMID: 19277881 DOI: 10.1007/s10552-009-9319-x]

19 **Wallner LP**, Morgenstern H, McGree ME, Jacobson DJ, St Sauver JL, Jacobsen SJ, Sarma AV. The effects of metabolic conditions on prostate cancer incidence over 15 years of follow-up: results from the Olmsted County Study. *BJU Int* 2011; **107**: 929-935 [PMID: 20880183 DOI: 10.1111/j.1464-

20   **Häggström C**, Stocks T, Ulmert D, Bjørge T, Ulmer H, Hallmans G, Manjer J, Engeland A, Nagel G, Almqvist M, Selmer R, Concin H, Tretli S, Jonsson H, Stattin P. Prospective study on metabolic factors and risk of prostate cancer. *Cancer* 2012; **118**: 6199-6206 [PMID: 23090855 DOI: 10.1002/cncr.27677]

21   **Tuohimaa P**, Tenkanen L, Syvälä H, Lumme S, Hakulinen T, Dillner J, Hakama M. Interaction of factors related to the metabolic syndrome and vitamin D on risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 302-307 [PMID: 17301263 DOI: 10.1158/1055-9965.EPI-06-0777]

22   **Pelucchi C**, Serraino D, Negri E, Montella M, Dellanoce C, Talamini R, La Vecchia C. The metabolic syndrome and risk of prostate cancer in Italy. *Ann Epidemiol* 2011; **21**: 835-841 [PMID: 21982487 DOI: 10.1016/j.annepidem.2011.07.007]

23   **Russo A**, Autelitano M, Bisanti L. Metabolic syndrome and cancer risk. *Eur J Cancer* 2008; **44**: 293-297 [PMID: 18055193 DOI: 10.1016/j.ejca.2007.11.005]

24   **Inoue M**, Noda M, Kurahashi N, Iwasaki M, Sasazuki S, Iso H, Tsugane S. Impact of metabolic factors on subsequent cancer risk: results from a large-scale population-based cohort study in Japan. *Eur J Cancer Prev* 2009; **18**: 240-247 [PMID: 19491612 DOI: 10.1097/CEJ.0b013e3283240460]

25   **Osaki Y**, Taniguchi S, Tahara A, Okamoto M, Kishimoto T. Metabolic syndrome and incidence of liver and breast cancers in Japan. *Cancer Epidemiol* 2012; **36**: 141-147 [PMID: 21890443 DOI: 10.1016/j.canep.2011.03.007]

26   **Beebe-Dimmer JL**, Dunn RL, Sarma AV, Montie JE, Cooney KA. Features of the metabolic syndrome and prostate cancer in African-American men. *Cancer* 2007; **109**: 875-881 [PMID: 17265528 DOI: 10.1002/cncr.22461]

27   **Beebe-Dimmer JL**, Nock NL, Neslund-Dudas C, Rundle A, Bock CH, Tang D, Jankowski M, Rybicki BA. Racial differences in risk of prostate cancer associated with metabolic syndrome. *Urology* 2009; **74**: 185-190 [PMID: 19428088 DOI: 10.1016/j.urology.2009.03.013]

28   **De Nunzio C**, Freedland SJ, Miano R, Trucchi A, Cantiani A, Carluccini A, Tubaro A. Metabolic syndrome is associated with high grade gleason score when prostate cancer is diagnosed on biopsy. *Prostate* 2011; Epub ahead of print [PMID: 21360562 DOI: 10.1002/pros.21364]

29   **Morote J**, Ropero J, Planas J, Bastarós JM, Delgado G, Placer J, Celma A, de Torres IM, Carles J, Reventós J, Doll A. Metabolic syndrome increases the risk of aggressive prostate cancer detection. *BJU Int* 2013; **111**: 1031-1036 [PMID: 22883053 DOI: 10.1111/j.1464-410X.2012.11406.x]

30   **Jeon KP**, Jeong TY, Lee SY, Hwang SW, Shin JH, Kim DS. Prostate cancer in patients with metabolic syndrome is associated with low grade Gleason score when diagnosed on biopsy. *Korean J Urol* 2012; **53**: 593-597 [PMID: 23060995 DOI: 10.4111/kju.2012.53.9.593]

31   **Cicione A**, Cantiello F, De Nunzio C, Tubaro A, Damiano R. Patients with metabolic syndrome and widespread high grade prostatic intraepithelial neoplasia are at a higher risk factor of prostate cancer on re-biopsy: a prospective single cohort study. *Urol Oncol* 2014; **32**: 28.e27-28.e31 [PMID: 23273912 DOI: 10.1016/j.urolonc.2012.10.004]

32   **Hsing AW**, Sakoda LC, Chua S. Obesity, metabolic syndrome, and prostate cancer. *Am J Clin Nutr* 2007; **86**: s843-s857 [PMID: 18265478]

33   **Xiang YZ**, Xiong H, Cui ZL, Jiang SB, Xia QH, Zhao Y, Li GB, Jin XB. The association between metabolic syndrome and the risk of prostate cancer, high-grade prostate cancer, advanced prostate cancer, prostate cancer-specific mortality and biochemical recurrence. *J Exp Clin Cancer Res* 2013; **32**: 9 [PMID: 23406686 DOI: 10.1186/1756-9966-32-9]

34   **MacInnis RJ**, English DR. Body size and composition and prostate cancer risk: systematic review and meta-regression analysis. *Cancer Causes Control* 2006; **17**: 989-1003 [PMID: 16933050 DOI: 10.1007/s10552-006-0049-z]

35   **Gong Z**, Neuhouser ML, Goodman PJ, Albanes D, Chi C, Hsing AW, Lippman SM, Platz EA, Pollak MN, Thompson IM, Kristal AR. Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 1977-1983 [PMID: 17035408 DOI: 10.1158/1055-9965.EPI-06-0477]

36   **Rodriguez C**, Freedland SJ, Deka A, Jacobs EJ, McCullough ML, Patel AV, Thun MJ, Calle EE. Body mass index, weight change, and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 63-69 [PMID: 17179486 DOI: 10.1158/1055-9965.EPI-06-0754]

37   **Wright ME**, Chang SC, Schatzkin A, Albanes D, Kipnis V, Mouw T, Hurwitz P, Hollenbeck A, Leitzmann MF. Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. *Cancer* 2007; **109**: 675-684 [PMID: 17211863 DOI: 10.1002/cncr.22443]

38   **Discacciati A**, Orsini N, Wolk A. Body mass index and incidence of localized and advanced prostate cancer--a dose-response meta-analysis of prospective studies. *Ann Oncol* 2012; **23**: 1665-1671 [PMID: 22228452 DOI: 10.1093/annonc/mdr603]

39   **Buschemeyer WC**, Freedland SJ. Obesity and prostate cancer: epidemiology and clinical implications. *Eur Urol* 2007; **52**: 331-343 [PMID: 17507151 DOI: 10.1016/j.eururo.2007.04.069]

40   **Price MM**, Hamilton RJ, Robertson CN, Butts MC, Freedland SJ. Body mass index, prostate-specific antigen, and digital rectal examination findings among participants in a prostate cancer screening clinic. *Urology* 2008; **71**: 787-791 [PMID: 18267334 DOI: 10.1016/j.urology.2007.11.036]

41   **Bañez LL**, Hamilton RJ, Partin AW, Vollmer RT, Sun L, Rodriguez C, Wang Y, Terris MK, Aronson WJ, Presti JC, Kane CJ, Amling CL, Moul JW, Freedland SJ. Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. *JAMA* 2007; **298**: 2275-2280 [PMID: 18029831 DOI: 10.1001/jama.298.19.2275]

42   **Grubb RL**, Black A, Izmirlian G, Hickey TP, Pinsky PF, Mabie JE, Riley TL, Ragard LR, Prorok PC, Berg CD, Crawford ED, Church TR, Andriole GL. Serum prostate-specific antigen hemodilution among obese men undergoing screening in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 748-751 [PMID: 19258472 DOI: 10.1158/1055-9965.EPI-08-0938]

43   **Dahle SE**, Chokkalingam AP, Gao YT, Deng J, Stanczyk FZ, Hsing AW. Body size and serum levels of insulin and leptin in relation to the risk of benign prostatic hyperplasia. *J Urol* 2002; **168**: 599-604 [PMID: 12131317 DOI: 10.1016/S0022-5347(05)64687-3]

44   **Freedland SJ**, Platz EA, Presti JC, Aronson WJ, Amling CL, Kane CJ, Terris MK. Obesity, serum prostate specific antigen and prostate size: implications for prostate cancer detection. *J Urol* 2006; **175**: 500-504; discussion 504 [PMID: 16406980 DOI: 10.1016/S0022-5347(05)00162-X]

45   **Pearce ML**, Dayton S. Incidence of cancer in men on a diet high in polyunsaturated fat. *Lancet* 1971; **1**: 464-467 [PMID: 4100347 DOI: 10.1016/S0140-6736(71)91086-5]

46   **Solomon KR**, Freeman MR. The complex interplay between cholesterol and prostate malignancy. *Urol Clin North Am* 2011; **38**: 243-259 [PMID: 21798387 DOI: 10.1016/j.ucl.2011.04.001]

47   **Platz EA**, Clinton SK, Giovannucci E. Association between plasma cholesterol and prostate cancer in the PSA era. *Int J Cancer* 2008; **123**: 1693-1698 [PMID: 18646186 DOI: 10.1002/ijc.23715]

48   **Platz EA**, Till C, Goodman PJ, Parnes HL, Figg WD, Albanes D, Neuhouser ML, Klein EA, Thompson IM, Kristal AR. Men with low serum cholesterol have a lower risk of high-grade prostate cancer in the placebo arm of the prostate cancer prevention trial. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 2807-2813 [PMID: 19887582 DOI: 10.1158/1055-9965.

EPI-09-0472]

49 **Mondul AM**, Clipp SL, Helzlsouer KJ, Platz EA. Association between plasma total cholesterol concentration and incident prostate cancer in the CLUE II cohort. *Cancer Causes Control* 2010; **21**: 61-68 [PMID: 19806465 DOI: 10.1007/s10552-009-9434-8]

50 **Batty GD**, Kivimäki M, Clarke R, Davey Smith G, Shipley MJ. Modifiable risk factors for prostate cancer mortality in London: forty years of follow-up in the Whitehall study. *Cancer Causes Control* 2011; **22**: 311-318 [PMID: 21116843 DOI: 10.1007/s10552-010-9691-6]

51 **Mondul AM**, Weinstein SJ, Virtamo J, Albanes D. Serum total and HDL cholesterol and risk of prostate cancer. *Cancer Causes Control* 2011; **22**: 1545-1552 [PMID: 21915616 DOI: 10.1007/s10552-011-9831-7]

52 **Shafique K**, McLoone P, Qureshi K, Leung H, Hart C, Morrison DS. Cholesterol and the risk of grade-specific prostate cancer incidence: evidence from two large prospective cohort studies with up to 37 years' follow up. *BMC Cancer* 2012; **12**: 25 [PMID: 22260413 DOI: 10.1186/1471-2407-12-25]

53 **Van Hemelrijck M**, Garmo H, Holmberg L, Walldius G, Jungner I, Hammar N, Lambe M. Prostate cancer risk in the Swedish AMORIS study: the interplay among triglycerides, total cholesterol, and glucose. *Cancer* 2011; **117**: 2086-2095 [PMID: 21523720 DOI: 10.1002/cncr.25758]

54 **Van Hemelrijck M**, Walldius G, Jungner I, Hammar N, Garmo H, Binda E, Hayday A, Lambe M, Holmberg L. Low levels of apolipoprotein A-I and HDL are associated with risk of prostate cancer in the Swedish AMORIS study. *Cancer Causes Control* 2011; **22**: 1011-1019 [PMID: 21562751 DOI: 10.1007/s10552-011-9774-z]

55 **Kok DE**, van Roermund JG, Aben KK, den Heijer M, Swinkels DW, Kampman E, Kiemeney LA. Blood lipid levels and prostate cancer risk; a cohort study. *Prostate Cancer Prostatic Dis* 2011; **14**: 340-345 [PMID: 21727905 DOI: 10.1038/pcan.2011.30]

56 **Jacobs EJ**, Stevens VL, Newton CC, Gapstur SM. Plasma total, LDL, and HDL cholesterol and risk of aggressive prostate cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Causes Control* 2012; **23**: 1289-1296 [PMID: 22692409 DOI: 10.1007/s10552-012-0006-y]

57 **Hayashi N**, Matsushima M, Yamamoto T, Sasaki H, Takahashi H, Egawa S. The impact of hypertriglyceridemia on prostate cancer development in patients aged ≥60 years. *BJU Int* 2012; **109**: 515-519 [PMID: 21812901 DOI: 10.1111/j.1464-410X.2011.10358.x]

58 **Wuermli L**, Joerger M, Henz S, Schmid HP, Riesen WF, Thomas G, Krek W, Cerny T, Gillessen S. Hypertriglyceridemia as a possible risk factor for prostate cancer. *Prostate Cancer Prostatic Dis* 2005; **8**: 316-320 [PMID: 16158078 DOI: 10.1038/sj.pcan.4500834]

59 **Moses KA**, Abd TT, Goodman M, Hsiao W, Hall JA, Marshall FF, Petros JA, Issa MM. Increased low density lipoprotein and increased likelihood of positive prostate biopsy in black americans. *J Urol* 2009; **182**: 2219-2225 [PMID: 19758611 DOI: 10.1016/j.juro.2009.07.039]

60 **Ulmer H**, Borena W, Rapp K, Klenk J, Strasak A, Diem G, Concin H, Nagel G. Serum triglyceride concentrations and cancer risk in a large cohort study in Austria. *Br J Cancer* 2009; **101**: 1202-1206 [PMID: 19690552 DOI: 10.1038/sj.bjc.6605264]

61 **Gann PH**, Daviglus ML, Dyer AR, Stamler J. Heart rate and prostate cancer mortality: results of a prospective analysis. *Cancer Epidemiol Biomarkers Prev* 1995; **4**: 611-616 [PMID: 8547827]

62 **Bonovas S**, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: a meta-analysis. *Diabetologia* 2004; **47**: 1071-1078 [PMID: 15164171 DOI: 10.1007/s00125-004-1415-6]

63 **Kasper JS**, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 2056-2062 [PMID: 17119028 DOI: 10.1158/1055-9965.EPI-06-0410]

64 **Bansal D**, Bhansali A, Kapil G, Undela K, Tiwari P. Type 2 diabetes and risk of prostate cancer: a meta-analysis of observational studies. *Prostate Cancer Prostatic Dis* 2013; **16**: 151-158, S1 [PMID: 23032360 DOI: 10.1038/pcan.2012.40]

65 **Zhang F**, Yang Y, Skrip L, Hu D, Wang Y, Wong C, Qiu J, Lei H. Diabetes mellitus and risk of prostate cancer: an updated meta-analysis based on 12 case-control and 25 cohort studies. *Acta Diabetol* 2012; **49** Suppl 1: S235-S246 [PMID: 23124624 DOI: 10.1007/s00592-012-0439-5]

66 **Pierce BL**. Why are diabetics at reduced risk for prostate cancer? A review of the epidemiologic evidence. *Urol Oncol* 2012; **30**: 735-743 [PMID: 23021557 DOI: 10.1016/j.urolonc.2012.07.008]

67 **Jayachandran J**, Aronson WJ, Terris MK, Presti JC, Amling CL, Kane CJ, Freedland SJ. Diabetes and outcomes after radical prostatectomy: are results affected by obesity and race? Results from the shared equal-access regional cancer hospital database. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 9-17 [PMID: 20056618 DOI: 10.1158/1055-9965.EPI-09-0777]

68 **Abdollah F**, Briganti A, Suardi N, Gallina A, Capitanio U, Salonia A, Cestari A, Guazzoni G, Rigatti P, Montorsi F. Does diabetes mellitus increase the risk of high-grade prostate cancer in patients undergoing radical prostatectomy? *Prostate Cancer Prostatic Dis* 2011; **14**: 74-78 [PMID: 20956995 DOI: 10.1038/pcan.2010.41]

69 **Moreira DM**, Anderson T, Gerber L, Thomas JA, Bañez LL, McKeever MG, Hoyo C, Grant D, Jayachandran J, Freedland SJ. The association of diabetes mellitus and high-grade prostate cancer in a multiethnic biopsy series. *Cancer Causes Control* 2011; **22**: 977-983 [PMID: 21562753 DOI: 10.1007/s10552-011-9770-3]

70 **Mitin T**, Chen MH, Zhang Y, Moran BJ, Dosoretz DE, Katin MJ, Braccioforte MH, Salenius SA, D'Amico AV. Diabetes mellitus, race and the odds of high grade prostate cancer in men treated with radiation therapy. *J Urol* 2011; **186**: 2233-2237 [PMID: 22019035 DOI: 10.1016/j.juro.2011.07.072]

71 **Hong SK**, Oh JJ, Byun SS, Hwang SI, Lee HJ, Choe G, Lee SE. Impact of diabetes mellitus on the detection of prostate cancer via contemporary multi (≥ 12)-core prostate biopsy. *Prostate* 2012; **72**: 51-57 [PMID: 21520162 DOI: 10.1002/pros.21405]

72 **Moses KA**, Utuama OA, Goodman M, Issa MM. The association of diabetes and positive prostate biopsy in a US veteran population. *Prostate Cancer Prostatic Dis* 2012; **15**: 70-74 [PMID: 21894176 DOI: 10.1038/pcan.2011.40]

73 **Kang J**, Chen MH, Zhang Y, Moran BJ, Dosoretz DE, Katin MJ, Braccioforte MH, Salenius SA, D'Amico AV. Type of diabetes mellitus and the odds of Gleason score 8 to 10 prostate cancer. *Int J Radiat Oncol Biol Phys* 2012; **82**: e463-e467 [PMID: 21944463 DOI: 10.1016/j.ijrobp.2011.07.003]

74 **Davies BJ**, Walsh TJ, Ross PL, Knight SJ, Sadetsky N, Carroll PR, Kane CJ. Effect of BMI on primary treatment of prostate cancer. *Urology* 2008; **72**: 406-411 [PMID: 18267336 DOI: 10.1016/j.urology.2007.11.032]

75 **Kheterpal E**, Sammon JD, Diaz M, Bhandari A, Trinh QD, Pokala N, Sharma P, Menon M, Agarwal PK. Effect of metabolic syndrome on pathologic features of prostate cancer. *Urol Oncol* 2013; **31**: 1054-1059 [PMID: 23020926 DOI: 10.1016/j.urolonc.2011.12.012]

76 **Han BK**, Choi WS, Yu JH, Han JH, Chang IH, Jeong SJ, Hong SK, Byun SS, Lee SE. The characteristics of prostate cancer with metabolic syndrome in Korean men. *Korean J Urol* 2007; **48**: 585-591 [DOI: 10.4111/kju.2007.48.6.585]

77 **Castillejos-Molina R**, Rodríguez-Covarrubias F, Sotomayor M, Gómez-Alvarado MO, Villalobos-Gollás M, Gabilondo F, Feria-Bernal G. Impact of metabolic syndrome on biochemical recurrence of prostate cancer after radical prostatectomy. *Urol Int* 2011; **87**: 270-275 [PMID: 21876327 DOI:

10.1159/000329280]

78   **Post JM**, Beebe-Dimmer JL, Morgenstern H, Neslund-Dudas C, Bock CH, Nock N, Rundle A, Jankowski M, Rybicki BA. The Metabolic Syndrome and Biochemical Recurrence following Radical Prostatectomy. *Prostate Cancer* 2011; **2011**: 245642 [PMID: 22096652 DOI: 10.1155/2011/245642]

79   **Asmar R**, Beebe-Dimmer JL, Korgavkar K, Keele GR, Cooney KA. Hypertension, obesity and prostate cancer biochemical recurrence after radical prostatectomy. *Prostate Cancer Prostatic Dis* 2013; **16**: 62-66 [PMID: 22907512 DOI: 10.1038/pcan.2012.32]

80   **Kwon YS**, Leapman M, McBride RB, Hobbs AR, Collingwood SA, Stensland KD, Samadi DB. Robotic-assisted laparoscopic prostatectomy in men with metabolic syndrome. *Urol Oncol* 2014; **32**: 40.e9-40.16 [PMID: 23820091 DOI: 10.1016/j.urolonc.2013.04.008]

81   **Cao Y**, Ma J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. *Cancer Prev Res* (Phila) 2011; **4**: 486-501 [PMID: 21233290 DOI: 10.1158/1940-6207.CAPR-10-0229]

82   **Hu MB**, Xu H, Bai PD, Jiang HW, Ding Q. Obesity has multifaceted impact on biochemical recurrence of prostate cancer: a dose-response meta-analysis of 36,927 patients. *Med Oncol* 2014; **31**: 829 [PMID: 24390417 DOI: 10.1007/s12032-013-0829-8]

83   **Chan JM**, Latini DM, Cowan J, Duchane J, Carroll PR. History of diabetes, clinical features of prostate cancer, and prostate cancer recurrence-data from CaPSURE (United States). *Cancer Causes Control* 2005; **16**: 789-797 [PMID: 16132789 DOI: 10.1007/s10552-005-3301-z]

84   **Wu C**, Aronson WJ, Terris MK, Presti JC, Kane CJ, Amling CL, Freedland SJ. Diabetes predicts metastasis after radical prostatectomy in obese men: results from the SEARCH database. *BJU Int* 2013; **111**: E310-E318 [PMID: 23305170 DOI: 10.1111/j.1464-410X.2012.11687.x]

85   **Strom SS**, Kamat AM, Gruschkus SK, Gu Y, Wen S, Cheung MR, Pisters LL, Lee AK, Rosser CJ, Kuban DA. Influence of obesity on biochemical and clinical failure after external-beam radiotherapy for localized prostate cancer. *Cancer* 2006; **107**: 631-639 [PMID: 16802288 DOI: 10.1002/cncr.22025]

86   **Stroup SP**, Cullen J, Auge BK, L'Esperance JO, Kang SK. Effect of obesity on prostate-specific antigen recurrence after radiation therapy for localized prostate cancer as measured by the 2006 Radiation Therapy Oncology Group-American Society for Therapeutic Radiation and Oncology (RTOG-ASTRO) Phoenix consensus definition. *Cancer* 2007; **110**: 1003-1009 [PMID: 17614338 DOI: 10.1002/cncr.22873]

87   **Palma D**, Pickles T, Tyldesley S. Obesity as a predictor of biochemical recurrence and survival after radiation therapy for prostate cancer. *BJU Int* 2007; **100**: 315-319 [PMID: 17617138 DOI: 10.1111/j.1464-410X.2007.06897.x]

88   **King CR**, Spiotto MT, Kapp DS. Obesity and risk of biochemical failure for patients receiving salvage radiotherapy after prostatectomy. *Int J Radiat Oncol Biol Phys* 2009; **73**: 1017-1022 [PMID: 18707829 DOI: 10.1016/j.ijrobp.2008.05.041]

89   **Merrick GS**, Galbreath RW, Butler WM, Waller KE, Allen ZA, Lief J, Adamovich E. Primary Gleason pattern does not impact survival after permanent interstitial brachytherapy for Gleason score 7 prostate cancer. *Cancer* 2007; **110**: 289-296 [PMID: 17549691 DOI: 10.1002/cncr.22793]

90   **Efstathiou JA**, Skowronski RY, Coen JJ, Grocela JA, Hirsch AE, Zietman AL. Body mass index and prostate-specific antigen failure following brachytherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008; **71**: 1302-1308 [PMID: 18262732 DOI: 10.1016/j.ijrobp.2007.11.073]

91   **van Roermund JG**, Hinnen KA, Battermann JJ, Witjes JA, Bosch JL, Kiemeney LA, van Vulpen M. Body mass index is not a prognostic marker for prostate-specific antigen failure and survival in Dutch men treated with brachytherapy. *BJU Int* 2010; **105**: 42-48 [PMID: 19519759 DOI: 10.1111/j.1464-

410X.2009.08687.x]

92   **Shetti MB**, Merrick GS, Butler WM, Galbreath R, Torlone A, Lief JH, Adamovich E, Wallner KE. The impact of diabetes mellitus on survival in men with clinically localized prostate cancer treated with permanent interstitial brachytherapy. *Am J Clin Oncol* 2012; **35**: 572-579 [PMID: 22134514 DOI: 10.1097/COC.0b013e31822dfd8a]

93   **Efstathiou JA**, Chen MH, Renshaw AA, Loffredo MJ, D'Amico AV. Influence of body mass index on prostate-specific antigen failure after androgen suppression and radiation therapy for localized prostate cancer. *Cancer* 2007; **109**: 1493-1498 [PMID: 17340594 DOI: 10.1002/cncr.22564]

94   **Smith MR**, Bae K, Efstathiou JA, Hanks GE, Pilepich MV, Sandler HM, Shipley WU. Diabetes and mortality in men with locally advanced prostate cancer: RTOG 92-02. *J Clin Oncol* 2008; **26**: 4333-4339 [PMID: 18779620 DOI: 10.1200/JCO.2008.16.5845]

95   **Keto CJ**, Aronson WJ, Terris MK, Presti JC, Kane CJ, Amling CL, Freedland SJ. Obesity is associated with castration-resistant disease and metastasis in men treated with androgen deprivation therapy after radical prostatectomy: results from the SEARCH database. *BJU Int* 2012; **110**: 492-498 [PMID: 22094083 DOI: 10.1111/j.1464-410X.2011.10754.x]

96   **Flanagan J**, Gray PK, Hahn N, Hayes J, Myers LJ, Carney-Doebbeling C, Sweeney CJ. Presence of the metabolic syndrome is associated with shorter time to castration-resistant prostate cancer. *Ann Oncol* 2011; **22**: 801-807 [PMID: 20880998 DOI: 10.1093/annonc/mdq443]

97   **Jasuja GK**, Travison TG, Davda M, Murabito JM, Basaria S, Zhang A, Kushnir MM, Rockwood AL, Meikle W, Pencina MJ, Coviello A, Rose AJ, D'Agostino R, Vasan RS, Bhasin S. Age trends in estradiol and estrone levels measured using liquid chromatography tandem mass spectrometry in community-dwelling men of the Framingham Heart Study. *J Gerontol A Biol Sci Med Sci* 2013; **68**: 733-740 [PMID: 23105044 DOI: 10.1093/gerona/gls216]

98   **Teloken PE**, Nelson CJ, Karellas M, Stasi J, Eastham J, Scardino PT, Mulhall JP. Defining the impact of vascular risk factors on erectile function recovery after radical prostatectomy. *BJU Int* 2013; **111**: 653-657 [PMID: 22758405 DOI: 10.1111/j.1464-410X.2012.11321.x]

99   **Wang Y**, Liu T, Rossi PJ, Watkins-Bruner D, Hsiao W, Cooper S, Yang X, Jani AB. Influence of vascular comorbidities and race on erectile dysfunction after prostate cancer radiotherapy. *J Sex Med* 2013; **10**: 2108-2114 [PMID: 23742221 DOI: 10.1111/jsm.12215]

100   **Sanda MG**, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, Lin X, Greenfield TK, Litwin MS, Saigal CS, Mahadevan A, Klein E, Kibel A, Pisters LL, Kuban D, Kaplan I, Wood D, Ciezki J, Shah N, Wei JT. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 2008; **358**: 1250-1261 [PMID: 18354103 DOI: 10.1056/NEJMoa074311]

101   **Montgomery JS**, Gayed BA, Hollenbeck BK, Daignault S, Sanda MG, Montie JE, Wei JT. Obesity adversely affects health related quality of life before and after radical retropubic prostatectomy. *J Urol* 2006; **176**: 257-261; discussion 261-262 [PMID: 16753415 DOI: 10.1016/S0022-5347(06)00504-0]

102   **Anast JW**, Sadetsky N, Pasta DJ, Bassett WW, Latini D, DuChane J, Chan JM, Cooperberg MR, Carroll PR, Kane CJ. The impact of obesity on health related quality of life before and after radical prostatectomy (data from CaPSURE). *J Urol* 2005; **173**: 1132-1138 [PMID: 15758721 DOI: 10.1097/01.ju.0000154973.38301.7f]

103   **Freedland SJ**, Haffner MC, Landis PK, Saigal CS, Carter HB. Obesity does not adversely affect health-related quality-of-life outcomes after anatomic retropubic radical prostatectomy. *Urology* 2005; **65**: 1131-1136 [PMID: 15913722 DOI: 10.1016/j.urology.2004.12.064]

104   **Brown JA**, Rodin DM, Lee B, Dahl DM. Laparoscopic radical prostatectomy and body mass index: an assessment of 151 sequential cases. *J Urol* 2005; **173**: 442-445 [PMID: 15643198 DOI: 10.1097/01.ju.0000148865.89309.cb]

105   **Mulholland TL**, Huynh PN, Huang RR, Wong C, Diokno AC, Peters KM. Urinary incontinence after radical retropubic prostatectomy is not related to patient body mass index. *Prostate Cancer Prostatic Dis* 2006; **9**: 153-159 [PMID: 16505832 DOI: 10.1038/sj.pcan.4500860]

106   **Ayyathurai R**, Manoharan M, Nieder AM, Kava B, Soloway MS. Factors affecting erectile function after radical retropubic prostatectomy: results from 1620 consecutive patients. *BJU Int* 2008; **101**: 833-836 [PMID: 18190627 DOI: 10.1111/j.1464-410X.2007.07409.x]

107   **Boorjian SA**, Crispen PL, Carlson RE, Rangel LJ, Karnes RJ, Frank I, Gettman MT. Impact of obesity on clinicopathologic outcomes after robot-assisted laparoscopic prostatectomy. *J Endourol* 2008; **22**: 1471-1476 [PMID: 18613784 DOI: 10.1089/end.2008.0056]

108   **Wiltz AL**, Shikanov S, Eggener SE, Katz MH, Thong AE, Steinberg GD, Shalhav AL, Zagaja GP, Zorn KC. Robotic radical prostatectomy in overweight and obese patients: oncological and validated-functional outcomes. *Urology* 2009; **73**: 316-322 [PMID: 18952266 DOI: 10.1016/j.urology.2008.08.493]

109   **Marien T**, Sankin A, Lepor H. Factors predicting preservation of erectile function in men undergoing open radical retropubic prostatectomy. *J Urol* 2009; **181**: 1817-1822 [PMID: 19233413 DOI: 10.1016/j.juro.2008.11.10]

110   **van Roermund JG**, van Basten JP, Kiemeney LA, Karthaus HF, Witjes JA. Impact of obesity on surgical outcomes following open radical prostatectomy. *Urol Int* 2009; **82**: 256-261 [PMID: 19440009 DOI: 10.1159/000209353]

111   **Wolin KY**, Luly J, Sutcliffe S, Andriole GL, Kibel AS. Risk of urinary incontinence following prostatectomy: the role of physical activity and obesity. *J Urol* 2010; **183**: 629-633 [PMID: 20018324 DOI: 10.1016/j.juro.2009.09.082]

112   **Briganti A**, Gallina A, Suardi N, Capitanio U, Tutolo M, Bianchi M, Passoni N, Salonia A, Colombo R, Di Girolamo V, Guazzoni G, Rigatti P, Montorsi F. Predicting erectile function recovery after bilateral nerve sparing radical prostatectomy: a proposal of a novel preoperative risk stratification. *J Sex Med* 2010; **7**: 2521-2531 [PMID: 20487236 DOI: 10.1111/j.1743-6109.2010.01845.x]

113   **Moskovic DJ**, Lavery HJ, Rehman J, Nabizada-Pace F, Brajtbord J, Samadi DB. High body mass index does not affect outcomes following robotic assisted laparoscopic prostatectomy. *Can J Urol* 2010; **17**: 5291-5298 [PMID: 20735909]

114   **Uffort EE**, Jensen JC. Impact of obesity on early erectile function recovery after robotic radical prostatectomy. *JSLS* 2011; **15**: 32-37 [PMID: 21902939 DOI: 10.4293/108680810X1292446 6009203]

115   **Khoder WY**, Trottmann M, Stuber A, Stief CG, Becker AJ. Early incontinence after radical prostatectomy: a community based retrospective analysis in 911 men and implications for preoperative counseling. *Urol Oncol* 2013; **31**: 1006-1011 [PMID: 22100069 DOI: 10.1016/j.urolonc.2011.10.00]

116   **Gacci M**, Sebastianelli A, Salvi M, De Nunzio C, Schiavina R, Simonato A, Tubaro A, Mirone V, Carini M, Carmignani G. Role of abdominal obesity for functional outcomes and complications in men treated with radical prostatectomy for prostate cancer: results of the Multicenter Italian Report on Radical Prostatectomy (MIRROR) study. *Scand J Urol* 2014; **48**: 138-145 [PMID: 23781856]

117   **Mandel P**, Kretschmer A, Chandrasekar T, Nguyen HG, Buchner A, Stief CG, Tilki D. The effect of BMI on clinicopathologic and functional outcomes after open radical prostatectomy. *Urol Oncol* 2014; **32**: 297-302 [PMID: 24332640 DOI: 10.1016/j.urolonc.2013.09.005]

118   **Latini DM**, Chan JM, Cowan JE, Arredondo SA, Kane CJ, Penson DF, DuChane J, Carroll PR. Health-related quality of life for men with prostate cancer and diabetes: a longitudinal analysis from CaPSURE. *Urology* 2006; **68**: 1242-1247 [PMID: 17141841 DOI: 10.1016/j.urology.2006.08.1096]

119   **Thong MS**, van de Poll-Franse L, Hoffman RM, Albertsen PC, Hamilton AS, Stanford JL, Penson DF. Diabetes mellitus and health-related quality of life in prostate cancer: 5-year results from the Prostate Cancer Outcomes Study. *BJU Int* 2011; **107**: 1223-1231 [PMID: 21070583 DOI: 10.1111/j.1464-410X.2010.09861.x]

120   **Merrick GS**, Butler WM, Galbreath RW, Stipetich RL, Abel LJ, Lief JH. Erectile function after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2002; **52**: 893-902 [PMID: 11958881 DOI: 10.1016/S0360-3016(01)02675-X]

121   **Macdonald AG**, Keyes M, Kruk A, Duncan G, Moravan V, Morris WJ. Predictive factors for erectile dysfunction in men with prostate cancer after brachytherapy: is dose to the penile bulb important? *Int J Radiat Oncol Biol Phys* 2005; **63**: 155-163 [PMID: 16111584 DOI: 10.1016/j.ijrobp.2004.12.056]

122   **Pinkawa M**, Gagel B, Piroth MD, Fischedick K, Asadpour B, Kehl M, Klotz J, Eble MJ. Erectile dysfunction after external beam radiotherapy for prostate cancer. *Eur Urol* 2009; **55**: 227-234 [PMID: 18375048 DOI: 10.1016/j.eururo.2008.03.026]

123   **Herold DM**, Hanlon AL, Hanks GE. Diabetes mellitus: a predictor for late radiation morbidity. *Int J Radiat Oncol Biol Phys* 1999; **43**: 475-479 [PMID: 10078625 DOI: 10.1016/S0360-3016(98)00460-X]

124   **Skwarchuk MW**, Jackson A, Zelefsky MJ, Venkatraman ES, Cowen DM, Levegrün S, Burman CM, Fuks Z, Leibel SA, Ling CC. Late rectal toxicity after conformal radiotherapy of prostate cancer (I): multivariate analysis and dose-response. *Int J Radiat Oncol Biol Phys* 2000; **47**: 103-113 [PMID: 10758311 DOI: 10.1016/S0360-3016(99)00560-X]

125   **Akimoto T**, Muramatsu H, Takahashi M, Saito J, Kitamoto Y, Harashima K, Miyazawa Y, Yamada M, Ito K, Kurokawa K, Yamanaka H, Nakano T, Mitsuhashi N, Niibe H. Rectal bleeding after hypofractionated radiotherapy for prostate cancer: correlation between clinical and dosimetric parameters and the incidence of grade 2 or worse rectal bleeding. *Int J Radiat Oncol Biol Phys* 2004; **60**: 1033-1039 [PMID: 15519772 DOI: 10.1016/j.ijrobp.2004.07.695]

126   **Vavassori V**, Fiorino C, Rancati T, Magli A, Fellin G, Baccolini M, Bianchi C, Cagna E, Mauro FA, Monti AF, Munoz F, Stasi M, Franzone P, Valdagni R. Predictors for rectal and intestinal acute toxicities during prostate cancer high-dose 3D-CRT: results of a prospective multicenter study. *Int J Radiat Oncol Biol Phys* 2007; **67**: 1401-1410 [PMID: 17241754 DOI: 10.1016/j.ijrobp.2006.10.040]

127   **Budäus L**, Bolla M, Bossi A, Cozzarini C, Crook J, Widmark A, Wiegel T. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. *Eur Urol* 2012; **61**: 112-127 [PMID: 22001105 DOI: 10.1016/j.eururo.2011.09.027]

128   **Andersson SO**, Wolk A, Bergström R, Adami HO, Engholm G, Englund A, Nyrén O. Body size and prostate cancer: a 20-year follow-up study among 135006 Swedish construction workers. *J Natl Cancer Inst* 1997; **89**: 385-389 [PMID: 9060961 DOI: 10.1093/jnci/89.5.385]

129   **Rodriguez C**, Patel AV, Calle EE, Jacobs EJ, Chao A, Thun MJ. Body mass index, height, and prostate cancer mortality in two large cohorts of adult men in the United States. *Cancer Epidemiol Biomarkers Prev* 2001; **10**: 345-353 [PMID: 11319175]

130   **Snyder CF**, Stein KB, Barone BB, Peairs KS, Yeh HC, Derr RL, Wolff AC, Carducci MA, Brancati FL. Does pre-existing diabetes affect prostate cancer prognosis? A systematic review. *Prostate Cancer Prostatic Dis* 2010; **13**: 58-64 [PMID: 20145631 DOI: 10.1038/pcan.2009.39]

131   **Freedland SJ**, Aronson WJ. Dietary intervention strategies to modulate prostate cancer risk and prognosis. *Curr Opin Urol* 2009; **19**: 263-267 [PMID: 19300265 DOI: 10.1097/MOU.0b013e328329ea6c]

132 **Ornish D**, Weidner G, Fair WR, Marlin R, Pettengill EB, Raisin CJ, Dunn-Emke S, Crutchfield L, Jacobs FN, Barnard RJ, Aronson WJ, McCormac P, McKnight DJ, Fein JD, Dnistrian AM, Weinstein J, Ngo TH, Mendell NR, Carroll PR. Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol* 2005; **174**: 1065-1069; discussion 1069-1070 [PMID: 16094059 DOI: 10.1097/01.ju.0000169487.49018.73]

133 **Frattaroli J**, Weidner G, Dnistrian AM, Kemp C, Daubenmier JJ, Marlin RO, Crutchfield L, Yglecias L, Carroll PR, Ornish D. Clinical events in prostate cancer lifestyle trial: results from two years of follow-up. *Urology* 2008; **72**: 1319-1323 [PMID: 18602144 DOI: 10.1016/j.urology.2008.04.050]

134 **Kushi LH**, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, Gapstur S, Patel AV, Andrews K, Gansler T. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin* 2008; **62**: 30-67 [PMID: 22237782 DOI: 10.3322/caac.20140]

135 **Liu Y**, Hu F, Li D, Wang F, Zhu L, Chen W, Ge J, An R, Zhao Y. Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. *Eur Urol* 2011; **60**: 1029-1044 [PMID: 21802197 DOI: 10.1016/j.eururo.2011.07.007]

136 **Rice KR**, Koch MO, Cheng L, Masterson TA. Dyslipidemia, statins and prostate cancer. *Expert Rev Anticancer Ther* 2012; **12**: 981-990 [PMID: 22845413 DOI: 10.1586/era.12.75]

137 **Platz EA**, Leitzmann MF, Visvanathan K, Rimm EB, Stampfer MJ, Willett WC, Giovannucci E. Statin drugs and risk of advanced prostate cancer. *J Natl Cancer Inst* 2006; **98**: 1819-1825 [PMID: 17179483 DOI: 10.1093/jnci/djj499]

138 **Jacobs EJ**, Rodriguez C, Bain EB, Wang Y, Thun MJ, Calle EE. Cholesterol-lowering drugs and advanced prostate cancer incidence in a large U.S. cohort. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 2213-2217 [PMID: 17971518 DOI: 10.1158/1055-9965.EPI-07-0448]

139 **Murtola TJ**, Tammela TL, Lahtela J, Auvinen A. Cholesterol-lowering drugs and prostate cancer risk: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 2226-2232 [PMID: 18006910 DOI: 10.1158/1055-9965.EPI-07-0599]

140 **Bonovas S**, Filioussi K, Tsavaris N, Sitaras NM. Statins and cancer risk: a literature-based meta-analysis and meta-regression analysis of 35 randomized controlled trials. *J Clin Oncol* 2006; **24**: 4808-4817 [PMID: 17001070 DOI: 10.1200/JCO.2006.06.3560]

141 **Mass AY**, Agalliu I, Laze J, Lepor H. Preoperative statin therapy is not associated with biochemical recurrence after radical prostatectomy: our experience and meta-analysis. *J Urol* 2012; **188**: 786-791 [PMID: 22818136 DOI: 10.1016/j.juro.2012.05.011]

142 **Scosyrev E**, Tobis S, Donsky H, Wu G, Joseph J, Rashid H, Messing E. Statin use and the risk of biochemical recurrence of prostate cancer after definitive local therapy: a meta-analysis of eight cohort studies. *BJU Int* 2013; **111**: E71-E77 [PMID: 23017100 DOI: 10.1111/j.1464-410X.2012.11527.x]

143 **Park HS**, Schoenfeld JD, Mailhot RB, Shive M, Hartman RI, Ogembo R, Mucci LA. Statins and prostate cancer recurrence following radical prostatectomy or radiotherapy: a systematic review and meta-analysis. *Ann Oncol* 2013; **24**: 1427-1434 [PMID: 23508824 DOI: 10.1093/annonc/mdt077]

144 **Wright JL**, Stanford JL. Metformin use and prostate cancer in Caucasian men: results from a population-based case-control study. *Cancer Causes Control* 2009; **20**: 1617-1622 [PMID:

19653109 DOI: 10.1007/s10552-009-9407-y]

145 **He XX**, Tu SM, Lee MH, Yeung SC. Thiazolidinediones and metformin associated with improved survival of diabetic prostate cancer patients. *Ann Oncol* 2011; **22**: 2640-2645 [PMID: 21415239 DOI: 10.1093/annonc/mdr020]

146 **Hitron A**, Adams V, Talbert J, Steinke D. The influence of antidiabetic medications on the development and progression of prostate cancer. *Cancer Epidemiol* 2012; **36**: e243-e250 [PMID: 22417708 DOI: 10.1016/j.canep.2012.02.005]

147 **Margel D**, Urbach DR, Lipscombe LL, Bell CM, Kulkarni G, Austin PC, Fleshner N. Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. *J Clin Oncol* 2013; **31**: 3069-3075 [PMID: 23918942 DOI: 10.1200/JCO.2012.46.7043]

148 **Spratt DE**, Zhang C, Zumsteg ZS, Pei X, Zhang Z, Zelefsky MJ. Metformin and prostate cancer: reduced development of castration-resistant disease and prostate cancer mortality. *Eur Urol* 2013; **63**: 709-716 [PMID: 23287698 DOI: 10.1016/j.eururo.2012.12.004]

149 **Murtola TJ**, Tammela TL, Lahtela J, Auvinen A. Antidiabetic medication and prostate cancer risk: a population-based case-control study. *Am J Epidemiol* 2008; **168**: 925-931 [PMID: 18700234 DOI: 10.1093/aje/kwn190]

150 **Currie CJ**, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia* 2009; **52**: 1766-1777 [PMID: 19572116 DOI: 10.1007/s00125-009-1440-6]

151 **Patel T**, Hruby G, Badani K, Abate-Shen C, McKiernan JM. Clinical outcomes after radical prostatectomy in diabetic patients treated with metformin. *Urology* 2010; **76**: 1240-1244 [PMID: 20627287 DOI: 10.1016/j.urology.2010.03.059]

152 **Azoulay L**, Dell'Aniello S, Gagnon B, Pollak M, Suissa S. Metformin and the incidence of prostate cancer in patients with type 2 diabetes. *Cancer Epidemiol Biomarkers Prev* 2011; **20**: 337-344 [PMID: 21148757 DOI: 10.1158/1055-9965.EPI-10-0940]

153 **Allott EH**, Abern MR, Gerber L, Keto CJ, Aronson WJ, Terris MK, Kane CJ, Amling CL, Cooperberg MR, Moorman PG, Freedland SJ. Metformin does not affect risk of biochemical recurrence following radical prostatectomy: results from the SEARCH database. *Prostate Cancer Prostatic Dis* 2013; **16**: 391-397 [PMID: 24100644 DOI: 10.1038/pcan.2013.48]

154 **Kaushik D**, Karnes RJ, Eisenberg MS, Rangel LJ, Carlson RE, Bergstralh EJ. Effect of metformin on prostate cancer outcomes after radical prostatectomy. *Urol Oncol* 2014; **32**: 43.e1-43.e7 [PMID: 23810664 DOI: 10.1016/j.urolonc.2013.05.005]

155 **Rothermundt C**, Hayoz S, Templeton AJ, Winterhalder R, Strebel RT, Bärtschi D, Pollak M, Lui L, Endt K, Schiess R, Rüschoff JH, Cathomas R, Gillessen S. Metformin in Chemotherapy-naive Castration-resistant Prostate Cancer: A Multicenter Phase 2 Trial (SAKK 08/09). *Eur Urol* 2014; **66**: 468-474 [PMID: 24412228 DOI: 10.1016/j.eururo.2013.12.057]

156 **Go AS**, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation* 2013; **127**: e6-e245 [PMID: 23239837 DOI: 10.1161/CIR.0b013e31828124ad]