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**Review Article**

# Association between metabolic syndrome, obesity, diabetes mellitus and oncological outcomes of bladder cancer: A systematic review

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**Abbreviations & Acronyms**
BCa = bladder cancer
BMI = body mass index
CI = confidence interval
CIS = carcinoma *in situ*
CPS II = Cancer Prevention Study II
FEV1 = forced expiratory volume first second
Me-Can = Metabolic syndrome and Cancer project
MetS = metabolic syndrome
NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III
NMIBCa = non-muscle-invasive bladder cancer
PCa = prostate cancer
RC = radical cystectomy
RR = relative risk
t2DM = type 2 diabetes mellitus
WHO = World Health Organization

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**Abstract:** Metabolic syndrome is a cluster of several metabolic abnormalities, its prevalence is increasing worldwide. To summarize the most recent evidence regarding the relationship between metabolic syndrome, its components and the oncological outcomes in bladder cancer patients, a National Center for Biotechnology Information PubMed search for relevant articles either published or e-published up to March 2014 was carried out by combining the following Patient population, Intervention, Comparison, Outcome terms: metabolic syndrome, obesity, body mass index, hyperglycemia, insulin resistance, diabetes, hypertension, dyslipidemia, bladder cancer, risk, mortality, cancer specific survival, disease recurrence and progression. Metabolic syndrome is a complex, highly prevalent disorder, and central obesity, insulin resistance, dyslipidemia and hypertension are its main components. Published findings would suggest that metabolic syndrome per se might be associated with an increased risk of bladder cancer in male patients, but it did not seem to confer a risk of worse prognosis. Considering the primary components of metabolic syndrome (hypertension, obesity and dyslipidemia), available data are uncertain, and it is no possible to reach a conclusion yet on either a direct or an indirect association with bladder cancer risk and prognosis. Only with regard to type 2 diabetes mellitus, available data would suggest a potential negative correlation. However, as the evaluation of bladder cancer risk and prognosis in patients with metabolic disorders is certainly complex, further studies are urgently required to better assess the actual role of these metabolic disorders.

**Key words:** bladder cancer, diabetes mellitus, metabolic syndrome, obesity, pathological outcomes.

## Introduction

MetS is a complex disorder described as a cluster of risk factors for cardiovascular diseases and t2DM including visceral obesity, glucose intolerance, high blood pressure, high triglyceride levels and low high-density lipoprotein cholesterol levels. Irrespective of MetS definition, MetS prevalence is increasing worldwide, and it has become a common clinical condition and a major public health problem with high socioeconomic costs in countries with high incidence of obesity and Western dietary patterns.[1] Current literature supports the hypothesis that MetS could act as a significant etiological factor for the development and progression of different cancers.[2] In this context, several pathways of correlations between MetS and cancer have been investigated, without being able to come to any real conclusion.[3] Dealing with urological cancers, most of the investigations evaluated the correlation between MetS and PCa.[4] Conversely, little is known about the potential association between MetS and BCa.

BCa is one of the most frequent malignant tumors in the urinary system, and a leading cause of cancer-related death.[5]

A potential positive correlation between MetS and an increased risk of BCa has been recently proposed.[2]

In contrast, data on the association between MetS and oncological outcomes (i.e. mortality, overall survival, cancer specific survival, disease recurrence, disease progression) in BCa are extremely limited and unconfirmed. Similarly, only a few studies have comprehensively evaluated the relationship between each single MetS component and BCa oncological outcomes.

In this context, one of the most important problems that characterize the correlation between MetS and cancer is the forced inclusion of different clinical entities in a single variable that might

be methodologically inappropriate. Combining all the multiple components of MetS in a single variable could change or confound the independent effect of each single component with cancer. Particularly, we do not know if the cumulative effect played by MetS is greater or lower than its single parts, and defining this effect for BCa would be the key to preventively improve the action on specific risk factors and, with regard to the oncological outcomes, to improve the prognosis.

The aim of the present critical systematic review was to summarize the most recent evidence regarding the relationship between MetS and, separately, its single components and the oncological outcomes in patients with BCa.

## Evidence acquisition

### Study selection

A literature search for English-language original and review articles either published or e-published up to March 2014 was carried out using the National Center for Biotechnology Information PubMed database regarding the association between MetS as a whole and its components – in particular DM and visceral obesity – with oncological outcomes of BCa. We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines for reporting systematic reviews.[6]

The patient population, intervention, comparison, outcome) terms used were: metabolic syndrome, obesity, body mass index, hyperglycemia, insulin resistance, DM, BCa, risk, mortality, cancer specific survival, overall survival, disease recurrence and disease progression.

### Inclusion criteria

We included studies if they reported the definition of MetS according to the most widely recognized criteria (traditional definitions), or if they used proxy indicators in the absence of original data (non-traditional definitions), or included at least three factors, even in the absence of the others.[4]

We also included studies that reported all standardized forms of RR for oncological outcomes (risk ratio, hazard ratio, odds ratio, likelihood ratio, standardize incidence ratio) with estimates of CI or with sufficient data to estimate CI.

Furthermore, relevant journal, bibliographies and review papers were manually searched for additional articles. Evidence was not only limited to human studies, but data from *in vitro* and *in vivo* animal studies were also included in the review. Each article and abstract was reviewed for their appropriateness with regard to the inclusion criteria; relevance was then graded using the Oxford Centre for Evidence-based Medicine, 2011 Levels of Evidence. Figure 1 presents the search strategy and study selection flow chart. Details of the selected references are summarized in Tables 1–3.

## Evidence synthesis

### MetS and BCa oncological outcomes: Clinical evidence

As reported, only a few studies evaluated the relationship between BCa and MetS. In a prospective cohort study of 580 000 people – carried out within the Me-Can – Haggstrom

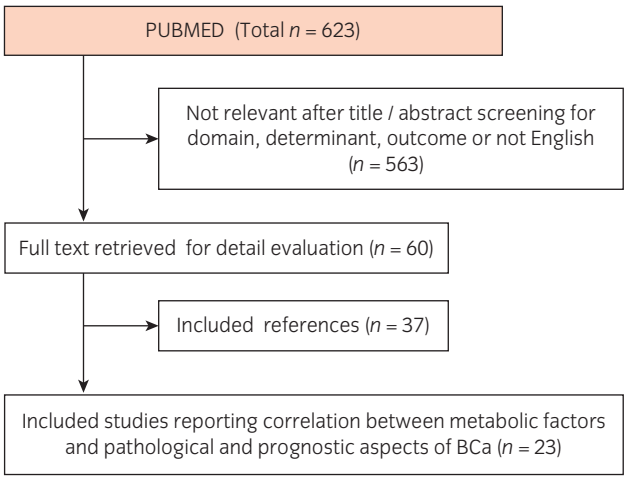


**Fig. 1** The flow diagram of the search results.

*et al*. showed that MetS was associated with a significantly increased risk of BCa in men (RR 1.10, 95%CI 1.01–1.18), whereas no association was observed in women.[7] Similarly, Russo *et al*. in an Italian population-based study and using a "non-traditional" pharmacologically based definition of MetS (i.e. individuals simultaneously treated with hypoglycemic, antihypertensive and hypolipemics drugs) observed an increased risk of BCa only in men (standardized incidence ratios – ratio between observed and expected cases [109, 95% CI 82–143]).[8] As a whole, in their meta-analysis, Esposito *et al*. estimated that in men the presence of MetS was significantly associated with BCa with a RR of 1.10 (95% CI 1.02–1.18).[2]

Similarly, little is known regarding the influence of MetS on pathological and prognostic factors of BCa, and if its cumulative effect is greater or lower than its single components. A recent study investigated this correlation in 262 consecutive patients undergoing RC for muscle-invasive urothelial BCa.[9] These authors showed that MetS, defined according to the NCEP ATP III criteria, did not emerge as an independent predictor of the risk of both a higher pathological stage, and lymph vascular invasion and lymph node invasion; conversely, BMI, considered as a surrogate of obesity, was found to be an independent predictor of both oncological conditions. Unfortunately, no data were available on other prognostic parameters. In their study carried out with a large cohort of patients within the Me-Can project, Haggstrom *et al*. showed that MetS did not predict the risk of cancer-specific mortality, while they observed in male patients that an increased blood pressure was the only independent risk factor of BCa mortality (RR 1.34, 95% CI 1.06–1.69).[7]

Consequently, MetS as a whole did not seem to confer a risk of worse prognosis, but two studies are few, and further clinical studies with a large cohort of patients are required.

### Metabolic factors and BCa oncological outcomes: Clinical evidence

#### Obesity and BCa

Obesity, considered as a single metabolic factor, continues to represent worldwide a growing health problem, even in

**Table 1** Relevant clinical studies of the relationship between MetS, obesity, and pathological and prognostic factors of BCa

| Author year (ref.no) | Country and study design | Population | Time period (years) | Definition/criteria | Age | Follow up | No. BCa deaths | Outcomes/comments | Covariates adjustment |
|---|---|---|---|---|---|---|---|---|---|
| MetS and pathological and prognostic factors of BCa | | | | | | | | | |
| Häggström, 2011[7] | Norway (prospective cohort study) | MeCan project 578 700 subjects | 1972–2005 | Non-traditional definition<br>MetS as a composite score including BMI, blood pressure, glucose, cholesterol, triglycerides | 44 years (mean) | 12 years (mean) | 274 | No relationship between MetS and BCa mortality<br>Blood pressure the only risk factor, exclusively among men<br>RR 1.34 (95% CI 1.06–1.69) | Smoking status, sex, BMI, birth year |
| Cantiello, 2014[9] | Italy (radical cystectomy cohort study) | 262 patients | 2008–2012 | NCEP ATP III definition of MetS | 71.0 years (median) | NA | NA | No relationship between MetS and pathological stage, lymph vascular invasion, lymph node metastasis at radical cystectomy | Age, sex, smoking status, waist circumference, blood glucose level, blood cholesterol and triglyceride level, hypertension |
| Obesity and pathological and prognostic factors of BCa | | | | | | | | | |
| Calle, 2003[17] | USA (prospective cohort study) | 900 053 subjects | 1982–1998 | BMI according to WHO classification | 57.0 years (mean) | 16.0 years (median) | 872 men<br>297 women | No significant correlation between increasing BMI and BCa mortality | Age, race, smoking status, education, physical activity, alcohol use, aspirin use, estrogen replacement therapy, marital status, fat and vegetable consumption |
| Batty, 2005[18] | England (prospective cohort study) | 18 403 subjects | 1967–1970 | BMI according to WHO classification | 52.0 years (median) | 28.1 years (median) | 144 | Positive correlation between BMI and BCa mortality<br>HR 1.68 (95% CI 1.06–2.65) overweight<br>HR 1.19 (95% CI 0.27–5.18) obese | Age, triceps skin fold thickness, plasma cholesterol, FEV1, systolic blood pressure, physical activity, smoking status, disease at study entry, blood glucose level, marital status, employment grade |
| Hafron, 2005[19] | USA (radical or partial cystectomy cohort study) | 300 patients (288 sufficient data available) | 1990–1993 | BMI according to WHO classification | 67.0 years (median)<br>65.4 ± 9.7 | 53.4 months (mean) | 203 | No significant association between BMI and overall or BCa-specific survival | Age, sex, smoking status |
| Maurer, 2009[20] | Germany (radical cystectomy cohort study) | 390 patients | 1986–2004 | BMI according to WHO classification | 68.0 years (median) | 5 and 10 years | NA | No significant correlation between increasing BMI and BCa 5-year and 10-year overall survival | Age, sex, urinary diversion, stage |
| Chromecki, 2013[21] | Multicentric radical cystectomy cohort study | 4118 patients | 1979–2008 | BMI according to WHO classification | 67.0 years (median) | 44.0 months (median) | 1121 | Obesity was an independent risk factor of disease recurrence (HR 1.67, 95% CI 1.46–1.91), cancer-specific mortality (HR 1.43, 95% CI 1.24–1.66), overall mortality (HR 1.81, 95% CI 1.60–2.05) | Age, sex, stage, grade, lymph vascular invasion, lymph node status, surgical margin, CIS, adjuvant chemotherapy |
| Cantiello, 2014[9] | Italy (radical cystectomy cohort study) | 262 patients | 2008–2012 | BMI according to WHO classification | 71.0 years (median) | NA | NA | BMI (continuous variable) was an independent risk factor for higher pathological stage (OR 1.3, 95% CI 1.09–1.55), lymph vascular invasion (OR 1.4, 95% CI 1.17–1.73) and lymph node metastasis (OR 1.2, 95% CI 0.95–1.51) | Age, sex, smoking status, waist circumference, blood glucose level, blood cholesterol and triglyceride level, hypertension |
| Kluth, 2013[22] | USA (non-muscle-invasive bladder cancer cohort study) | 892 patients | 1996–2007 | BMI 30 kg/m$^2$ or greater *vs* less than 30 kg/m$^2$ | 68.0 years (median) | 42.8 months (median) | 59 | BMI ≥ 30 kg/m$^2$ was an independent predictor of disease recurrence (HR 2.66, 95% CI 2.12–3.32), progression (HR 1.49, 95% CI 1.00–2.21), cancer specific mortality (HR 3.15, 95% CI 1.74–5.67), any cause mortality (HR 1.42, 95% CI 1.06–1.92) | Age, sex, concomitant CIS, tumor size, number of tumors and intravesical therapy |
| Wyszynski, 2014[23] | USA (non-muscle-invasive bladder cancer cohort study) | 726 patients | 1994–2001 | BMI according to WHO classification | NA | 6.0 years (median) | NA | BMI associated with an increased risk or recurrence<br>HR 1.33 (95% CI 0.94–1.89)<br>HR 2.24 (95% CI 1.14–6.28) higher BMI with smoking status | Age, sex, smoking status, stage, grade, tumor size, multiplicity and intravesical therapy |

BCa, bladder cancer; BMI, body mass index; CI, confidence interval; CIS, carcinoma in situ; FEV1, forced expiratory volume 1st second; HR, hazard ratio; MetS, metabolic syndrome; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; OR, odds ratio; RR, risk ratio; WHO, World Health Organization.

**Table 2** Relevant clinical studies of the relationship between diabetes mellitus and pathological and prognostic factors of BCa

| Author year (ref.no) | Country and study design | Population | Time period (years) | Definition/criteria | Age (years) | Follow up (mean or median) | No. BCa deaths | Outcomes/comments | Covariates adjustment |
|---|---|---|---|---|---|---|---|---|---|
| Diabetes mellitus and pathological and prognostic factors of BCa | | | | | | | | | |
| Coughlin, 2004[26] | USA (prospective cohort study) | Cancer Prevention Study II<br>467 922 men<br>588 321 women | 1982–1998 | Diabetes status was ascertained by a self reported questionnaire<br>26 617 (5.7%) men<br>26 186 (4.5%) women | 57 (mean) | 16 years | Men<br>996 BCa death<br>83 diabetics<br>913 non diabetics<br>Women<br>363 BCa death<br>23 diabetics<br>340 non diabetics | Diabetes was a significant predictor of bladder cancer mortality only in men<br>RR = 1.43 (95% CI 1.14–1.80)<br>RR 1.30 (95% CI 0.85–2.00, *P* = ns) women | Age, sex, race, BMI, years of education, family history of that cancer in a first-degree relative, physical activity, smoking status, alcohol consumption, total red meat consumption, citrus fruit/juice consumption, vegetable consumption, replacement estrogens (women) |
| Campbell, 2012[27] | USA (prospective cohort study) | Cancer Prevention Study II<br>467 143 men<br>586 688 women | 1982–2008 | Diabetes status was ascertained by a self reported questionnaire<br>26 565 (5.6%) men<br>26 090 (4.4%) women | Stratified | 26 years | Men<br>2108 BCa death<br>121 diabetics<br>1987 non diabetics<br>Women<br>801 BCa death<br>37 diabetics<br>764 non diabetics | Diabetes was a significant predictor of bladder cancer mortality only in men<br>RR = 1.22 (95% CI 1.01–1.47)<br>RR 1.13 (95% CI 0.81–1.59, *P* = ns) women | Age, sex, smoking status, BMI, level of education, amount of physical activity during work and leisure time, aspirin intake, usual daily intake of beer, wine, and hard liquor, average weekly dietary intakes of red and processed meats and vegetables +<br>Women: parity, age of menarche, menopausal status, postmenopausal hormone use, oral contraceptives and age of first birth |
| Jee, 2005[29] | South Korea (prospective cohort study) | Korean Cancer Prevention Study<br>829 770 men<br>468 615 women | 1992–2002 | Diabetes status was ascertained on the basis of self-report, medication use, fasting serum glucose level greater than 126 mg/dL, or a combination of these<br>42 380 (5.1%) men<br>21 087 (4.5%) women | 45.3 (mean) men<br>49.6 (mean) women | 10 years | NA | Fasting serum glucose >126 mg/dL was significant associated with bladder cancer mortality only in men<br>HR 1.57 (95% CI 1.00–2.50)<br>HR 1.23 (95% CI 0.97–1.56, *P* = ns) women | Age, sex, smoking status, alcohol use |
| Tseng, 2009[28] | Taiwan (prospective cohort study) | Taiwan Cancer register (nationwide) | 1995–1998 recruiment | 113 347 men and 131 573 women with medical diagnosis of diabetes | Sex-specific mortality rates for age 25–64, 65–74, and ≥75 years | 11 years<br>1995–2006 | Men 494 overall BCa death<br>Women 2291 overall BCa death | Diabetes was correlated with BCa mortality, most of all in younger patients<br>The relative risk of bladder cancer mortality for diabetic patients was 2.18 (95% CI 1.75–2.72), 2.50 (95% CI 2.06–3.04), and 5.95 (95% CI 4.57–7.74) in men, and 1.34 (95% CI 0.96–1.89), 2.48 (95% CI 1.92–3.19), and 7.44 (95% CI 5.46–10.15) in women, for ages ≥75, 65–74, and 25–64 years, respectively | Age, sex, smoking status, BMI, alcohol use |

**Table 2** *Continued*

| Author year (ref.no) | Country and study design | Population | Time period (years) | Definition/criteria | Age (years) | Follow up (mean or median) | No. BCa deaths | Outcomes/comments | Covariates adjustment |
|---|---|---|---|---|---|---|---|---|---|
| Lam, 2011[30] | Asia + Australia (36 prospective cohort studies) | Asian Pacific Cohort Study Collaboration 367 361 subjects | NA | Diabetes status was ascertained on the basis of self-report 23 560 (6.4%) diabetics | 48 (mean) | 4 years (median) | 105 overall BCa death | Positive trend of association between diabetes and bladder cancer mortality HR 1.42 (95% CI 0.70–2.86) overall | Age, sex, smoking status, BMI, alcohol use, education, diagnosis region |
| Seshasai, 2011[31] | Europe + North America (multicentric cohort study) | Emerging Risk Factors Collaboration 820 900 subjects | NA | Diabetes status was ascertained on the basis of self-report, medication use, fasting serum glucose level greater than 126 mg/dL, or a combination of these 40 851 (4.9%) diabetics | 55 (mean) | 13.6 years (median) | 834 overall BCa death | Positive trend of association between diabetes and bladder cancer mortality HR 1.40 (95% CI 0.91–2.17) overall | Age, sex, smoking status, BMI When available, adjustment were also carried out for systolic blood pressure, lipid levels, PCR, fibrinogen levels, alcohol use, estimated glomerular filtration rate, indicators of socioeconomic status |
| Liu, 2012[32] | Sweden (cohort study) | Swedish cancer register (nationwide) | 1961–2008 | 16 123 patients with medical diagnosis of diabetes | NA | 7 years (mean) | 294 overall BCa death | Diabetes was associated with BCa mortality HR 1.33 (95% CI 1.18–1.49) overall | Age, sex, BMI, smoking status, alcohol use, socioeconomic status, diagnosis region |
| Rieken, 2014[36] | Multicentric radical cystectomy retrospective cohort study | 1502 | 1992–2008 | Diabetes status was ascertained on the basis of a history of DM and medical therapy | 66.0 (median) | 34 months (median) | 402 overall BCa death | Diabetes was associated with increased risk of bladder cancer mortality (HR 1.53) and any cause mortality (HR 1.52) | Age, sex, BMI, smoking status, stage, grade, lymph vascular invasion, lymph nodes metastasis, concomitant CIS, surgical margins, adjuvant chemotherapy |
| Hwang, 2011[38] | South Korea (non-muscle-invasive bladder cancer retrospective cohort study) | 251 patients | 2000–2010 | Diabetes status was ascertained on the basis of a history of DM, medical therapy, fasting serum glucose level greater than 126 mg/dL Evaluation of HbA1c levels | 67.0 (median) | 34 months (median) | NA | Diabetes was an independent factor for recurrence free survival (HR 2.1), progression free survival (HR 9.3) HbA1c ≥7% was associated with a higher rate of multiplicity ($P = 0.001$, tumor grade ($P = 0.03$), and intravesical treatment ($P = 0.04$) | Age, sex, smoking status, hypertension, intravesical treatment, stage, grade, size, multiplicity, serum creatinine |
| Rieken, 2013[37] | Multicentric non-muscle-invasive bladder cancer retrospective cohort study | 1117 patients | 1996–2007 | Diabetes status was ascertained on the basis of a history of DM and medical therapy | 67.0 (median) | 64 months (median) | 50 overall BCa death | Diabetes was associated with increased risk of disease recurrence (HR 1.45, 95% CI 1.09–1.45) and progression (HR 2.3, 95% CI 1.40–4.06) | Age, sex, stage, grade, size, multiplicity, concomitant CIS, primary *vs* recurrent tumors |

**Table 3** Relevant clinical studies of the relationship between hypertension, dyslipidemia and pathological and prognostic factors of BCa

| Author year (ref.no) | Country and study design | Population | Time period (years) | Definition/criteria | Age year (mean or median) | Follow up (mean or median) | No. BCa death | Outcomes/comments | Covariates adjustment |
|---|---|---|---|---|---|---|---|---|---|
| Hypertension and pathological and prognostic factors of BCa | | | | | | | | | |
| Batty, 2003[48] | England (prospective cohort study) | Whitehall Study 17 498 subjects | 1967–1970 recruiment | WHO definition | 40–64 years | 25 years | 92 | No correlation was found between BCa mortality and hypertension<br>For 10 mmHg increase aging adjusted pooled OR = 1.01 (95% CI 0.87–1.18)<br>And multiply covariates adjusted pooled OR = 1.08 (95% CI 0.92–1.27) | Age, employment grade, smoking status, blood pressure-lowering medication, marital status, disease at study entry, BMI, triceps skinfold thickness, FEV1, cholesterol blood level |
| Stocks, 2012[49] | Sweden (prospective cohort study) | MeCan project 577 799 subjects | 1972–2005 | WHO definition | 44.0 years (mean) | 12.0 years (mean) | 274 | A positive correlation was found between BCa mortality and hypertension only in men<br>For 10 mmHg increase HR 1.26 (95% CI 1.05–1.51, $P = 0.08$) | Smoking status, sex, BMI, birth year |
| Dyslipidimia (statin use) and pathological and prognostic factors of BCa | | | | | | | | | |
| da Silva, 2013[56] | USA (radical cystectomy cohort study) | 1502 patients<br>Statin use 642 patients (42.8%) | 1998–2002 | — | 65.5 (mean) | 34.0 months (median) | 402 (26.8%) | No correlation between statin use and BCa mortality<br>HR = 1.04 (95% CI 0.84–1.28) | Age, sex, smoking status, stage, grade, positive soft tissue surgical margin, lymph vascvular invasion, lymph node invasion, concomitant CIS |
| Crivelli, 2013[57] | USA (non-muscle-invasive bladder cancer study cohort) | 1117 patients<br>Statin use 341 patients (30.5%) | 1996–2007 | — | 65.0 (mean) | 62.7 months (median) | – | Statin use was not associated with disease recurrence<br>HR = 1.08 (95% CI 0.89–1.31, $P = 0.41$), disease progression HR = 0.99 (0.66–1.51, $P = 0.97$), cancer-specific mortality HR = 1.23 (0.69–2.19, $P = 0.49$) or any-cause mortality HR = 1.14 (0.89–1.44, $P = 0.30$) | Age, sex, smoking status, stage, grade, concomitant CIS, tumor size, multiplicity and intravesical therapy |

developing countries. Its prevalence has dramatically increased over the past few years, reaching epidemic proportions. BMI is generally used to define the grade of obesity, which is usually stratified according to the World Health Organization and the National Institutes of Health classification criteria (overweight as a BMI ≥ 25 kg/m$^2$ and obesity as BMI ≥ 30 kg/m$^2$).

Data from the 2011–2012 National Health and Nutrition Examination Survey reported that the age-adjusted prevalence of obese Americans was 34.9%, and it has been estimated that in 2015, 75% of Americans adults will be overweight and 41% will be obese.[10] In Europe, we have lower mean percentages of obesity, with a peak of nearly 30% in some countries, such as Italy and Spain.[11]

There is a growing body of literature showing the negative influence of obesity on genitourinary malignancies.[12]

As for the risk of BCa, the data are not unique, with several epidemiological studies showing a positive relationship between obesity and an increased risk of BCa,[13,14] whereas others did not outline any statistical correlation.[7,15] Qi *et al*. recently meta-analyzed the findings of 11 cohort studies showing an overall significant correlation between obesity and an increased risk of BCa (RR 1.10, 95% CI 1.06–1.16).[16]

Likewise, a few studies have investigated the influence of obesity on pathological factors and prognosis of BCa, with conflicting results.

Calle *et al*., for instance, carried out a large prospective study on 900 000 USA adults investigating the role of obesity in the mortality risk of many types of cancer.[17] Their findings showed that the risk of mortality of both PCa and kidney cancer significantly increased with increasing BMI values, whereas they did not find a significant association with BCa.

Conversely, Batty *et al*., in a prospective cohort study regarding more than 18 000 middle-aged men enrolled in a medical examination between 1967 and 1970 with a median follow up of 28.1 years, showed that there was an elevated risk of BCa-related mortality in men who were either overweight (HR 1.68, 95% CI 1.06–2.65) or obese (HR 1.19, 95% CI 0.27–5.18).[18]

Hafron *et al*. in a retrospective cohort study including 288 consecutive patients undergoing either radical or partial cystectomy, showed that there was no significant association between increasing BMI and the overall survival, the cancer-specific survival and a higher pathological stage; in contrast, age greater than 65 years, a positive soft tissue surgical margin and smoking status kept their independent predictor status for both overall and cancer-specific survival (all $P < 0.05$).[19]

Similarly, using a retrospective cohort of 390 patients undergoing RC, Maurer *et al*. found no significant difference in terms of overall survival rates at 5-year follow up between normal and overweight patients either receiving ileal conduits ($P = 0.14$) or ileal neobladders ($P = 0.12$).[20]

Finally, Chromecki *et al*. found that obese patients were older ($P < 0.001$), had higher tumor grade ($P < 0.001$) and were more likely to have positive soft tissue margin ($P < 0.006$).[21] In addition, after adjusting for standard clinicopathological features, obesity emerged as an independent predictor of cancer recurrence (HR 1.67, 95% CI 1.46–1.91), cancer-specific mortality (HR 1.43, 95% CI 1.24–1.66) and overall mortality (HR 1.8, 95% CI 1.60–2.05). Comparably, in a retrospective cohort study of 262 patients, Cantiello *et al*. showed that higher BMI values were associated with a higher pathological stage (OR 1.30, 95% CI 1.09–1.55), a higher risk of lymph vessel invasion (OR 1.43, 95% CI 1.17–1.74) and lymph nodes metastasis (OR 1.20, 95% CI 0.95–1.51), although no data on survival were available.[9]

Recently, two studies analyzed the role of obesity in terms of prognosis of superficial BCa. Kluth *et al*., in a retrospective cohort study of 892 patients with primary superficial high-grade BCa, showed that obese patients experienced worse outcomes than their non-obese counterparts.[22] More specifically, after adjusting for the effects of sex, concomitant carcinoma *in situ*, tumor size, number of tumors and previous intravesical therapy, at a median follow up of 42.8 months, obesity was associated with an increased risk of disease recurrence (HR 2.66, 95% CI 2.12–3.32), disease progression (HR 1.49, 95% CI 1.00–2.21), cancer-specific mortality (HR 3.15, 95% CI 1.74–5.67) and any cause of mortality (HR 1.42, 95% CI 1.06–1.92). Similarly, Wyszynski *et al*., in a USA population-based study of 726 patients with superficial BCa and a 6-year median follow up, reported that high BMI values at diagnosis were modestly associated with an increased risk of recurrence (HR 1.33, 95% CI 0.94–1.89).[23] The same data also suggested that among current smokers, being overweight increased more than twofold the risk of recurrence as compared with individuals of normal weight (HR 2.67, 95% CI 1.14–6.28).

As a whole, these not univocal findings would suggest a possible correlation between pathological factors and prognosis of BCa and obesity, but further clinical studies are required to better elucidate this possible relationship.

## DM and BCa

DM is a highly prevalent and growing health problem worldwide that determines severe acute and chronic complications. Several studies suggest that patients with t2DM have an increased risk of developing many different types of cancer.[24] It is not clear whether the association between DM and cancer is either direct – thus because of poor glycemic control and of DM-related derangements, such as insulin resistance with hyperinsulinemia – or it is indirect and a consequence of common risk factors, first of all obesity. In this context, most studies suggested a positive association between t2DM and a greater risk of BCa.[25]

Furthermore, besides its role as an independent risk factor for the development of BCa, DM could have a further significant impact on pathological outcomes and prognosis. Throughout the past decade, several studies have been published documenting an increased BCa mortality in individuals with t2DM. Coughlin *et al*. in a large prospective mortality study related to a cohort of 1.2 million Americans and a follow-up of 16 years (CPS II), suggested that DM may be an independent risk factor for BCa-related deaths in men (RR 1.43, 95% CI 1.14–1.80), with an elevated although not significant rate in women (R.R 1.30, 95% CI 0.85–2.00).[26] The 26-year follow-up findings of CPS II study have recently been published; in this updated analysis, Campbell *et al*. replicated the earlier findings regarding BCa: an increased risk of death in diabetic patients was observed only in male individuals (RR 1.22, 95% CI 1.01–1.47).[27]

In an Asian prospective cohort study, Tseng *et al*. reported a higher risk of BCa mortality in diabetic patients, which was more remarkable in the group of younger patients.[28]

A 10-year prospective cohort study, including 1.3 million Koreans aged 30–95 years, found a linear trend of increasing mortality along with an increased fasting glucose level in all cancer patients and for cancers of several sites, such as the pancreas, liver, esophagus and colon/rectum.[29] In the cohort of patients with BCa, a significant association was found only for those male patients with a fasting serum glucose level of 126 mg/dL or higher, after adjusting for age, smoking status and alcohol use.

Another recent Asian cohort study showed a positive trend of association between t2DM and BCa mortality (HR 1.42, 95% CI 0.70–2.86).[30]

These findings were confirmed by the results of a relevant European and North American multicenter cohort study, which showed a positive trend of correlation between DM and a BCa-related premature mortality (HR 1.40, 95% CI 0.91–2.17), with a linear association between fasting glucose levels greater than 100 mg/dL and the risk of death.[31] Likewise, a large Swedish cohort study confirmed that patients with BCa and t2DM were at increased risk for cancer-specific mortality compared with patients without t2DM (HR 1.33, 95% CI 1.18–1.49).[32] Finally, a recent cumulative meta-analysis showed that DM was positively associated with BCa mortality in both men (RR 1.55, 95% CI 1.30–1.82) and women (RR 1.50, 95% CI 1.05–2.14).[33]

A further controversial debate is related to the possible anticancer effect of several drugs used for the management of t2DM. Among them, metformin, the most commonly used drug in patients with t2DM, primarily acts through an improvement of insulin sensitivity and a concomitant decrease of hepatic gluconeogenesis.[34] Metformin treatment has potential antineoplastic activity including adenosine monophosphate kinase pathway activation, p-53 activation, downregulation of cyclin D1, inhibition of the mammalian target of rapamycin pathway and suppression of the HER2 oncoprotein expression, which showed in both *in vivo* and *in vitro* models a decreased growth of different malignant cell types, thus including human BCa cells.[35]

A retrospective analysis of a cohort of 1502 patients with muscle-invasive BCa submitted to RC showed that t2DM patients who did not use metformin had both an increased risk of cancer-specific mortality (HR 1.53, 95% CI 1.12–2.09) and any cause mortality (HR 1.52, 95% CI 1.16–2.09) as compared with those t2DM patients who have been regularly treated with metformin.[36]

Likewise, a potential protective role of metformin was also reported for NMIBCa patients; indeed, NMIBCa patients with concomitant t2DM who did not take metformin had a significantly shorter recurrence-free survival and progression free survival than their counterparts either without t2DM or with t2DM but under metformin treatment.[37] In another retrospective study of 251 patients with NMIBCa, Hwang *et al*. showed that a poor glycemic control (HbA1c ≥7%) was associated with tumor-related recurrence or risk factors for progression (i.e. grade, multiplicity).[38]

Thiazolidinediones have been shown to promote BCa cell migration and invasion,[39] and a number of epidemiological studies supported the hypothesis that long-term treatment with thiazolidinediones (namely, pioglitazone) was associated with an increased risk of BCa.[40] However, a clear association was never established between pioglitazone and either recurrence or progression of BCa or an increased mortality.

Finally, some *in vitro* studies provided evidence of a potential risk of BCa associated with insulin use. Indeed, insulin seemed able to activate epidermal growth factors and to cause a time- and dose-dependent proliferation of RT4 BCa cell lines.[41] Another recent *in vitro* study suggested that high-dose human insulin or long-acting insulin analogous glargine could promote T24 BCa cell proliferation through activation of protein kinase B.[42] In addition, both hyperinsulinemia, as a result of endogenous hypersecretion, and exogenous insulin administration might activate the insulin-like growth factor pathway, which stimulates BCa cell proliferation and inhibits apoptosis. In a recent USA case–control study, diabetic patients treated with insulin had a not-significant 2.2-fold higher risk of BCa compared with individuals without DM, but the analysis had several limitations inherent to the case–control design, thus including small numbers of diabetic patients both in the control and the BCa group, a failure to differentiate between different types of DM and DM duration, and the different forms of insulin used.[43] A recent observational study that used data from the CPS II cohort study showed a higher risk of invasive BCa among insulin users compared with diabetics who did not use insulin.[44] A large Taiwanese population-based study showed a correlation between human insulin use and BCa only in age-sex adjusted multivariate models, which became insignificant when results were adjusted for all covariates.[45] The same study also showed that human insulin was predictive of BCa mortality after adjusting for all important confounders, thus including DM duration and smoking habit.

As a whole, according to the available epidemiological data, t2DM seemed to be associated with worse BCa oncological outcomes, although further studies have to be implemented in order to define if prevention and treatment of DM could eventually influence the evolution of BCa diagnosis and treatment.

## Hypertension and BCa

Whether hypertension or antihypertensive agents influence cancer incidence and mortality is still a matter of debate.[46] Grossman *et al*. reported the findings of a meta-analysis based on 10 longitudinal studies with a total of 47 119 patients; they found that hypertension was associated with an age- and smoking-adjusted pooled OR of 1.23 (95% CI 1.11–1.36) for all cause cancer mortality, with the most pronounced association between hypertension and renal cell carcinoma mortality (OR 1.75, 95% CI 1.61–1.90).[47] No data were specifically available for BCa. However, the limitations of that study included the lack of data on several covariates, such as the use of antihypertensive medication, which could have influenced risk estimates. In another study including 17 498 participants, after adjusting for several potential confounding factors – such as antihypertensive drugs – blood pressure was inversely associated with mortality from leukemia and pancreatic cancer, but positively associated with liver and rectal cancer.[48] With regard to BCa mortality, no correlation was found for a 10-mmHg increase with aging – adjusted pooled OR of 1.01 (95% CI

0.87–1.18, $P = 0.87$) and multiple covariates-adjusted pooled OR of 1.08 (95% CI 0.92–1.27, $P = 0.36$). However, that study was hampered by small study size, and by the issue of confounding and reverse causality (cancer caused hypertension).

More recently, most of the previous limitations have been overcome in a large study of seven European prospective cohorts aimed at evaluating the association between blood pressure, and cancer incidence and mortality (Me-Can project).[49] Cancer risk increased linearly with increasing blood pressure levels and, for both incidence and mortality, the association was stronger for men than for women. With regard to BCa, a positive correlation was also found for incidence and mortality only in men, but not in women, with HR per 10-mmHg increment of 1.12 (95% CI 1.04–1.21, $P = 0.02$) and of 1.26 (95% CI 1.05–1.51), respectively.

The role of antihypertensive drugs use on cancer is yet uncertain. Over the past few years, several observational prospective trials suggested that a lot of classes of antihypertensives (beta-blockers, calcium channel blockers, diuretic drugs) could be associated with an increased risk of cancer; however, all these studies are certainly difficult to interpret because of their small simple size, short follow up, and inherent selection and ascertainment biases. A recent meta-analysis by Sipahi *et al*. showed a modestly increased risk of cancer (1–2%) with a newer class of antihypertensives (angiotensin receptor blockers), but several limitations were acknowledged by the investigators, such as few trials included and post-hoc analyses.[50] A further recent meta-analysis evaluating 70 randomized controlled trials, showed no different risk of cancer between the antihypertensive treatment groups, thus including angiotensin-receptor blockers, and no difference in cancer mortality.[51] However, the authors showed a slightly increased risk of cancer when an angiotensin-receptor blocker was given along with an angiotensin-converting enzyme inhibitor, therefore concluding that it should not be considered a preferred combination for long-term treatment of high blood pressure. More specifically, as for BCa, there is only a small USA study evaluating the correlation between antihypertensive drugs and this cancer, with striking results and in contrast.[52] In a population of 1585 individuals, the authors showed that the history of hypertension was not related to BCa; however, among hypertensive individuals, there was a significant difference in BCa risk related to the use of diuretics or antihypertensive drugs ($P$ for heterogeneity = 0.004). Indeed, hypertensive individuals who regularly used diuretics/antihypertensives had a similar risk of BCa as compared with individuals without hypertension (OR 1.06, 95% CI 0.86–1.30), whereas untreated hypertensive individuals had a 35% risk reduction (OR 0.65; 95% CI 0.48–0.88).

In conclusion, data on the correlation between BCa and hypertension are uncertain and inconclusive. Similarly, the eventual correlation between antihypertensive drugs, and BCa risk and mortality would need to be better clarified, even regardless of final blood pressure levels.

### Dyslipidemia and BCa

A number of studies have examined the correlation between cholesterol levels and site-specific cancers. Strohmaier *et al*. recently examined the findings of a prospective cohort study including data from the Me-Can project; overall, total cholesterol levels were associated with decreasing risk of cancer in women, and with decreasing risk of cancer at several sites for both men (liver/intrahepatic bile duct, pancreas, non melanoma of skin and lymph/hematopoietic tissue) and women (gallbladder, breast, melanoma of skin and lymph/hematopoietic tissue).[53] Likewise, a positive association was only found for colon cancer in men. With regard to BCa incidence, no significant correlation was found in both sexes. In addition, in the lag-time analysis, some inverse associations persisted, thus suggesting that although competing risk (cardiovascular mortality before cancer diagnosis) and reverse association (blood cholesterol-related metabolic depression in cancer patients) could explain the major inverse associations, some etiological roles cannot be ruled out.

All published studies are limited by the lack of information regarding the use of antihypercholesterol medications, such as statins. In terms of BCa, a large population-based case–control study showed that a prolonged (more than 4 years) use of statins was associated with an increased risk of BCa (OR 1.29).[54] Conversely, several cohort studies and a recent meta-analysis were not able to highlight any significant correlation between statins use and an increased risk of BCa.[55]

In patients with MIBCa treated with RC, statin users were not at higher risk for disease recurrence and cancer-specific mortality.[56] Similarly, in a retrospective analysis of 1117 patients with NMIBCa, statin users did not experience different outcomes as compared with non-users.[57] In addition, statins use did not affect the efficacy of bacillus Calmette–Guérin immunotherapy, thus supporting no modification or discontinuation from statin therapy in patients with high-risk NMIBCa.[58,59] In contrast, a single study with a limited cohort of 84 patients showed that the discontinuation of statin therapy during BCG immunotherapy could improve the clinical outcome, as the use of statins was significantly associated with an increased risk of tumor progression and a subsequent need for RC.[60]

## Conclusions

Currently, published findings would suggest that MetS, as a whole, might be associated with an increased risk of BCa in male patients, although its cumulative effect does not seem to be superior to its individual components in terms of both cancer-specific mortality and worse oncological outcomes after surgery. However, further studies with adjustment for appropriate confounders are urgently required to better elucidate the relationship between MetS, its components and BCa, along with potential pathogenic pathways behind this association.

Considering the primary components of MetS (hypertension, obesity and dyslipidemia) individually evaluated, available data are uncertain, and it is not possible to reach a conclusion yet on either a direct or an indirect association with BCa risk and prognosis. Only with regard to t2DM, available data would suggest a potential negative correlation. However, as the evaluation of BCa risk and prognosis in patients with metabolic disorders is certainly complex, because of the different clinical combinations of the various metabolic abnormalities, further studies are required to assess the actual role of these metabolic disorders.

## Conflict of interest

None declared.

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