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European Association of Urology

Review – Bladder Cancer

Epidemiology of Bladder Cancer in 2023: A Systematic Review of Risk Factors

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Abstract

Context: Bladder cancer (BC) is common worldwide and poses a significant public health challenge. External risk factors and the wider exposome (totality of exposure from external and internal factors) contribute significantly to the development of BC. Therefore, establishing a clear understanding of these risk factors is the key to prevention.
Objective: To perform an up-to-date systematic review of BC's epidemiology and external risk factors.
Evidence acquisition: Two reviewers (I.J. and S.O.) performed a systematic review using PubMed and Embase in January 2022 and updated it in September 2022. The search was restricted to 4 yr since our previous review in 2018.
Evidence synthesis: Our search identified 5177 articles and a total of 349 full-text manuscripts. GLOBOCAN data from 2020 revealed an incidence of 573 000 new BC cases and 213 000 deaths worldwide in 2020. The 5-yr prevalence worldwide in 2020 was 1 721 000. Tobacco smoking and occupational exposures (aromatic amines and polycyclic aromatic hydrocarbons) are the most substantial risk factors. In addition, correlative evidence exists for several risk factors, including specific dietary factors, imbalanced microbiome, gene-environment risk factor interactions, diesel exhaust emission exposure, and pelvic radiotherapy.
Conclusions: We present a contemporary overview of the epidemiology of BC and the current evidence for BC risk factors. Smoking and specific occupational exposures are

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the most established risk factors. There is emerging evidence for specific dietary factors, imbalanced microbiome, gene-external risk factor interactions, diesel exhaust emission exposure, and pelvic radiotherapy. Further high-quality evidence is required to confirm initial findings and further understand cancer prevention.

Patient summary: Bladder cancer is common, and the most substantial risk factors are smoking and workplace exposure to suspected carcinogens. On-going research to identify avoidable risk factors could reduce the number of people who get bladder cancer.

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1. Introduction

In 2018, bladder cancer (BC) was the tenth commonest cancer worldwide [1]. Incidence rates were higher in men for whom it was the sixth commonest cancer. Highest incidence rates were seen in the developed world [1]. Most BC cases are urothelial carcinoma (UC) in subtype (the remainder includes squamous cell, sarcoma, lymphoma, and adenocarcinoma), and approximately 75% of these are non–muscle-invasive BC (NMIBC) [2]. NMIBC has a high prevalence due to its indolent natural history and high recurrence rate. Around one-quarter of BC cases, and most non-UC subtypes, are muscle invasive, which require systemic chemotherapy and/or immunotherapy, radical treatment (cystectomy or radiotherapy [RT]), or palliation [3]. Most BC cases present with either haematuria or storage lower urinary tract symptoms, while the remainder of cases are asymptomatic or incidental findings [4].

The demographics of BC are evolving, reflecting an improved understanding of the human exposome and the changing nature of industrialisation [5]. For example, around half of BC cases are attributed to cigarette smoking, although the rate of smoking has declined in many countries [6–8]. Similarly, workplace regulations have reduced exposure to high-risk carcinogens [9]. Here, we update previous reports [10,11] by searching the literature to compile a contemporary picture of BC demographics and epidemiology.

2. Evidence acquisition

A systematic literature search was performed using PubMed and Embase on January 21, 2022 and September 6, 2022 utilising a combination of subject headings and free text words. Further details of the search strategy are provided in the Supplementary material. The search was restricted to manuscripts published since 2018. Studies were excluded if these were not in English, had <50 participants (for epidemiological studies), or were not human studies. Conference abstracts were also excluded. Two authors (I.J. and S.O.) reviewed the abstracts using a priori inclusion and exclusion criteria and Covidence software (Cochrane Library). Conflicts were resolved between the authors or with the involvement of a third author (M.G.C.). Reference lists of included manuscripts were also searched. Systematic reviews (SRs) and meta-analyses (MAs) were included. We report our findings in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [12]. The review was registered with the PROSPERO database (CRD42022341359) on July 20, 2022.

3. Evidence synthesis

The literature search, after removal of duplicates, identified 5177 studies, of which 334 full-text articles were included. A total of 15 articles were identified by searching references leading to the inclusion of 349 full-text articles (Fig. 1). Information on study type, number of study participants, or number of studies and confounding factors adjusted for were extracted for quality assessment. For MAs, specific information on included studies and heterogeneity was extracted (Supplementary Table 1).

3.1. Epidemiology, incidence, prevalence, and mortality of BC

According to GLOBOCAN, there were 573 000 new BC cases and 213 000 deaths worldwide in 2020 [13–15]. Over three-quarters of new BC cases occurred in men. Age-standardised incidence rates (ASRs; per 100 000 persons per year) for both sexes combined were highest in Europe (11), North America (11), North Africa (8.9), and West Asia (8.6), and lowest in West (2.0) and Middle (1.6) Africa, Central America (2.2), and South-Central Asia (1.9). Male:female ratios of ASRs for incidence (per 100 000 persons) vary by region from 6:1 to 2:1. In West Asia, the ASR for incidence is 15 versus 2.6 for men versus women (ratio of 6:1), and in East Africa, the ASR for incidence is 4.2 versus 2.4 for men versus women (ratio of 2:1). The 5-yr prevalence worldwide in 2020 was 1 721 000 cases. The combined age-standardised mortality rates (per 100 000 persons per year) for both sexes were highest in North Africa (5.2), South Europe (3.3), and West Asia (3.2). GLOBOCAN world maps of BC incidence and mortality rates are shown in Figures 2–4.

In men, BC is the sixth commonest cancer worldwide (5% of all cancers excluding nonmelanoma skin cancer) and in women it is the 17th commonest cancer site (1.5% of female cancer incidence). BC has the ninth highest 5-yr prevalence (22 per 100 000 persons) overall. With regard to disability-adjusted life years, BC ranks 15th (54 yr of total health lost per 100 000 individuals) [16].

Globally, estimated ASRs for incidence have not changed significantly from 1990 to 2019, reflecting diverging incidence trends in different world areas. According to estimates, there have been significant increases in East Asia (percentage change: 56%), North Africa and Middle East

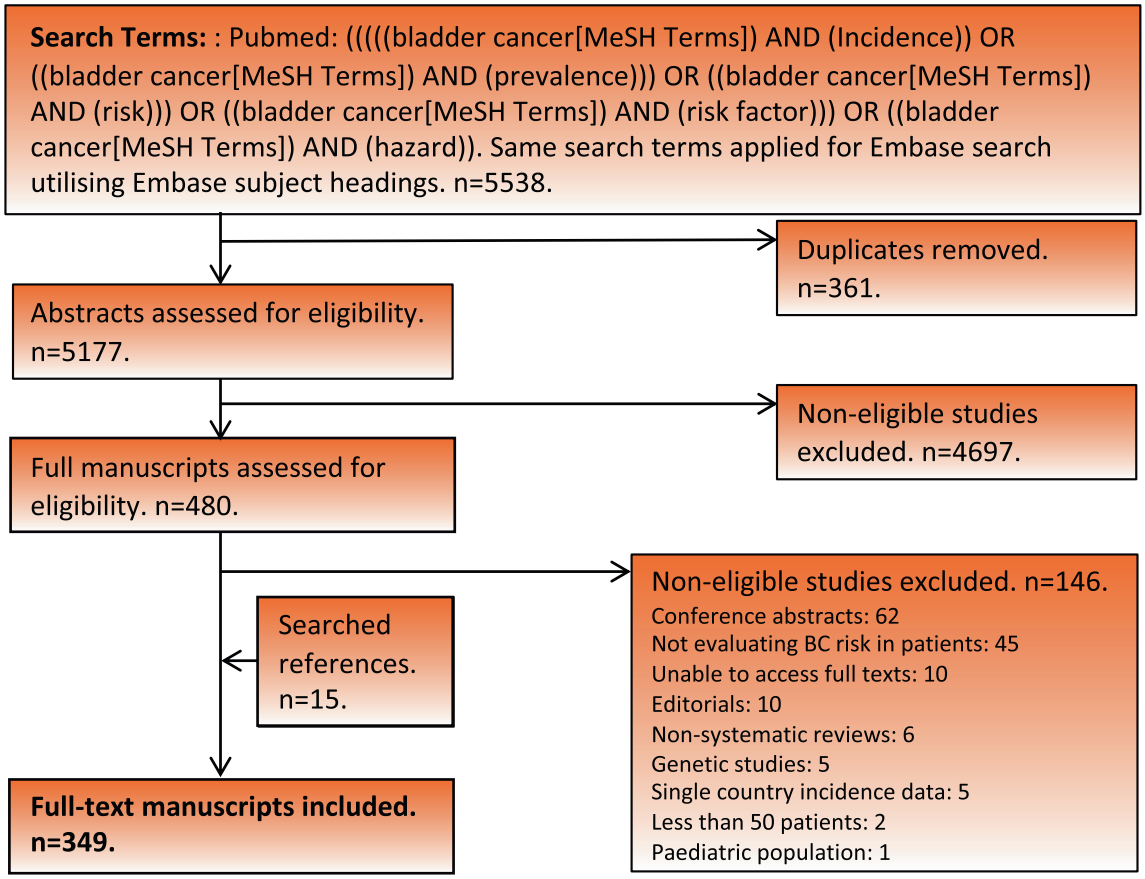

Fig. 1 – CONSORT diagram. Search captured all articles from April 1, 2018 until September 6, 2022. BC = bladder cancer.

(53%), and Central Europe (50%). With regard to estimated age-standardised mortality rates, there were overall decreases worldwide, but a significant increase was noted in central Asia (18%) [17]. GLOBOCAN predictions of future BC disease burden (based on demographic changes only) by continent estimate that the greatest percentage increases in incident BC cases from 2020 to 2040 will be in Africa (101%), Latin America and the Caribbean (85%), Asia (79%), and Oceania (70%; Fig. 5) [18].

3.2. *Risk factors for BC*

Most BC cases are associated with external risk factors. In total, 4.3% of BC patients have a first-degree relative with BC [19], and up to 50% of urothelial cancer patients have a family history of cancer [20]. The International Agency for Research on Cancer (IARC) has reported sufficient evidence for the following risk factors in BC: tobacco smoking, various occupational exposures (aluminium production, rubber production, painting, firefighting, occupational exposure to various dyes [eg, magenta and auramine] or dye intermediates [eg, 4-aminobiphenyl]), environmental exposures (X radiation or gamma radiation, and arsenic), medications (cyclophosphamide and chlornaphazine), opium consumption, and *Schistosoma* infection (Table 1) [21].

3.2.1. *Smoking*

Approximately 50% of BC cases are caused by tobacco smoking [22]. A cohort study of 422 010 participants with 30 yr follow-up demonstrated between two and three times increased risks of BC with smoking (hazard ratio [HR]: 2.32, 95% confidence interval [CI]: 1.98–2.73 in males and HR: 2.75, 95% CI: 2.07–3.64 in females) [23].

In a pooled analysis of seven Australian cohorts (including 364 426 patients), the percentage BC risk attributed to ever smoking was estimated to be 44% (95% CI: 35–52%) overall, 53% (95% CI: 43–62%) in men, and 19% (1.1–33%) in women [24]. However, significantly higher values have been reported previously [22].

In a MA of 52 studies, BC risk is directly proportional to smoking intensity up to 20 cigarettes per day (risk ratio [RR]: 2.52, 95% CI: 2.41–2.64 for ten cigarettes per day and RR: 3.27, 95% CI: 3.16–3.38 for 20 cigarettes per day) but plateaus thereafter. In contrast, BC risk increases without plateau with smoking duration [25].

BC risk decreases with time since smoking cessation. In a prospective cohort of 143 279 postmenopausal women, BC risk in ex-smokers was 25% lower within the first 10 yr following smoking cessation (HR: 0.75, 95% CI: 0.56–0.99) and continued to decrease with time. However, risks of BC remained higher in ex-smokers than in never smokers 30 yr after quitting smoking (HR: 1.92, 95% CI: 1.43–2.58) [26].

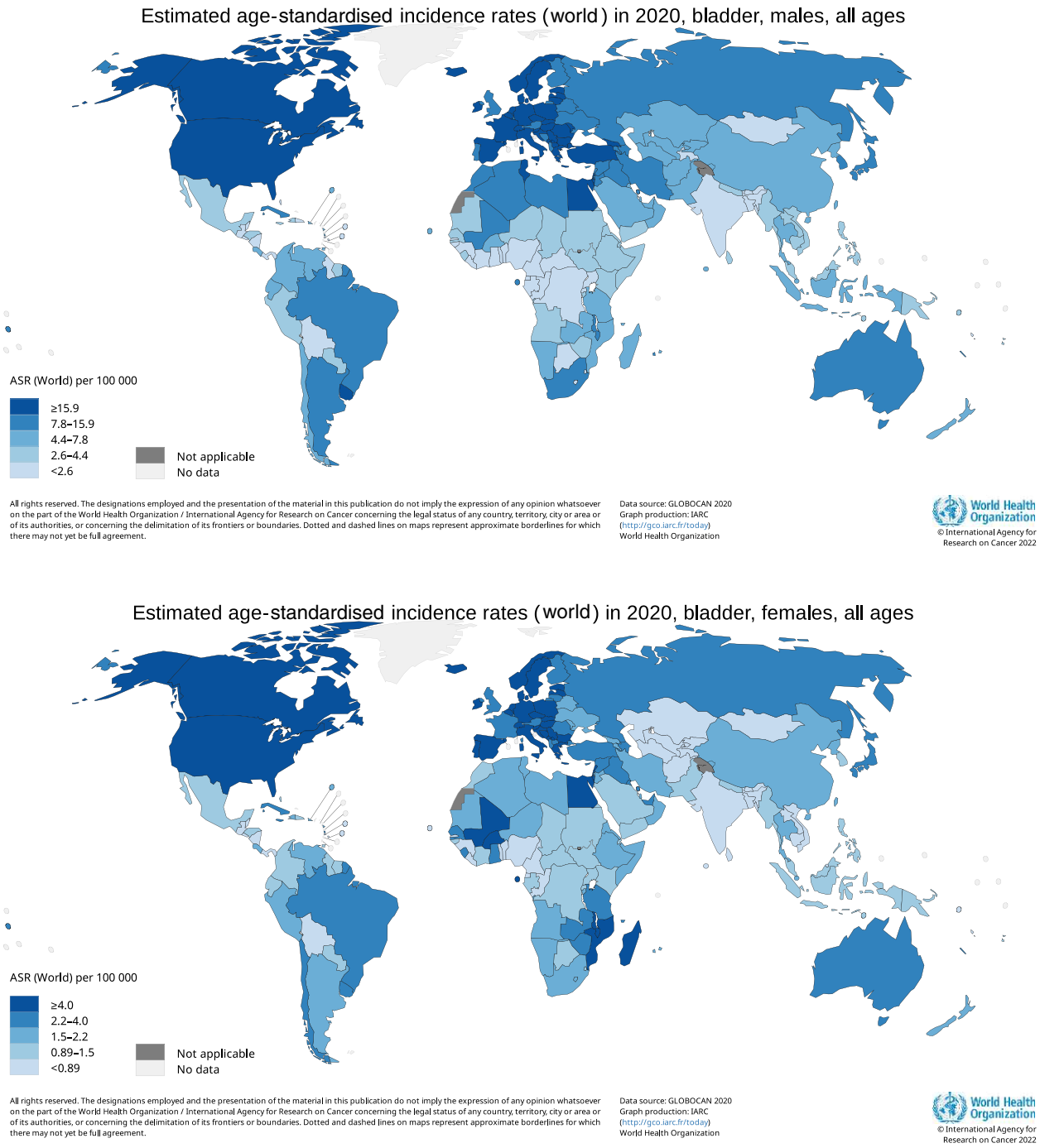

Fig. 2 – Global map of incidence (age-standardised) rates for males and females in 2020. From Global Cancer Observatory: Cancer Today tool [13] by the International Agency for Research on Cancer. ASR = age-standardised rate.

A MA of 14 studies (646 526 participants) demonstrated an increased BC risk with lifetime second-hand smoking exposure in non-smokers (RR: 1.22, 95% CI: 1.06–1.40) compared with unexposed non-smokers [27].

3.2.2. *E-cigarette use*

E-cigarette vapour may contain a number of carcinogenic compounds (eg, formaldehyde and acrolein). A study of 23 patients found two carcinogenic compounds (o-toluidine and 2-napthylamine) at higher concentrations in the urine of e-cigarette users [28]. Similarly, a SR of 22 studies found numerous carcinogenic compounds linked to BC in the urine of e-cigarette users [29].

3.2.3. *Cannabis*

Previous data on cannabis and BC risk have been inconsistent, with two previous studies reporting both increased and decreased BC risk, respectively. A cohort study of over

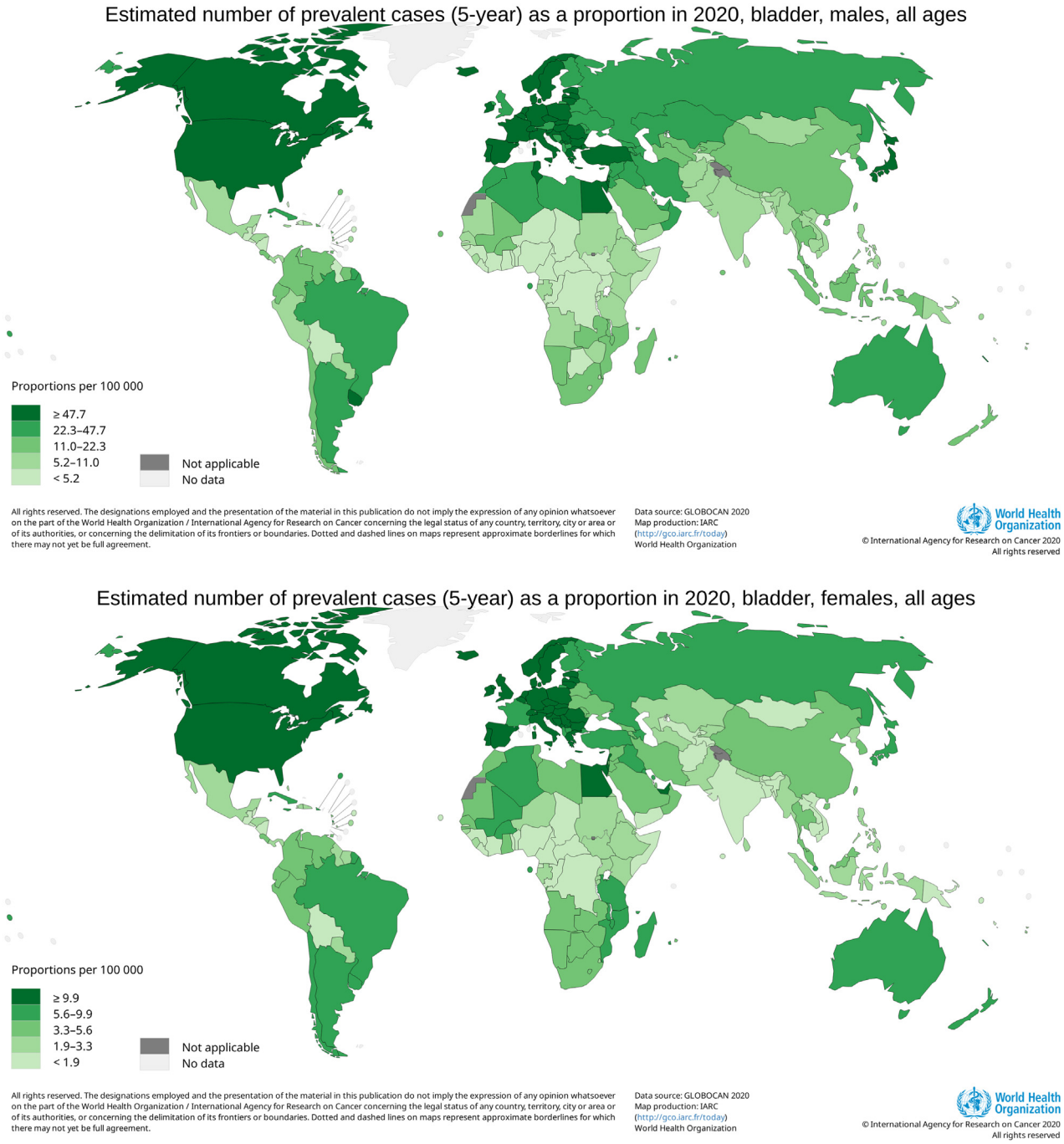

Fig. 3 – Global map of prevalence for males and females in 2020. From Global Cancer Observatory: Cancer Today tool [13] by the International Agency for Research on Cancer.

150 000 patients reported no association between previous cannabis use and BC risk overall, but a reduced BC risk in female patients on a subgroup analysis (HR: 0.42, 95% CI: 0.19–0.94) [30]. This study is limited by a potential recall bias and a lack of adjustment for key confounding factors such as occupation.

3.2.4. *Opium consumption*

Opium consumption has previously been linked to an increased BC risk in several case-control studies. A prospective cohort study of over 50 000 patients with a median 10 yr of follow-up showed an increased BC risk for ever users of opium (smoking and ingestion) compared with never users (HR: 2.86, 95% CI: 1.47–5.55) [31].

3.2.5. *Occupational carcinogen exposure*

Occupational carcinogen exposure is the second most frequent BC risk factor for industrialised countries. An estimated 5.7% of new BC cases are due to occupational carcinogen exposure [32].

A Nordic cohort study of 14.9 million patients (including 111 458 BC cases) reported the highest smoking-adjusted

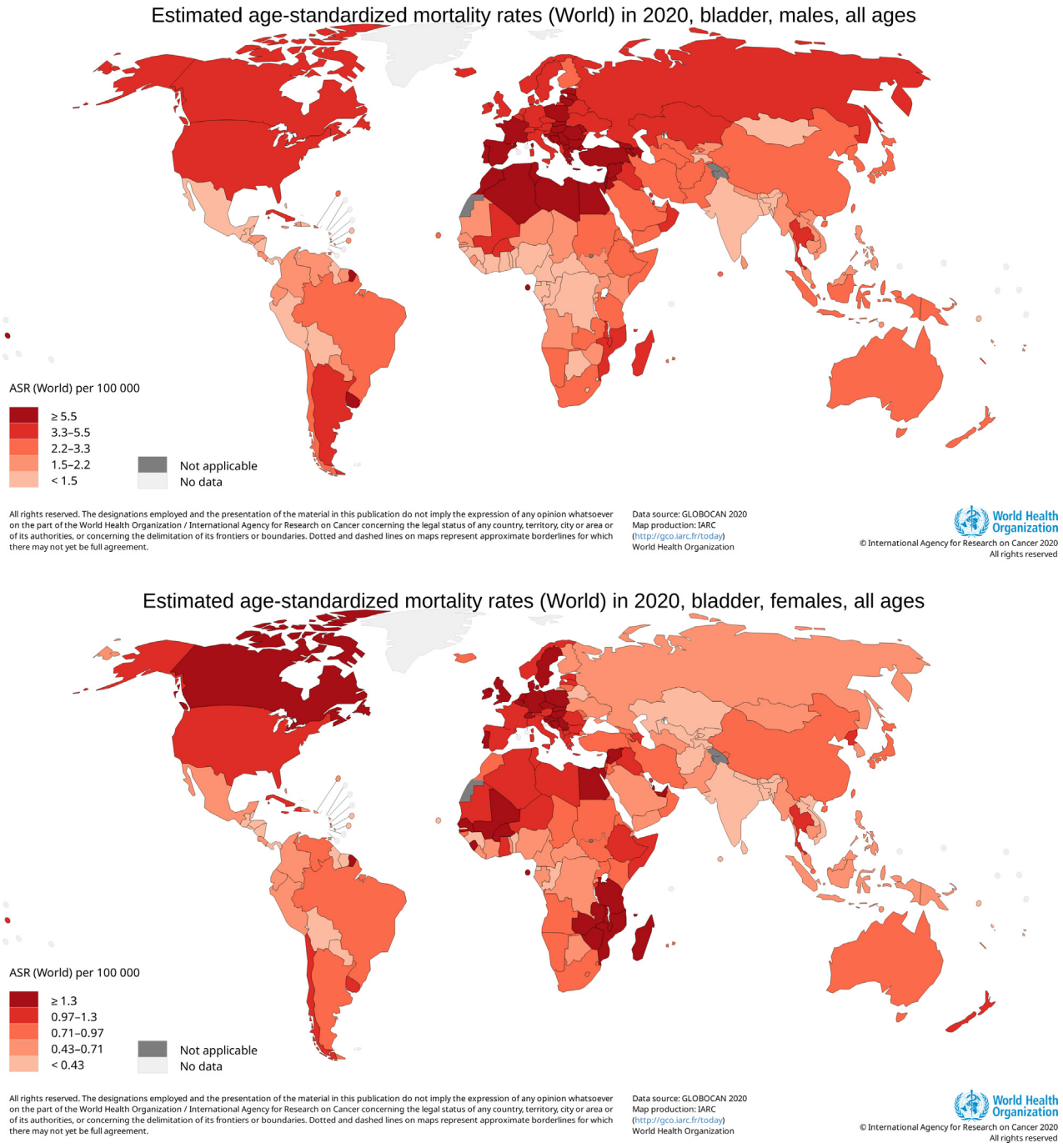

Fig. 4 – Global map of mortality (age-standardised) rates for males and females in 2020. From Global Cancer Observatory: Cancer Today tool [13] by the International Agency for Research on Cancer. ASR = age-standardised rate.

standardised incidence ratios (SIRs) in chimney sweeps (SIR: 1.29, 95% CI: 1.05–1.56), waiters (SIR: 1.22, 95% CI: 1.07–1.38), hairdressers (SIR: 1.14, 95% CI: 1.02–1.26), cooks and stewards (SIR: 1.12, 95% CI: 1.01–1.25), printers (SIR: 1.11, 95% CI: 1.04–1.18), seamen (SIR: 1.09, 95% CI: 1.03–1.14), and drivers (SIR: 1.08, 95% CI: 1.05–1.10) [33].

Firefighters are exposed to multiple compounds in smoke such as acetaldehyde, formaldehyde, sulphur dioxide, benzene, toluene, and ethylbenzene. A MA of 14 studies demonstrated an increased BC risk in firefighters (summary risk estimate: 1.12, 95% CI: 1.04–1.21) [34]. However, it is important to note that the individual studies had varying levels of adjustment for potential confounders, and there was poorly defined exposure information [34].

3.2.6. *Dietary factors*

Previous studies investigating diet/fluid consumption and BC risk have yielded inconsistent results. The World Cancer Research Fund Continuous Update Project reported that there was limited suggestive evidence of a reduced BC risk with fruit and vegetables and tea intake [35].

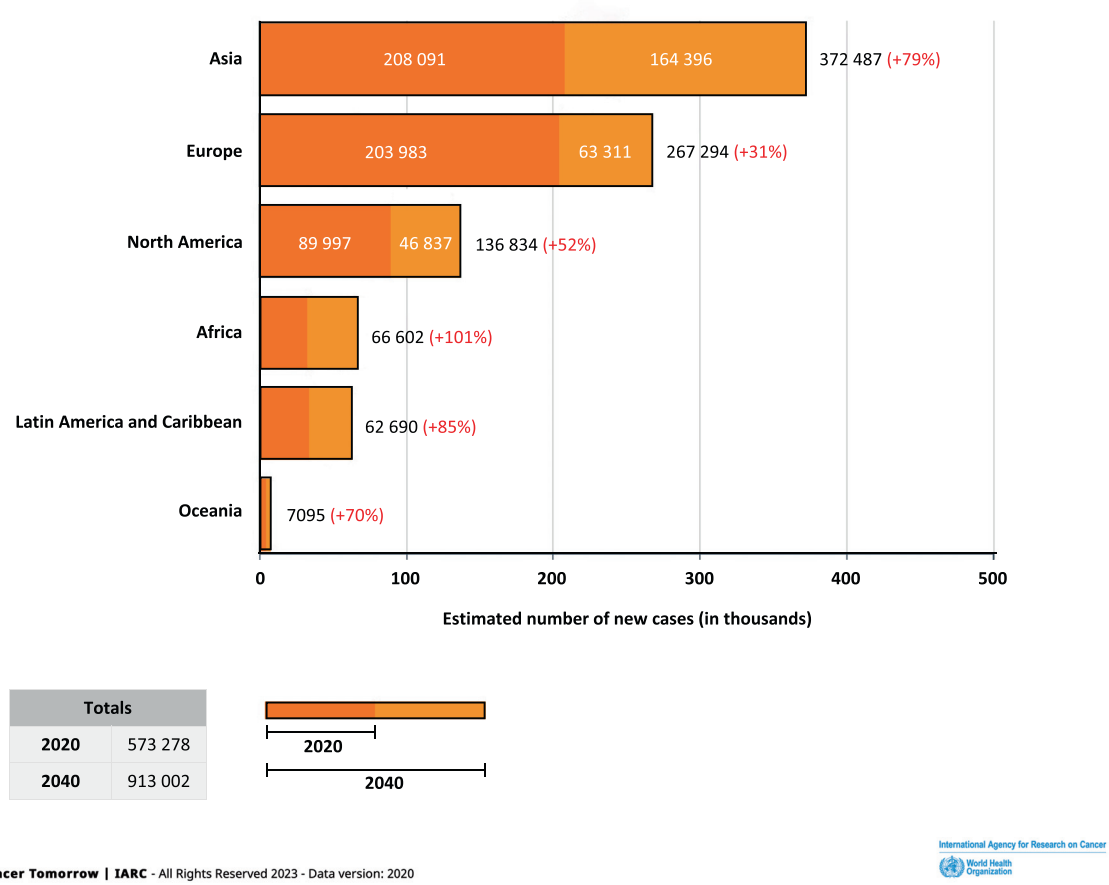

Fig. 5 – Estimated number of new bladder cancer cases between 2020 to 2040 (Both Sexes). Adapted from Global Cancer Observatory: Cancer Tomorrow tool [18] by the International Agency for Research on Cancer.

Table 1 – BC risk factor summary according to IARC monographs

Smoking 1. Tobacco smoking[a]	Occupational agents 1. Benzidine (dye manufacturing)[a] 2. 4-Aminobiphenyl (dye and rubber manufacturing)[a] 3. Ortho-toluidine (dye and rubber manufacturing)[a] 4. 2-Naphthylamine (dye and rubber manufacturing)[a] 5. 4-Chloro-ortho-toluidine[b] (dye manufacturing) 6. 2-Mercaptobenzothiazole[b] (rubber manufacturing) 7. Tetrachloroethylene[b] (dry cleaning, automotive, and metalwork industries) 8. Soot[b] 9. Coal tar pitch[b]
Occupations 1. Aluminium production[a] 2. Rubber manufacturing industry[a] 3. Dye industry (magenta, auramine)[a] 4. Painter[a] 5. Firefighter[a] 6. Dry cleaning[b] 7. Hairdressers or barbers[b] 8. Printing processes[b] 9. Textile manufacturing[b]	
Environmental factors 1. Arsenic and inorganic arsenic compounds[a] 2. X and gamma radiation[a] 3. Outdoor air pollution[b] 4. Diesel exhaust[b]	Diseases and medications or drugs 1. Chlornaphazine[a] 2. Schistosomiasis[a] 3. Cyclophosphamide[a] 4. Opium consumption[a] 5. Pioglitazone[b]

Adapted IARC list of risk factors for bladder cancer with sufficient or limited evidence in humans [21]. BC = bladder cancer; IARC = International Agency for Research on Cancer.
[a] Agents with sufficient evidence for bladder cancer in humans. These correspond to a group 1 IARC classification (carcinogenic to humans).
[b] Agents with limited evidence for bladder cancer in humans.

3.2.6.1. Regional diets. A MA of 13 studies (including 646 222 participants) demonstrated a reduced BC risk with high adherence to a Mediterranean diet overall (HR: 0.85, 95% CI: 0.77–0.93). A subgroup analysis showed reduced BC risks in males and not in females [36]. In contrast, Western diet was associated with an exaggerated BC risk overall (HR for highest vs lowest tertile: 1.54, 95% CI: 1.37–1.72). A subgroup analysis revealed increased risks in males, with no observed differences noted in females [37].

3.2.6.2. Grain and fibre. A MA of 13 cohort studies (including 574 726 patients) reported a reduced BC risk with a higher intake of total whole grain (HR for highest vs lowest tertile: 0.87, 95% CI: 0.77–0.98). Similar findings were reported for total dietary fibre (HR for highest vs lowest tertile: 0.86, 95% CI: 0.76–0.98) [38].

3.2.6.3. Alcohol. The association between BC and alcohol is controversial. While there was no association between increased alcohol intake and BC risk overall in an Australian cohort of 226 162 patients [39], a MA subgroup analysis of a Japanese population demonstrated an increased BC risk with heavy alcohol consumption (moderate alcohol intake defined as $\leq$30 g of ethanol per day and heavy intake defined as the most heavy volume of alcohol consumed; RR: 1.31, 95% CI: 1.08–1.58) [40]. Furthermore, heavy consumption of spirit drinks was associated with an increased BC risk in males (RR: 1.42, 95% CI: 1.15–1.75) [40].

3.2.6.4. Dietary fluid consumption. Previous data on dietary fluid consumption and BC risk have been conflicting.

Increased fluid may reduce carcinogen exposure by diluting urine. However, increased fluid may increase exposure to potential carcinogens such as arsenic. In a MA of 20 studies, while total fluid intake did not correlate with BC risk overall, a subgroup analysis by sex demonstrated male predisposition to BC development with increased fluid intake (RR: 1.37, 95% CI: 1.04–1.81 for highest vs lowest intake). Increased BC risks were also observed with a total fluid intake of >3000 ml/day and with tap water consumption (RR: 1.33, 95% CI: 1.02–1.73 for highest vs lowest categories) [41] but not with non–tap water. However, most studies evaluated were retrospective, and categories of fluid intake were often poorly defined.

3.2.6.5. Caffeine. A pooled analysis of 12 cohorts (including 501 604 patients) reported an increased BC risk with coffee consumption of >500 ml/day (HR: 1.56, 95% CI: 1.38–1.77) and 180–500 ml/day (HR: 1.39, 95% CI: 1.23–1.58) compared with no coffee consumption. However, an analysis stratified by sex and smoking demonstrated that the link was restricted to male smokers, suggesting that the findings may have been influenced by residual confounding of smoking [42].

3.2.6.6. Tea. Greater tea consumption was associated with a reduced BC risk overall in a pooled analysis of 12 cohort studies (HR: 0.84, 95% CI: 0.75–0.95 for high consumption). However, no evidence of association was seen for females and never smokers in a subgroup analysis [43], suggesting a possible modulation of the effect by tobacco carcinogens. This study is limited by the lack of granularity in tea consumption data and the lack of data on other potential confounding factors, for example, occupation.

3.2.6.7. Cow's milk and dairy. A Swedish cohort study previously reported a 38% reduced BC risk with high culture milk intake [44]. However, overall, the literature on dairy products has previously been inconsistent. Dairy products were not associated with BC risk overall in a pooled analysis of 13 studies, but reduced BC risks were seen for yoghurt (HR: 0.85, 95% CI: 0.75–0.96 for moderate consumption) [45]. This analysis did not adjust for occupation.

3.2.6.8. Meat and fish. There has previously been inconsistent data on the relationship between meat and BC risk. A MA of 11 studies (including 518 545 individuals) demonstrated an increased BC risk with a high intake of organ meat (HR for highest vs lowest tertile: 1.21, 95% CI: 1.05–1.38). On a subgroup analysis, fish consumption was linked with a lower BC risk in men (HR: 0.79, 95% CI: 0.65–0.97) but not in women [46]. This work is limited by a lack of data on food preparation methods and other potential BC risk factors such as occupation.

3.2.6.9. Fruits and vegetables. A pooled analysis of 13 cohort studies (including 535 713 patients) demonstrated a small decrease in BC risk only in women (HR: 0.92, 95% CI 0.85–0.99) with increasing fruit consumption by 100 g/day but not in men [47]. Potential explanations for the sex difference include hormonal factors and micturition habits. A pooled analysis of 13 cohort studies showed that a higher intake of total vegetables was associated with a reduced BC risk in women but not in men (highest vs lowest tertile HR: 0.79, 95% CI: 0.64–0.98) [48]. An important limitation of these studies is the limited data on confounding factors.

3.2.6.10. Inflammatory diets. Chronic inflammation has previously been implicated in BC, and diet is reported to modulate inflammation. Results from three North American prospective cohort studies (including 218 074 participants) did not demonstrate an association between diets with a greater inflammatory potential and BC risk [49].

3.2.6.11. Vitamins. A SR of six studies evaluated the association between vitamin D levels and BC. In total, five out of the six studies demonstrated an association between low serum vitamin D levels and BC risk (ORs [odds ratios] ranging from 1.28 to 3.71) [50].

An increased BC risk was reported with high vitamin B1 consumption (HR: 1.14, 95% CI: 1.01–1.29) compared with low consumption. A subgroup analysis showed this association only in men [51]. This study is limited by the absence of data on numerous potential confounding factors.

3.2.7. Environmental carcinogens

Arsenic in the drinking water, which the IARC has classified as a group 1 carcinogen [52], has established links with BC risk. Air pollution is classified by the IARC as a group 1 carcinogen based on associations with lung cancer.

3.2.7.1. Arsenic. Although there is significant evidence that high levels of arsenic in drinking water is a risk factor for BC, there has previously been uncertainty about the exposure levels required for carcinogenicity. A MA of eight studies specifically evaluating low levels of exposure (exposure >150 μg/L was excluded) did not show a statistically significantly increased risk of BC with an increase in arsenic levels of 10 mg/L (RR: 1.02, 95% CI: 0.97–1.07) [53]. This suggests that arsenic is carcinogenic only at higher levels.

3.2.7.2. Air pollution. Diesel exhaust emissions and outdoor air pollution exposure have been established as carcinogens by the IARC based on evidence for lung cancer (group 1) [21,54] and are both reported to have limited evidence for BC. A pooled analysis of two case-control studies (5121 patients) reported an increased BC risk (OR: 1.61, 95% CI: 1.08–2.40) with a high level of cumulative diesel exhaust exposure [55].

There were no statistically significant associations with BC for air pollution in a pooled analysis from a European cohort [56] or a Spanish case-control [57] study.

3.2.7.3. Nitrates. Previous studies on nitrates and BC risk have not been conclusive. A MA of five studies showed no significant association between nitrates in drinking water and BC risk [58]. Most study populations were in developed countries with relatively low nitrate concentrations.

3.2.7.4. Trihalomethanes. In a cohort study of 58 672 individuals with 16 yr of follow-up, there was no association

between high drinking water trihalomethane (THM) exposure and BC risk. This study evaluated THM concentrations up to around 20 μg/l, reflecting European chlorinated drinking water. However, individual drinking water consumption data were lacking [59].

3.2.7.5. Routine personal hair dye use. Although there is some evidence of an increased cancer risk with occupational exposure to hair dyes, previous data on personal hair dye use and BC risk have been conflicting. A prospective cohort study (including 117 200 women) reported no significant association between ever users of permanent hair dyes and BC [60].

3.2.8. Race and comparative genomic landscape across different ancestries

A UK cohort study of 52 779 123 patients reported lower age-standardised rates for BC in Asian and Black ethnic categories compared with White [61]. These data should be interpreted with caution as the differences in BC incidence rates between races can reflect different smoking patterns and environmental exposures. An analysis of the molecular effects of ancestry in cancer demonstrated enrichment in HRAS mutations in BC cases from patients of East Asian ancestry compared with those of European ancestry [62].

3.2.9. Socioeconomic position

An analysis of the GLOBOCAN data demonstrated positive correlations between gross domestic product per capita and BC incidence in men (r = 0.48) and women (r = 0.44). However, this association was not significant in multivariable linear regression adjusting for tobacco smoking [63].

A cohort study reported a higher BC incidence in more deprived socioeconomic groups in Canada (based on income and education levels) over an 18-yr period [64]. An important drawback of these is the absence of data on smoking.

3.2.10. Physical activity

A North American prospective cohort study of 141 288 postmenopausal women demonstrated a reduced BC risk with more physical activity (≥15 metabolic equivalent of task [MET] hours per week of total physical activity HR: 0.74, 95% CI: 0.59–0.94; ≥8.75 MET h/wk of walking HR: 0.79, 95% CI: 0.63–0.98; and ≥11.25 MET h/wk of moderate to vigorous activity HR: 0.76, 95% CI: 0.61–0.94) [65]. In contrast, data from a Japanese cohort of 76 795 individuals [66] and a Korean cohort of 162 220 individuals [67] reported no association with BC risk.

3.2.11. Gene-environment interaction

N-acetyltransferase 2 and glutathione S transferases are enzymes involved in the detoxification of carcinogens linked with BC, such as arylamines and polycyclic aromatic hydrocarbons (PAHs). Previous reports on the role of N-acetyltransferase 2 (*NAT-2*) and glutathione S transferase (*GSTM1* and *GSTT1*) gene polymorphisms and BC risk have been inconsistent.

In a MA of 54 case-control studies (including 31 929 patients), the slow acetylator genotype of *NAT-2*, an enzyme important for catalysing N-acetylation of arylamines, was associated with an increased BC risk compared with the rapid and intermediate genotype (OR: 1.46, 95% CI: 1.30–1.63) [68].

An analysis of genetic associations of plasma metabolites revealed an association between caffeine metabolite 5-acetylamino-6-formylamino-3-methyluracil (AFMU), a potential BC carcinogen that is a product of NAT2 activity, and single nucleotide polymorphism (SNP) rs1495741 near the N-acetyltransferase 2 (*NAT2*) gene that showed linkage disequilibrium with an SNP, rs35246381, which has previously been reported to be associated with urinary AFMU [69].

A MA of 84 studies demonstrated that both the GSTM1 and the GSTT1 null genotype were associated with an increased BC risk in the overall population (OR: 1.40, 95% CI: 1.31–1.48 for GSTM1 and OR: 1.11, 95% CI: 1.01–1.22 for GSTT1) [70]. A MA of 34 case-control studies showed that the *GSTP1* gene polymorphism (313 A/G rs1695) was also associated with an increased BC risk (GG vs AA; OR: 1.33, 95% CI 1.04–1.69) [71].

A SR of five studies demonstrated that arsenic (+3 oxidation state) methyltransferase (AS3MT) gene polymorphisms (rs3740393 and rs11191438 polymorphisms) were associated with an increased BC risk potentially because of regulating inorganic arsenic metabolism [72].

3.2.12. Microbiome

Owing to the complex interplay between host, disease, and microbiome, many diseases are thought to be associated with shifts from the "normal", leading to an imbalanced microbiome termed dysbiosis.

3.2.12.1. Urinary microbiome. Early evidence highlights an increased abundance of *Acinetobacter*, *Anaerococcus* [73], *Fusobacterium*, and *Campylobacter* [74] in the urine of BC patients. While the association of chronic *Schistosoma haematobium* infection with BC is well established, coinfections with N-nitrosamine–forming bacteria (ie, *Pseudomonas*, *Proteus*, and *Escherichia coli*) are thought to act synergistically in BC initiation [75]. Similarly, a MA of microbial signatures has suggested a metabolic link between PAH degraders (i.e. *Acinetobacter*, *Micrococcus*, and *Pseudomonas*) and BC oncogenesis through potent PAH intermediates formed by the bacteria (Fig. 5) [76].

Studies investigating the microbial population differences in BC have further implicated the role of *Lactobacillus* in BC prevention [77]. Among the few urinary microbiome studies in BC, the majority have consistently reported loss of this abundant genera in BC [78,79]. While *Lactobacillus* species itself is cytotoxic to human BC cell lines ex vivo [80], it is possible that an increased abundance of *Lactobacillus* in healthy patients is reflective of urinary biome homoeostasis and protective effects of probiotics (Fig. 6) [81].

3.2.12.2. Gut microbiome and BC risk. Gut microbial signatures in BC patients are poorly understood, and thus far only two studies have been conducted in BC [82,83]. As such, any currently available data on microbial differences may reflect general dysbiosis rather than BC-specific alterations. However, results of the initial study by He et al. [82] demonstrated a reduction of *Prevotella* and *Clostridium* in BC

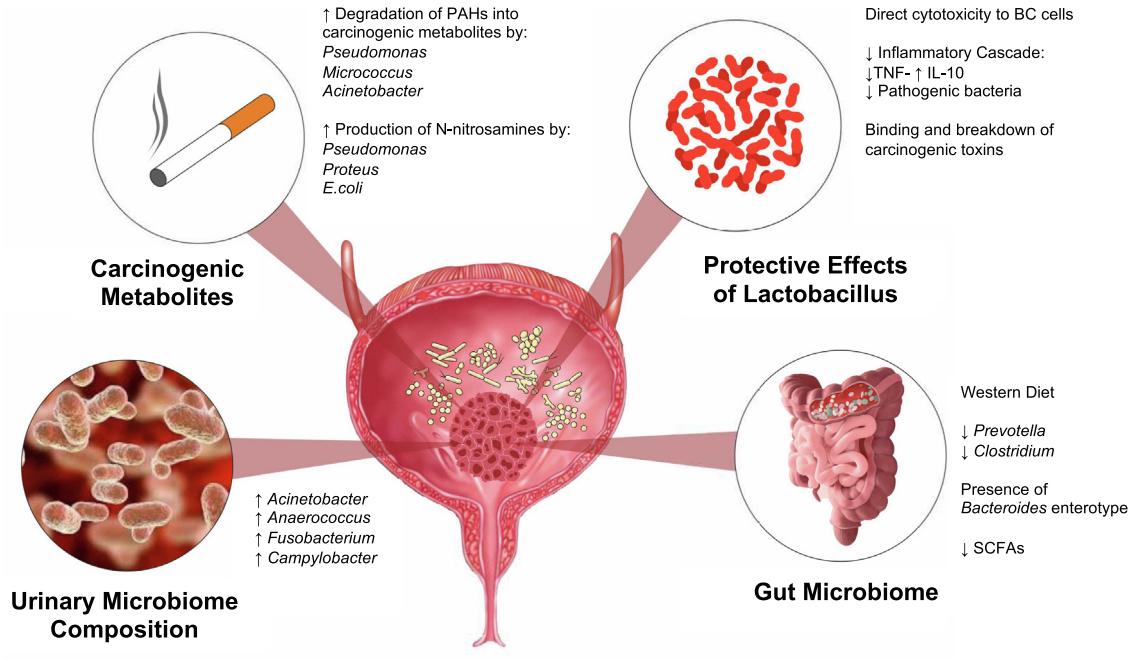

Fig. 6 – Bladder cancer risk modulation by the urine and gut microbiome. BC = bladder cancer; IL = interleukin; PAH = polycyclic aromatic hydrocarbon; SCFA = short-chain fatty acid; TNF = tumour necrosis factor.

patients compared with healthy donors. Similarly, other studies have supported the role of a "healthy" gut microbiome in the prevention of BC, illustrating that patients with *Bacteroides* dominant enterotype were more likely to harbour aggressive BC than patients with *Prevotella* dominant enterotype [83]. Historically, patients on a high animal fat diet (Western diet) aggregate within the *Bacteroides* enterotype [84], likely a reflection of decreased short-chain fatty acid–producing bacteria and a chronic inflammatory state (Fig. 5). However, both studies are underpowered to fully delineate the confounders and variation by disease stage and treatment.

3.2.13. Urinary tract inflammation

3.2.13.1. Urinary tract infection. While the association between schistosomiasis and BC risk is well established [21], the association with non-schistosomiasis urinary tract infection is less well defined. A MA of eight studies demonstrated an increased BC risk with urinary tract infections (RR: 1.33, 95% CI: 1.14–1.55) [85].

3.2.13.2. Neurogenic bladder and long-term catheter. There have been previous reports of an increased BC risk in neurogenic bladder patients with a higher incidence of squamous cell histology, but the causes are unclear. The proposed pathophysiology is secondary to chronic irritation due to long-term catheters (LTCs) and recurrent urinary tract infections. A cohort study with 7004 patients reported that BC was diagnosed in 0.5% of spinal cord injury (SCI) patients. Of the BC cases, 95% had >10-yr latency between the onset of SCI and BC diagnosis. LTCs were the bladder emptying method in 22% of BC cases, suggesting a BC risk independent of LTCs. An important limitation is the absence of data on key BC risk factors, that is, smoking [86]. A SR of 15 studies reported a comparable overall incidence of BC of 0.33% (range: 0.11–7.4%) in the neurogenic bladder population [87].

A Canadian cohort study of 147 612 individuals demonstrated an increased BC risk with LTCs (HR: 4.80, 95% CI: 4.26–5.42). BC risk was highest among patients in the two longest catheter duration quintiles (2.9–5.9 and 5.9–15.5 yr) [88].

3.2.13.3. Urolithiasis. Previous work on urolithiasis and BC has been inconsistent. A MA of 13 studies demonstrated an increased risk of BC in patients with urolithiasis (OR: 1.87, 95% CI: 1.45–2.41) [89]. This may be due to the associated chronic irritation and inflammation. The BC risk was increased with bladder (OR: 2.17, 95% CI: 1.52–3.08) and kidney (OR: 1.39, 95% CI: 1.06–1.82) stones. Important potential confounders such as smoking and occupation were not adjusted for in the majority of included studies. There is also a potential surveillance bias as patients with urolithiasis are likely to have had more follow-up imaging than the general population.

3.2.13.4. Benign prostate hyperplasia and bladder diverticula. Benign prostate hyperplasia (BPH) has previously been proposed as a risk factor possibly due to prolonged contact time of urothelium with urine carcinogens, but the data have been inconsistent. A retrospective cohort study of 35 092 patients demonstrated an increased risk of BC with BPH (HR: 4.11, 95% CI: 2.70–6.26) [90].

A cohort study of 10 662 individuals demonstrated an increased BC risk with bladder diverticula (HR: 2.63, 95% CI: 1.74–3.97) [91]. This may be due to prolonged urothelial contact with urinary carcinogens due to urinary stasis. This

study did not evaluate the association between bladder diverticula and intradiverticulum BC cases specifically.

3.2.14. Medical conditions

Previous studies have evaluated medical conditions, but the evidence for certain conditions has been inconsistent. As numerous medical conditions and treatments are intrinsically linked, it is difficult to ascertain the effect of specific conditions and treatments on BC risk.

3.2.14.1. Pelvic RT. Previous studies investigating secondary BC following pelvic radiotherapy (RT) have had inconsistent results. A cohort study of 440 792 patients with 6 yr of follow-up reported an increased BC risk with external beam RT for prostate cancer compared with radical prostatectomy (HR: 1.41, 95% CI: 1.33–1.51) [92]. There were similar findings in a cohort of 84 397 patients [93] and a MA of 15 studies (including 619 479 patients) [94]. A cohort study (including 318 058 patients) with a median follow-up of approximately 10 yr demonstrated an increased BC risk with brachytherapy (HR: 1.58, 95% CI: 1.46–1.72) [95]. Whole-exome sequencing of muscle-invasive BC cases demonstrated distinct genomic profiles in BC cases with previous RT (increased frequency of short insertions and deletions [indels]) [96].

Increased secondary BC risks were also reported following RT for gynaecological cancer (HR: 2.69, 95% CI: 2.29–3.16) [97].

3.2.14.2. Obesity. Previous data on obesity and BC risk are inconsistent. A cohort study of 11 823 876 men demonstrated increased BC risks with higher body mass index (BMI) categories but only in participants with waist circumference >90 cm, suggesting abdominal obesity to play a key role [98].

A pooled analysis of six cohort studies (including 811 633 patients) showed no significant association between raised BMI and BC risk overall in men, but an inverse association between raised BMI and BC risk overall in women (HR: 0.90, 95% CI: 0.82–0.99). An analysis of BC subtypes showed an association between raised BMI and NMIBC in men (HR: 1.09, 95% CI: 1.01–1.18) [99]. This study is limited by a lack of data on potential confounders such as comorbidities and physical activity.

3.2.14.3. Metabolic syndrome. Previous research on metabolic syndrome (which comprises central obesity, insulin resistance, hypertriglyceridemia, hypercholesterolaemia, hypertension, and reduced high-density lipoprotein) and BC risk has been inconclusive. A SR and MA of four studies demonstrated an increased BC risk with metabolic syndrome (RR: 1.09, 95% CI: 1.02–1.17) [100]. This study did not specify the confounding factors that were adjusted for in individual studies, and there may be a confounding effect from medications.

3.2.14.4. Diabetes. In a cohort of 95 796 patients, there was no significantly increased risk of BC in the type 2 diabetes mellitis (T2DM) group after 16 yr of follow-up [101]. Similar findings were reported in a cohort of 148 208 women [102]. However, an increased BC risk was reported in a Korean cohort of over 25 million patients with a mean follow-up period of 8.6 yr (HR: 1.28, 95% CI: 1.23–1.33). This study is limited by potential misclassification of diabetic patients and did not adjust for smoking and diabetic medications [103].

3.2.14.5. Hypertension and hyperlipidaemia. A pooled prospective cohort study of 811 633 men and women reported no association between raised cholesterol and BC risk. However, there was an increased BC risk with increasing blood pressure in men (HR: 1.09, 95% CI: 1.02–1.17) but not in women. An important limitation is the potential confounding effect of drug treatments, and occupational and environmental exposures on the results [99].

3.2.14.6. Stroke. A cohort study of 944 633 patients reported an increased BC risk in the stroke population (HR: 1.43, 95% CI: 1.17–1.76) [104]. However, smoking status and other specific medical comorbidities were not adjusted for.

3.2.14.7. Asthma. Previous reports on asthma or atopic disease and BC risk have had inconsistent results. A MA of seven studies (2 171 549 individuals) found an increased BC risk in patients with current or previous asthma (HR: 1.46, 95% CI: 1.18–1.80) [105]. A proposed mechanism relates to the associated oxidative stress, reactive oxygen species, and resulting DNA damage.

3.2.14.8. Autoimmune and rheumatological conditions. A MA of ten cohort studies reported an increased BC risk (HR: 1.92, 95% CI: 1.15–3.21) with systemic lupus erythematosus [106]. Similar findings have been reported for vasculitis. A cohort study of 9910 individuals reported an increased BC risk with antibody-associated vasculitis (HR: 2.70, 95% CI: 1.20–6.10) [107]. Similarly, a cohort study of 359 860 individuals reported an increased BC risk with gout (HR: 1.15, 95% CI: 1.01–1.30) [108]. These studies did not adjust for treatments in their analyses. There was no significant association between inflammatory bowel disease and BC risk in two MAs [109,110].

3.2.14.9. Solid organ transplantation. Several studies have previously reported an increased BC risk following kidney transplant believed to be due to immunosuppressive therapy. However, there have also been conflicting reports previously. A cohort study (including 3069 patients) reported an incidence of solid organ malignancy of 3.6% in kidney transplant recipients. Of the solid organ malignancies reported, 5.3% were BC cases (0.20% BC overall in kidney transplant patients) [111].

A study of 11 004 liver transplant patients reported a risk of de novo malignancy of 2.1% at 1 yr, 13% at 5 yr, and 28% at 10 yr. Of the reported malignancies, 1.1% were BC cases [112]. It is important to note that the potential effect of key BC risk factors such as smoking were not considered.

3.2.14.10. Associations with other cancers. A cohort study of 10 734 men with non-seminomatous testicular cancer demonstrated an increased BC risk compared with the general population (SIR: 1.47, 95% CI: 1.07–1.59) potentially

related to the effects of cisplatin-based chemotherapy, radiation from surveillance imaging, and RT [113].

3.2.15. Medications

The IARC has classified cyclophosphamide and chlornaphazine as having sufficient evidence for BC [21]. Exploratory evidence showed increased BC risks for pioglitazone [114,115], ranitidine [116], levothyroxine [117], and angiotensin 2 receptor blockers [118]. No significant association was seen for SGLT2 inhibitors [119], metformin [120], aspirin [121,122], statins [123], angiotensin-converting enzyme inhibitors, calcium channel blockers, or diuretics [118]. There were mixed results for reports on androgen deprivation therapy [124] and 5-alpha reductase inhibitors [125–127].

4. Conclusions

BC is a significant global health problem. While the incidence of BC has not significantly changed globally, increased incidence and mortality have been noted in specific regions of the world, likely to represent evolving carcinogen exposures. Smoking and specific occupational exposures are the most established risk factors. There is emerging evidence for a number of risk factors including specific dietary factors, gene-external risk factor interactions, and pelvic RT.

Our updated analysis builds on our previous report [11], and highlights the recent evidence for opium consumption and firefighting as risk factors for BC. This updated analysis also reports the emerging evidence for the imbalanced microbiome and diesel exhaust emission exposure. Further work with standardised reporting and robust adjustment for potential confounding risk factors is needed to confirm preliminary findings, explore the underlying mechanisms behind reported associations with BC, and further understand cancer prevention.

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Study concept and design: Jubber, Ong, Cumberbatch, Catto.
Acquisition of data: Jubber, Ong.
Analysis and interpretation of data: Jubber, Ong.
Drafting of the manuscript: Jubber, Ong, Bukavina, Cumberbatch, Catto.
Critical revision of the manuscript for important intellectual content: Bukavina, Black, Compérat, Kamat, Kiemeney, Lawrentschuk, Lerner, Meeks, Moch, Necchi, Panebianco, Sridhar, Znaor, Catto, Cumberbatch.
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