

REVIEW

Obesity and urogenital cancer in men: biological mechanisms and clinical implications

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Abstract

Obesity is a highly prevalent global health issue, affecting more than 890 million adults worldwide, with over 2.5 billion adults being overweight. In men, obesity is a leading determinant of morbidity and premature mortality, contributing to cardiovascular, metabolic and oncological diseases, including urogenital cancers, such as renal, bladder, and prostate cancers, as they are highly susceptible to the adverse effects of obesity on metabolic, inflammatory, hormonal, and immune pathways. Excess adiposity predominantly acts as a biological modifier of tumor aggressiveness, progression, and clinical outcomes. Chronic inflammation, insulin resistance, dysregulation of the insulin-like growth factor axis, adipokine imbalance, oxidative stress, and endocrine disruption create a pro-tumorigenic environment that facilitates malignant transformation and disease progression. In men, these mechanisms are amplified by increased visceral fat and obesity-related hypogonadism. Renal cell carcinoma (RCC) is the urogenital malignancy most strongly associated with obesity, with an approximately 30–35% increase in RCC risk for every 5 kg/m² increase in body mass index (BMI). Globally, RCC accounts for approximately 2.2% of all newly diagnosed cancers, with more than 430,000 new cases annually, highlighting its growing public health burden. Conversely, in bladder and prostate cancers, obesity, besides increasing the risk of cancer development, affects tumor characteristics, treatment response, and disease outcomes. Interestingly, typical anthropometric measurements, such as BMI, are insufficient to determine obesity-related cancer risk, thus, a better evaluation of body composition, with determination of fat mass, fat-free mass, and intra- and extra-cellular water through bioelectrical impedance analysis, is needed. This review discusses the link between obesity and development of urogenital cancers, its potential negative influences on treatment responses and clinical outcomes, as well as the putative pathogenic mechanisms underlying these associations. We focused on kidney, bladder, and prostate cancers, excluding testicular and penile tumors, for which the association between obesity and cancer appears to be weaker.

Keywords

Obesity; Urogenital cancer; Renal cancer; Bladder cancer; Prostate cancer; Metabolic dysfunction; Men's health

1. Introduction

Obesity represents one of the most severe public health problems worldwide, with a steadily increasing prevalence, particularly among adult men. According to the World Health Organization, more than 890 million adults are obese, while over 2.5 billion are overweight. In Europe, approximately one in four adult men is obese, and the prevalence continues to increase across all age groups, making obesity one of the leading contributors to cardiovascular disease, type 2 diabetes, chronic kidney disease, and several malignancies [1–3].

Although traditionally regarded primarily as a lifestyle-related condition, obesity is now recognized as a heterogeneous and multifactorial disease that encompasses an array of metabolic, inflammatory, hormonal, and immunological alterations, including disturbances in glycemic and lipid homeostasis, increased production of pro-inflammatory cytokines, altered circulating levels of insulin and sex hormones, and impaired immune responses [4–6]. Importantly, these changes extend beyond an imbalance between energy intake and expenditure or simple adipose

tissue expansion, as they have been shown to have broad impacts on the functioning of diverse organ systems, in particular the cardiovascular system, thus affecting disease susceptibility to several obesity-related conditions, including diabetes, ischemic heart disease, hypertension, male infertility, and even cancer [4, 7–12]. The relationship between obesity and cancer has received increasing attention in recent years, with substantial epidemiological evidence supporting an association between excess adiposity and a higher incidence, greater aggressiveness, and increased mortality across a wide range of cancers [12, 13].

At the biological level, obesity-related metabolic, pro-inflammatory, hormonal, and immunological dysregulation has been proposed to create a pro-tumorigenic microenvironment at both systemic and local tissue levels [13–15] that contributes not only to tumor initiation, but also to subsequent disease progression. In men, this biological framework is further influenced by sex-specific patterns of adipose tissue distribution and endocrine regulation, with visceral adiposity assuming a particularly important pathogenic role [16, 17]. At the molecular level, obesity-driven carcinogenesis is sustained by the persistent activation of several oncogenic signaling pathways, including Nuclear Factor kappa-light-chain-enhancer of activated B cell (NF- κ B), Janus Kinase/Signal Transducer and Activator of Transcription 3 (JAK/STAT3), Phosphoinositide3-kinase/Protein Kinase B/Mechanistic Target of Rapamycin (PI3K/AKT/mTOR), Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase (MAPK/ERK), Hypoxia-inducible factor-1 α (HIF-1 α), and Wntless Int-1/beta catenin (Wnt/ β -catenin) signaling. Collectively, activation of these pathways promotes cell proliferation, inhibits apoptosis, stimulates angiogenesis, induces epithelial-to-mesenchymal transition, and facilitates immune evasion, thereby creating a microenvironment that favors tumor initiation, progression, and metastatic dissemination [12, 14].

Urogenital cancers constitute a major source of morbidity in male populations worldwide. Among them, kidney, bladder, and prostate cancers represent the most common urogenital malignancies in men, accounting for a substantial proportion of the global cancer burden [18, 19]. According to the Global Burden of Disease Study 2021, prostate cancer accounts for approximately 7.3% of all newly diagnosed cancers worldwide, bladder cancer for approximately 3.0%, and kidney cancer for approximately 2.2%, corresponding to more than 1.5 million, 610,000, and 430,000 new cases annually, respectively [18]. Despite major advances in early diagnosis, including the development of liquid biopsy approaches, urinary biomarkers, circulating tumor DNA (ctDNA), and multiparametric molecular profiling, as well as significant improvements in minimally invasive and robot-assisted surgery and the introduction of novel oncological therapies, including immune checkpoint inhibitors, patient outcomes remain strongly influenced by host-related factors, such as metabolic health and body composition. In this context, increased fat mass together with a decrease in lean mass and alterations in intra- and extra-cellular water distribution may have important clinical implications and eventually affect the pharmacokinetics and bioavailability of

oncological drugs [20].

There is growing evidence suggesting that obesity is not only a coincidental comorbid condition in men with urogenital cancer, but also an independent modifier of tumor biology, disease aggressiveness, and response to therapy [21–24]. Renal cell carcinoma has one of the strongest and most consistent associations with obesity among all solid tumors, which provides biological plausibility for a direct mechanism by which excess adiposity contributes to renal carcinogenesis [22, 25]. Conversely, in bladder and prostate cancers, the relationship seems more complex, with obesity having an increasing impact on tumor progression, aggressiveness, and clinical outcomes rather than on incidence itself [23, 24, 26, 27]. The different effect of obesity across different cancer types might also reflect the heterogeneity in the definition of obesity among different studies.

Traditional measures such as body mass index (BMI) are being increasingly acknowledged as insufficient proxies for obesity-related cancer susceptibility. BMI does not account for body fat distribution, visceral adiposity, sarcopenia, or metabolic health, which have been recognized as relevant determinants of oncologic outcomes [28]. This limitation has contributed to conflicting observations, including the so-called “obesity paradox” (*i.e.*, better cancer-specific and overall survival in obese patients), particularly in kidney cancer, and highlights the importance of refining obesity phenotyping in both research and clinical practice [29–31]. From a clinical point of view, obesity represents a challenge with a wide array of implications for urogenital cancer management. Obesity can hinder cancer diagnosis, increase surgical difficulties, alter medication kinetics, and affect responses to immune therapy [32]. In addition, obesity is commonly associated with cardiovascular disease, diabetes, and endocrine disorders, which further increase the risk of mortality [33].

Epidemiological studies indicate that obesity accounts for approximately 44% of type 2 diabetes cases, 23% of ischemic heart disease cases, and up to 41% of selected obesity-related cancers worldwide [1]. Moreover, obese individuals have a two- to four-fold higher risk of developing type 2 diabetes and a substantially increased risk of hypertension, dyslipidemia, hypogonadism, and cardiovascular mortality [7, 9, 34]. These indicate a need for metabolic and lifestyle factors to be addressed in urologic cancer management, especially from a men’s health perspective. Within this context, the aim of this narrative review is to present an interdisciplinary analysis of the relationship between obesity and urogenital tract malignancies in males. Discussions on the general pathogenic mechanisms linking obesity and cancer, and their impact on malignancies of the kidney, bladder and prostate, could help elucidate the biological basis underlying this relationship and its clinical implications for urologic oncology, as well as inform future preventive measures and development of more holistic approaches for cancer management among men.

2. Methodology

A literature review was performed to determine the relationship between obesity and urogenital cancer, together with the potential biological mechanisms underlying this association.

We searched three databases (Google Scholar, Scopus, and PubMed) to identify clinical studies, preclinical studies, systematic reviews, meta-analyses, and book chapters addressing the role of obesity in cancers of the urogenital tract in terms of prevalence and pathogenic mechanisms. Our search encompassed a period of 20 years (*i.e.*, from January 2006 to January 2026), which, in our opinion, represents the period during which the role of obesity in carcinogenesis in general, and in urogenital oncology in particular, has been the subject of increasing clinical and preclinical research. Abstracts and meeting proceedings were excluded. The key terms used for the search were male obesity, renal cancer, kidney cancer, bladder cancer, and prostate cancer. MM, LR, CS, AC and AM independently reviewed the literature regarding kidney cancer; SC, PPP, DA, and CM reviewed literature on bladder cancer, and LS, ST, LN and FC reviewed literature on prostate cancer. This was followed by cross-evaluation between the groups (*i.e.*, each group also evaluated the work performed by the other groups), and any disagreements were discussed. Overall, 120 records were initially identified through the literature search. After screening the titles and the full-text articles, 95 publications were considered eligible and included in this narrative review based on their scientific quality, methodological rigor, and relevance to the objectives of the study.

3. Obesity and cancer: general pathogenic mechanisms

The relationship between obesity and cancer has been supported by numerous evidence, placing excess adiposity in a fundamental biological role in carcinogenesis rather than a coincidental or associative condition [35]. We consider that obesity should be viewed as a chronic systemic illness that can significantly affect metabolism, immune function, and endocrine regulations, which, in turn, contribute to the creation of a modified cellular and molecular environment in which cancer can arise and progress [36]. For males, in particular, such alterations are important in view of sex-related differences in fat distribution and endocrine regulation, with visceral adiposity now identified as a leading pathogenic factor [37]. Rather than acting through a single isolated pathway, obesity promotes cancer initiation and progression through a complex and interconnected network of mechanisms that operate at both systemic and tissue-specific levels, creating a pro-tumorigenic environment in various organ systems, including the urogenital tract.

3.1 Metabolic inflammation and growth-promoting signaling

Among the many biological features associated with obesity, inflammation is one of the most common and prominent, typically referred to as metabolic inflammation [38, 39]. During adipose tissue expansion, particularly in visceral fat, adipocytes enlarge and become functionally stressed [40]. This, in turn, triggers local hypoxia, endoplasmic reticulum stress, and adipocyte apoptosis, which in turn promote homing and activation of immune cells, particularly macrophages, causing pro-inflammatory changes [41]. In

obese adipose tissues, macrophages tend to accumulate around dead adipocytes in the form of crown-like structures, thus perpetuating the release of inflammatory mediators [41, 42]. Elevated levels of cytokines such as tumor necrosis factor- α , interleukin-6, and interleukin-1 β not only result in local inflammation, but also contribute to a systemic inflammatory state affecting tissues beyond adipose tissue [43, 44]. These mediators trigger the activation of key oncogenic signaling pathways such as nuclear factor kappa B and Signal Transducer and Activator of Transcription 3, which regulate genes involved in cell division, survival, angiogenesis, and immune evasion. The persistent activation of these pathways creates a tumorigenic environment favoring the development of neoplastic cells. In addition, the inflammatory process induces epigenetic changes, including variations in DNA methylation patterns and microRNA expression [45, 46]. These changes lead to long-lasting alterations in gene regulation that favor carcinogenesis. In urogenital tissues, prolonged exposure to inflammatory signals may compromise epithelial structure and facilitate early neoplastic transformation. Closely linked to inflammatory signaling, obesity-related insulin resistance represents a central metabolic abnormality that further amplifies pathways known to promote cancer. Reduced insulin sensitivity in peripheral tissues causes compensatory hyperinsulinemia, with chronic exposure of cells to high insulin levels [47]. Apart from its metabolic effects, insulin acts as a growth factor, exerting mitogenic and anti-apoptotic effects. Hyperinsulinemia inhibits hepatic production of insulin-like growth factor-binding proteins, thereby increasing the bioavailability of insulin-like growth factor 1. Insulin and insulin-like growth factor 1 activate intracellular signaling cascades, such as the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin and mitogen-activated protein kinase pathways, which are frequently perturbed in cancer [48]. Chronic stimulation of these pathways drives cell division, protein synthesis, and angiogenesis, together with an increase in resistance to apoptosis, all of which are hallmarks of tumor growth and survival. In metabolically sensitive organs, such as the kidney and prostate, sustained activation of insulin and insulin-like growth factor signaling may accelerate tumor progression and favor more aggressive disease phenotypes [49].

3.2 Adipose tissue as an endocrine and metabolic driver of cancer

Adipose tissue is an endocrine organ that actively secretes a wide variety of adipokines, which exhibit systemic and local biological effects. During obesity, the adipokine secretion profile is markedly altered in a way that favors the creation of a pro-tumorigenic environment [50]. On one hand, leptin concentrations are elevated in proportion to fat mass and, in addition to appetite regulation, leptin also plays a major role in a variety of biological processes. For instance, leptin induces cell proliferation, migration, and angiogenesis, also activating inflammatory signaling, with its receptors found to be expressed in different urogenital tissues [51]. On the other hand, the level of adiponectin, an adipokine with anti-inflammatory, insulin-sensitizing, and anti-proliferative effects, is markedly

reduced in individuals with obesity. Low adiponectin levels are inversely associated with cancer risk and are also associated with higher tumor aggressiveness and worse patient prognosis. In fact, the leptin–adiponectin imbalance removes an important protective brake on uncontrolled cell growth and promotes oncogenic signaling [52].

In addition, adipose tissue is actively engaged in tumor–stroma crosstalk through direct metabolic interactions with cancer cells. Fat cells can provide free fatty acids and other metabolic substrates that fuel the high energy demands and biosynthesis rate of cancer cells. The crosstalk between tumor and adipose tissue is particularly important in malignancies directly adjacent to one or more adipose depots, such as kidney tumors surrounded by perirenal fat, although it may also exert systemic effects on tumors located far from adipose tissue. Through these mechanisms, adipose tissue is not merely a passive energy reservoir, but becomes an active contributor to tumor growth [53].

3.3 Hormonal, oxidative, and immune dysregulation in obese men

Obesity can change the hormonal milieu in men, mostly due to the increased aromatase activity in fat tissues. Aromatase converts androgens into estrogens, leading to lower circulating testosterone levels and a relative excess of estrogens. The altered estrogen-to-androgen ratio contributes to obesity-related hypogonadism and is particularly relevant in hormone-sensitive tissues. Androgen signaling is crucial in the prostate for maintaining cell differentiation and homeostasis. Obesity-induced hormonal changes can disrupt this balance, thereby favoring the development of poorly differentiated and aggressive tumor clones [54, 55]. It is somewhat surprising that low testosterone levels have been linked to higher-grade prostate cancer at diagnosis, suggesting that inflammatory and metabolic stress might override normal androgen-driven mechanisms of carcinogenesis.

Hormonal imbalances are also closely linked to oxidative stress and immune dysfunction. Nutrient surplus, mitochondrial dysfunction, and inflammation are major factors contributing to increase in reactive oxygen species (ROS), while antioxidant defenses may be insufficient to counteract ROS generation. High levels of oxidative stress, when sustained, cause DNA strand breaks, base modifications, and chromosomal instability, which in turn increase the mutation load and trigger malignant transformation [56, 57]. Over time, the buildup of genetic and epigenetic changes results in tumor heterogeneity and progression, especially in urogenital tissues, which are continuously exposed to metabolic and hormonal changes.

Interestingly, despite the presence of chronic inflammation, obesity is associated with reduced antitumor immunity. Both innate and adaptive immune responses are altered by excess adiposity, leading to T-cell exhaustion, loss of cytotoxicity, and weakened immune surveillance. Such an immune-dysfunctional state facilitates tumor immune evasion and may also affect the response to immunotherapeutic strategies. Immune mechanisms significantly contribute to disease control in urogenital cancers, and therefore obesity-related immune

dysfunction represents an important factor that may influence treatment success and overall survival [58].

4. Obesity and kidney cancer

Kidney cancer, especially renal cell carcinoma (RCC), is the urogenital cancer most closely and consistently linked to obesity. Compared with other solid tumors, the epidemiological pattern of RCC shows a particularly clear association with increasing adiposity, thus making the kidney a model organ for obesity-driven cancer development in men [59]. Several large prospective cohort studies and meta-analyses have convincingly shown that the greater the amount of excess body weight, the higher the risk of developing RCC, with a dose-dependent association that remains significant even after adjustment for major confounders correlated with both obesity and RCC, such as smoking and hypertension [60]. The link between obesity and RCC is more evident in men than in women, likely reflecting sex-specific differences in fat distribution, metabolic profile, and endocrine regulation. Visceral adiposity, which predominates in the male population, has emerged as a more relevant determinant of RCC risk and aggressiveness than BMI alone, highlighting the limitations of traditional anthropometric measures in capturing obesity-related cancer risk [61].

4.1 Metabolic and inflammatory vulnerability of the kidney

Obesity-driven metabolic and inflammatory changes can strongly affect the kidneys, which, because of their high vascularity, are continuously exposed to blood-borne hormones, growth factors, lipids, and inflammatory signals. In obesity, long-term insulin resistance causes hyperinsulinemia and ongoing insulin–Insulin-like Growth Factor (IGF) signaling, thereby promoting renal tubular epithelial cell proliferation and reducing apoptosis. These growth-promoting signals can make cells more likely to become cancerous, especially after long-term metabolic stress. Obesity often coexists with dyslipidemia and abnormal fatty acid metabolism, leading to lipid buildup in kidney tissues and tubules [62]. This lipotoxic state impairs mitochondrial function, induces ROS generation and causes oxidative DNA damage. Over time, oxidative stress can lead to the accumulation of genetic and epigenetic changes that destabilize the genome and may trigger tumor development [63].

Chronic low-grade inflammation can further aggravate renal damage because cytokines such as interleukin-6 and tumor necrosis factor- α promote endothelial dysfunction, fibrosis, and persistent cellular stress in renal tissue. Obesity can also alter renal microcirculation and oxygen delivery, resulting in local hypoxia. Reduced oxygen availability activates hypoxia-responsive pathways, including hypoxia-inducible factors, which are central to the molecular pathogenesis of RCC. Obesity-driven hypoxia can activate these pathways even in the absence of typical genetic changes, tying systemic metabolic dysfunction to the molecular hallmarks of clear cell RCC [64].

4.2 Role of perirenal adipose tissue and local tumor microenvironment

Perirenal fat plays a major role in obesity-associated kidney carcinogenesis [65]. The kidney is surrounded by large amount of fat tissues in close proximity to both normal and cancerous areas. In obesity, perirenal fat undergoes significant changes, including immune cell infiltration, adipocyte expansion, reduced oxygen levels, and altered adipokine production. This adipose tissue is not just a bystander, but represents an active participant in the cross-talk between the tumor and its microenvironment. The perirenal adipocytes can supply free fatty acids and other energy sources to RCC cells and secrete leptin, interleukin-6, and Vascular Endothelial Growth Factor (VEGF), which promote growth and neoangiogenesis, and immune evasion. This microenvironment created by obesity may cause cancers to become aggressive [66]. As a consequence of this active cross-talk, cancer can signal changes to the fat tissues, which, in turn, promotes an environment favorable to cancer progression. Thus, perirenal fat should be considered an important contributor to RCC progression in obese men.

4.3 Tumor biology, clinical implications, and the obesity paradox

In obese patients, RCC may exhibit distinct biological characteristics. Recent transcriptomic and metabolomic studies have linked these tumors to alterations in lipid metabolism, inflammation, and immune regulation in clear cell RCC, systemic and local metabolic dysregulation may intensify its lipid-rich phenotype, supporting oncogenic signaling and tumor survival. Obesity-driven oxidative stress may also increase intratumoral heterogeneity, which could affect disease course and treatment response.

Obesity is linked to higher RCC risk, yet some observational studies have found that obese patients may have better cancer-specific and overall survival, a phenomenon known as the obesity paradox [67, 68]. One possible explanation is that patients with a higher BMI may adequately preserve their fat and muscle mass, thus allowing a better nutritional status and potentially gaining a survival advantage by delaying the onset of cachexia. An alternative explanation for the obesity paradox may involve differences in the expression of fatty acid metabolism genes. Fatty acid synthase (FASN) is an enzyme that regulates de novo fatty acid biosynthesis, an essential process for tumor growth. Interestingly, FASN is downregulated in patients with obesity and higher FASN expression has been shown to be associated with worse survival. An upregulation of FASN may confer cancer cells a survival advantage, making it a potential metabolic oncogene.

BMI is an imperfect surrogate for biologically distinct body composition compartments, such as visceral adipose tissue and muscle mass, and inferences about the overall metabolic state based on BMI alone are therefore incomplete. Growing evidence indicates that visceral fat, sarcopenia, and metabolic dysfunction may predict prognosis more accurately than BMI, and when these factors are considered, the apparent “protective” effect of obesity often weakens [69].

Clinically, obesity affects kidney cancer treatment in men. Excess body fat increases surgical complexity during partial or

radical nephrectomy and may increase the risk of perioperative complications [70]. Obesity-related comorbidities, such as hypertension, diabetes, and cardiovascular disease, can also affect treatment selection, tolerance, and long-term outcomes. These considerations underline the importance of metabolic assessment and improvement in RCC management. Addressing obesity through lifestyle modification and metabolic control should be viewed not only as a preventive strategy, but also as a potential adjunct to oncologic treatment within a comprehensive men’s health framework.

5. Obesity and bladder cancer

Bladder cancer is among the most frequent cancers of the male urogenital system and remains a major cause of cancer-related morbidity and mortality worldwide. When comparing renal cell carcinoma and bladder cancer, the link between obesity and bladder cancer seems less clear in terms of incidence [71]. However, an increasing body of evidence is showing that obesity has an important impact on tumor biology, disease severity, and clinical outcomes. In men with a higher prevalence of visceral obesity and metabolic syndrome, excess adiposity may act as a systemic promoter of cancer development rather than as an isolated etiological factor.

5.1 Metabolic and inflammatory mechanisms in bladder carcinogenesis

Obesity may promote bladder cancer through metabolic and inflammatory changes that indirectly affect the urothelium. Chronic low-grade inflammation is an important factor, marked by persistently elevated levels of Interleukin-6 (IL-6), Tumor Necrosis Factor- α (TNF- α), and C-reactive protein. These mediators are capable of promoting urothelial cell growth, reducing apoptosis, altering DNA repair mechanisms, and raising genomic instability. Over time, chronic inflammatory signaling can drive malignant changes and tumor progression.

Insulin resistance and compensatory hyperinsulinemia may also contribute to obesity-linked bladder carcinogenesis. Insulin-IGF signaling is implicated in the stimulation of urothelial cell growth through the PI3K/AKT and MAPK pathways, which are often linked to urothelial carcinoma progression [72]. In obese or diabetic patients, hyperglycemia may increase urinary glucose levels, thereby fostering bladder tumor growth. In this setting, obesity often coexists with other metabolic disorders that may synergistically enhance carcinogenic risk [73].

Oxidative stress represents an additional link between obesity and bladder cancer. Increased production of ROS and weaker antioxidant defenses can induce oxidative DNA damage in urothelial cells. Chronic oxidative stress may accelerate the accumulation of genetic alterations and increase tumor heterogeneity, especially in patients with long-term metabolic dysfunction [74].

5.2 Obesity, immune dysregulation, and tumor microenvironment

In addition to metabolic and inflammatory mediators, obesity has been shown to profoundly affect the immune system in ways that have important consequences for bladder cancer. Although obesity is known to be associated with chronic inflammation, it has paradoxically been shown to be associated with dysfunctional antitumor immunity. Immune cell dysfunction in obesity includes reduced cytotoxic T-cell function, T-cell exhaustion, and altered macrophage polarization, which may contribute to tumor immune escape [75, 76].

Antitumor immunity is critical in controlling bladder cancer, and obesity-related immune dysfunction may affect immune surveillance during early tumor development. Furthermore, altered adipokine signaling pathways due to excessive levels of certain mediators, such as leptin, may also affect immune cell function. This may contribute to inadequate antitumor immune responses in the tumor microenvironment [77]. Immune dysfunction in obesity has also been proposed to affect the efficacy of intravesical and systemic immunotherapeutic agents. However, current literature remains heterogeneous, and the relationship between metabolic alterations and antitumor immunity represents an important area of ongoing investigation in bladder cancer.

5.3 Clinical impact, disease aggressiveness, and therapeutic outcomes

Clinical studies have linked obesity with more aggressive forms of bladder cancer and worse patient outcomes. Several studies have reported that obese patients more frequently present with high-grade disease and muscle-invasive tumors. This pattern suggests that metabolic dysfunction may be more closely linked to subsequent tumor progression rather than being a trigger of tumor development [78]. Obesity is also associated with higher perioperative morbidity after radical cystectomy, including increased complication rates, longer operative times, and prolonged hospital stays [79].

Obesity may also influence treatment response and long-term outcomes. Changes in pharmacokinetics, technical challenges during surgical and radiotherapy procedures, and impaired immune function may act together to reduce treatment response. Obesity-related inflammation and reduced immune function may limit the response to intravesical treatment and increase the risk of recurrence, although further research is needed to confirm and clarify these associations [80]. From a broader men's health perspective, bladder cancer often occurs in patients who also have obesity-related conditions such as diabetes, cardiovascular disease, and metabolic syndrome. These comorbidities not only increase competing mortality risks, but may also complicate oncologic management.

Lastly, based on the suggested role of obesity and dietary factors in bladder cancer, adoption of a Mediterranean diet rich in fruits and vegetables, as opposed to a Western diet rich in fat and red meat, has been suggested as a potential preventive measure against bladder cancer. The understanding of obesity as a modifying factor in bladder cancer biology and disease course also highlights the importance of evaluating and managing metabolic abnormalities as part of the comprehensive

management of bladder cancer. Therefore, addressing obesity may improve cancer outcomes and overall health in men with bladder cancer.

6. Obesity and prostate cancer

Prostate cancer is the most common cancer diagnosed in men and remains a major cause of cancer-related mortality worldwide. Among urogenital tumors, it has one of the most complex and debated associations with obesity. Although obesity has not been consistently associated with an increased incidence of prostate cancer, a large number of studies have clearly shown that it is associated with more aggressive disease features, advanced stage, and elevated prostate cancer-specific mortality [81]. The discrepancy between findings on incidence and aggressiveness suggests that the effect of obesity may be more pronounced on prostate cancer progression than on its initiation, thereby identifying metabolic dysfunction as a key modifier of the natural history of prostate cancer.

6.1 Hormonal dysregulation and androgen-estrogen imbalance

Hormonal alterations may represent a key pathway through which obesity contributes to prostate cancer progression. In obese men, higher aromatase activity in adipose tissue increases the conversion of androgens to estrogens, resulting in reduced circulating testosterone levels and a relative excess of estrogen. This shift in the estrogen-to-androgen balance may contribute to obesity-associated hypogonadism and affect the normal maintenance of prostate tissue. Androgen signaling plays a crucial role in maintaining normal cell differentiation and limiting uncontrolled growth. When this regulation is disrupted, tumors may be more likely to develop features associated with greater aggressiveness and poorer differentiation [82].

Paradoxically, men with low testosterone levels at diagnosis are more likely to present with higher-grade prostate cancer and worse oncological outcomes. Rather than protecting against tumor growth, obesity-related hypogonadism may exert selective pressure that favors the survival and expansion of androgen-independent or androgen-insensitive cancer clones. Estrogens may also directly promote cell proliferation and inflammation in prostate tissue through estrogen receptor-mediated pathways. These hormonal alterations interact with metabolic and inflammatory stress, strengthening oncogenic signaling and contributing to tumor aggressiveness in obese men [83].

6.2 Metabolic stress, inflammation, and tumor progression

Besides endocrine dysfunction, the metabolic and inflammatory alterations associated with obesity are also essential for the development of prostate cancer. Hyperinsulinemia resulting from insulin resistance is a key factor in the continuous stimulation of the insulin-IGF signaling pathway, resulting in the proliferation, survival, and resistance to apoptosis through PI3K/AKT/mTOR signaling. The overexpression of these signaling pathways has been observed in aggressive forms of

prostate cancer and has been implicated in the development and resistance to treatment of the disease [84]. Additionally, chronic low-grade inflammation contributes to the development of a tumor-supporting microenvironment in the prostate. The secretion of inflammatory cytokines and adipokines by visceral adipose tissue influences stromal epithelial interactions, angiogenesis, and immune evasion. Specifically, leptin has been found to promote the proliferation, migration, and invasion of prostate cancer cells, while decreased secretion of adiponectin abolishes the inhibitory effects of the latter on the growth of the tumor cells. Additionally, obesity increases ROS production in the body, further increasing the instability of the genome of the cells in the prostate. ROS overproduction, combined with the decreased production of antioxidants, results not only in the development of DNA damage and the accumulation of deleterious mutations in the cells, but also the development of aggressive phenotypes of the disease over time [85].

6.3 Diagnostic challenges, treatment outcomes, and clinical implications

Obesity has important implications for prostate cancer detection and management. A widely recognized diagnostic issue is Prostate-Specific Antigen (PSA) dilution, in which higher plasma volume in individuals with obesity can lead to lower measured serum PSA concentrations. This phenomenon may delay cancer detection and referral for biopsy, which may result in diagnosis at a more advanced stage. Technical difficulties during digital rectal examination and prostate biopsy in obese patients may also reduce the likelihood of early detection.

From a clinical perspective, obesity is linked to poorer outcomes across several treatment modalities. Patients with obesity who undergo radical prostatectomy may face greater technical difficulty, a higher risk of perioperative complications, and less favorable pathological findings, including positive surgical margins. Similarly, obesity can complicate radiotherapy planning and delivery, which may increase toxicity and reduce treatment efficacy. In systemic treatment settings, metabolic dysfunction may alter drug pharmacokinetics and the response to androgen deprivation therapy, which may be associated with earlier disease progression [86].

From a broader men's health perspective, prostate cancer in men with obesity often occurs alongside metabolic and cardiovascular comorbidities that complicate oncologic management and increase competing mortality risks. These considerations support the need to incorporate metabolic assessment, weight management, and lifestyle interventions as routine components of prostate cancer care. Obesity management should be considered not only as a preventive measure, but also as a potential adjunct to standard cancer treatments, with the goal of improving both treatment outcomes and overall health in men [87].

The pathogenic mechanisms and level of supporting evidence whereby obesity may favor urogenital cancers are summarized in Table 1 (Ref. [13, 15, 32, 33, 39, 40, 47, 49–57, 75, 76]).

7. Discussion

Obesity is a major and active biological determinant of urogenital cancer behavior in men. Across renal, bladder, and prostate cancers, obesity acts as a systemic modifier of tumor biology, influencing carcinogenesis, tumor aggressiveness, treatment responsiveness, and clinical outcomes. Carcinogenesis due to excess adiposity results from the interaction of multiple, but not independent, mechanisms. Chronic low-grade inflammation, insulin resistance, dysfunction of the insulin/insulin-like growth factor axis, adipokine imbalance, oxidative stress, hormonal imbalance, and immune dysfunction represent dynamically interacting mechanisms that produce a systemic and local tumor-supportive microenvironments favoring carcinogenesis [7, 9] (Fig. 1). Moreover, in men, a major role is also played by sex-specific factors, including preferential visceral adiposity accompanied by obesity-related hypogonadism, which may have important effects on the urogenital system because of its high sensitivity to metabolic and hormonal perturbations.

The effects of excess adiposity are not uniform, but vary among different urogenital cancers. Renal cell carcinoma represents the urogenital cancer with the strongest and most consistent evidence of an association between carcinogenesis and excess adiposity, with clear epidemiological gradients and well-established links with metabolic stress, hypoxia signaling, and interactions with perirenal adipose tissue. Bladder and prostate cancers show more complex interactions with excess adiposity, with the latter playing a major role as a modifier of tumor progression, aggressiveness, and treatment responsiveness rather than tumor initiation alone. An additional important topic is the inadequacy of BMI as a surrogate predictor of obesity-related cancer risk. BMI does not adequately reflect important determinants of obesity-related cancer risk, such as visceral adiposity, metabolic disorders, sarcopenia, and inflammation, all of which have been shown to affect tumor biology and outcomes [15, 16]. This inadequacy has led to seemingly paradoxical results, such as the “obesity paradox”, particularly in the context of renal cancer. In this regard, increasing evidence shows that when body composition and metabolic status are assessed in a more refined manner, the so-called protective role of obesity is attenuated or may no longer retains its significance. Therefore, in our opinion, there is a need for a more uniform approach to assessing obesity to obtain more consistent results regarding its association with different diseases, including cancer.

Clinically, the impact of obesity is evident in several ways throughout the treatment pathway for urogenital malignancies. Diagnostic challenges, such as dilution of PSA in obese individuals, difficulties with imaging and biopsy procedures, and delayed detection of malignancy, may contribute to diagnosis at a more advanced disease stage. Moreover, obesity may increase surgical technical difficulty as well as the risk of perioperative complications [88]. Obesity also, substantially increases the technical complexity of urological surgery. Meta-analyses have shown that obese patients undergoing radical prostatectomy, radical cystectomy, or partial nephrectomy experience significantly longer operative times (approximately 20–40 minutes), greater estimated blood loss, higher rates of wound complications and surgical-site infections (odds ratio

TABLE 1. Obesity-related pathogenic mechanisms in urogenital cancers and level of supporting evidence.

Mechanism	Biological and Molecular Pathways	Kidney Cancer	Bladder Cancer	Prostate Cancer	Clinical Implications	Highest Level of Evidence	Key Supporting References
Chronic low-grade inflammation	Persistent cytokine release (TNF- α , IL-6, IL-1 β); NF- κ B and STAT3 activation	Tumor initiation and progression	Increased aggressiveness	Tumor progression and high-grade disease	Pro-tumorigenic microenvironment, angiogenesis, immune evasion	Systematic reviews and preclinical studies	[13], [15], [33], [39], [40]
Insulin resistance and insulin-IGF axis	Hyperinsulinemia; increased IGF 1 bioavailability; PI3K/AKT/mTOR and MAPK activation	Biological and epidemiological association	Contribution to progression	Aggressive phenotypes	Increased proliferation; resistance to apoptosis	Translational and observational studies	[47], [49]
Adipokine dysregulation	Increased leptin; reduced adiponectin; altered adipocyte-tumor signaling	Perirenal fat crosstalk	Sustained inflammatory milieu	Enhanced proliferation and invasion	Poor prognosis; disease progression	Systematic reviews and preclinical studies	[50], [51], [52], [53]
Hormonal dysregulation	Increased aromatase; reduced testosterone; relative estrogen excess	Limited role	Minimal role	Central mechanism of aggressiveness	Selection of poorly differentiated clones	Clinical observational and mechanistic studies	[54], [55]
Oxidative stress and DNA damage	Increased ROS; impaired antioxidant defenses	Genomic instability	Increased mutational burden	Tumor heterogeneity	Cancer initiation and progression	Experimental and translational studies	[56], [57]
Immune dysfunction	T-cell exhaustion; impaired immune surveillance; altered macrophage polarization	Immune escape	Reduced response to immunotherapy	Tumor microenvironment modulation	Treatment resistance; disease progression	Translational, experimental, and systematic review evidence	[15], [32], [75], [76]

TNF: Tumor necrosis Factor; IL: Interleukin; NF- κ B: Nuclear Factor kappa-light-chain-enhancer of activated B cells; STAT3: Signal Transducer and Activator of Transcription 3; IGF: Insulin-like Growth Factor; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; mTOR: Mechanistic Target of Rapamycin; MAPK: Mitogen-Activated Protein Kinase; ROS: Reactive Oxygen Species.

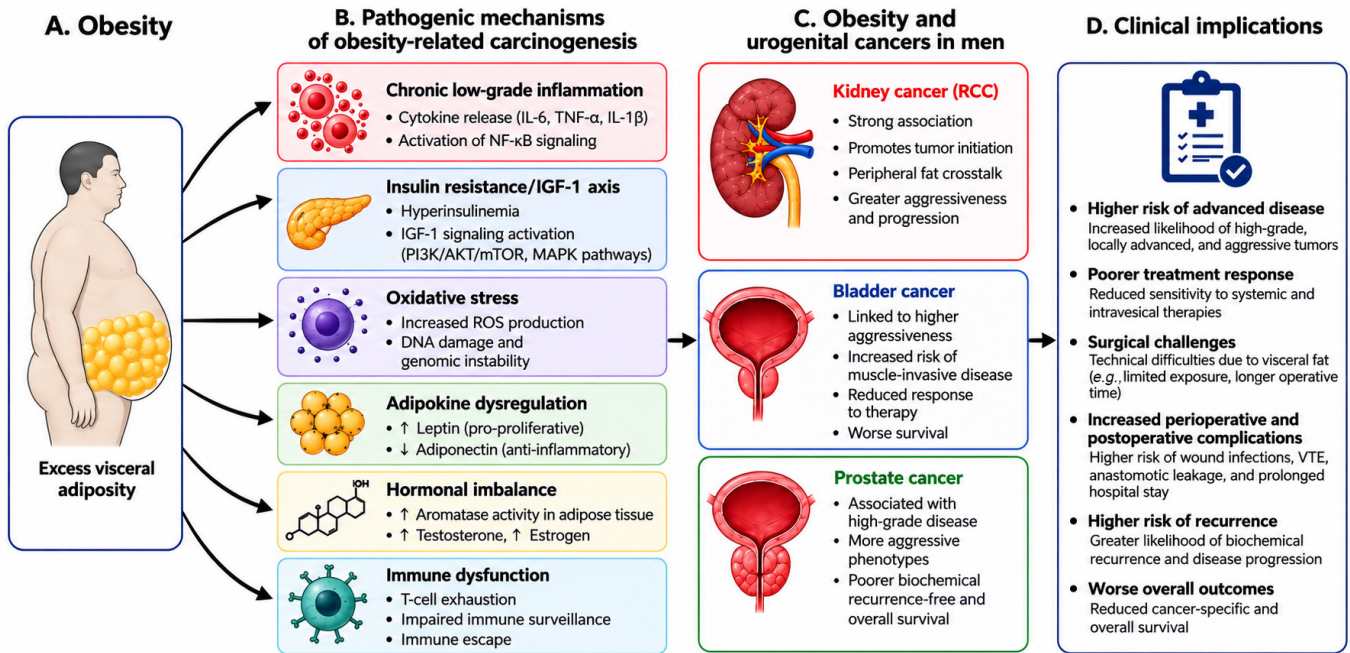


FIGURE 1. Biological pathways linking obesity to urogenital cancers in men. Visceral adiposity (A); Pathogenic mechanisms underlying obesity-related carcinogenesis (B); Most frequent urogenital cancers associated to obesity (C); Obesity-related clinical implications in urogenital cancers (D). IL: Interleukin; TNF: Tumor Necrosis Factor; NF- κ B: Nuclear Factor kappa-light-chain-enhancer of activated B cells; IGF: Insulin-like Growth Factor; PI3K: Phosphoinositide 3-kinase; AKT: protein kinase B; mTOR: mechanistic Target of Rapamycin; MAPK: Mitogen-Activated Protein Kinase; ROS: Reactive Oxygen Species; RCC: renal cell carcinoma; VTE: venous thromboembolism.

approximately 1.3–1.6), and an approximately 20–30% higher overall risk of postoperative complications compared with normal-weight patients [70, 79, 88, 89]. Obesity is also associated with a higher likelihood of conversion to open surgery during minimally invasive procedures and with longer hospital stays [70].

Metabolic changes may also affect the pharmacokinetics of anticancer drugs and the tolerance of obese individuals to radiation therapy. Obesity may alter the pharmacokinetics of anticancer drugs by increasing the volume of distribution of lipophilic agents, modifying hepatic metabolism and renal clearance, and reducing drug penetration into poorly vascularized adipose tissue. These alterations may result in either suboptimal drug exposure or increased toxicity, depending on the therapeutic agent [90]. In radiation oncology, obesity may reduce treatment accuracy because of greater setup variability, organ displacement, and increased tissue thickness, potentially leading to greater irradiation of surrounding healthy tissues and reduced dose conformity [21].

Moreover, obese patients may exhibit immune dysfunction that could specifically affect the response to treatment of the underlying urogenital malignancy. Obesity-associated immune dysfunction is characterized by chronic T-cell exhaustion, impaired cluster of differentiation 8 (CD8⁺) cytotoxic activity, expansion of immunosuppressive regulatory T cells and myeloid-derived suppressor cells, together with polarization of macrophages toward a pro-tumorigenic phenotype. These alterations reduce immune surveillance and may impair the efficacy of intravesical Bacillus Calmette–Guérin therapy, immune checkpoint inhibitors, and other immunotherapeutic

strategies currently used in urological oncology [33].

Despite the rising recognition of the negative role of obesity, several issues still need to be addressed. In particular, it should be considered that the classic anthropometric marker of obesity (*i.e.*, BMI) does not completely reflect the complexity of the condition and that variability in the methods used to define obesity may account for inconsistencies among different studies regarding the role of obesity in urogenital cancer development. There is also a need for prospective research that integrates body composition data with oncologic outcomes. Despite these challenges, this review supports the concept that the management of cancer in general, and urogenital cancer in particular, should also incorporate the treatment of obesity, and obesity-associated comorbidities, such as impaired glucose and lipid metabolism. The importance of identifying and managing the negative impact of obesity may, therefore, have an important impact on the management of urogenital cancers in men [21]. Table 2 (Ref. [21–25, 27, 60, 61, 65–74, 81–87]) summarizes the impact of obesity on aggressiveness and outcomes in specific urogenital cancers.

Considering that obesity may also affect diagnosis, increase the complexity of surgery, influence treatment response or tolerance, and affect clinical outcomes through associated cardiovascular and metabolic comorbidities, the treatment of obesity represents a unique opportunity to reduce risk and improve outcomes in urologic cancers [89]. In this regard, besides lifestyle modifications, including an appropriate dietary pattern and exercise, glucagon-like peptide-1 receptor agonists (GLP-1RAs) are increasingly prescribed for glycemic control in type 2 diabetes and have recently gained popularity for the

TABLE 2. Impact of obesity on incidence, aggressiveness, and clinical outcomes of urogenital cancers in men.

Cancer Type	Association with Obesity	Cancer Incidence	Tumor Aggressiveness	Diagnostic Implications	Clinical Outcomes	Highest Level of Evidence	Key Supporting References
Kidney cancer (RCC)	Strong	Dose-dependent increase in incidence	Increased growth and progression	Not applicable	Obesity paradox reported; visceral adiposity and metabolic health may influence prognosis	Meta-analyses, prospective cohort studies, translational studies	[22], [25], [60], [61], [65], [66], [67], [68], [69], [70]
Bladder cancer	Moderate	Modest or inconsistent increase	Higher grade and muscle-invasive disease	Not applicable	Increased perioperative morbidity; possible reduction in treatment efficacy	Meta-analyses, observational cohort studies, translational studies	[27], [24], [71], [72], [73], [74]
Prostate cancer	Complex	No clear increase; possible reduction in low-grade disease	Association with high-grade and advanced-stage disease	PSA dilution; delayed diagnosis	Higher prostate cancer-specific mortality and worse treatment outcomes	Meta-analyses, prospective cohort studies, systematic reviews	[21], [23], [81], [82], [83], [84], [85], [86], [87]

Since body mass index (BMI) may underestimate the impact of visceral adiposity and metabolic dysfunction on urogenital cancer risk and prognosis, body composition parameters and metabolic health could be considered when possible. RCC: Renal cell carcinoma.

management of obesity [90]. However, their long-term impact on urogenital cancer risk is not fully understood. For kidney cancer, a recent study by Dai *et al.* [91] reported a marginally elevated risk associated with the use of GLP-1RAs. GLP-1RAs exert effects on kidney function that are mediated by GLP-1RA-induced changes in the renal vasculature, although these changes are not associated with increased mitogenesis. The biological mechanisms underlying a potential increase in kidney cancer risk remain unclear. In addition, GLP-1RA, as well as other antidiabetic medications, do not appear to decrease the risk of bladder cancer [92]. In contrast, for prostate cancer, a recent review article by Murphy *et al.* [93] indicated that GLP-1RAs, together with other therapeutic approaches to control metabolic syndrome and obesity, might be useful as a therapeutic strategy, having been demonstrated to cause tumor reduction and inhibition of cell proliferation in Lymph Node Carcinoma of the Prostate (LNCaP) cells. Also, GLP-1RAs have been suggested as promising, novel, therapeutic agents, especially in advanced and metastatic prostate cancer when standard therapies become insufficient [93, 94].

This review has several limitations. In particular, the studies cited in this review employ varying definitions of obesity, including BMI thresholds, waist circumference, or body fat percentage. The variability in the definition of obesity across different studies may affect comparisons among studies and contribute to conflicting findings, such as the obesity paradox in kidney cancer. Another limitation is that we did not include the role of obesity in testicular and penile cancers. However, the evidence linking these two cancer types to obesity is more

limited compared with kidney, bladder, and prostate cancers, which influenced our decision. In particular, regarding the role of obesity in penile cancer, to our knowledge, there are very few reports on the possible association between adiposity and the risk of penile cancer. A very recent Norwegian cohort study including more than 800,000 men showed that a high BMI was associated with an increased risk of penile cancer, highlighting the need for further studies to investigate the possible underlying mechanisms [95].

8. Conclusions

Increasing evidence supports the concept that obesity is not merely a concomitant condition in kidney, bladder, and prostate cancers, but also a factor that actively influences the development, progression, and behavior of these malignancies through a complex interplay of metabolic, inflammatory, hormonal, and immune-mediated pathways. In men, the link between obesity and urogenital cancer relies on the concept that visceral adipose tissue may cause hormonal imbalances, insulin resistance, adipokine abnormalities, and chronic inflammation, which may act synergistically to create a tumor-supporting milieu that favors the development of aggressive phenotypes of the disease and hampers the management of these malignancies. Renal cell carcinoma is most frequently and consistently associated with obesity, reflecting a direct biological relationship mediated by the effects of metabolic stress, hypoxia signaling, and interactions between tumor cells and the adjacent perirenal adipose tissue. In bladder and prostate cancers, the effects of obesity

appear to be more pronounced on disease progression, aggressiveness, and treatment responsiveness than on disease onset, emphasizing the importance of host-related factors in determining tumor behavior. From a men's health perspective, urogenital cancers are often found in patients with multiple comorbidities secondary to obesity, such as diabetes, cardiovascular disease, and metabolic syndrome. Aside from increasing the risk for other causes of mortality, these comorbidities can also affect cancer management and survival. Addressing obesity, therefore, represents an opportunity to improve not only cancer-specific outcomes, but also overall health and quality of life in male patients. Additional research is needed on improving obesity phenotyping, defining the underlying pathogenic mechanisms and evaluating the potential effectiveness of targeted metabolic therapies as adjuncts to the standard treatment of urogenital cancers.

AVAILABILITY OF DATA AND MATERIALS

Not applicable. This manuscript is a narrative review based exclusively on previously published studies. No new datasets were generated or analyzed for the purposes of this review.

AUTHOR CONTRIBUTIONS

MM and LR—conceived and designed the study and drafted the manuscript. ST, DA, CM, LS, LN, PPP, AM, SC and CS—performed the literature search and analysis. FC, AC and CS—critically reviewed the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable. This article does not involve any studies with human participants, human data, or animal subjects.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Lorenzo Romano is serving as one of the Editorial Board members of this journal. We declare that Lorenzo Romano had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial

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