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Review article

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Global trends in the epidemiology of bladder cancer: challenges for public health and clinical practice

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Abstract

Bladder cancer is among the ten most common cancers globally, causes considerable morbidity and mortality and is, therefore, a substantial burden for health-care systems. The incidence of bladder cancer is affected by demographic trends, most notably population growth and ageing, as well as exposure to risk factors, especially tobacco smoking. Consequently, the incidence has not been stable throughout the world over time, nor will it be in the near future. Further primary prevention efforts are of the utmost importance to reduce the medical and financial burden of bladder cancer on populations and health-care systems. Simultaneously, less-invasive and lower-cost approaches for the diagnosis of both primary and recurrent bladder cancers are required to address challenges posed by the increasing shortage of health-care professionals and limited financial resources worldwide. In this regard, urinary biomarkers have demonstrated promising diagnostic accuracy and efficiency. Awareness of the risk factors and symptoms of bladder cancer should also be increased in society, particularly among health-care professionals and high-risk groups. Studies investigating the associations between lifestyle factors and bladder cancer outcomes are scarce and should be a research priority. In this Review, we outline global trends in bladder cancer incidence and mortality, and discuss the main risk factors influencing bladder cancer occurrence and outcomes. We then discuss the implications, challenges and opportunities of these epidemiological trends for public health and clinical practice.

Sections

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Key points

- The rising incidence of bladder cancer, a growing shortage of health-care professionals worldwide and limited financial resources underline the need to reduce the substantial burden of bladder cancer globally.
- Awareness regarding risk factors for and symptoms of bladder cancer should be increased in society, particularly among both health-care professionals and high-risk groups.
- Given the undisputed association between smoking and bladder cancer, further efforts focused on primary prevention should be undertaken, most importantly through greater implementation of tobacco control policies worldwide.
- Less-invasive and cheaper approaches for the diagnosis of primary and recurrent bladder cancers in clinical practice are urgently needed.
- Literature on the potential associations between lifestyle factors and bladder cancer outcomes is scarce. Given the observational data indicating beneficial effects of a healthy lifestyle on clinical outcomes in other cancer types, this aspect should be a priority for bladder cancer research.

Introduction

Bladder cancer is a highly heterogeneous disease entity. More than 90% of patients with this disease are diagnosed with urothelial carcinoma, with the remainder having squamous cell carcinoma, adenocarcinoma or neuroendocrine tumours[1]. Moreover, several molecular and genetic subtypes of bladder cancer have been established through comprehensive profiling efforts, such as The Cancer Genome Atlas project[2]; however, these subtypes are not yet widely considered in clinical practice owing to insufficient evidence supporting their additional prognostic and predictive value. In addition, bladder cancers are typically categorized as either muscle-invasive bladder cancers (MIBCs) that have spread into or through the detrusor muscle or non-muscle-invasive bladder cancers (NMIBCs) that are restricted to the mucosa or submucosal connective tissue (Fig. 1), which account for approximately 25% and 75% of patients with newly diagnosed bladder cancer, respectively. Patients with NMIBC have a good prognosis with a 5-year bladder cancer-specific mortality of 0.5%, 1.7% and 6.8% among patients with grade 1, 2 and 3 tumours, respectively[3]. The disease does, nevertheless, recur frequently after transurethral resection of the bladder tumour(s) (TURBT) and intravesical chemotherapy or Bacillus Calmette–Guérin (BCG) instillations; depending on initial tumour stage and grade, recurrences can occur in >50% of patients[4–6]. Despite local therapy, NMIBC can also eventually progress to MIBC, resulting in inferior survival even compared with that associated with de novo MIBC (5-year overall survival 37% versus 49%)[4,7,8]. Such progression occurs in 10–40% of patients with high-risk NMIBCs, such as Tis (carcinoma in situ) and grade 3 Ta or T1 tumours[9]. Patients with MIBC have a poor prognosis (5-year overall survival <50%)[10], with no substantial improvement over the past few decades.

Although rarely perceived as such by the general public, bladder cancer is among the most common cancers, especially among men[11], and is also one of the most economically costly cancers because of the intensive treatment and monitoring it requires, placing a high burden on both patients and health-care systems[12,13]. Up to 50% of bladder cancers are likely to be caused by exposure to lifestyle-related or environmental carcinogens, with a highly prominent role for tobacco smoking[14]. Geographical and temporal trends in the risk of bladder cancer can be partly explained by differences and changes in such exposures. Herein, we first summarize global trends in bladder cancer incidence and mortality. We then discuss the key contributing risk factors and, finally, the clinical and public health implications.

Bladder cancer incidence and mortality

The validity of geographical and temporal comparisons of bladder cancer burden is dependent on the existence of high-quality cancer registries. Approximately 24% of the world populace is covered by national or subnational population-based cancer registries, with lower coverage in South America (19% of the total population), Asia (15%) and Africa (13%)[15]. Cause of death registries also vary in coverage and quality. This variation requires some extent of extrapolation and modelling of data to enable comparisons across countries[15]. Additionally, not all registries document the occurrence of non-invasive bladder tumours (stages Tis and Ta) similarly (Fig. 1). In this section, most incidence and mortality data are derived from the GLOBOCAN 2020 database, which includes non-invasive tumours[11,16].

Incidence

Globally, bladder cancer is the tenth most common cancer type in terms of absolute number of cases, with approximately 573,000 new diagnoses in 2020, more than three-quarters occurring in men (in whom it is the sixth most common cancer) owing predominantly to a historically higher smoking prevalence in men than in women[11]. However, the incidence of bladder cancer varies considerably across countries (Fig. 2). The estimated age-standardized incidence rates among men range from 40 cases per 100,000 person-years in Greece to <1 case per 100,000 person-years in several African countries, such as Côte d'Ivoire and Liberia[16]. Among women, the age-standardized incidence rates are highest in Hungary (9 per 100,000 person-years) and lowest in several African and Eastern Mediterranean countries (<1 case per 100,000 person-years)[16]. Of note, these rates do not necessarily represent the true bladder cancer 'risk' per country, owing to differences in life expectancy, health-care infrastructure and cultural health-seeking behaviour as well as incomplete registries. The majority of bladder cancers (an estimated 356,600 cases in 2020) occur in countries with a very high human development index (HDI), which is associated with long life expectancy[16,17]. Even after age-standardization, however, countries with a very high HDI have much higher incidence rates than countries with lower HDIs (Fig. 2), with 10.2 cases per 100,000 person-years compared with 4.1, 1.9 and 2.6 cases per 100,000 person-years in countries with high, medium and low HDIs, respectively[16].

Over the past 15 years, bladder cancer incidence rates among men have been declining by ~1% per year in most parts of the world[17]. In Europe, however, large differences in temporal trends are observed with stronger decreasing trends in Ireland (−2.7% per year) and the UK (−4.3% per year) but also strong increasing trends in the southern and eastern part of Europe (most prominently in Bulgaria with an increase of 3.7% per year)[17]. Overall, the same trends are observed in women, with the exception of western Europe[17]. Unlike the decreasing trend in men, bladder cancer incidence among women has increased in western Europe (with the highest increase of +1.6% per year in the Netherlands)[17].

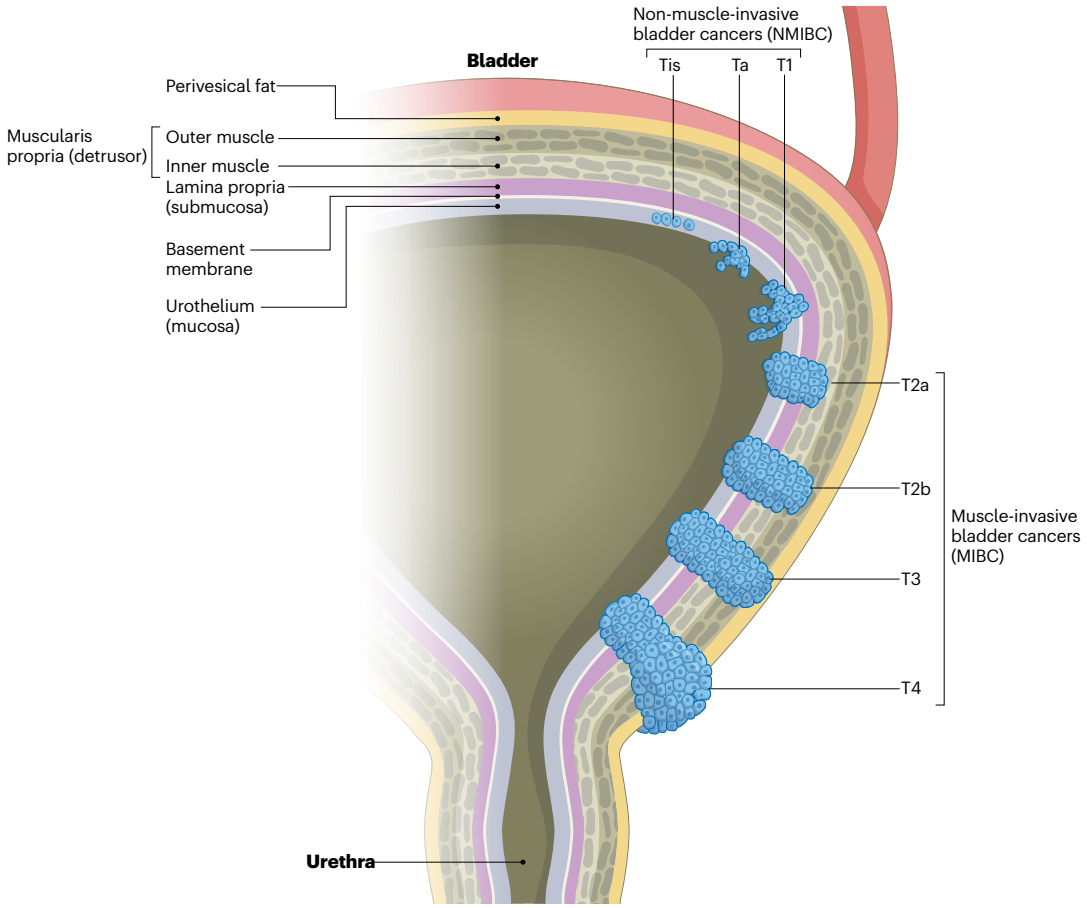
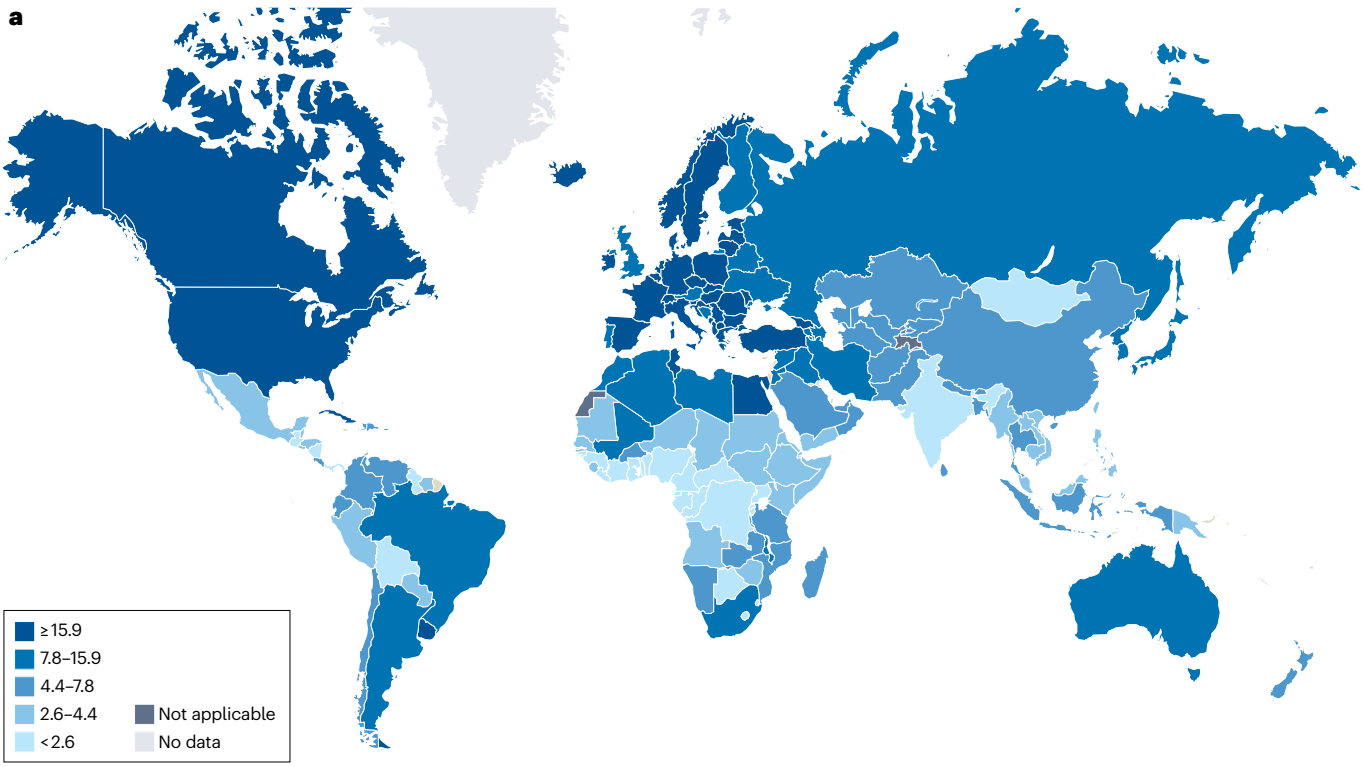


Fig. 1 | Bladder wall and different stages of tumour invasion. In bladder cancer staging, non-muscle invasive bladder cancers (NMIBC) include carcinoma in situ (Tis, flat tumour), Ta papillary non-invasive carcinomas and T1 tumours infiltrating the lamina propria; muscle invasive bladder cancers (MIBC) include T2a tumours infiltrating the superficial detrusor muscle, T2b tumours infiltrating the deep detrusor muscle, T3 tumours infiltrating perivesical fat tissue, and T4 tumours infiltrating perivesical organs (prostate, uterus, vagina or abdominal/pelvic wall). In urology practice, the distinction between NMIBC and MIBC has important clinical implications, given that NMIBC is usually treated conservatively with transurethral resection of the tumour and intravesical chemotherapy or Bacillus Calmette–Guérin instillations, whereas MIBC is treated with removal of the bladder or chemoradiotherapy and/or systemic chemotherapy or immunotherapy. Ta and most T1 NMIBC tumours develop through pathways very different from those involved in MIBC development[190]. Paradoxically, Tis NMIBC tumours develop through the same pathways as MIBC, and are therefore the most aggressive subtype of NMIBC.

Trends in the demographic composition of populations have an important role in projecting the future incidence of bladder cancer. In absolute terms, future incidence is mostly determined by population size and growth rate as well as the proportion of older people in the population[18], given that ageing is the strongest determinant of bladder cancer risk. In addition to these demographic factors, the prevalence of tobacco smoking also strongly affects the incidence of bladder cancer[19]. We have graphically depicted these four aspects for 226 countries and territories worldwide, for both sexes (Fig. 3a,b). The vast majority of countries have a growing population, with 69% of the world population living in countries with growth rates of ≥5% over the last decade (2010–2020)[20]. Overall, older people (aged ≥65 years) account for an estimated 9.6% of the world population[20]. Notably, however, countries with the highest levels of population growth (>25%) because of high fertility rates over the last decade mostly have low proportions of older people[20] (typically <5%) (Fig. 3a,b). The prevalence of smoking in these countries is also generally low among both men and women[21] (typically <20% and <5%, respectively) (Fig. 3a,b). With anticipated increases in smoking prevalence, environmental pollution and ageing associated with a rising HDI, such countries will probably show strong increases in bladder cancer incidence over the coming decades. We have also provided a graphical summary of the degree to which these demographic factors that influence the future incidence of bladder – that is, population growth, proportion of older people and smoking prevalence – apply to each country (Fig. 3c).

Countries with low population growth (0–10%) and consequently high proportions of older people include most European, Northern American and some Western Pacific countries (Fig. 3a,b), with historically the highest HDI scores. These countries with very high HDIs have a much higher smoking prevalence among women than countries with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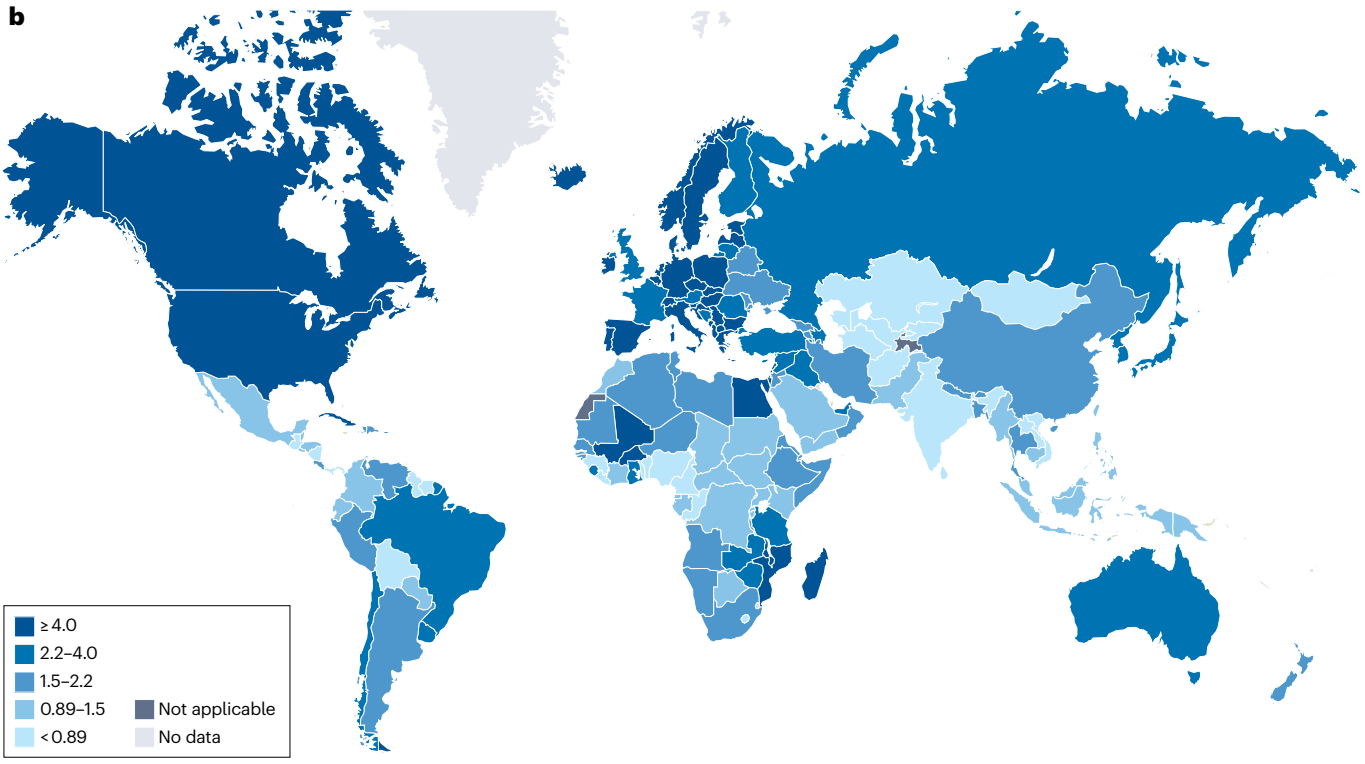
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Fig. 2 | Bladder cancer incidence worldwide in 2020. The shading indicates the estimated age-standardized incidence rates of bladder cancer in men (part **a**) and women (part **b**), based on data from GLOBOCAN 2020 (ref. [16]), © International Agency for Research on Cancer.

lower HDIs[18]. The smoking prevalence in countries with very high HDIs has been reduced considerably among men and to a lesser extent among women over the past few decades but remains high[18]. This decrease started much earlier and is of greater magnitude among men than women in most countries with a very high HDI, and therefore the age-standardized incidence of bladder cancer is decreasing among men but is likely to continue to increase in the near future among women.

Mortality

Worldwide, approximately 213,000 people died of bladder cancer in 2020, with this disease ranking as the 13th most common cause of cancer-related death (and ninth among men). Three out of four bladder cancer deaths were in men[11]. Age-standardized mortality rates were highest in Northern African and European countries among men and in Northern American, European and several African countries, including Tanzania, Burkina Faso, Malawi and Mozambique, among women (Fig. 4). In most countries around the globe, age-standardized mortality rates have decreased over the past 15 years, ranging from a decrease of 0.1% per year (among women in Ireland) to as much as 6.1% per year (among women in Iceland)[17].

Future total bladder cancer mortality will primarily be determined by the projected increases in the absolute incidence of the disease, while age-standardized mortality rates might continue to decrease owing to reductions in smoking prevalence and, to a much lesser extent, improvements in bladder cancer diagnosis and treatment. Such changes have contributed to the stabilization or slight decreases in mortality rates in most countries with high and very high HDIs, but not yet in countries undergoing rapid economic transition (including Central and South American countries, such as Brazil, and some central, southern and eastern European countries, such as Bulgaria)[17].

Impact of the incidence and mortality trends on health care

Worldwide, the increase in bladder cancer incidence is expected to continue and will have direct effects on the need for diagnostic procedures and primary treatment. A higher incidence of the disease will also lead to a higher prevalence, which in turn has enormous consequences for clinical follow-up. For NMIBC, an increasing number of patients will require intensive follow-up monitoring with cystoscopy for diagnosis of recurrent and progressive disease as well as repeated TURBT to manage recurrences. For MIBC, more patients will need costly systemic treatments (in both the perioperative setting and the metastatic setting), imaging assessments, radiotherapy and hospital admissions associated with radical cystectomy. Ultimately, the increasing incidence and prevalence of bladder cancer translates into a growing demand on health-care resources and capacity.

In many countries with a large proportion of older people, including most European countries and Japan, an additional complication relates to the fact that the ratio of working-age people to older people is decreasing at an increasing rate, which can contribute to shortages of health-care staff[22,23]. This issue underlines the need for more efficient (that is, less labour-intensive) strategies for the diagnosis, treatment and follow-up of patients with bladder cancer.

New therapies for bladder cancer, such as immune-checkpoint inhibitors, have been introduced into clinical practice and are currently being transitioned from the palliative to the perioperative[24] and even NMIBC settings[25]. However, these treatments will not considerably improve survival at the population level globally because they will only be available for a small proportion of patients and provide modest benefits over established therapies[26,27].

All these trends together emphasize the absolutely crucial role of prevention of tobacco exposure worldwide to curb the rising incidence of bladder cancer and the associated burden on society. In addition, innovations are needed that make the management of bladder cancer better but, even more importantly, more efficient.

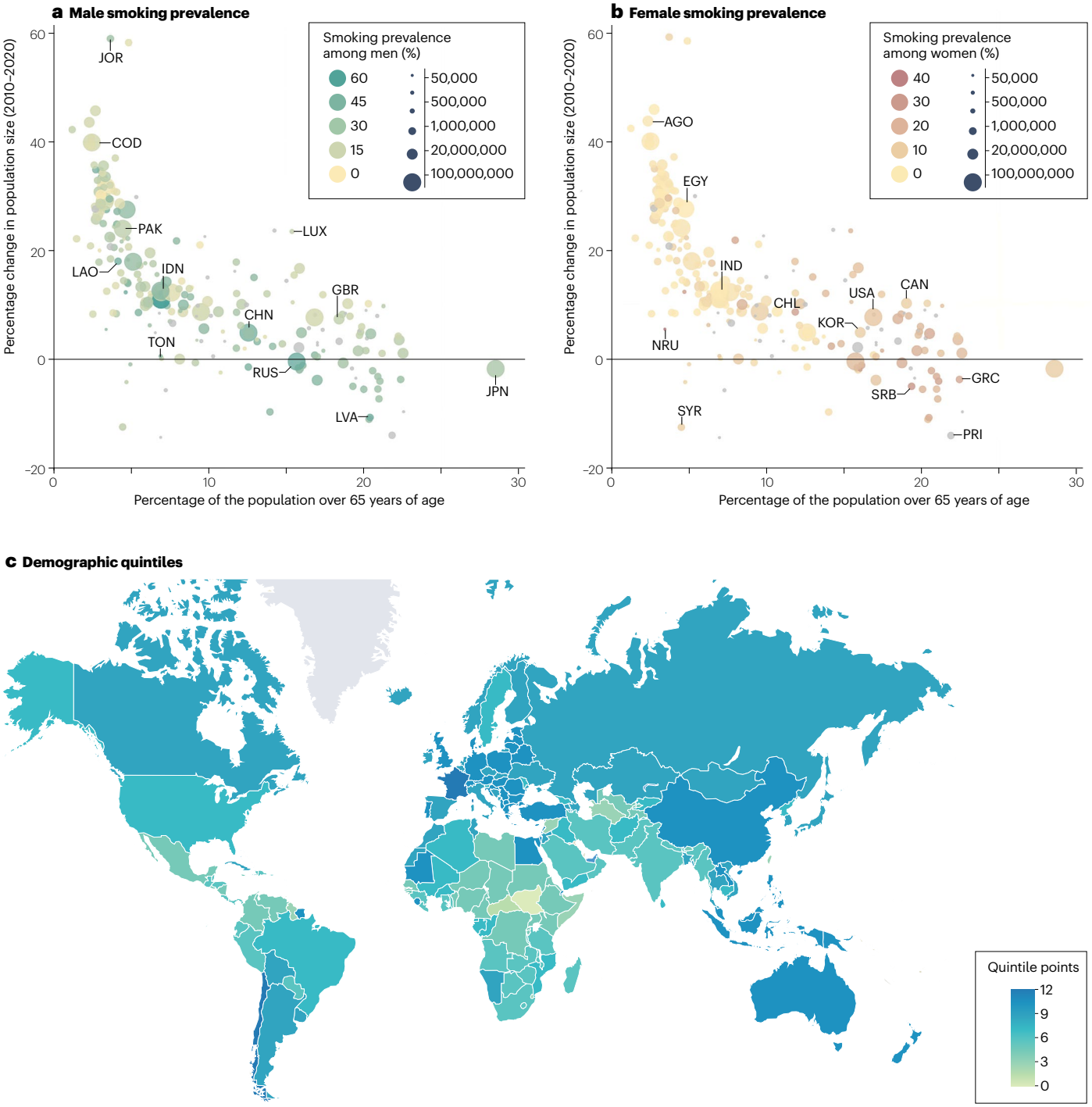
Risk factors

Numerous factors have been studied as potential risk factors for bladder cancer, although almost exclusively with regard to urothelial carcinoma because it is by far the most common, and thus the best studied, histological subtype (Table 1). Tobacco smoking and urinary tract infections, such as schistosomiasis, are the only established risk factors for squamous cell carcinoma[28].

Lifestyle-related factors

Smoking. Tobacco contains many known carcinogenic compounds, including aromatic amines and *N*-nitroso compounds, which are excreted in the urine and therefore come into close contact with the bladder lining[29]. After entering urothelial cells, these compounds can result in DNA adducts that can induce different mutational spectra[30,31]. Smoking is the most important risk factor for bladder cancer, a conclusion strongly supported by a meta-analysis of 83 studies[32]. Ever-smokers have a twofold to threefold increased risk of the disease compared with never-smokers, increasing up to a fivefold relative risk in heavy smokers (>20 cigarettes per day), with strengths of the associations being similar in men and women[33]. Although most studies have focused on the association with urothelial carcinoma, a pooled analysis of nine European case–control studies including 146 patients with other forms of bladder cancer also identified smoking as an important cause of squamous cell bladder carcinoma, with odds ratios ~5.3 in current smokers and ~2.2 in former smokers, increasing to 11.3 and 3.7, respectively, in those in the highest tertile of pack-years (>40.5, equivalent to 20 cigarettes per day for 40.5 years or 40 cigarettes per day for 20.25 years), compared with non-smokers; the risk of squamous cell carcinoma was similar to that observed for urothelial cancer in this study[34]. Smoking cessation decreases the relative risk of bladder cancer by 20–30% in the first 5 years, although an approximately 1.5-fold increased risk remains beyond even 25 years after cessation[35,36].

The population attributable risks (PAR; that is, the fraction of bladder cancers attributable to cigarette smoking) were 66% in men and 30% in women according to an International Agency for Research on Cancer (IARC) report published in 2004 (ref. [37]), with a more recent meta-analysis of 89 observational studies providing fairly similar results[27]. The lower PAR in women probably reflects the later smoking epidemic among women. Indeed, studies focused on more recent population cohorts indicate that the PARs are comparable in men and women. In the USA, for example, the NIH-AARP Diet and Health Study spanning 1995–2006 estimated PARs of 50% in men and 52% in women[38]. These findings emphasize the fact that the PAR of smoking for



bladder cancer is not a natural constant; this proportion is calculated using the risk ratio of smoking for bladder cancer and the prevalence of smoking in the population, both of which are situation-dependent estimates (and this is the reason for us not reporting PARs in Table 1). Furthermore, given the strong differential trends in smoking prevalence worldwide, it is important to combine the risk ratio of smoking for bladder cancer with the prevalence of smoking in the calendar period at least 20–30 years earlier than the occurrence of the incident bladder cancers. In most studies, whether this latency period was accounted for is unclear. The PAR values should therefore be considered as very crude estimates.

Electronic cigarettes. Currently, no robust data exist regarding the risk of bladder cancer associated with the use of electronic cigarettes (or 'vaping'). This habit is too recent to have reached the long latency period of bladder cancer. A systemic review of urinary carcinogens related to vaping showed higher concentrations of 63 toxic or carcinogenic metabolite biomarkers in people who smoke electronic

Fig. 3 | Summary of demographic characteristics that are relevant to bladder cancer incidence across countries worldwide. Population size and growth, proportion of older inhabitants and smoking prevalence are shown for men (part **a**) and women (part **b**). Each country or territory is represented as a circle in part **a** and part **b**, with the size of each circle corresponding to the population size in the respective country or territory in 2020. The position of the circles according to the *y*-axis indicates the percentage population growth (or decline) in the corresponding countries during the period 2010–2020, and their position relative to the *x*-axis indicates the proportion of inhabitants aged >65 years in 2020. The shading of the circles indicates the smoking prevalence during the period 2015–2020. The distributions of population growth, proportion of older people and smoking prevalence (50:50 average of men and women) across countries were divided by quintiles, and the countries were assigned scores for each of these three factors (0 if in the lowest quintile up to 4 if in highest), which were then summed and are plotted in part **c**. In part **c**, darker colours indicate countries with more demographic characteristics that are likely to contribute to higher absolute numbers of bladder cancer cases in the future. AGO, Angola; CAN, Canada; CHL, Chile; CHN, China; COD, Congo Democratic Republic; EGY, Egypt; GBR, Great Britain; GRC, Greece; IDN, Indonesia; IND, India; JOR, Jordan; JPN, Japan; KOR, South Korea; LAO, Laos; LUX, Luxembourg; LVA, Latvia; NRU, Nauru; PAK, Pakistan; PRI, Puerto Rico; RUS, Russia; SRB, Serbia; SYR, Syria; TON, Tonga; USA, United States of America. Data on population size, growth rate and proportion of older inhabitants were derived from the International Database of the US Census Bureau[20]; smoking prevalence data were sourced from refs. [21,191,192].

cigarettes compared with the concentrations in non-smoking controls[39]. Therefore, we are confronted with a possible new risk factor for bladder cancer in its infancy, warranting efforts to prevent this habit becoming endemic.

Fluid intake and diet. High intake of fluids has frequently been hypothesized to reduce the risk of bladder cancer by diluting the urinary concentrations of lifestyle-related or environment-related metabolites, or by decreasing the duration of exposure of the bladder epithelium to such compounds owing to more frequent voiding. Conversely, high fluid intake might increase the risk if the fluids contain carcinogens, simply because of a higher cumulative dose[40] and/or owing to higher junctional permeability of the urothelium with a more extensive bladder filling[41] (see the 'Drinking water' section below). To date, the findings of epidemiological studies on fluid intake and the risk of bladder cancer have been inconsistent[42]. Case–control studies have suggested several associations for various dietary factors[43], but have been hampered by the possibility of recall bias because data collection takes place after diagnosis[44]. The World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) Continuous Update Project report on diet, nutrition, physical activity and bladder cancer, published in 2018 (ref. [45]), focused on prospective cohort studies and randomized controlled trials with lifestyle-related data collected before diagnosis. This report states that only limited suggestive evidence has been found for a protective effect of high levels of fruit and vegetables or tea consumption on the risk of bladder cancer[45]. Any protective effect of fruit and vegetables might be attributable to their content of antioxidants, minerals, dietary fibres, phenols, flavonoids and phytochemicals. These components might reduce oxidative stress and DNA damage caused by free radicals as well as influence cell proliferation and apoptosis[45]. Tea contains polyphenol compounds, which also have antioxidative and antiproliferative effects[45]. The evidence for effects of other dietary factors on the risk of bladder cancer is inconclusive[45].

BMI and physical activity. The results of a meta-analysis of 15 cohort studies encompassing >14.2 million individuals, including 38,072 patients with bladder cancer, indicate that a high BMI (≥25 kg/m^2) is a risk factor for bladder cancer: RR 1.07 (95% CI 1.01–1.14) for overweight (BMI 25.00–29.99 kg/m^2) and RR 1.10 (95% CI 1.06–1.14) for obesity (BMI ≥ 30 kg/m^2), both relative to normal weight (BMI 18.50–24.99 kg/m^2), with the risk increasing linearly by 4.2% for each 5 kg/m^2 increment[46]. Conversely, a meta-analysis of 15 studies with a total of 5.4 million participants, including 27,784 with bladder cancer, suggested that high levels of physical activity decreases the risk of bladder cancer (summary RR 0.85, 95% CI 0.74–0.98, relative to low levels)[47]. The biological mechanisms underlying the associations of BMI and physical activity with the risk of bladder cancer are not well understood. Evidence indicates that obesity and physical inactivity are associated with elevated production of insulin and chronic low-grade systemic inflammation, which can modify cell proliferation, differentiation and apoptosis, and angiogenesis[46,47]. However, owing to insufficient evidence for biological plausibility and substantial heterogeneity between studies, the WCRF–AICR classifies the evidence for BMI and physical activity as inconclusive[45]. Thus, despite numerous studies, the overall evidence for effects of lifestyle-related factors on the risk of bladder cancer is inconclusive, except for smoking.

Sex. As mentioned previously, men have a much higher lifetime risk of bladder cancer than women. This imbalance might be partly explained by the higher historical prevalence of smoking and exposure to occupational carcinogens among men, but studies have shown that these factors do not fully explain the male predominance of bladder cancer[48,49]. Several other mechanisms might underlie the difference in risk[50]. At the molecular level, sex differences in certain hepatic metabolic pathways seem to lead to differences in the degradation of carcinogens, resulting in differential exposure of the urothelium to carcinogenic compounds[51,52]. Although the evidence is limited, sex hormones might also have a role, as late age at menarche (≥15 years), parity, and oestrogen and progestogen therapy have been associated with a decreased risk of bladder cancer (with hazard ratios of 0.57, 0.76 and 0.53, respectively, in a study of 127,361 women with incident bladder cancer identified in 198)[53,54]. Nevertheless, the sex ratio of bladder cancer closely follows that of lung cancer in all countries, suggesting smoking as the most relevant factor[33].

Although the incidence of bladder cancer is higher among men, in women the disease is more often diagnosed at a higher stage, which is associated with a worse prognosis[53,55,56]. This disparity is partly explained by a delay in diagnostic work-up among women presenting with haematuria[57], who are more likely than men with the same sign to be diagnosed incorrectly with urinary tract infections and less likely to be referred to a urologist and undergo abdominal or pelvic imaging[58–60]. The worse prognosis in women might also be related to a thinner bladder wall (which is on average 4.6 ± 1.3 mm in men and 4.2 ± 1.5 mm in women, at a low filling volume of 20–50 ml)[61]. With a thinner bladder wall, bladder cancer cells might more easily disseminate, but this hypothesis is very difficult to study.

As alluded to above, outcomes of bladder cancer also differ between men and women. The differences in stage at diagnosis only account for part of this divergence because, even after adjusting for disease stage, women have a lower relative survival rate[56] and a higher cancer-specific mortality risk[62]. The reason for these differences in outcomes is unclear, but might relate in part to sex differences in the use of certain therapies[63] and treatment effectiveness[64].

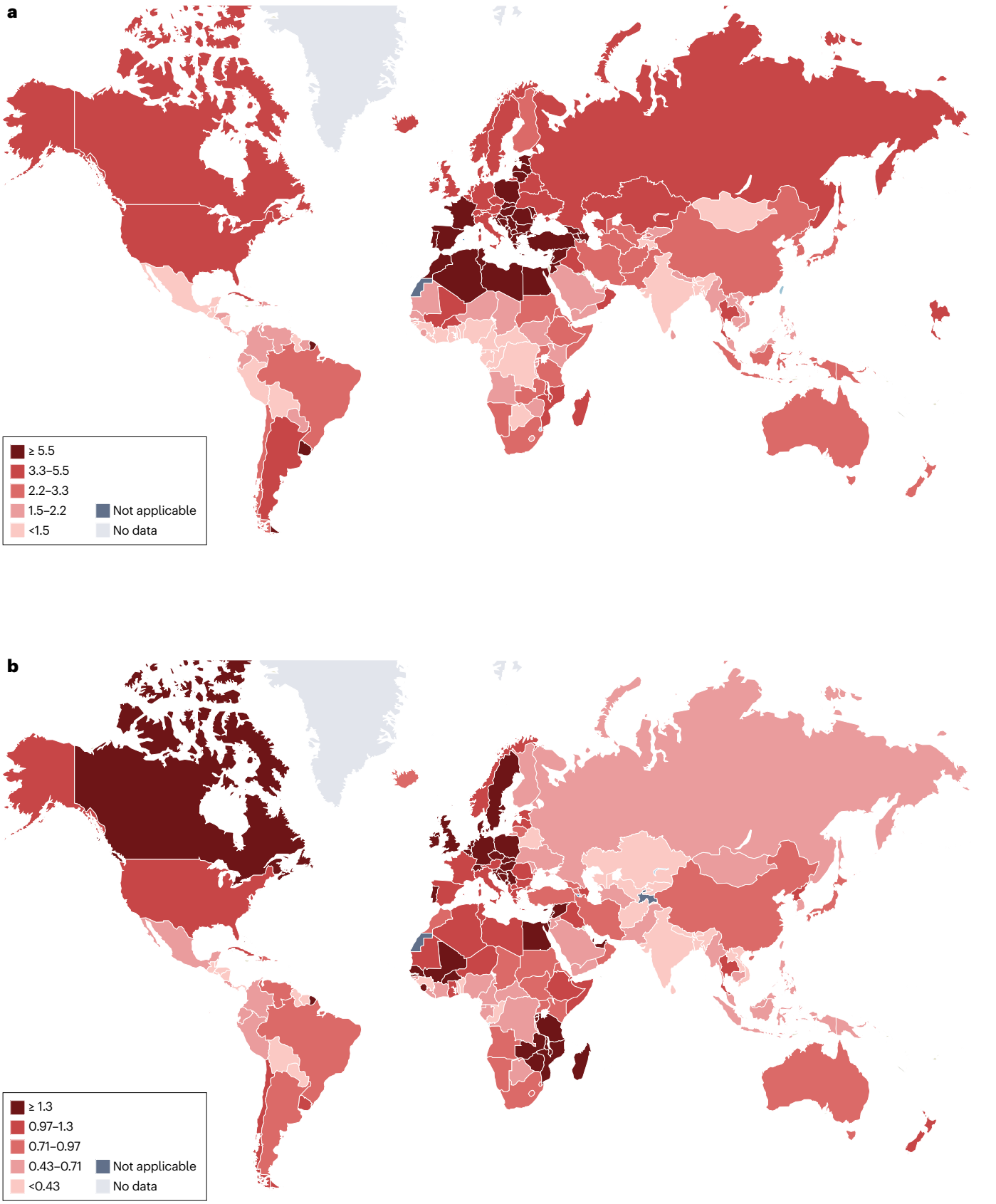

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Fig. 4 | Bladder cancer mortality worldwide in 2020. The shading indicates the age-standardized mortality rates in men (part **a**) and women (part **b**) in 2020, based on data from GLOBOCAN 2020 (ref. [16]), © International Agency for Research on Cancer.

Genetic susceptibility. Bladder cancer is not a disease with a strong genetic component. However, reports have suggested the existence of rare monogenic susceptibility forms of bladder cancer[65]. Data indicate that carriers of mutations in the retinoblastoma gene (*RB1*) or patients with bilateral retinoblastoma have a strongly increased risk of bladder cancer[66–68], but this finding was refuted by a long-term study published in 2021 involving >2,000 patients with retinoblastoma[69]. In addition, some patients with Costello syndrome, caused by activating germline *HRAS* mutations, developed bladder cancer at an extremely young age (10, 11 and 16 years, with the youngest patient developing recurrences twice before the age of 15 years), suggesting a monogenic cause of bladder cancer[70]. The risk of urothelial cancer is also increased in families with Lynch syndrome harbouring a mismatch repair gene mutation; most studies have shown the highest risk with *MSH2* mutations[71,72]. Periodic screening for urothelial cancers among carriers of such mutations is a subject of debate. Several sequencing studies have revealed an increased frequency of pathogenic or probably pathogenic germline mutations in DNA damage response genes such as *ERCC2*, *ERCC3*, *MSH2*, *MSH6*, *BRCA1*, *NBN* and *RAD50* among patients with bladder cancer, especially high-grade bladder cancer[73–78]. Nevertheless, familial clustering of bladder cancer is modest (HR 1.8, 95% CI 1.3–2.7, among first-degree relatives); families with more than two patients related in the first degree are rare[79]. These findings mean that germline counselling and testing of all patients with (high-grade) bladder cancer to identify high-risk family members, as sometimes advocated[73], is unlikely to be cost-effective.

In addition to rare high-penetrance mutations, early studies of candidate genes and, more recently, genome-wide association studies have revealed more than two dozen genetic variants that increase the risk of bladder cancer[80]. Together, these variants explain ~12% of the familial risk of bladder cancer[81]. The variants lie in or near genes that are mainly active in carcinogen metabolism (such as *NAT2*, *GSTM1* and *UGT1A6*), cell cycle control (*TP63*, *CCNE1*, *MYC* and *FGFR3*) and DNA repair (*XRCC1* and *XRCC3*, *ERCC2*, *ERCC4* and *ERCC5*, and *NBN*), but also in, for example, telomere maintenance (*TERT*) or other cellular processes[80]. Many studies have consistently found gene–environment interactions between some of these variants and exposure to cigarette smoke[82,83]. So far, the relevance of all these genetic variants is mainly in expanding our knowledge of the aetiology of bladder cancer. Some researchers advocate for the construction of polygenic risk scores (PRSs) that can be used for preventive purposes, such as identifying high-risk individuals for inclusion in early detection and/or intervention programmes. However, the predictive ability of such PRSs can only be adequate if they include many genetic variants, owing to the small effect size of individual variants. In that case, the risk distribution will take the form of a gaussian curve, and therefore the choice of a cut-off point for the 'high-risk' group will be arbitrary. The importance of low-penetrance genetic risk variants for public health is therefore not clear yet.

Occupational risk factors. Aside from tobacco smoking, specific occupational exposures are the most important risk factors for bladder cancer. Six different categories of carcinogenic exposures in the workplace have been reported to be risk factors for bladder cancer in IARC monographs: *ortho*-toluidine; arsenic and inorganic arsenic compounds; X-ray radiation and γ-radiation; 2-naphthylamine; 4-aminobiphenyl; and benzidine[84] (Table 1). Exposure to these carcinogens can particularly occur in industrial metal workers and people working with dyes (for example, textile manufacturers). Studies on occupational risk factors might be hampered by some degree of bias related to the difficulty in accurately assessing exposure levels, classifying occupations and fully adjusting for smoking behaviour[85], although for these six categories of carcinogens the evidence for an increased risk of bladder cancer is sufficiently robust. In addition, the IARC classifies several occupations and industries, including painting, the rubber industry, aluminium production, auramine production, magenta production and firefighting, as risk factors for bladder cancer with sufficient evidence[84].

Drinking water. Strong evidence indicates that drinking water containing arsenic at concentrations of >50 μg/l increases the risk of bladder cancer in a dose-dependent manner[40] (Table 1). Some studies have shown an increased the risk of bladder cancer at levels of exposure to arsenic at concentrations of <10 μg/l, but the overall evidence is less conclusive than that for exposure to higher levels[86]. A high level of arsenic exposure is particularly relevant in countries such as Taiwan, Bangladesh, India, Cambodia, Argentina, Chile and Mexico, where natural deposits of arsenic present in the earth or the use of arsenic-containing compounds in agricultural and industrial practices can lead to contamination of drinking water[87,88]. However, high levels of arsenic have also been measured in groundwater of specific regions in the USA and several countries in Europe. Arsenic can increase the risk of bladder cancer owing to its genotoxic and mutagenic properties, and can also result in aberrant methylation of oncogenes and tumour suppressor genes as well as oxidative stress that promote tumorigenesis[45].

Chlorinated drinking water, which is common in many countries[89], might also increase the risk of bladder cancer (OR 1.4, 95% CI 1.2–1.7, for ≥40 years of exposure in a meta-analysis of eight studies including >6,200 patients with and >10,800 individuals without bladder cancer)[90]. This effect might occur via the reaction of chlorine with organic or inorganic compounds in the water, resulting in the formation of undesirable disinfection by-products with carcinogenic, mutagenic or genotoxic properties[91].

Air pollution. In our increasingly industrialized world, air pollution might have become a risk factor for bladder cancer. A report published by the European Environment Agency in 2022 states that exposure to air pollution, carcinogenic chemicals, radon, UV radiation and second-hand smoke together might account for >10% of the cancer burden in Europe[92]. In a study involving >6.3 million residents living within 30 miles of an oil refinery in Texas, USA, the risk of several cancers was higher in persons living closer to the refinery, with the greatest risk observed for metastatic bladder cancer (RR 1.30, 95% CI 1.02–1.65, among residents living within 0–10 miles versus 21–30 miles from the refinery)[93]. By contrast, a pooled analysis of 15 population-based cohort studies including >300,000 people across eight European countries was unable to identify an increased risk of bladder cancer associated with exposure to nitrogen oxides, particulate matter of different diameters, organic carbon or traffic density at individuals' home addresses[94]. Although an aetiological link is biologically plausible, obtaining robust evidence for a causal role of air pollution in bladder

Table 1 | Risk factors for bladder cancer and level of supporting evidence

Risk factors	Direction and strength of association[a]
Proven risk factors	
Cigarette smoking	↑↑
Genetic susceptibility: variants in or near genes active in carcinogen metabolism (including *NAT2*, *GSTM1* and *UGT1A6*), cell cycle control (*TP63*, *CCNE1*, *MYC* and *FGFR3*) and/or DNA repair (*XRCC1*, *XRCC2*, *XRCC3*, *ERCC2*, *ERCC4*, *ERCC5* and *NBN*)	↑
Infection with *Schistosoma haematobium*	↑↑
Arsenic in drinking water	↑
Occupational exposures: aromatic amines and dyes (4-aminobiphenyl, benzidine, 2-naphthylamine and *ortho*-toluidine)	↑↑
Occupations and industries: painting, rubber industry, aluminium production, auramine production, magenta production and firefighting	↑
Medications: cyclophosphamide, chlornaphazine, phenacetin, aristolochic acid (also a dietary risk factor) and pioglitazone	↑↑
Family history	↑
Ionizing radiation (X-ray radiation and γ-radiation)	↑
Probable risk factors, based on substantial evidence	
Disinfection by-products in drinking water	↑
Occupational exposures: diesel engine exhaust emissions, 4-chloro-*ortho*-toluidine, coal, tar and/or pitch, soot, tetrachloroethylene and perchloroethylene, metal working fluids	↑
Occupations and industries: barbers and hairdressers, dry cleaning industry, printing, textile industry	↑
Pipes and cigars	↑
Type 2 diabetes	↑
Weak risk factors, if risk factors at all, based on substantial evidence	
Parity	↓
Tea consumption	↓
Fruit and vegetable consumption	↓
Physical activity	↓
Risk factors with inconsistent findings or data to date too limited	
Air pollution	↑
Hair dyes	↑
Diet: cereals (grains) and their products, pulses (legumes), meat, poultry, fish, dairy products, drinks (including coffee, juices and soft drinks), energy intake, macronutrients, micronutrients and bioactive compounds, multivitamin supplements, dietetic foods and artificial sweeteners	↑ or ↓
Fluid intake	↓
Alcohol consumption	↑
Obesity	↑
Infections (other than *S. haematobium*)	↑
Medications: barbiturates and NSAIDs	↓

Adapted with permission from ref. [33], Oxford University Press. [a]Evaluations of direction and strength of the associations are expert opinions based on all available human, animal and in vitro data, with the Bradford Hill criteria for causation used for guidance[189]. Arrows indicate the approximate magnitude of the relationship: ↑, slight-to-moderate increase in risk; ↑↑, moderate-to-large increase in risk; ↓, slight-to-moderate decrease in risk. Although the strength of a relationship is dependent on the definition of an exposure (for example, having ever been a painter versus number of years working as a painter) as well as the characteristics of the population (that is, effect measures are not natural constants), ↑ can be approximately equated to an odds ratio/risk ratio of 1–2, ↑↑ to an odds ratio/risk ratio of >2, and ↓ to an odds ratio/risk ratio of 0.5–1. NSAIDs, non-steroidal anti-inflammatory drugs.

cancer development will be very difficult because the association is probably weak.

***Schistosoma* infection.** Bladder cancer can be caused by urogenital schistosomiasis, a parasitic disease caused by trematodes (also known as blood flukes or flatworms) of the species *Schistosoma haematobium*. This parasite spreads via eggs that are excreted from infected humans in urine into freshwater and, after involvement of a snail host, subsequently generate larvae (cercariae) that can penetrate human skin[95]. After maturation within the vesical venous plexus (a group of veins at the lower portion of the bladder) of their human host, the parasitic flatworms again produce eggs that can penetrate into the bladder; however, some of the eggs can become lodged in the bladder wall and induce a granulomatous host response and tissue inflammation that result in pathological lesions, including benign and malignant bladder tumours[95]. Schistosomiasis is an endemic disease that affects hundreds of millions of people in sub-Saharan Africa and some parts of the Middle East, causing an estimated 200,000 deaths annually[96]. Bladder cancers caused by schistosomiasis usually have a squamous cell morphology (>80%) and occur a decade earlier than other types of bladder cancer[96]. Notably, schistosomiasis is often accompanied by chronic bacterial superinfection, which might in itself predispose to squamous cell bladder cancer[96].

In Egypt, where the prevalence of schistosomiasis was extremely high (>40%) until the 1980s, bladder cancer was the most frequently diagnosed cancer and the most common cause of death in men aged 20–44 years, and in women it was the second most frequent solid cancer, second only to breast cancer. The odds ratio of a history of urogenital schistosomiasis for the risk of bladder cancer was 1.72 (95% CI 1.0–2.9); in up to 16% of all individuals with bladder cancer in this population the cancer could be explained by a schistosomiasis infection[97]. Through mass treatment with the effective anthelmintic drug praziquantel, and improvements in the water supply and sanitation, the prevalence of schistosomiasis has been reduced to 1–2%, leading to a spectacular decrease in the occurrence of squamous cell bladder cancer in Egypt[96]. Preventive treatment through mass administration of praziquantel is now the cornerstone of the control of endemic schistosomiasis in regions of Africa[98].

Medical conditions and interventions. Patients with type 2 diabetes have an increased risk of bladder cancer. In a meta-analysis of nine case–control and 19 cohort studies in patients with bladder cancer as well as eight cohort studies in patients with diabetes, the summary odds ratio was found to be 1.35 (95% CI 1.17–1.56; $P < 0.001$)[99]. Antidiabetes therapy is a potential mediator in this association; specifically, the use of pioglitazone increases the risk of bladder cancer (HR 1.63, 95% CI 1.22–2.19, compared with other antidiabetic drugs in a cohort of >145,000 patients)[100]. Associations with bladder cancer have also been reported for other classes of drugs or drug compounds, such as analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), aristolochic acid and barbiturates[33].

Chronic bacterial infections can occur in patients with urinary tract stones and in patients with spinal cord injury (SCI) who use an indwelling urinary catheter (IDC). In a historical US cohort of 3,670 patients with SCI, of whom approximately a half had an IDC, 21 patients were diagnosed with bladder cancer and the use of an IDC increased the risk of bladder cancer 25-fold[101]. The patients with SCI without an IDC had a fivefold increased risk of bladder cancer compared with the risk in the general population. Despite these findings, clinical guidelines for

SCI make no statements about screening for bladder cancer in patients with an IDC[102,103]. Patients with a history of bladder stones seem to have an increased risk of bladder cancer. In a meta-analysis of 13 studies, the pooled odds ratio for bladder stones was found to be 2.17 (95% CI 1.52–3.08), and for kidney stones was 1.39 (95% CI 1.06–1.82)[104].

Other medical interventions might also increase the risk of bladder cancer, specifically certain drugs and radiotherapy. In the 1950s, the 2-naphthylamine derivative chlornaphazine was used for the treatment of polycythaemia and Hodgkin lymphoma; however, the use of this drug was stopped when patients were found to have an enormously increased risk of bladder cancer[105,106]. In a study from Denmark involving 61 patients treated with chlornaphazine for polycythaemia vera, 13 patients developed bladder cancer during 20 years of follow-up, and among five patients who were treated with ≥200 g, four developed invasive bladder cancer[107]. Similarly, the analgesic phenacetin is believed to be a risk factor for bladder cancer (OR 2.2, 95% CI 1.3–3.8, in a study of 366 patients and 456 individuals without bladder cancer)[108], although its association with upper urinary tract tumours is stronger[109]. Because of this effect in increasing the risk of upper urinary tract cancers, phenacetin was banned from the market in most countries in the late 1960s, leading to a significant reduction in renal pelvis cancer incidence in Australia, especially among women[110]. Paracetamol, a metabolite of phenacetin, is not a risk factor for bladder cancer[108]. Cyclophosphamide, a drug that is still frequently used in oncology, is known to cause bladder cancer in a cumulative dose-dependent manner, with a relatively large proportion (26%) of tumours having a non-urothelial cell histology and muscle invasion (48%)[111]. The same is true for radiotherapy to the lower pelvis (for example, for prostate or cervical cancer), although the absolute risk of radiotherapy-induced bladder cancer is very low[112–114]. Nevertheless, health-care professionals should be alert for bladder cancer symptoms in cancer survivors who were treated with radiotherapy to the lower pelvis. Newer radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), could possibly decrease the risk, given the lower radiation doses delivered to non-target tissues in the pelvis. In a study based on the Netherlands Cancer Registry and published in 2020, patients with prostate cancer treated with IMRT indeed had a non-significantly lower risk of bladder cancer than patients treated with the older 3D conformal radiation techniques (HR 0.56, 95% CI 0.27–1.18 (by the Fine and Gray method))[113]. However, the risk of bladder cancer among patients with prostate cancer treated with IMRT was still higher than in the general population (standardized incidence ratio 1.6, 95% CI 0.98–2.47)[113]. Definitive conclusions to support the hypothesis that IMRT to the pelvis is associated with a lower risk of bladder cancer than older radiotherapy protocols cannot be drawn yet owing to the sparsity of data[114].

Under acidic conditions, glucuronide conjugates of aromatic amines in cigarette smoke or occupational exposures can be rapidly hydrolysed, undergo further metabolic activation and form DNA adducts in cells of the urothelium. Interestingly, therefore, data from a study in Spain indicate that a consistently acidic urinary pH (≤6.0 across 4 days) is associated with an increased risk of bladder cancer (OR 1.5, 95% CI 1.2–1.9)[115]. Because this study had a case–control design and urinary pH was measured after the diagnosis of bladder cancer, acidic pH might have been a consequence rather than a cause of the bladder cancer. However, in an independent group of 14 patients, the researchers showed that the average pre-admission pH did not differ from the pH measured after hospital discharge[115]. Furthermore, the pH was not found to be dependent on the number of red blood cells in the urine, nor on the grade or stage of the bladder cancer, suggesting that acidic pH is a risk factor for, rather than a consequence of, bladder cancer[115]. The study also found risk estimates for current smokers to be higher among those with consistently acidic urine (OR 8.8–23.8, depending on smoking intensity) compared with smokers without consistently acidic urine. Although these findings remain to be replicated, an interesting question for future studies is whether modification of urinary pH through dietary interventions could reduce the risk of recurrence in patients with NMIBC.

Influence of lifestyle on treatment, rehabilitation and outcomes

Contrary to the abundant research on risk factors for bladder cancer, limited data are available regarding the effect of lifestyle-related factors on bladder cancer outcomes (that is, tertiary prevention). This knowledge gap is unfortunate, given that a cancer diagnosis might provide patients with a window of opportunity for lifestyle change and, thus, a way to regain some control over their fate.

Smoking

Cigarette smoking might reduce the immunostimulatory effect of intravesical BCG instillation, thereby reducing the effectiveness of such immunotherapy in patients with NMIBC, although only one[116] of two historical studies[116,117] found that efficacy was compromised in current smokers. In patients undergoing radical cystectomy, smoking might be associated with an increased risk of major postoperative complications, infections and mortality[118–120]. Furthermore, the results of a meta-analysis indicate that non-smokers and never-smokers undergoing neoadjuvant chemotherapy followed by radical cystectomy have a higher complete, but not partial, response rate than current smokers (HR 0.47, 95% CI 0.29–0.75)[118]. Although these findings are inconsistent and require confirmation in prospective studies, they suggest that smokers who are diagnosed with bladder cancer should be informed about and referred to smoking cessation programmes before BCG immunotherapy or radical cystectomy. Future studies should investigate whether an intensive stop-smoking intervention starting at least 4 weeks prior to therapy can reduce the risk of postoperative complications and improve survival[121].

Smoking is also an important risk factor for bladder-cancer-specific outcomes[122,123]. In a meta-analysis of 24 studies involving a total of >13,100 patients with bladder cancer, smokers with NMIBC had a higher risk of local recurrence than never-smokers with NMIBC (HR 1.27, 95% CI 1.09–1.46, for current smokers, and HR 1.13, 95% CI 1.00–1.25, for former smokers)[122]. No association between smoking status and progression to MIBC has been found, but the studies were probably not sufficiently powered with regard to this outcome. Among patients with MIBC, the aforementioned meta-analyses found that current smokers have a higher risk of disease-specific mortality than never-smokers (HR 1.23, 95% CI 1.02–1.44)[122]. Smoking cessation within 1 year before to 3 months after diagnosis has been associated with a lower risk of disease recurrence after diagnosis among patients with NMIBC in two historical cohort studies[124,125]. In one of these studies, the 3-year recurrence-free survival among continued smokers, non-smokers, ex-smokers and quitters was 45%, 57%, 62% and 70%, respectively[125]. In the other study, the hazard ratio for continued smokers compared with ex-smokers and quitters was 1.40 (95% CI 1.03–1.91)[124]. However, no high-quality prospective studies are available yet on the effect of smoking cessation on bladder cancer outcomes.

Body weight

It has been hypothesized that excess body fat is related to bladder cancer outcomes owing to its association with increased insulin and

insulin-like growth factor concentrations and with low-grade systemic inflammation. Certain diagnostic and surgical procedures are more complicated in patients with obesity. In a meta-analysis of historical cohort studies, patients with NMIBC and obesity but not those who were overweight were found to be at higher risk of recurrence (HR 1.51, 95% CI 1.05–2.16), progression (HR 1.88, 95% CI 1.41–2.50) and cancer-specific mortality (HR 2.01, 95% CI 1.39–2.90) than patients with a normal BMI[126]. By contrast, patients with MIBC who were overweight were at lower risk of cancer-specific mortality (HR 0.77, 95% CI 0.67–0.89)[126], with a similar trend observed for patients with obesity (HR 0.68, 95% CI 0.25–1.84)[126]. This inverse association might be explained by a higher prevalence of sarcopenia in patients with a normal BMI, which has been associated with increased risk of any-cause and cancer-specific mortality in patients with non-metastatic bladder cancer[127].

Diet

Malnutrition in patients undergoing radical cystectomy has an estimated prevalence of 16–55% and has been associated with a higher risk of postoperative complications and mortality[128]. Parenteral nutrition has also been associated with a higher risk of complications in such patients, whereas early introduction of food after surgery, enteral feeding and immunonutrition supplements with a focus on a high protein diet might improve surgical outcomes[129]. The 30-day complication rate after radical cystectomy in patients receiving specialized immunonutrition from 5 days before to 5 days after surgery is being compared with the rate in patients receiving oral nutritional support in a phase III trial involving 200 patients[130]. Further well-designed trials are needed to investigate the effect of nutritional interventions on clinical outcomes in patients undergoing radical cystectomy.

Several randomized controlled trials testing dietary supplementation have been conducted in patients with NMIBC, evaluating the effects of the retinoids etretinate and fenretinide, vitamin B_6, vitamin E, multivitamins, selenium and *Lactobacillus casei* on disease recurrence (reviewed elsewhere[42,131,132]). Some of these studies demonstrated beneficial effects, with *L. casei* probiotic supplementation emerging as the most promising approach; however, the trials generally had small sample sizes and the results were inconsistent[132]. Population-based studies investigating associations between dietary factors and bladder cancer outcomes are scarce (also reviewed elsewhere[42,131,132]). No associations between intake of vitamin A[133], total intake of fluids[134,135], consumption of (alcoholic) drinks[135,136], or total intake of fruit and vegetables[137,138] and the risk of disease recurrence, progression or bladder-cancer-specific mortality were found. However, the studies were limited by their small sample size[133,134,136,137] or the use of non-validated food-frequency questionnaires[135,138]. One prospective cohort study showed that patients with NMIBC who best adhered to a 'Western' dietary pattern before diagnosis were at increased risk of disease recurrence (HR 1.48, 95% CI 1.06–2.06, relative to patients within the lowest tertile of adherence); no association was observed for a 'fruit and vegetables', 'low-fat' or 'Tex-Mex' dietary pattern[139]. Solid evidence for the effects of diet on bladder cancer outcomes is very limited, and the results of high-quality prospective cohort studies in this space (for example, CoBlance[140], UroLife[141] and Be-Well[142]) are eagerly awaited.

Exercise

Evidence suggests that exercise in patients with bladder cancer before and/or after radical cystectomy improves health-related quality of life, cardiorespiratory fitness, functional capacity and muscle strength[143,144]. However, the studies conducted to date were limited by a lack of information on the type of exercise intervention used and recruitment and/or eligibility rates, small sample sizes and substantial patient attrition during the follow-up period[143–145]. The results from ongoing[145] and future prospective trials should provide better insight into the benefits of both aerobic exercise and strength training in relation to different treatments during all stages of the care pathway in patients with bladder cancer[146]. The results of cohort studies evaluating the association between physical activity and bladder cancer outcomes are not available.

Multimodal prehabilitation

Multimodal prehabilitation — consisting of aerobic and resistance exercise, diet therapy and relaxation techniques — prior to radical cystectomy has been investigated in one randomized controlled trial[147]. However, no clear differences in functional capacity and secondary outcomes such as postoperative complication severity and length of hospital stay were observed between the intervention and the control groups[147]. Further studies with larger sample sizes should be conducted to obtain better insight into the effect of multimodal prehabilitation on postoperative complications in patients with bladder cancer.

Prevention — advances made to date and future opportunities

Smoking policies worldwide

Primary prevention of bladder cancer relies mainly on reducing smoking prevalence and improving occupational hygiene. The WHO classifies tobacco control policies into six categories, together known as MPOWER: monitoring (M) tobacco use (for example, through periodic population or school-based surveys); protecting (P) people from tobacco smoke (for example, introducing smoke-free laws to decrease second-hand smoke exposure); offering (O) help to quit tobacco use by providing and covering the costs of smoking-cessation programmes; warning (W) people about the dangers of tobacco (for example, with mandatory health warning labels); enforcing (E) bans on tobacco advertising; and raising (R) taxes on tobacco products. These approaches are outlined in the WHO Framework Convention on Tobacco Control that has been in force since 2005 after unanimous adoption by all WHO member states[148]. Subsequently, an increase in implementation across the world has been observed in all six categories, with the best implementation in high-income countries. In 2020, optimal monitoring policies (M) were in place in 78 out of 195 countries encompassing 4.4 billion people among the world population of 7.8 billion; for the other five control policies (P, O, W, E and R), this was the case for 1.8 billion (67 countries), 2.5 billion (26 countries), 4.7 billion (73 countries), 1.6 billion (57 countries) and 1.0 billion people (40 countries), respectively[149] (Fig. 5). Thus, a lot of room for improvement remains. For example, even with an increasing focus on low-income and middle-income countries (LMICs), in 2019, the largest cigarette and smokeless-tobacco companies still spent US $8.2 billion on advertising and promotional expenses in the USA alone[150]. Additionally, despite all the knowledge about the detrimental effects of smoking accumulated over 70 years of research, the global prevalence of smoking in 2020 was still 17.5% (32.6% and 6.5% among men and women, respectively), equating to almost 1.2 billion smokers[149,151]. The declines in smoking have been particularly limited in most LMICs, with over half of all men in large populations in Asia (including China and Indonesia) and the Pacific Islands continuing to smoke[151]. Government policies, such as tax increases and bans, seem to be more effective than individual counselling and intervention programmes[152,153]. To prevent an epidemic of smoking-related diseases such as bladder cancer in LMICs, if still possible, governments

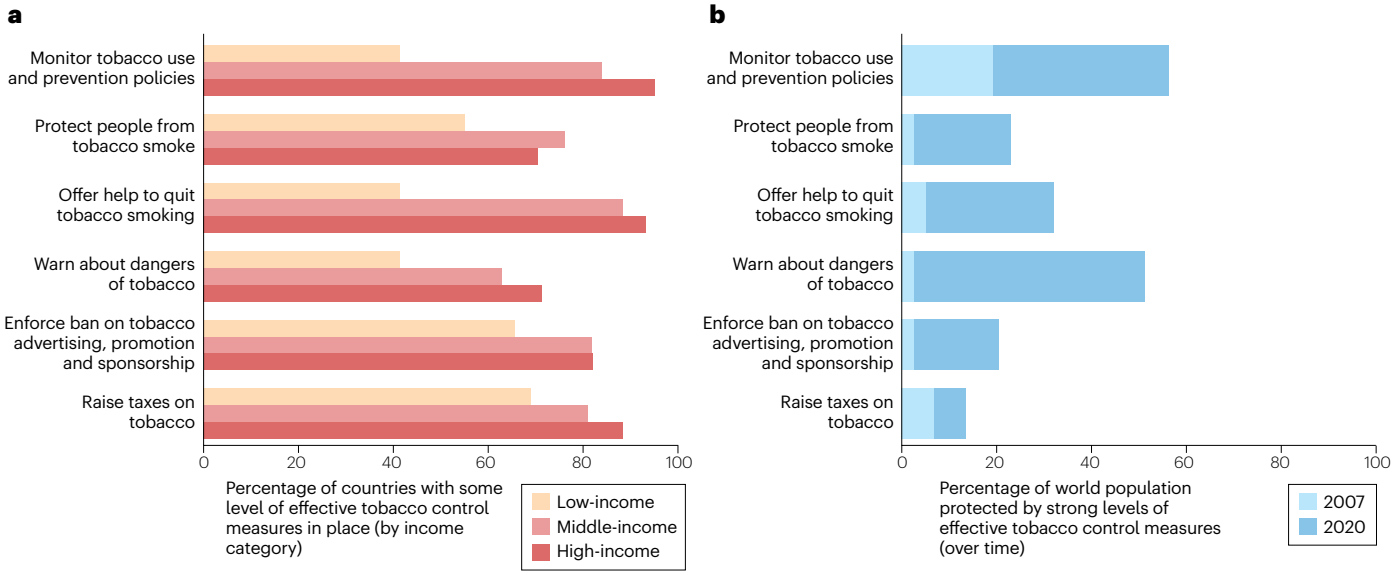

Fig. 5 | Worldwide implementation of effective tobacco control measures. **a**, Percentages of countries that had implemented tobacco control interventions in 2020 according to the six 'MPOWER' categories defined by the WHO. **b**, Percentages of the world population protected by strong tobacco control measures in 2007 and 2020 according to the six 'MPOWER' categories defined by WHO. Despite improvements, the strong tobacco control programmes cover only a minority of the world population, with a particular need for improvement in the introduction of such measures in low-income countries. All the data presented were derived from the 2021 WHO report on the global tobacco epidemic[149].

should adopt the WHO policies with more urgency and force. A simulation study indicated that stricter MPOWER policy adoption by more countries in 2009 could have resulted in there being up to 100 million fewer smokers globally in 2017 (ref. [154]).

Occupational hygiene

Labourers, in particular in the tobacco, dye, rubber, printing, leather, aluminium and oil/petroleum industries, have an increased risk of bladder cancer; sailors, hairdressers/barbers, nurses, chimney sweeps, metal workers, mechanics and cleaners might also be at increased risk[155]. Occupational hygiene has been substantially improved in Western societies during the past decades, although exposure to occupational carcinogens still occurs. Moreover, occupation-associated bladder cancers will continue to occur for decades to come owing to the long latency time of this disease. In the European Union (EU), workers are currently protected against cancer-causing or mutation-causing substances under three main directives. The overarching Occupational Safety and Health Framework Directive (89/391/EEC) lays out the main principles of health and safety in the workplace, while the Chemical Agents Directive (98/24/EC) and the Carcinogen and Mutagens Directive (CMD; 2004/37/EC, plus four amendments) are focused specifically on chemical risks. The CMD sets general minimum requirements to eliminate or reduce exposure to a relatively short list of 41 chemicals, including bladder carcinogens such as *ortho*-toluidine[156]. Furthermore, the CMD establishes occupational exposure limit values for certain carcinogens and mutagens with a view to protecting workers. Employers must identify and assess exposure-associated risks for workers; where risk occurs, exposure must be prevented. If technically possible, the process or agent concerned must be substituted with a non-hazardous or less-hazardous process or agent. If substitution is not possible, chemical carcinogens/mutagens must be used in a closed system, or worker exposure reduced to as low a level as is technically possible. Employers are also obliged to ensure that occupational exposure limit values are not exceeded. In many parts of the world beyond the EU, especially in LMICs, less formal legislation and enforcement probably exists, leaving substantial room for improvement in occupational hygiene.

Advances in diagnosis and follow-up monitoring

Given the increasing incidence of bladder cancer and the actual or anticipated shortage of health-care workers as a result of demographic trends, innovations are needed to lower the burden of this disease on health-care systems. In this regard, much can be gained from more efficient follow-up investigations in patients with NMIBC. For example, the European Association of Urology guidelines advise that patients with high-risk NMIBC should undergo up to 14 cystoscopy procedures over 5 years as well as annual upper tract imaging[157]. The number of follow-up investigations could potentially be decreased safely considering that the risk of disease progression is limited in a large proportion of these patients. In a large multicentre study involving 3,400 patients with NMIBC, the group with the lowest predicted risk (encompassing >50% of all patients) had a 5-year risk of progression of <1% (95% CI 0.49–1.70). The findings of the first cystoscopy assessment 3 months after TURBT have high prognostic value, but the value of subsequent follow-up cystoscopy is based on low-level evidence[158]. Active surveillance, that is, leaving recurrent low-grade Ta tumours in situ, is another option in the follow-up management of NMIBC. A meta-analysis of seven studies encompassing 558 patients found this approach to be safe in a selected subgroup with low-risk disease (that is, fewer than five tumours of low grade and <10 mm diameter, and with negative cytology)[159]. With a median active surveillance time of 15.6 months, upstaging to T1 was observed in 8% and upstaging to T2 in <1%[159].

Using urinary markers instead of cystoscopy could be an additional step to lower health-care consumption in a safe way. Urinary marker tests, such as the Xpert Bladder Cancer Monitor and the Bladder EpiCheck methylation test, have a negative predictive value for disease recurrence of up to 99% in patients with high-grade NMIBC[160–162]. Thus, in the case of a negative urine test, cystoscopy might be safely postponed, reducing the burden on patients and the health-care system.

The efficiency of follow-up monitoring might also be improved by increasing the diagnostic performance of cystoscopy, for example, through optimized imaging predicated on photodynamic diagnosis (PDD). PDD, which is performed using violet light after intravesical instillation of 5-aminolaevulinic acid or hexaminolaevulinic acid[163], improves bladder tumour detection and is especially useful in patients with carcinoma in situ[164]. A meta-analysis of 12 randomized studies involving a total of 2,288 patients with NMIBC demonstrated a lower risk of recurrence with the use of PDD compared with white-light cystoscopy (RR 0.75, 95% CI 0.62–0.91, at 24 months)[165]; progression and mortality rates were not evaluated. PDD is more costly than white-light cystoscopy. Nevertheless, several studies have shown that PDD can be cost-effective[166,167], by yielding more complete detection and resection[168]. Notwithstanding, the upfront costs of PDD are not affordable in all countries.

Screening

In order to implement a screening strategy, several requirements, as described by Wilson and Jungner[169] and advocated by the WHO[170], should be met, which is not yet the case for bladder cancer. A small US population-based screening study evaluating the use of a home dipstick for the detection of haematuria in 1,575 men aged ≥50 years found no bladder-cancer-related deaths after 14 years of follow-up among the 21 patients with bladder cancer in the screening group, whereas 20.5% of 509 patients with bladder cancer in the same age group who were captured in a local tumour registry died of the disease ($P = 0.02$), probably owing to (earlier) diagnosis of NMIBC that had not yet progressed to MIBC with screening[171]. Because haematuria is a non-specific symptom, the majority of men with microhaematuria did not have bladder cancer; that is, the positive predictive value was only 8%[171]. The investigators therefore suggested that the focus should be on a higher-risk population and the dipstick test should be combined with other diagnostic markers[172]. The Dutch Bladder Cancer Urine Marker Project (BLU-P) study evaluated the feasibility of population-based screening using home-based haematuria testing and, for those with a positive result, additional molecular-based triage testing for specific urine markers for bladder cancer (comprising a NMP22 test, an *FGFR3* mutation assay, microsatellite analysis and a custom DNA methylation-specific multiplex PCR panel), to reduce the number of cystoscopies[173,174]. The authors found that the number of cystoscopies was indeed markedly reduced (by 82.5%, from potentially 378 to 66 among a total of 1,611 participants)[173,174]; however, the diagnostic yield was low (only four bladder cancers and one kidney cancer were detected)[173,174] because the study was performed in an unselected, asymptomatic, all-male population.

Screening in high-risk populations

Smokers. The low incidence of bladder cancer in the general population provides a rationale for a focused screening strategy for high-risk groups. Currently, no screening policies focusing on smokers have been implemented, but some smoker-oriented screening studies have been performed. An exploratory cohort study in Austria evaluated a bladder cancer detection programme for heavy smokers, defined as those with a smoking history of ≥40 pack-years[175]. Screening urine samples in this high-risk group using a dipstick test for haematuria resulted in diagnosis of malignancies in six of 183 participants (3.3%), of which three were bladder tumours (two Tis and one Ta grade 1)[175]. Other studies focused on smokers with other risk factors for bladder cancer, such as advanced age or environmental or occupational exposures[48,176,177]. For example, the investigators of a study performed in the USA selected asymptomatic men or women aged ≥50 years with a smoking history of ≥10 pack-years and/or environmental or occupational exposure to known carcinogenic agents of ≥15 years to undergo urine-based screening with the NMP22 BladderChek test[178]. Two Ta tumours (one low grade and one high grade) were detected among 1,502 screened participants. Among 1,309 screened participants in whom 1-year follow-up data were available, another two low-grade tumours were diagnosed[178]. After a median follow-up duration of 6.5 years, the diagnostic yield remained limited: a total of 11 of 925 evaluable individuals (1.2%) were diagnosed with bladder cancer, all of which were Ta tumours[177].

Groups exposed to occupational carcinogens. Some studies have addressed the efficacy of bladder cancer screening strategies in populations with high levels of occupational carcinogen exposure[179–182], although research in this area remains limited. For example, a study performed in an industrialized region of Germany evaluated the performance of urinary tumour markers (using a quantitative NMP22 assay plus a fluorescence in situ hybridization test for gains at chromosomes 3, 7 and 17 and loss of 9p21 (the UroVysion test)) in a high-risk population of chemical workers exposed to aromatic amines[183]. These researchers concluded that screening using urinary markers could not be recommended owing to the associated high costs and the high number of false-positive tests (3% with the NMP22 test)[183]. Furthermore, the occurrence of 'occupational bladder cancer' is decreasing owing to the banning of carcinogenic aromatic amines from dyes in Western countries[183].

Other high-risk groups. Other high-risk groups could also be considered for a targeted bladder cancer screening approach. A scoping review published in 2022 evaluated the performance of screening using cytology and cystoscopy in patients with neurogenic bladder (the consequences of which, such as secondary infections, might increase the risk of bladder cancer)[184]. The authors found that thus far, the performance, costs and safety of bladder cancer surveillance in this patient population has not been evaluated, and therefore they could not support the idea of screening in this population[184]. Individuals with a strong family history of bladder cancer, inhabitants of regions where schistosomiasis is endemic, patients with conditions such as mycosis fungoides, aristolochic acid nephropathy or Lynch syndrome, or those treated with radiotherapy to the pelvic area or with certain drugs (such as cyclophosphamide) are also candidate populations for potential screening studies. However, data to support this hypothesis are scarce.

Overall, it is doubtful whether any bladder cancer screening programme will be cost-effective. The potential benefits of such screening do not outweigh the disadvantages[185]. Routine screening for bladder cancer is therefore not recommended anywhere in the world[157,186–188]. Especially for bladder cancers associated with smoking and occupational hazards, increased effort should definitely be focused on primary prevention, instead of screening.

Conclusions

Bladder cancer is a frequently occurring disease with a considerable burden on public health. Because of an ageing population, the numbers of patients with bladder cancer will rise all over the world, in some regions despite decreasing age-standardized rates. This rise in absolute numbers will be much stronger in LMICs because smoking prevalence will be stable or even increase owing to the strong marketing of cigarettes by the tobacco industry. The best way to decrease the risk of bladder cancer is by introducing a firm governmental policy against smoking with bans and tax increases; Australia and Norway are countries that might function as positive examples. Protection from occupational exposures to bladder carcinogens is also an area with large potential for improvement in several parts of the world. Even though bladder cancer is among the most frequently occurring cancers, population screening programmes aiming to lower the number of patients diagnosed with advanced-stage disease and, thus, bladder cancer deaths are not and probably never will be cost-efficient. Screening of higher risk groups is possible, but the pros and cons have to be balanced and accurate urinary biomarkers are needed to avoid the need for periodic cystoscopy. Screening of one of the highest risk groups (former and current heavy smokers) raises additional ethical issues, such as providing benefits to these groups and not others (that is, non-smokers), besides the lack of efficacy and cost-efficiency.

A large gap exists between the substantial research focus placed on the roles of lifestyle factors in the risk of bladder cancer and the limited attention devoted to their influence on bladder cancer outcomes. In other cancer types, including breast, prostate and colorectal cancers, convincing observational data indicate that more physical activity improves cancer-specific clinical outcomes such as cancer-specific death. The evidence for other lifestyle factors such as diet is less mature. For bladder cancer, hardly any data exist regarding the effects of lifestyle on cancer-specific outcomes. This area should be a research priority.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

The authors declare no competing interests.

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