Review

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Review

Is Insulin Resistance a Potential Pathophysiological Mechanism Underlying the Association Between Bladder Cancer and Its Known Risk Factors?

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Highlights

1. Bladder cancer (BC) cases and deaths are projected to increase by over 70% and 85% respectively, by 2040.
2. Emerging BC risks arise from environmental sources like air pollution, microplastics, and contaminated drinking water.
3. Insulin resistance (IR) is presented as the primary, unifying mechanism that connects various BC risk factors.
4. A key consequence of IR is chronic hyperinsulinemia. Hyperinsulinemic state contributes to cancer both by accelerating cell growth and by creating a pro-tumor environment through inflammation and oxidative stress.
5. Established risk factors like obesity, smoking, and poor diet are all identified as drivers of IR.
6. Managing IR through metabolic interventions is a promising and modifiable strategy for preventing BC.
7. Physical activity is a key protective factor, with evidence showing it decreases BC risk by improving insulin sensitivity and reducing inflammation.

Abstract

Growing evidence suggests that insulin resistance (IR) might be a core, unifying mechanism linking various established risk factors for bladder cancer (BC). While factors like smoking, central obesity, sedentary lifestyle, and high-fat diets are known to increase BC risk, a common thread among them is their role in driving IR due to chronic hyperinsulinemia. Hyperinsulinemia promotes BC development in several ways. It acts as a potent growth factor, stimulating the proliferation and inhibiting the programmed cell death of malignant cells by activating the insulin/IGF signaling pathway. Furthermore, IR is closely associated with chronic low-grade inflammation and oxidative stress, both of which contribute to a pro-tumorigenic microenvironment. This convergence of growth-promoting and inflammatory signals highlights the central role of IR. While more research is needed to fully elucidate these complex interactions, the available data suggest that metabolic interventions aimed at improving insulin sensitivity could be a valuable, modifiable strategy for BC prevention.

Keywords: bladder cancer; insulin resistance; obesity; type2 diabetes mellitus; ambient toxicity

1. Introduction

In 2022, more than 600,000 people were diagnosed with BC worldwide and more than 220,000 people died from the disease [1]. Considering the predicted 73% and 87% increase in annual BC cases and deaths by 2040, respectively, there is an urgent need to develop and accelerate BC control

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initiatives for high-risk populations to tackle global BC burden and narrow its geographical disparities [2].

Epidemiological patterns reveal striking demographic disparities: BC is four times more common in men than women and predominantly affects older adults, with over 70% of diagnoses occurring in individuals aged 65 or older [3]. Based on the latest GLOBOCAN data, BC accounts for 3% of global cancer diagnoses and is especially prevalent in the developed world [4].

2. Aim/Methods

The objective of this narrative review was to provide an overview of the literature concerning the mechanistic pathways linking known risk factors to BC pathogenesis and to explore the novel perspective of IR as a potential common pathway.

The search strategy utilized keywords and synonyms related to hyperinsulinemia, insulin sensitivity/resistance, BMI, obesity, abdominal adiposity, metabolic syndrome, and BC risk factors. The searched databases were PubMed, Scopus, Web of Science, and Google Scholar. Gray literature sources, such as government reports and conference proceedings, were not considered. During the preparation of this work the author used AI in order to proofread the manuscript and generate Tables and the Figure. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

3. Results

3.1. The Controversial Role of the Increased Body Weight

An absolute increase in circulating insulin, or hyperinsulinemia, is associated with obesity [5]. Investigation by Jung et al. confirmed these correlations through experimental data [6], indicating that these factors increase the risk of cancer, as also evidenced by findings from Kim et al. [7]. A significant dose-response meta-analysis, which pooled data from 15 cohort studies involving 38,072 BC cases among over 14 million participants, concluded that obesity is associated with a linearly increased risk of BC. This analysis found that for every 5 kg/m^2 increase in BMI, there was a 4.2% increased risk of BC. When comparing BMI categories to normal weight, the pooled relative risks were 1.07 for pre-obese individuals and 1.10 for obese individuals [8].

A study comprehending 17,777 men newly diagnosed with BC analyzed data from the National Health Insurance System and National Health Checkups databases in South Korea with the aim of assessing the association between metabolic health status and the incidence of BC. When compared to the metabolically healthy-normal-weight group, the multivariable-adjusted hazard ratios (HRs) were higher in other categories: Metabolically obese-obese individuals had the highest HR at 1.3; the metabolically obese-normal-weight group showed an HR of 1.18; even the metabolically healthy-obese group exhibited a slightly elevated HR of 1.07. These findings indicate that both obesity and metabolic dysfunction i.e., the presence of at least three metabolic syndrome components, contribute to an increased risk of BC in men [9]. A previous meta-analysis of 14 prospective cohort studies, encompassing 12,642 BC cases, investigated the relationship between BMI and BC risk. The dose-response analysis revealed a nonlinear positive association between BMI and BC risk showing a summary relative risk (RR) of 1.03. This suggests that for every 5 kg/m^2 increase in BMI, there is an approximate 3% rise in BC risk, with this increase being particularly notable when BMI exceeds 30 kg/m^2 [10]. Beyond overall BMI, emerging research also points to specific fat distributions, such as abdominal subcutaneous adipose tissue and the ratio of abdominal subcutaneous to gluteofemoral adipose tissue, as potentially increasing BC risk [11].

A more recent meta analysis of eleven cohort studies demonstrated a statistically significant association between obesity and an increased risk of BC in the overall study population with a RR of 1.10. Furthermore, among the nine studies that controlled for the confounding effect of cigarette smoking, the pooled RR for BC in obese individuals remained statistically significant at 1.09 [12]. Interestingly, patients with non-muscle invasive BC, who had general or abdominal obesity, did not

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experience a higher risk of recurrence, but these forms of obesity might be connected to an increased risk of the disease worsening [13,14]. Among the metabolic syndrome components, central obesity, was positively associated with BC (HR = 1.39), [15]. Nevertheless, BMI warrants further investigation when making therapeutic decision [16]. Unexpectedly, research indicates that a higher BMI could be associated with better survival rates for some individuals with BC, suggesting that obese patients may have a more favorable prognosis, according to the obesity paradox [17].

Until recently major clinical guidelines, including those from the American Urological Association and the Society of Urologic Oncology, did not consider obesity to be an established risk factor for BC [18]. For instance, the International Agency for Research on Cancer (IARC) Working Group considered the evidence "presently inadequate" for BC a stance that contrasts with other experts who have more recently suggested an increased risk [19]. Similarly, the World Cancer Research Fund/American Institute for Cancer Research report on BC, which synthesized findings from numerous prospective cohort studies, also judged the evidence for an association of obesity with BC risk as limited and inconclusive [20]. In line with American Cancer Society, selecting what types of cancer are linked with excess body weight, BC is not included [21]. In parallel, according to the 2020 report from the IARC, there is strong evidence that obesity increases the risk of 13 different cancers; however, this association was not found for BC [22]. This position of scientific societies conflicted with previous studies.

3.2. Rather Established and Vague Risk Factors

After reviewing 1,496 articles, researchers identified several key factors influencing BC risk. They found significant increases in risk associated with: Smoking (cigarettes, pipes, or cigars), obesity, high consumption of processed meat. Conversely, the study found a lower risk linked to increased physical activity, higher body levels of selenium, vitamin D, vitamin A, vitamin E, and folate. Certain occupations also carried a higher risk, with tobacco workers, dye workers, and chimney sweeps showing the highest associations. The likelihood of individual factors causing BC varied widely, from 4% to 68% [23].

A summary of modifiable and non-modifiable risk factors and their molecular mechanisms are provided in Table 1.

Table 1. Risk Factors for Bladder Cancer and Mechanicistic Biochemical Levels.

Category	Risk Factor	Description	Mechanisms
Modifiable	Smoking (Tobacco Use)	The leading risk factor; accounts for ~50% of cases. Carcinogens in smoke (i.e., nitrosamines, polycyclic aromatic hydrocarbons) are absorbed and excreted in urine, damaging bladder epitelium.	DNA damage and mutations in TP53 and RB1 genes [24]. Activation of MAPK/ERK pathway (promotes cell proliferation), [25]. Oxidative stress and inflammation via NF-κB pathway [26].
Modifiable	Occupational Chemical Exposure	Exposure to aromatic amines (i.e., benzidine, 2-naphthylamine) in industries like dye, rubber, leather, and painting. These chemicals are	Metabolic activation via cytochrome P450 enzymes and N-acetyltransferase polymorphisms [27]. DNA adduct formation leading to mutations in FGFR3 and HRAS genes [28]. PI3K/AKT pathway dysregulation (enhances cell survival), [29].

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		metabolized into bladder carcinogens.	
Modifiable	Arsenic in Drinking Water	Chronic exposure from contaminated water (i.e., in certain regions like parts of Asia and South America). Arsenic is a known carcinogen.	Induction of oxidative stress and DNA hypomethylation. Activation of EGFR and MAPK pathways (promotes angiogenesis and proliferation). Inhibition of DNA repair pathways (base excision repair), [30].
Modifiable	Chronic Bladder Irritation/Infections	Repeated urinary tract infections, bladder stones, or long-term catheter use; also linked to parasitic infections like schistosomiasis (common in Africa/Middle East).	Chronic inflammation via NF-κB and COX-2 pathways (leads to squamous cell carcinoma), [31]. Nitrosamine formation from nitrates in urine, causing DNA alkylation, [32]. Upregulation of STAT3 pathway (enhances immune evasion and tumor growth), [33].
Modifiable	Low Fluid Intake/Dehydration	Insufficient water consumption leads to concentrated urine, prolonging exposure to carcinogens in the bladder.	Increased concentration of urinary carcinogens, amplifying DNA damage. Indirect activation of oxidative stress pathways (ROS-mediated damage), [34]. Potential link to altered metabolic pathways like urea cycle dysregulation, [35].
Modifiable	Certain Medications/Treatments	Prior use of cyclophosphamide (chemotherapy) or pelvic radiation therapy for other cancers.	Alkylating agents cause DNA cross-links and mutations in TP53. Radiation induces double-strand breaks, activating ATM/ATR DNA damage response pathways. PI3K/AKT/mTOR pathway overactivation (promotes cell survival post-damage), [36].
Non-Modifiable	Age	Risk increases significantly after age 55; ~90% of cases occur in people over 55.	Accumulation of somatic mutations over time (i.e., in FGFR3 and TERT genes). Age-related decline in DNA repair pathways (nucleotide excision repair).Telomere shortening and senescence bypass via p16/RB pathway [37].
Non-Modifiable	Gender (Male)	Men are 3-4 times more likely to develop BC, possibly due to higher smoking rates and occupational exposures historically.	Hormonal influences (androgen receptor signaling may promote tumor growth), [38]. Genetic factors like X-chromosome inactivation in females providing protective effects [39].

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			Interaction with smoking-related pathways (enhanced CYP1A1 metabolism in males), [40].
Non-Modifiable	Family History/Genetics	Inherited predisposition (i.e., Lynch syndrome or polymorphisms in genes like GSTM1, NAT2). Family history increases risk by 1.5-2 times.	Germline mutations in mismatch repair genes (MSH2 in Lynch syndrome), leading to microsatellite instability [41]. Polymorphisms in detoxification pathways (GST and NAT enzymes affecting carcinogen metabolism), [42]. Hereditary activation of Wnt/β-catenin or RAS pathways, [43].
Non-Modifiable	Race/Ethnicity	Higher incidence in White populations compared to Black or Asian; possibly due to genetic and environmental factors.	Genetic variations in drug-metabolizing enzymes (CYP2D6 polymorphisms), [44]. Epigenetic changes influencing pathways like histone modification. Interaction with environmental exposures amplifying TP53 mutations [45].

Legend to Table 1: BC, bladder cancer. ROS, reactive oxygen species.

Many risk factors converge on common pathways, such as: DNA Damage Response: Involves TP53 and RB1 genes, leading to loss of cell cycle control. Oncogenic Signaling: FGFR3 mutations (common in non-muscle-invasive bladder cancer) and PI3K/AKT (in muscle-invasive types). Inflammation: NF-κB pathway drives chronic irritation to cancer. Metabolic Activation: Liver enzymes (i.e., CYP450) convert exposures into active carcinogens that target the bladder. Key signaling pathways contributing to aberrant proliferation include hypoxia-inducible factor 1 (HIF-1), nuclear factor-kappa B (NF-κB), the phosphoinositide 3-kinase/Akt (PI3K/Akt) pathway, insulin-like growth factor receptor 1 (IGF-1R), Wnt signaling, and dysregulated cell cycle associated proteins. Evidence Level: Smoking and chemical exposures are the strongest links, supported by large cohort studies. Others are associative.

3.3. Smoking

Smoking is a major cause of BC [47]. Recent findings from the NIH-AARP Diet and Health Study (started in 1995) show that current smokers face a higher risk of BC compared to never-smokers. This increased risk is more pronounced than what was observed in studies from earlier cohorts (1963-1987), suggesting that the link between smoking and BC risk in the U.S. has strengthened over time [48]. Studies indicate that smokers with a higher BMI often consume more cigarettes daily and may experience a greater level of nicotine dependence than smokers who are leaner [49]. Among 499,504 adults studied, a clear link was found between smoking and obesity. The more a person smoked, the higher their risk of obesity. Additionally, the risk of obesity for former smokers decreased the longer they had been smoke-free. Notably, former heavy smokers were 60% more likely to be obese than former light smokers [50].

Data from the Korea National Health and Nutrition Examination Survey were analyzed to explore the relationship between smoking and IR, which was defined by the triglyceride-glucose index (TyG). Participants were classified based on urinary metabolite levels into continuous-smokers, past-smokers, current-smokers, and non-smokers. Multiple logistic regression indicated that continuous-smokers and past-smokers (both men and women) had an increased risk of high IR. This observation suggests that smoking cessation could be protective against insulin resistance [51].

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Nicotine appears to cause IR in skeletal muscle by activating the mTOR pathway. This suggests that developing treatments to block mTOR activation in skeletal muscle could help prevent IR in people who cannot quit smoking or are regularly exposed to secondhand smoke [52]. Research indicates that both active smoking and exposure to secondhand smoke are associated with impaired glucose tolerance and impaired fasting glucose [53]. Indeed, high prevalence of e-cigarette was noted among obese population [54], but the malignant potential of e-cigarettes for BC remains unknown and is likely less than that of combustible cigarettes [55].

3.4. Microplastics

Very recent investigation identified a statistically significant spatial clustering of BC incidence. This clustering was predominantly observed in geographical areas exhibiting elevated chemical risk-screening environmental indicator scores, particularly those correlated with documented bladder carcinogens and the presence of microplastic (MP) waste [56]. The demonstrated tumorigenic potential of bisphenol (BP) A and BP S, absorbed onto MP surfaces, coupled with their established ligand-receptor binding affinities and the presence of cognate receptors within the bladder urothelium, collectively suggest a plausible mechanistic involvement of these BPs in the pathogenesis of BC [57].

The precise implications of MP exposure on human health remain an area of ongoing investigation. However, laboratory animal models and cell culture studies collectively indicate that these xenobiotics may contribute to the etiology of obesity through multifaceted mechanisms [58].

Polystyrene (PS) microplastics and nanoplastics have been shown in recent laboratory studies to cause IR in skeletal muscle cells. This happens because the MP lead to mitochondrial dysfunction, which in turn generates an excess of mitochondrial ROS, [59].

For better understanding of the health hazards posed by MP, past studies in mice show that PS can worsen metabolic disorders like IR. The effect, observed when comparing mice on a normal diet to those on a high-fat diet, was obtained by disrupting gut microbiota, leading to pro-inflammatory responses [60]. Beyond the physical properties of the MP themselves, plastic additives constitute a significant concern as co-contaminants. Numerous such additives, including organotins, phthalates, and various toxic metals beyond bisphenols, are recognized for their capacity to modulate adipocyte differentiation and interfere with the expression and function of proteins crucial for lipid and glucose metabolism [61]. These additives activate specific cellular components, including nuclear receptors, peroxisome proliferator-activated receptors (alpha, beta, and gamma), and the retinoid X receptor. This activation, in turn, triggers a range of negative effects such as oxidative stress, cell toxicity, harm to the immune system, disruption of thyroid hormones, and changes in fat cell development and energy production [62]. Notably, BP A, a ubiquitous monomer in plastic synthesis, is a well-established endocrine-disrupting chemical. A exposure is positively associated with IR in humans [63]. Such endocrine disruption can profoundly impact metabolic regulation and predispose individuals to weight gain.The escalating global prevalence of overweight and obesity represents a substantial public health challenge, given their strong association with an increased risk of severe co-morbidities, including but not limited to type 2 diabetes mellitus (T2DM) and various neoplastic conditions.The promotion of SOCS-3 expression by BP A may inhibit insulin signal transduction, thereby contributing to the development of IR [64].

3.5. Smog

Researchers conducted an umbrella review of seven studies (five meta-analyses and two systematic reviews) to determine how air pollutants affect obesity. They examined the impacts of common pollutants like PM1, PM2.5, PM10, NO2, SO2, and O3. Most studies indicated that exposure to air pollution was linked to a higher risk of obesity, although the effects varied among different pollutants [65]. A systematic review of 37 studies and meta-analysis of 21 epidemiological studies suggests a significant connection between exposure to air pollution and an increased risk of urological cancers. Specifically authors found that for every 5 $\mu g/m^3$ increase in PM2.5, the risk of BC

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rises by 7%. Similarly, a 10 μg/m³ increase in NO2 is associated with a 4% higher risk of BC. These findings highlight the potential for public health interventions. If these links are indeed causal, lowering PM2.5 levels to 5.8 μg/m³ could lead to a reduction of 1.5 to 27 urological cancer cases per 100,000 people (age-standardized rate) in the countries most affected by high PM2.5 and urological cancer burden [66].

It is not fully understood how environmental air pollutants cause cancer, but the dose and duration of exposure play a role. Carcinogens found in air pollution, whether individually or in mixtures, disrupt several molecular processes. They can cause direct damage or indirect damage through systemic inflammation and oxidative stress. This leads to the inactivation of tumor suppressor genes, the activation of oncogenes, and changes in the cell cycle dependent on p53 activation. Additionally, these pollutants can cause energy dysregulation, chromosome instability, inhibition of apoptosis, and increased cell proliferation in somatic cells. This information was reviewed in recent article [67]. Evidence suggests ambient PM2.5 – even at low concentrations – can diminish metabolic insulin sensitivity. This lends plausibility to the idea that air pollution exposure potentiates T2DM development [68].To corroborate earlier findings, long-term exposures to PM2.5, PM10, NO2 or SO2 are indeed associated with the odds of IR. Among the analyzed pollutants, inhalable particulate matters appear to exert greater impacts on IR [69].

3.6. Drinking Water

Groundwater contamination by arsenic has emerged as a significant worldwide issue, posing a severe health risk to millions [70]. Arsenic exposure increases blood sugar levels and the risk of hyperglycemia by increasing IR. This effect is more pronounced in females than in males [71].

A comprehensive review of 30 years of epidemiological research, encompassing 40 qualifying studies, reveals that the majority of these (28 out of 40) found a clear link between arsenic in drinking water and BC. Specifically, meta-analyses predicted the risk of BC incidence to be 2.7, 4.2 and 5.8 times higher at arsenic levels of 10, 50, and 150 μg/L. This means that at an exposure level of just 50 μg/L, there was an 83% probability of increased BC incidence and a 74% probability of higher mortality from the disease [72].

3.7. Public Water Disinfection

A statistically significant difference was observed in female serum cholesterol levels, with higher concentrations found in communities with chlorinated water supplies [73]. On the contrary, short-term exposure to chlorinated drinking water at 20 ppm appears to have no significant impact on parameters of lipid in healthy humans [74]. Most interestingly, daily intake of water with fluoride concentrations >1.5 mg/l produces IR [75]. One meta analysis involving over 17,000 individuals from European and North American populations suggests that drinking chlorinated water may increase the risk of BC. In this analysis of six case-control and two cohort studies, men who ever consumed chlorinated water had a 40% higher chance of developing BC while women drinking water showed a 20% higher chance. The risk appeared to be dose-dependent, with a 40% increased risk for long-term exposure. Furthermore, the study indicated a linear increase in risk over time, with a 27% increase after 40 years of exposure for both sexes combined [76]. The interaction of disinfectants with wastewater's organic constituents can yield byproducts, including trihalomethanes (THM). Of the sixteen BC susceptibility genetic variants identified via genome-wide association studies, a single nucleotide polymorphism at locus rs907611, situated within the lymphocyte-specific protein 1 region at 11p15.5, exhibited the most robust association with BC risk, especially with elevated THM exposure via potable water [77].

In multivariate models adjusted for potential confounders, participants with a BMI ≥30 had significantly higher odds of T2DM (OR=8.42) compared to those with normal weight, via insulin signaling disruption. Similarly, individuals in the highest tertile of urinary brominated (Br)-THM levels had nearly four times the risk of T2DM (OR=3.99) compared to those in the lowest tertile. Furthermore, among participants with a BMI ≥25, urinary Br-THM concentrations were significantly

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elevated in diabetic individuals compared to healthy controls [78]. Consuming contaminant-free water and increasing intake of plant-based foods can help prevent BC [79].

3.8. Does Sleep Affect Cancer Risk?

Insufficient sleep significantly perturbs the intricate network of hormones controlling appetite. Sleep restriction is associated with a decrease in circulating levels of leptin, an adipokine with satiety-promoting effects, and a concurrent increase in ghrelin concentrations, a potent orexigenic peptide. This hormonal imbalance, coupled with extended sleeplessness providing increased opportunities for caloric intake, is hypothesized to promote hyperphagia and subsequent obesity [80]. Sleep deprivation, whether total or partial, initiates a cascade of physiological alterations that contribute to metabolic dysfunction. This includes an elevation in sympathetic nervous system activity and circadian disruption of endocrine rhythms, specifically observed as increased nocturnal cortisol levels and elevated diurnal GH concentrations. These neuroendocrine shifts collectively contribute to compromised metabolic homeostasis, primarily through the induction of IR and diminished glucose tolerance [81]. Beyond direct metabolic and appetite-related effects, chronic sleep reduction and its sequelae, such as somnolence and fatigue, are implicated in reducing overall energy expenditure. This reduction is attributed to decreased participation in voluntary physical activity and a reduction in non-exercise activity thermogenesis [82,83]. The aforementioned deleterious effects are frequently exacerbated in individuals who are overweight or obese, particularly in the presence of sleep-disordered breathing (SDB). SDB, including obstructive sleep apnea (OSA) central sleep apnea, as well as sleep-related hypoventilation and hypoxemia, is a recognized independent risk factor for IR, thus accelerating the progression of metabolic derangements initiated by sleep loss [84,85]. A study including 380,042 UK Biobank participants showed that both healthy sleep and lifestyle patterns were significantly associated with a reduced risk of BC (HR = 0.61), compared to those with unhealthy patterns [86]. Epidemiological evidence from large community studies indicates that obesity is a strong determinant but not a prerequisite for OSA; the greater proportion of people with OSA have a BMI in the non-obese range [87]. Data from 12 studies since 1814, involving over 9.2 million participants, show a significant link between OSA and an increased risk of BC. A quantitative analysis of nine of these studies found that OSA patients had a 76% higher risk [88].

3.9. Red and Processed Meat

It is biologically plausible that what individuals eat can affect BC risk. This is because both helpful and harmful substances from diet pass through the urinary tract and come into direct contact with the bladder epitelium. Despite this, studies examining the link between diet and BC have often shown conflicting results [89].

To understand the relationship between meat consumption and BC, researchers analyzed five cohort studies involving over one million participants and eight case-control studies with more than 27,000 participants. The findings suggested different impacts for red meat and processed meat. Case-control studies indicated that for every 100-gram daily increase in red meat consumption, the risk of BC rose by 51%. However, cohort studies did not observe this association with red meat. When looking at processed meat, a combined analysis of both study types showed a 20% increase in BC risk for every 50-gram daily increase. The hypothetic mechanism consists in the generation of low ppb levels of mutagenic/carcinogenic heterocyclic amines, during frying and grilling [90].

Furthermore, a systematic review of 21 studies and a meta-analysis of 18 studies (encompassing a massive 1,135,661 participants) points to a strong connection between red and processed meat intake and obesity. The meta-analysis, which included 113,477 individuals, concluded that higher consumption of these meats is a risk factor for obesity, increasing the odds by 37% [91].

Evidence from various populations indicates that the consumption of meat, especially processed and unprocessed red meat, is a significant risk factor for T2DM [92]. These findings suggest that a reduction in meat consumption is a crucial public health measure that should be incorporated into dietary guidelines. High to moderate consumption of meat is linked to a higher risk of IR in women

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who do not have T2DM. Reducing the amount and changing the type of meat people eat could help lower the chances of developing IR [93]. Meat consumption affects blood sugar and insulin levels through several key mechanisms: Nitrosamines can harm the beta cells in the pancreas; saturated fat can lead to obesity, a primary factor in the development of IR; heme iron, advanced glycation end products, and specific amino acids (like leucine), all of which can influence how insulin is secreted [94].

3.10. Alcohol Intake

The relationship between alcohol consumption and BC risk is complex and research findings can be inconsistent. Chronic heavy alcohol consumption may contribute to the development of T2DM by causing pancreatic beta-cell dysfunction, possibly by decreasing the expression of glucokinase, and/or by reducing insulin sensitivity through the inhibition of the insulin receptor [95].

Analyzing nine prospective cohort studies including 1,971,396 individuals no consistent evidence was found to definitively link alcohol consumption to an increased risk of BC [96], even though alcohol is a risk factor for obesity [97]. Other studies suggest a nuanced relationship. One meta-analysis found a 23% increase in BC risk in men [9]. The same meta-analysis by Lao et al. specifically highlighted that consumption of alcohol from liquor or spirits was associated with an increased risk of BC, with a dose-response relationship (i.e., a one-drink increment per day from liquor/spirits increased risk by 9%). Some studies have shown no association with wine consumption, while beer consumption has even been associated with a reduced risk in one study [99]. Research in East Asian populations suggests that individuals with inactive ALDH2 alleles, which affect alcohol metabolism and lead to higher acetaldehyde exposure (a known carcinogen), may have an increased risk of BC with alcohol consumption [100].

3.11. The Advantage of Physical Activity

Physical activity is associated with decreased risk of BC according to a systematic review and meta analysis comprehending 15 studies with 5,402,369 subjects and 27,784 BC cases [101]. While the exact biological ways physical activity prevents BC are not fully understood, research suggests it works through several mechanisms. It may boost the body's ability to remove cancer-causing substances, repair damaged DNA, and regulate cell growth, specialization, and programmed cell death. Physical activity decrease visceral fat, which in turn ameliorates chronic, low-grade inflammation leading to IR [102]. Preventing obesity and T2DM is an effective strategy for reducing the risk of BC, as both conditions are established risk factors. Beyond these direct effects, physical activity might also offer indirect protection by helping people reduce smoking [103]. Understanding the connections between metabolic health, physical activity, and cancer requires a crucial appreciation for the role of mitochondria [104].

3.12. Microbiome and Bladder Cancer

Growing evidence shows the human microbiota drives cancer development through three main pathways: Promoting inflammation; migrating to distant tissues; producing DNA-damaging genotoxins. This microbial risk combines with the danger posed by environmental pollutants. Enzymes like cytochrome P450 metabolize these pollutants, either activating them into potent carcinogens or deactivating them [105]. Proving a direct causative link between specific microbes or microbial patterns and BC remains a significant challenge, despite observed associations [106].

The gut-bladder axis has recently become a key area of focus in BC research. This inter-organ communication is also facilitated by neural pathways, such as vagal signaling, and by shared receptors like the farnesoid X receptor and toll-like receptor 4 [107].

The urinary microbiome engages in complex inter-system crosstalk, notably with the gut microbiome [108]. Current literature review pinpoints that the core mechanisms the regulation of

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SCFAs and gut hormones, both of which are critical modulators of glucose metabolism and inflammation, influencing IR [109].

A systematic review of 27 studies, which included 926 BC patients and 412 control individuals, found that the composition of urinary microbiota is altered in patients with BC. However, the studies varied significantly in their findings regarding the specific types of bacteria that were different [110]. On the other hand population-level studies consistently demonstrate a significant reduction in the abundance of the probiotic genus *Bifidobacterium* within the gut microbiota of current smokers (high risk subjects) compared to non-smokers, a phenomenon observed across diverse ethnic groups [111]. Research has revealed a mechanism where the metabolism of carcinogens by gut microbiota may promote chemically induced carcinogenesis in the bladder. To investigate this link, the scientists utilized a standard mouse model of BC, which is reliably induced by chronic exposure to N-butyl-N-(4-hydroxybutyl)-nitrosamine, examining the microbiota's impact on both carcinogenesis and the compound's toxicokinetics [112].

4. Discussion

What interventions on risk factors should be adopted to reduce the cancer burden? First of all it should be emphasized that BC is typically caused by a combination of risk factors consisting in the existence of a latency period (years or decades) between exposure to carcinogens and the development of BC and an inter-individual variation in the susceptibility to BC based on genetic background, lifestyle, and environmental exposures.

Many of the risks attributed to "obesity alone" are actually mediated by the underlying IR. When studies adjust for markers of IR (like HOMA-IR, fasting insulin levels), the independent effect of BMI on cancer risk often diminishes [113,114]. Therefore, IR is the central metabolic risk factor because it is the active, pathophysiological driver of the pro-growth, pro-inflammatory, and pro-angiogenic environment that BC cells need to initiate, thrive, and progress. Researchers are pushing into new areas to treat IR, whose primary causes are: Chronic consumption of high-calorie diets, particularly those rich in refined carbohydrates and saturated fats, leads to excessive nutrient influx that overwhelms cellular metabolic capacity and impairs insulin signaling; elevated levels of circulating free fatty acids interfere with insulin receptor substrate (IRS) phosphorylation, disrupting the normal cascade of insulin-mediated glucose uptake in muscle and adipose tissue [115,116]; ectopic fat accumulation in non-adipose tissues such as liver, muscle, and pancreas creates lipotoxic conditions that directly impair insulin signaling pathways through the formation of toxic lipid metabolites like diacylglycerols and ceramides [117]; chronic low-grade inflammation, characterized by elevated pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β, activates serine kinases that phosphorylate IRS proteins at inhibitory serine residues rather than activating tyrosine residues [118]; adipose tissue dysfunction in obesity leads to aberrant secretion of adipokines, with decreased adiponectin and increased resistin and leptin levels that collectively promote inflammatory signaling and IR [119]; activation of the inflammasome pathway and nuclear factor-kappa B (NF-κB) in metabolic tissues creates a self-perpetuating cycle of inflammation that progressively worsens insulin sensitivity [120]; mitochondrial dysfunction reduces oxidative capacity and leads to incomplete fatty acid oxidation, resulting in accumulation of lipid intermediates that activate protein kinase C isoforms which inhibit insulin signaling [121]; endoplasmic reticulum stress triggered by nutrient excess activates the unfolded protein response, which includes kinases like JNK and IKK that directly phosphorylate IRS proteins at inhibitory sites [122,123]; oxidative stress and excessive ROS production damage cellular components and activate stress-sensitive kinases that interfere with normal insulin receptor signaling cascades [124]; genetic polymorphisms in genes encoding insulin receptor, IRS proteins, glucose transporters, and enzymes involved in glucose metabolism can predispose individuals to reduced insulin sensitivity [125,126]; epigenetic modifications including DNA methylation and histone acetylation patterns altered by environmental factors can silence genes essential for proper insulin signaling or activate pro-inflammatory pathways [127]; growth hormone excess and elevated glucagon levels create counter-regulatory hormonal environments that oppose insulin's metabolic

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effects and promote hepatic glucose output [128,129]; disrupted circadian rhythms and sleep deprivation alter the temporal coordination of metabolic processes, leading to desynchronization of insulin secretion and peripheral insulin sensitivity [130]; dysbiosis of the gut microbiome alters the production of short-chain fatty acids and increases intestinal permeability, allowing bacterial endotoxins like lipopolysaccharides to enter circulation and trigger systemic inflammation [131,132]; sedentary lifestyle reduces skeletal muscle glucose transporter-4 (GLUT4) expression and impairs muscle capillary density, diminishing the tissue's capacity for insulin-mediated glucose disposal [133]; aging is associated with progressive accumulation of senescent cells that secrete inflammatory factors, coupled with declining muscle mass and increased visceral adiposity, all contributing to deteriorating insulin sensitivity [134].

Although the underlying mechanisms of the association between IR and tumor remain unclear, it may rely upon several mechanisms and is not necessarily the same for different types of cancers. It is clear that IR-related factors, including chronic persistent hyperinsulinemia, INSRs, IGF1Rs and INSR/IGF1R hybrids, as well as chronic inflammation, ncRNAs and microbiota, have been suggested as factors that may play a role in all tumor stages. Recent studies indicate that gut microbiota may be a contributing factor in the relationship between IR and cancer, due to gut dysbiosis [135]. An imbalance in the gut microbiome, is a key factor in cancer development and progression. This disruption affects the ecosystem of gut, altering immune function and metabolism. These changes can create an environment that promotes tumor growth [136–138].

IR is closely associated with visceral adipose dysfunction and systemic inflammation4, both of which favor creating an environment conducive to tumorigenesis [139]. Additionally, epigenetic modifications which are triggered by IR and other environmental factors and chronic disease often involve in oncogenesis, such as DNA methylation, histone modifications, and non-coding RNA [140,141]. Furthermore, the MAPK insulin pathway is the basis of many obesity-related malignancies that control cell growth and mitosis [142], whereas insulin can directly promote cell proliferation and survival via the PI3K/Akt and Ras/MAPK pathways [143].

The molecular initiation events are summarized in Table 2.

Table 2. Mechanisms of Insulin Resistance.

Molecular Mechanism	Cellular Consequence	Key Molecular Players	References
Insulin/IGF-1 signaling	Hyperinsulinemia activates insulin/IGF-1 signaling, promoting cell proliferation and survival in BC cells.	Insulin, IGF-1, IGF1R, IR	144, 145
PI3K/AKT/mTOR pathway	IR activates PI3K/AKT/mTOR pathway, leading to increased cell growth, proliferation, and survival in BC cells.	PI3K, AKT, mTOR, PTEN	146, 147
Inflammation and oxidative stress	IR induces chronic inflammation and oxidative stress, which can lead to DNA damage and BC initiation.	TNF-α, IL-6, NF-κB, ROS	148, 149
Adipokine imbalance	IR alters adipokine secretion, including decreased adiponectin and increased leptin, which can promote BC cell growth and survival	Adiponectin, leptin, adiponectin receptor	150, 151
Epigenetic modifications	IR can lead to epigenetic changes, such as DNA methylation and histone	DNMT1, HDAC1, HAT1	152, 153

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	modification, which can silence tumor suppressor genes and activate oncogenes in BC.		
Circadian rhythm disruption	IR can disrupt circadian rhythms, leading to altered expression of clock genes and increased risk of BC.	PER2, PER3, CRY1, CRY2	1534, 155
MicroRNA dysregulation	Insulin resistance can alter microRNA expression, including miR-21, miR-143, and miR-145, which can contribute to BC development and progression.	miR-21, miR-143, miR-145, Dicer	156, 157
Stem cell regulation	IR can affect stem cell self-renewal and differentiation, leading to increased cancer stem cell populations and BC initiation.	OCT4, SOX2, NANOG, BMI1	158, 159

Legend to Table 2: BC, bladder cancer; IR, insulin resistance.

(Main Text) The mechanicistic biochemical level of IR in cancer is detailed in Figure 1.

Insulin Resistance

↓

Metabolic Dysregulation

↓

Chronic Hyperinsulinemia → 🔴 Increased Free Fatty Acids 🔴

↓

Activation of Insulin/IGF-1 Receptors

↓

PI3K/AKT/mTOR Pathway 🟢 Proliferative Signaling 🟢

↓

Enhanced Cell Proliferation ← 🟡 Inhibition of Apoptosis 🟡

↓

Cyclin D Overexpression → Bcl-2 Upregulation

↓

Uncontrolled Cell Cycle → Resistance to Cell Death

↓

Chronic Low-Grade Inflammation →

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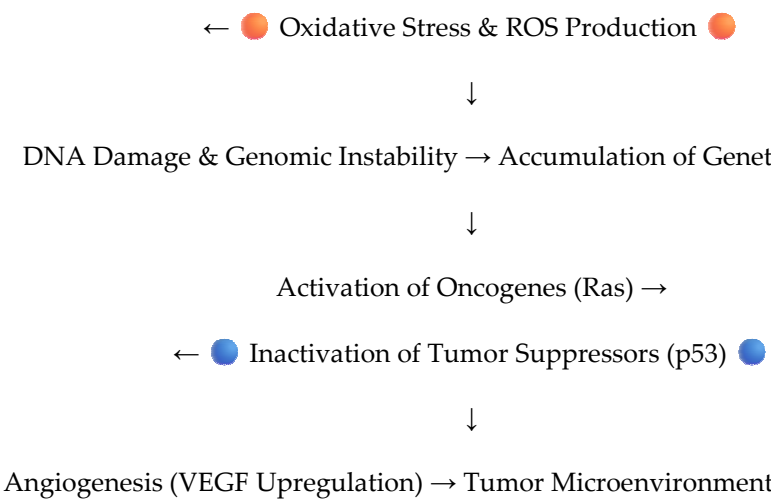

Legend to Figure 1:VEGF, vascular endothelial growth factor; IGF, insulin growth factor. Arrows (↓, →, ←): Indicate direction of influence or progression. Downward arrows show the main cascade; side arrows represent interactions or feedback loops. Colors: Metabolic stress (i.e., fatty acids), : Growth/proliferation signals, Anti-apoptotic effects, Inflammatory/oxidative damage, Genetic/oncogenic alterations.

Figure 1. Insulin Resistance and Cancer: A Mechanistic Flowchart.

(Main Text) Medications that can reduce IR with their downstream signaling events are shown in Table 3.

Table 3. Drugs favorably impacting on Insulin Resistance.

Drug Class	Examples	Mechanism of Action	References
Biguanides	Metformin	Enhances glucose uptake in peripheral tissues by increasing GLUT4 expression and promoting its movement to the cell surface.	160
GLP-1RA	Albiglutide, Dulaglutide, Liraglutide, Semaglutide	Reduces inflammation and oxidative stress, regulates lipid metabolism, and promotes glucose transporter protein expression in insulin-dependent tissues.	161
SGLT2 inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin, Tofogliflozin	Blocks renal glucose reabsorption, leading to increased glucose excretion. Also enhances insulin sensitivity by lowering body weight and reducing glucose toxicity.	162
Sulfonylureas	Glimepiride, Glipizide	Stimulates insulin receptor activity, thereby boosting glucose transporter protein numbers and improving insulin sensitivity.	163
Thiazolidinediones	Pioglitazone, Rosiglitazone	Improves insulin-stimulated glucose uptake, reduces pro-	164

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	inflammatory cytokine production, and stimulates adiponectin release.

Legend to Table 3: SGLT 2, sodium-glucose transport protein 2; GLP-1RA, glucagon-like peptide-1 receptor agonist; GLUT4, glucose transporter protein type-4.

Obesity is a major risk factor for cancer risk primarily because it is the most common cause of IR. For effective diagnosis and treatment, clinicians must distinguish between IR linked to high adiposity and IR arising from other independent causes. This differentiation supports a precision medicine approach, allowing healthcare providers to move beyond a simple diagnosis of IR and tailor interventions based on the primary driver, whether it is systemic inflammation from excess adipose tissue or a distinct metabolic or genetic disorder. Just like with other cancers linked to obesity, weight loss is a core component of BC care trough diet, exercise, weight reduction surgery, behavior therapy, and drug therapy. Note worthy, IR is a fundamental pathophysiological mechanism underlying T2DM [165].

The development of a novel cancer therapeutic strategy, which exploits the GLP-1AR mechanism, represents a major, potentially paradigm-shifting advancement in oncology. In fact, some studies have suggested that GLP-1RA agonists may be associated with a reduced risk of certain cancers, particularly those linked to obesity and T2DM. This is often attributed to their positive effects on weight loss and insulin sensitivity. In a large, 15-year study of 1.2 million patients with T2DM, who had not previously taken medication for the condition, GLP-1RAs were linked to a reduced risk of colorectal cancer. The risk was significantly lower compared to insulin (HR, 0.56) and metformin (HR, 0.75), as well as other drugs like sulfonylureas. The risk was also lower compared to DPP-4 inhibitors, though this difference was not statistically significant [166].There is a pressing need for safe, effective, and sustainable solutions to enhance the prognosis and quality of life of breast cancer patients with obesity. Initial data on GLP-1RA, based on comprehensive review of literature from 1996 to 2024, is reassuring, but more extensive studies are required to definitively establish their role in this context [167]. Recent clinical data demonstrate that GLP-1RAs improved lung cancer-specific outcomes and augmented response to immunotherapy. Mechanistic preclinical evidence suggests this benefit is confined to an obesity context and is mediated by the immune modulation of the tumor microenvironment [168]. Use of GLP-1RAs was linked to a significantly lower risk of three cancers—endometrial, meningioma, and ovarian—while a potential increased risk for kidney cancer was not statistically significant [169]. Very recently, an association between GLP-1RAs and increased kidney cancer risk was observed, necessitating long-term follow-up to elucidate the mechanisms and clinical relevance [170]. The most common and well known side effects include nausea, vomiting, constipation, and diarrhoea, which occur in up to 40% of people taking GLP-1RA drugs [171]. The cumulative burden of these side effects and chemotherapy-induced symptoms severely compromises quality of life. Adding cannabis or cannabinoids to standard antiemetic regimens may effectively reduce nausea and vomiting in patients where chemotherapy treatment has otherwise been unsuccessful [172].This raises the question of whether they could offer similar benefits in the context of GLP-1-based treatments, even though the question of whether cannabis and/or cannabinoids can improve the results of other supportive care is unresolved [173].

However, other studies on GLP-1AR have suggested a potential increase in the risk of certain cancers, including BC, though the evidence is not conclusive and requires further investigation [174]. A recent meta-analysis comprehending a total of 9 retrospective cohort studies with 1,270,179 patients revealed that metformin intake was associated with an increased recurrence-free survival (HR = 0.55) improved progression-free survival (HR = 0.70), and prolonged cancer-specific survival (HR = 0.57), indicating that metformin intake could improve the prognosis of BC patients [175]. Researchers examined the risk of cancer in 43,317 adults with obesity taking a GLP-1 medicine in comparison to 43,315 matched nonusers. They found a 17% reduction in overall cancer risk, a 25% reduction in endometrial cancer, a 47% reduction in ovarian cancer, and a 31% reduction in meningioma. For other cancers such as BC they found reductions that were not statistically significant [176]. The association

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between long-term GLP-1RA use and a slightly higher cancer incidence is currently viewed with caution. It is likely explained by statistical or observational biases (survival/detection) and/or the pre-existing high cancer risk of the patient population (BMI confounding), rather than being definitively attributed to a direct cancer-causing effect of the drug class [177].

Some research has suggested that the use of the T2DM medicine pioglitazone might be linked with an increased risk of BC. The risk seems to get higher when higher doses are used [178]. A "higher" intake of fluids and foods like fruits, vegetables, yogurt, whole grains, and dietary fiber is linked to a reduced risk of BC. This preventive effect is attributed to nutrient-rich foods, particularly fruits and vegetables, which can modulate numerous signaling pathways. For example, apples may modulate pathways related to apoptosis, proliferation, cell growth, and mitotic catastrophe. Similarly, pomegranate can modulate pathways for angiogenesis, immune response, cell proliferation, glycolysis, and the cell cycle, in addition to apoptosis [179]. Citrus fruits also contribute by modulating several pathways, including ROS production and the inhibition of cell growth and the cell cycle [180]. A current meta-analysis comprehending 12 studies showed that Mediterranean diet has protective effects on BC risk, although more research is needed to confirm the findings [181]. Combining structured exercise with dietary support is more effective for weight loss than either method alone. This approach also has the strongest positive effect on blood biomarkers linked to common cancers, such as IR and inflammatory markers [182].

5. Conclusion

IR appears to be less of a stand-alone risk and more of a common mechanism that helps connect other risk factors for BC. Conditions that promote the development of IR are often linked to BC because IR causes chronic hyperinsulinemia, which over activates the PI3K/AKT/mTOR pathway to drive uncontrolled cell proliferation and suppress apoptosis.This metabolic state simultaneously generates oxidative stress and inflammation, leading to DNA damage and genetic mutations.The combination of sustained growth signals and accumulating mutations inactivates tumor suppressors (i.e., p53) and activates oncogenes (i.e., Ras). These processes converge to promote angiogenesis and create a tumor microenvironment contributive to cancer development. Given its role as a key biological bridge, managing IR is proposed as a promising avenue to potentially reduce overall BC risk. Shifting the focus from merely describing this mechanism toward developing actionable, prescriptive IR-based risk stratification strategies could potentially improve their adoption into clinical practice and increase their real-world utility.

6. Future Directions

The association between obesity and BC is complex and actively debated in the scientific community, but the evidence linking anthropometric measures of obesity to an increased risk of developing BC is accumulating and generally supported by a causal biological mechanism. Results from a dose-response meta-analysis comprehending 15 cohort studies with 38,072 BC cases among 14,201,500 participants suggested obesity is associated with linear-increased risk of BC [183]. The central finding of a very recent meta-analysis is a clear association between metabolic syndrome (comprehending IR) and its individual components and an elevated risk of developing BC [184].The TyG index, a surrogate marker for IR is a significant predictor of BC presence, outperforming other metrics, provides direct evidence that IR itself is a powerful independent risk factor [185].To confirm previous data, prospective studies should be conducted to better understand the temporal and causal relationship.

A retrospective study conducted in 2020 on hospitalized patients found that the occurrence of Non-Alcoholic Fatty Liver Disease (NAFLD), recently renamed MASLD, was higher in patients with BC compared to those in a control group [186]. The link between NAFLD and BC is part of broader association between NAFLD and various extra-hepatic cancers, often attributed to an underlying metabolic dysregulation, namely IR, which they share [187]. There is evidence linking hepatic lipid

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accumulation to the development of IR, including the accumulation of triacylglycerol and lipid metabolites, such as diacylglycerol and ceramides [188]. Animal studies on Bifidobacteria have shown promising results in improving intestinal barriers, immune function, and metabolism [189]. Future research should investigate if probiotics, especially when combined with prebiotics, and a healthy lifestyle, by improving lipid profile, inflammatory and oxidative markers, SFAs production and microbiota composition, can effectively reduce IR in people [190], in the light of recent surprising findings that early metabolic changes with weight loss, i.e., improving insulin sensitivity, in humans are unlikely to be mediated by changes to the gut microbiome [191]. In this context, the Mediterranean diet raises as a highly effective approach for greater improvement of IR in obese individuals, and long-term obesity management, often exceeding the efficacy of other popular dietary patterns, including low-fat and low-carbohydrate regimens [192,193].

Both sleep physicians and urologists should further clarify the relationship between spleen disorders and BC to ensure appropriate patient management and improved outcome.

A recent systematic review and meta-analysis, encompassing eleven multiadjusted observation studies, reveals that OSA is associated with an elevated risk of BC. While initial findings suggest OSA does not negatively impact prognosis, available mortality data remain scarce[194]. While stepwise analysis identified obesity as the main driver of IR, sleep-disordered breathing indices were also shown to be independent predictors of IR. Once again, the link between OSA and IR held true regardless of the patient's obesity status [195]. It is now a well-established fact that people with OSA have a significantly higher likelihood of also having T2DM, and vice versa.[196].

Further research is required to elucidate the specific mechanisms linking smoking to IR. Studies show that smoking cessation leads to a reduction in chronic low-grade inflammation and increased levels of adiponectin, suggesting a potential pathway for improved insulin sensitivity [197]. Alcohol is considered a carcinogen because its metabolite, but there was no association between genetically-predicted alcohol assumption and BC risk [198]. Deepening its role as risk co-factor of smoking for BC is crucial, as well as clarifying that "excessive" fluid intake may increase the risk of BC [199]. The effects of arsenic in drinking water are highly gender-specific, demonstrating a critical gap in research that must be addressed. Disparities begin with higher exposure for women through household water management duties. Susceptibility could be further influenced by biological factors, including hormonal control over metabolism in women, genetic differences in arsenic biotransformation, and the effect of nutritional status on metal absorption [200]. Compared to insufficient concentrations, high concentrations of total and estimated free 25(OH)D were found to be significantly associated with a diminished risk of BC [201]. Vitamin D supplementation significantly improved both insulin secretion and sensitivity, according to the results [202]. To confirm the positive effect of this therapeutic approach in BC patients, further investigation via well-designed clinical trials is warranted.

For non-muscle-invasive bladder tumors, downregulated adiponectin expression was an independent predictor of recurrence. Conversely, for muscle-invasive bladder tumors, upregulated leptin expression independently predicted progression [203]. Although a direct adiponectin therapy, as antagonist of IR, is not yet available, researchers are developing therapeutic strategies using peptide or small molecule agonists to mimic its beneficial effects.

Abbreviations

BC, bladder cancer; IR, insulin resistance; GLOBOCAN, global cancer observation; BMI, body mass index; HR, hazard ratio; NMIBC, non-muscle invasive BC; IARC, International Agency for Research on Cancer; RR, relative risk; TP53, tumor protein 53; RB1, retinoblastoma protein; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; FGFR3, fibroblast growth factor receptor 3; HRAS, Harvey rat sarcoma virus; PI3K/AKT, phosphoinositide 3-kinase/protein kinase B; EGFR, epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; COX, cyclooxygenate; STAT3, signal transducer and activator of transcription 3; ROS, reactive oxygen species; mTOR, mammalian target of rapamycin; ATM/ATR, ataxia-telangiectasia mutated/ataxia

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telangiectasia and Rad3-related protein; FGFR3, fibroblast growth factor receptor 3; TERT, telomerase reverse transcriptase; CYP1A1, Cytochrome P450; GST, glutathione S-transferase; NAT, N-acetyltransferase; IGF-1R, Insulin-like Growth Factor Receptor 1; MP, microplastic; BPA, bisphenol A; T2DM, type 2 diabetes mellitus; SOCS-3; suppressor of cytokine signaling 3; THM, trihalomethanes; GH, growth hormone; SDB, sleep-disordered breathing; OSA, obstructive sleep apnea; ALDH2, aldehyde dehydrogenase; SCFA; short-chain fatty acids; INSRs, insulin receptors; TNF-α, tumor necrosis factor- alpha; IL-6, interleukin-6; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; DNMT1, DNA-methyltransferase 1; HDAC1, histone deacetylase 1**;** HAT1, histone acetyltransferase 1; PER2/PER3/CRY1/CRY2, genes coding for core components of the mammalian circadian clock; OCT4/SOX2/NANOG/BMI1, embryonic stem cell transcription factors; TyG, triglycerides-glucose index; GLP-1RA, glucagon-like peptide-1 receptor agonist.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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