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Epidemiology of Bladder Cancer: A Systematic Review and Contemporary Update of Risk Factors in 2018

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Abstract

Context: Bladder cancer (BC) is a significant health problem, and understanding the risk factors for this disease could improve prevention and early detection.

Objective: To provide a systematic review and summary of novel developments in epidemiology and risk factors for BC.

Evidence acquisition: A systematic review of original articles was performed by two pairs of reviewers (M.G.C., I.J., F.E., and K.P.) using PubMed/Medline in December 2017, updated in April 2018. To address our primary objective of reporting contemporary studies, we restricted our search to include studies from the last 5 yr. We subdivided our review according to specific risk factors (PICO [Population Intervention Comparator Outcome]).

Evidence synthesis: Our search found 2191 articles, of which 279 full-text manuscripts were included. We separated our manuscripts by the specific risk factor they addressed (PICO). According to GLOBOCAN estimates, there were 430 000 new BC cases and 165 000 deaths worldwide in 2012. Tobacco smoking and occupational exposure to carcinogens remain the factors with the highest attributable risk. The literature was limited by heterogeneity of data.

Conclusions: Evidence is emerging regarding gene-environment interactions, particularly for tobacco and occupational exposures. In some populations, incidence rates are declining, which may reflect a decrease in smoking. Standardisation of reporting may help improve epidemiologic evaluation of risk.

Patient summary: Bladder cancer is common worldwide, and the main risk factors are tobacco smoking and exposure to certain chemicals in the working and general environments. There is ongoing research to identify and reduce risk factors, as well as to understand the impact of genetics on bladder cancer risk.

1. Introduction

Bladder cancer (BC) is the ninth most common cancer worldwide with a yearly incidence of approximately 430 000 cases [1], and it ranks 13th in terms of yearly mortality from cancer [1]. There is a male predominance, and it is the seventh most common cancer worldwide in men [2]. In the USA, BC is the fourth most common cancer in men [3]. BC is a cancer of industrialized nations with an age-standardized incidence rate, which is three-fold greater in high-resource versus low-resource countries [4]. The highest incidence rates are in North America, Europe, and parts of Western Asia. However, mortality rates are greater in developing regions [5].

Urothelial BC is the most common subtype. Approximately 75% of patients present with non–muscle-invasive disease, confined to the bladder mucosa/submucosa. This stage is usually managed with local treatment and surveillance, and has a particularly high prevalence due to the nonaggressive natural history of this disease [6]. The remaining 25% have muscle-invasive disease and often undergo cystectomy, multimodal therapy (transurethral resection, chemotherapy, and radiation therapy), or palliation [7].

In 2013, Burger et al [8] published a detailed review on the epidemiology of BC and its risk factors. In our work, we have searched contemporary series to compile a current-day picture of BC epidemiology, and provide a discussion of further work that is needed to impact environmental causes of BC.

2. Evidence acquisition

A systematic review of original articles was performed using PubMed/Medline in December 2017 and again in April 2018. We used the following search terms (Fig. 1): ((Bladder cancer [MeSH terms] and incidence [MeSH terms]) (OR) (Bladder cancer [MeSH terms] and prevalence [MeSH]) (OR) (Bladder cancer [MeSH terms] and risk) (OR) (Bladder cancer [MeSH terms] and risk factor [MeSH terms]) (OR) Bladder cancer [MeSH terms] and hazard)). Manuscripts were excluded if they were not in English, had <50 patients, were not about humans, and were not published since 2012. Conference abstracts were also excluded. Two pairs of reviewers (M.G.C., I.J., F.E., and K.P.) reviewed the abstracts using a priori exclusion/inclusion criteria and Covidence software

(Cochrane Library). Conflicts were resolved between the authors or with the involvement of a senior author. Reference lists of included manuscripts were also searched. Systematic reviews and meta-analysis were included because our primary objective was to identify significant/relevant studies that had been published since 2012.

We report our findings in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Supplementary Table 1) [9]. The review was a priori registered with the PROSPERO database.

3. Evidence synthesis

Our search found 2191 articles, of which 279 full-text manuscripts were included. We separated our manuscripts by the specific risk factor they addressed (PICO [Population Intervention Comparator Outcome]), for example, tobacco smoking (Table 1) [10].

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

We provide an overview of BC incidence, mortality, and prevalence worldwide using the Cancer Incidence in Five Continents Series GLOBOCAN 2012 and World Health Organization Mortality databases held at the International Agency for Research on Cancer [2,11,12], as well as other studies published using the databases above.

According to estimates, there were 430 000 new BC cases and 165 000 deaths worldwide in 2012 [2]. Three-quarters of new cases occurred in men, with incidence rates in men being consistently higher than those in women and male:female ratios varying from 6:1 to 2:1 in different regions worldwide [2]. The risk of BC increased with age, with age-specific curves increasing steeply after the age of 50 yr [11]. A particular caveat for interpreting geographical patterns and temporal trends of BC incidence are large variations in diagnostic and cancer registration practices in distinguishing muscle-invasive (MIBC) and non–muscle-invasive (NMIBC) BC [1,11]. Owing to inclusion of NMIBC in reporting and the fact that 75% of newly diagnosed BCs are NMIBCs, as well as the fact that these tumours have a good prognosis, there was a high disease prevalence, with over 1.3 million prevalent cases (5-yr prevalence) worldwide

[2]. Age-standardised incidence and mortality rates varied widely, with the highest rates occurring in Europe and North America as well as some countries in Northern Africa and Western Asia, while the lowest rates occurred in Latin America, Sub-Saharan Africa, and South East Asia [1,2]. Figures 2 and 3 are maps of BC incidence and mortality rates in men and women worldwide [2].

According to the latest observed data from the period 2008 to 2012 from 343 registries in 65 countries published in CI5 Vol XI, age-standardised BC incidence rates (world standard population) in men varied from >30/100 000 in cancer registries in Italy and Spain to <3/100 000 in several registries from India, China, and Sub-Saharan Africa [11]. Large geographic variations reflect differences in exposures to known risk factors, notably smoking prevalence, occupational exposures, and *Schistosoma haematobium* infection (the latter relevant in Africa and Western Asia and causing squamous cell carcinoma, otherwise rare in the urinary tract), but also result from different diagnostic and registration practices [1,11].

Overall, BC incidence and mortality are higher in higher-income than in lower-income countries [2,5]. Several studies have explored correlations between the Human Development Index (HDI) and BC incidence and mortality [12,13]. The study by Greiman et al [4] showed a moderately strong inverse correlation (r = –1.02, r^2 = 0.80) between HDI and mortality to incidence ratio (MIR), thus indicating increasing survival with higher HDI levels. MIR was further shown to be higher in women than in men in most populations worldwide, which could possibly be explained by sex-specific differences in the biology of the disease, time to diagnosis, treatment decisions, and other factors [14].

The study of recent international trends of BC incidence and mortality by Antoni et al [1] reported diverging incidence trends with decline or stabilisation in men versus increases in women observed in many populations worldwide. In contrast, mortality rates have uniformly been decreasing in most populations worldwide (Fig. 4) [1].

Observed global geographical patterns and temporal trends in incidence largely reflect trends in smoking prevalence, even if other factors, such as *S. haematobium* infection and occupational exposures, are important in selected

populations. Standardisation of practices for reporting BC in cancer registries is necessary to improve the ability to compare incidence data worldwide.

3.2. Risk factors for BC

3.2.1. Smoking

This is the most important risk factor for BC with an attributable risk of approximately 50% [15]. Tobacco is a rich source of known carcinogenic compounds such as aromatic amines and N-nitroso compounds [16]. These compounds result in DNA damage in the form of double-stranded breaks, base modifications, and bulky adduct formation [16]. Such genomic events are implicated in gene-smoking interactions.

The strongest support for the association of tobacco use and BC is a meta-analysis of 83 studies, in which the pooled relative risk (RR) for current versus never smokers was 3.47 (95% confidence interval [CI] 3.07–3.91) and for ex-smokers 2.04 (95% CI 1.85–2.25) [15]. The lower rate for former smokers suggests that smoking cessation may reduce the risk for BC development [17]. The meta-analysis also found that disease-specific mortality (DSM) is greater in current smokers versus ex-smokers (1.53 [95% CI 1.12–2.09]) and 1.44 [95% CI 0.99–2.11], respectively). Limitations cited by the authors of the meta-analysis were the heterogeneity with which smoking histories were obtained and the cut-points used for stratifying smoking intensities and durations. This is important, as there is strong evidence that smoking duration and intensity are positively correlated with an increased risk of BC [18–21].

BC may also be associated with opium smoking. Afshari et al [22] conducted a meta-analysis of 17 studies and found an odds ratio (OR) of 3.85 (95% CI 3.05–4.87), which increased in magnitude if there was concomitant tobacco use.

A large cohort study of 34 000 cannabis smokers in California [23] found no association with BC over an 11-yr follow-up period. With increased legalisation of cannabis use in the USA, more data will emerge regarding its impact on BC rates.

The impact of e-cigarette use on BC risk will also be important to evaluate, since there is evidence for similar carcinogens in the urine of e-cigarette and regular cigarette users [24].

Interestingly, in a study by Westhoff et al [25], BC survivors often have little idea of what may have caused their disease, suggesting an increasing need for smoking cessation awareness.

3.2.2. Occupational carcinogen exposure

We found 20 articles published in the last 5 yr on occupational BC. The largest study was by Cumberbatch et al [26], which reviewed 263 publications. An increased BC incidence was seen in 42/61 occupations and DSM was raised in 16/40 (not all studies assessed DSM). The highest pooled RR was in tobacco workers (RR 1.72 [95% CI 1.37–2.15]) and dye workers (RR 13.4 [95% CI 1.5–48.2]). The highest pooled DSM RR was in metal workers (10.2 [95% CI 6.89–15.09]). Overall, occupational carcinogen exposure amounts to 5–6% of the attributable-risk of BC [25].

A limitation of occupational risk studies is that often there is exposure heterogeneity in the classification of occupations. There are classification systems in place such as the NYK and ISCO-1958 (Nordisk Yrkesklassificering, or Nordic Occupational Classification, and the International Standard Classification of Occupations); however, it is known that chemical exposure derives from the actual "task" that is being conducted within a workplace, and occupational classifications may group individuals who have different exposures to bladder carcinogens and have disparate risk profiles. Furthermore, not all studies adjust for smoking. Agents with a suspected/established role as an occupational bladder carcinogen include 2-naphthylamine, 4-aminobiphenyl, toluene, 4,4'-methylenebis(2-chloroaniline), metal working fluids, polyaromatic hydrocarbons (PAH), perchloroethylene, and diesel exhaust [26,27] (Table 2).

3.2.3. Dietary factors

As for many diseases**,** BC risk has been investigated for dietary factors. We found 29 articles reporting a link with BC and dietary components.

3.2.3.1. Alcohol

Whilst some small reports suggest a link with BC risk [28], a multicentre epidemiologic study (European Prospective Investigation into Cancer and

Nutrition [EPIC]) involving 476 160 persons followed up over 13.9 yr showed no association [29]. Those who reported high intake have an increased risk of BC, but there was no dose response, suggesting possible confounding lifestyle factors. No increased risk was observed in Asian populations with a deficient alcohol dehydrogenase enzyme (this metabolises acetaldehyde in alcohol, which may be carcinogenic) [30].

3.2.3.2. Vitamins/antioxidants

Several large recent studies evaluated the link between vitamins and antioxidants (such as flavonol, lignans, and plasma carotenoids) and BC [31,32]. These agents are thought to possess anticarcinogenic properties and are excreted in the urine. Animal studies have suggested a protective role, but two meta-analyses in our search reported conflicting results [33,34]. A meta-analysis of seven (two cohort and five case-control) studies suggested that a pooled RR for the lowest category versus the highest category of vitamin D was 1.34 (95% CI 1.17–1.53) [35]. The limitation is the use of different criteria for vitamin D deficiency. Furthermore, a meta-analysis of five (two cohort and three case-control) studies demonstrated a protective effect of a high serum vitamin D level on BC risk (RR 0.75, 95% CI 0.65–0.87) [36].

3.2.3.3. Dietary fluid consumption

Drinking coffee was recently evaluated by the International Agency for Research on Cancer (IARC) Cancer Monographs Working Group as “unclassifiable as to its carcinogenicity to humans” (group 3). They reviewed 10 cohort and several case-control studies from Europe, the USA, and Japan, and found no consistent evidence of association between drinking coffee and BC [37].

A meta-analysis of 24 (six cohort and 18 case-control) studies found no association between BC incidence and consumption of tea [38], cola, decaffeinated or energy drinks [39], or dairy products [40]. Some argue that higher levels of hydration may reduce BC incidence by diluting carcinogen contact with the urothelium and promoting more frequent voiding of urine, but no significant link has been established [41–43]. However, due to the possible presence of disinfection by-products (chlorination), some authors have cited an

increased BC risk with elevated tap water consumption due to the presence of trihalomethanes [43,44].

3.2.3.4. Fruits and vegetables

There is no consensus on the attributable risk from dietary components. Generally, the data are conflicting. However, a meta-analysis of 15 prospective cohort studies showed a summary RR for an increase of one serving per day of 0.97 (95% CI 0.95–0.99) for vegetables and fruits [45]. In particular, cruciferous vegetables and citrus fruits show favourable outcomes [46–48]. Limitations of these studies include publication bias (small studies), recall bias, (self-reported), and heterogeneity of "food dose" levels.

3.2.3.5. Meat

Within our dataset, two case-control studies found an association of processed meats and animal protein with BC. The concern arises from the possible presence of nitroso compounds in processed meat, but the finding requires additional confirmation [49–51].

3.2.3.6. Diet diversity

A balanced and "Mediterranean diet" has been assessed through the EPIC study and large case-control studies using consumption questionnaires for specific food items, but the results have been inconclusive [52,53].

3.2.4. Environmental carcinogens

3.2.4.1. Arsenic

Exposure to arsenic in drinking water is a recognised cause of BC [54–56]. The largest study in our series (a systematic review of 40 studies and a meta-analysis of 17 studies) showed a risk effect of 2.7 (95% CI 1.2–4.1) for 10 μg/l and 5.8 (2.9–8.7) for 140 μg/l. Limitations included exposure misclassifications between studies, which restricted greater data pooling [57]. Interestingly, a case-control study found that people who are poor at methylating inorganic arsenic are at higher risks of BC [58].

3.2.4.2. Nitrates/selenium/cadmium

In our series, a meta-analysis of five studies (mixed cohort/case-control) showed no difference from exposure to nitrate-containing drinking water [59], but additional studies are needed. A randomised controlled trial (RCT) secondary analysis with a median follow-up of 7.1 yr demonstrated no protective effect of selenium on BC risk [60].

3.2.4.3. Nuclear power plant and shale gas extraction

An ecologic study [61] found a statistically significant RR of BC in persons living inside 20 km from a nuclear power plant (RRmen 1.08 [95% CI 1.00–1.17], RRwomen 1.19 (95% CI 1.02–1.39]). However, the study used proximity as a proxy for exposure and did not assess blood profiles. Similarly, an observational study showed increased BC rates in areas of shale gas drilling, but the study had limited confounder control and small populations [62].

3.2.4.5. Routine personal hair dye use

A meta-analysis of 15 case-control and two cohort studies, involving 617 937 persons [63], showed a pooled RR for BC of 0.93 (0.82–1.05) for ever use and 1.29 (0.98–1.71) for use of dark-coloured dyes.

3.2.5. Gender, race, and socioeconomic factors

3.2.5.1. Gender

Reasons for sex differences in BC incidence and survival (higher in males) are thought to be related to a few (likely in combination) factors such as differences in access to health care, delayed diagnosis (haematuria or lower urinary tract symptoms being attributed to cystitis in women), occupational exposures, and smoking patterns [8]. Potential molecular mechanisms include disparate metabolic detoxification of carcinogens and difference in the sex steroid hormone pathways [64].

3.2.5.2. Hormonal and reproductive factors

A cohort study showed that parous women had a lower incidence of BC compared with nulliparous women (IRR 0.80, 95% CI 0.72–0.89). Absence of

data on menstrual history, use of exogenous hormones, and smoking were important limitations within this study [65].

3.2.5.3. Race

More historical Surveillance Epidemiology and End Results (SEER) data from the USA suggested that black people have a lower incidence but higher mortality. Explanations for higher mortality include lack of access to health care and advanced disease at presentation [66].

3.2.5.4. Socioeconomic status

In the USA, BC was related to those receiving Medicaid health benefits [67]. These factors may be surrogate markers for urban living [68], smoking, and occupational risk.

3.2.6. Gene-environment interaction

The genetic basis of BC is gaining increased attention and evidence. The Cancer Genome Atlas provided comprehensive molecular characterisation of MIBC based on somatic changes (eg, increased somatic copy number of FGFR3 and *KRAS* genes), but most of these represent acquired and not inherited mutations [69]. The role of germline genetic polymorphisms in increasing BC susceptibility in persons exposed to carcinogens is established. Here, we investigated gene-risk factor interactions for the main attributable factors.

3.2.6.1. Occupation-gene interactions and BC risk

The main polymorphisms associated with BC involve two carcinogen-detoxification genes—*NAT2* and *GSTM1*—since abnormalities in these genes leads to longer exposure to carcinogens. Links with N-acetyltransferase 2 (NAT2) acetylation status and GSTM1 copy number are well documented to be associated with the risk of BC. Our series reports on recent studies that have added to this field. Figueroa et al [70] examined whether established common single-nucleotide polymorphisms (SNPs), which have been associated with BC risk from candidate gene studies or genome-wide association studies (GWAS), modify the association between employment in high-risk occupations and BC,

using data from the New England Bladder Cancer Study and the Spanish BC Study. It was observed that three BC susceptibility variants displayed statistically significant evidence of additive interactions, specifically the GSTM1 deletion polymorphism, rs11892031 (UDP glucuronyltransferase 1A [UGT1A]), and rs798766 (TMEM129-TACC3-FGFR3).

In a case-control study, patients were genotyped for polymorphisms in NAT2, GSTM1, GSTT1, UGT1A, rs9642880 (close to c-MYC), and rs710521 (close to TP63) in relation to occupational BC [71]. Increased risks were seen with GSTM1 (in individuals exposed to aromatic amines and carbolineum, painters, and varnishers) and UGT1A (in individuals exposed to carbolineum, crack test spray, and PAH, and in painters and varnishers). In another case-control study, null or low-activity genotypes of the GSTA1, T1, and P1 did not contribute independently towards the risk of BC in males [72]. However, in association with occupational exposure, low-activity GSTA1 and GSTM1-null as well as GSTT1-active genotypes increase individual susceptibility. GSTM1-null genotype was over-represented among cases (OR 2.1, 95% CI 1.1–4.2). Low-activity GSTA1 genotype and GSTM1- and GSTT1-active patients showed an enhanced BC risk among individuals exposed to solvents and pesticides (GSTT1 active). Pesch et al [73] used data from the EPIC study to show that occupational exposure to aromatic amines and PAH was associated with an increased BC risk (OR 1.37, 95% CI 1.02–1.84, and OR 1.50, 95% CI, 1.09–2.05, respectively). NAT2 slow acetylation did not modify these risk estimates.

A multicentre case-control study examined associations between pesticide exposure, genetic polymorphisms for NQO1 and SOD2, and BC risk among male agricultural workers. There was an increased BC risk among participants with combined genotypes for low NQO1 and high SOD2 (RR 2.14 [95% CI 1.19–3.85]) activities [74].

3.2.6.2. Smoking-gene interactions and BC risk

The most convincing contemporary data are derived from two GWAS. These are observational studies that assess traits between a genome-wide set of variants and human disease. A meta-analysis by Garcia-Closas et al [75] included a total of 3942 cases and 5680 controls of European background in seven studies

participating in the National Cancer Institute (NCI) GWAS. This analysis evaluated 12 SNPs previously identified as susceptibility variants. Six of 12 variants showed significant additive gene-smoking (ever vs never) interactions: 8p22 NAT2, 2q37.1 UGT1A6, 1p13.3 GSTM1, 8q24.3 PSCA, 8q24.21 (MYC), 22q13.1 CBX6 APOBEC3A. NAT2 was also the only variant to show significant multiplicative gene-smoking interactions. A similar pattern was seen when comparing current and former smokers with never smokers, but weaker evidence for interactions was found when comparing current with former smokers. This study was limited by the use of a "weighted allele" approach, which is a summary measure of weights for each allele related to a risk factor. Selinski et al [76] addressed this by pooling data (IFADo-NBCS groups) and cited four variant combinations associated with BC:rs1014971[AA] near apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A (APOBEC3A) and chromobox homolog 6 (CBX6), solute carrier family 1s4 (urea transporter), member 1 (Kidd blood group; SLC14A1) exon SNP rs1058396[AG, GG], UDP glucuronosyltransferase 1 family, polypeptide A complex locus (UGT1A) intron SNP rs11892031[AA], and rs8102137[CC, CT] near cyclin E1 (CCNE1).

Figueroa et al [77] conducted a GWAS based on primary scan data from the NCI BC GWAS (including 2422 BC cases and 5751 controls) and showed an association between smoking and BC risk; rs1711973 (FOXF2) on 6p25.3 was a susceptibility SNP for never smokers (OR 1.34, 95% CI 1.20–1.50) and rs12216499 (RSPH3-TAGAP-EZR) on 6q25.3 was a susceptibility SNP for ever smokers (OR0.75, 95% CI 0.67–0.84). However, in an updated analysis by the same group using a larger dataset, no evidence was found for these associations. Genome-wide significance was found for rs6104690 (gene-desert) and rs4907479 (MCF2L) [78].

A meta-analysis of 26 case-control studies assessed the association between variations in the x-ray repair cross-complementing group 1 (XRCC1) DNA repair gene, smoking, and BC [79]. Results suggested that the XRCC1 R399Q polymorphism might play a protective role against BC among smokers. Associations have also been seen for the *XRCC6* gene [80], but not for XRCC3

[81]. Polymorphisms in the *VEGF* gene were also shown to have associations with BC and smoking in two NRT [82,83].

3.3. Medical conditions and treatments

3.3.1. Diabetes mellitus

The largest meta-analysis included 36 (nine case-control and 27 cohort) studies and showed an increased RR of BC in diabetes mellitus (DM; pooled RR 1.35, 95% CI 1.17–1.56). The RR of BC was negatively correlated with the duration of DM, with the higher risk of BC found among patients diagnosed within <5 yr [84]. However, this meta-analysis suffered from significant heterogeneity in study design and adjustment for confounders.

3.3.2. Thiazolidinedione use

Two large meta-analyses have shown statistically significantly increased risks of BC with the oral antidiabetic agent pioglitazone. Subgroup analysis showed the risk of BC to be greatest with >28.0 g daily of pioglitazone [85,86].
However, the first cohort study to assess long-term use of pioglitazone (based on up to 16 yr of follow-up) demonstrated no increased risk of BC, although the authors concluded that they could not exclude an association [87].

3.3.3. Metformin, sulphonylurea, and insulin

A large cohort study demonstrated a reduced risk of BC with the use of oral antidiabetic agents metformin and sulphonylurea [88]. With regard to insulin, the largest cohort study found no association with BC risk [89].

3.3.4. Systemic lupus erythematosus

A meta-analysis of seven studies showed a pooled RR of 2.11 (95% CI 1.12–3.99) for BC risk [90]. However, there were confounding factors such as the use of cytotoxic drugs and coexistence of overlapping syndromes. Similar findings were seen for systemic sclerosis [91] and inflammatory bowel disease [92].

3.3.5. Anthropometric measures/physical activity

Sun et al [93] reported pooled RRs of BC of 1.07 (95% CI 1.01–1.14) and 1.10 (1.06–1.14) for overweight and obesity, respectively. Body mass index (BMI) was associated with BC risk in a linear fashion, and the risk increased by 4.2% for each 5 kg/m^2 increase. A limitation is that higher BMIs are likely to be associated with other unhealthy behaviours such as lower physical activity levels and poorer diet. However, data across studies are conflicting [94].

3.3.6. Analgesics

A meta-analysis of 17 (eight cohort and nine case-control) studies showed that paracetamol and aspirin were not associated with BC risk (or reduction). However, the use of nonaspirin nonsteriodal anti-inflammatory drugs was significantly associated with a 43% reduction in BC risk among nonsmokers (RR 0.57, 95% CI 0.43–0.76), but not among current smokers [43,95].

3.3.7. Statins

A meta-analysis of 13 (three RCT and 10 observational) studies showed a nonsignificant increase in BC risk amongst statin users (RR 1.07, 95% CI 0.95, 1.21) [96].

3.3.8. Radiation

Radiotherapy (RT) to treat cancers of the ovary, testis, cervix, uterus, and prostate, and non-Hodgkin lymphoma has been associated with developing second malignancies of the bladder. In a meta-analysis of 21 studies looking at radiation of the prostate, BC risk was elevated with a hazard ratio (HR) of 1.67 (95% CI 1.55–1.80) [97]. In a retrospective cohort study from SEER data, Abern et al [98] found an RR of 1.7 for RT-treated prostate cancer (PC; 95% CI 1.57–1.86). All forms of RT showed an elevated risk, with the greatest risk at >10 yr lag. Older age at diagnosis was associated with increased BC risk, and nonwhite race reduced risk. Histologically, the number of non–urothelial cell carcinoma tumours was greater than usual and carcinoma in situ was more common. Anatomically, BCs were more frequently found at the trigone. Interestingly, stage and grade at diagnosis did not differ with prior radiation, and a nonsignificant increase in lymph node positivity was found. However, when controlled for

competing risk (PC), cumulative hazard curves revealed that patients had 30% increased BC mortality if previously treated with radiation [98].

3.3.9. Metabolic syndrome

A case-control study demonstrated that patients with metabolic syndrome reported a two-fold increase in BC risk [99].

3.3.10. Recurrent urinary tract infections

A case-control study showed that urinary tract infections (UTIs) were associated with an increased risk of BC [100]. However, two studies have shown a protective effect for those treated with antibiotics for the UTI [101].

3.3.11. Spinal cord injury

A large cohort study (54 401 patients) showed no significant difference in risk (HR 0.91, 95% CI 0.72–1.16) [102]. Conversely, a smaller study on 1816 patients with spinal cord injury (SCI), matched with patients with chronic indwelling urinary catheters without an SCI and healthy control patients, showed a higher risk of BC among those with SCI (HR 6.51, 95% CI 2.56–16.52) [103]. However, these papers did not comment on tumour cell type.

3.3.12. Renal transplant

A meta-analysis of 11 retrospective observational studies revealed a pooled RR of 3.18 (95% CI 1.34–7.53). There was a lack of adjustment and exclusion of BC prior to the transplant as the patients were not screened [104].

4. Conclusions

BC is common, and a significant proportion of the cases are attributable to tobacco use as well as occupational and environmental factors (Table 2 summarises the best-known risk factors).

Incidence patterns and trends are dependent on changes in smoking behaviour and shifting occupational and environmental regulations, such as workplace sanctions on known or suspected carcinogens. The evidence is growing for the role of genetic susceptibility and interplay with other risk factors.

One of the problems with the identification and quantification of BC risk factors is the heterogeneous phenotype of the disease. For the future, it will be important to arrive at standardised subclassifications of BC and stratify analyses according to these subtypes.

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Study concept and design: Cumberbatch, Jubber, Catto.
Acquisition of data: Cumberbatch, Jubber, Black, Esperto, Figueroa, Kamat, Kiemeney, Lotan, Pang, Silverman, Znaor, Catto.
Analysis and interpretation of data: Cumberbatch, Jubber.
Drafting of the manuscript: Cumberbatch, Jubber, Black, Esperto, Figueroa, Kamat, Kiemeney, Lotan, Pang, Silverman, Znaor, Catto.
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Fig. 1 – CONSORT diagram. Search captured all articles from 1 May 2012 until 9 April 2018. BC = bladder cancer.

Fig. 2 – International variation in estimated age-standardised bladder cancer incidence rates in (A) men and (B) women [2]. Age-standardised rates (ASR; world standard population) per 100 000.

Fig. 3 – International variation in estimated age-standardised bladder cancer mortality rates in (A) men and (B) women [2]. Age-standardised rates (ASR; world standard population) per 100 000.

Fig. 4 – Estimated annual percent change in (A) age-standardised incidence and (B) mortality rates of bladder cancer in men (top) and women (bottom) in selected countries (last 15 yr of available data). Regional incidence data from Gharbiah (Egypt); Blantyre (Malawi); Harare (Zimbabwe); Kampala (Uganda); Antofagasta (Chile);Villa Clara (Cuba); Cali (Colombia); Quito (Ecuador); SEER (USA); Alberta, British Columbia, Manitoba, Northwest Territories, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador, Ontario, and Saskatchewan (Canada); Miyagi, Nagasaki, and Osaka (Japan); Hong Kong and Shanghai (China); Chiang Mai (Thailand); Manila (Philippines); Chennai and Mumbai (India); Izmir (Turkey); Riyadh (Saudi Arabia); Cracow City, Kielce, and Lower Silesia (Poland); St Petersburg (Russian Federation); Granada, Murcia, Navarra, and Tarragona (Spain); City of Torino, Modena, Parma, Romagna, Ragusa, and Varese provinces (Italy); Geneva and St. Gall-Appenzell (Switzerland); Berlin, Brandenburg, Mecklenburg, Saxony, Saxony-Anhalt, Schleswig-Holstein, and Thuringia (Germany); Doubs, Isere, Haut-Rhin, Herault, and Tarn (France); and Australian Capital Territory, New South Wales, Northern Territory, Queensland, South Australia, Tasmania, Victoria, and Western Australia (Australia). Data from Cuba are presented with Central and South America. [a] A change significantly different than 0. Reproduced from Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder cancer incidence and mortality: a global overview and recent trends. Eur Urol 2017;71:96–108 [1].

Table 1 – Number of reports by section

Subject	Number of articles included in review
Incidence and mortality patterns	6
Tobacco smoking	15
Occupational carcinogen exposure	20
Dietary associations	29
Medical disease and treatments	91
Environmental carcinogen exposure	23
Genetic associations	87
Gender, socioeconomic group, and racial differences	8

Table 2 – BC risk factor summary

Risk factors for bladder cancer summary	
Tobacco smoking	
Occupations • Aluminium production • Rubber production industry • Dye industry • Coal-tar pitch [a] • Dry cleaning [a] • Hairdressers and barbers [a] • Printing [a] • Textile manufacturing [a]	Occupational carcinogens • 2-Naphthylamine • Benzidine • 4-aminobiphenyl • 4,4′-methylene-bis (2-chloroaniline) • Ortho-toluidine • Metal working fluids [a] • Tetrachloroethylene [a] • Diesel exhaust [a] • Polyaromatic hydrocarbons [a] • Combustion and pyrolysis products from natural gas [a]
Dietary factors • Low hydration [a] • Low intake of citrus fruit, cruciferous vegetables, vitamin A, folate, and vitamin D [a] • Processed meat and animal protein [a]	Environmental factors • Arsenic and inorganic arsenic compounds • Disinfection by-products [a] • Nitrates [a]
Age • Median age at diagnosis is 73 yr	Race • White race

Gender
- Male sex
- Hormone and reproductive factors [a]

Medical disease
- Radiotherapy
- Schistosomiasis
- NSAIDs (reduced risk)
- Cyclophosphamide
- Phenobarbital (reduced Risk)
- Pioglitazone [a]

Socioeconomic status
- Industrialised regions

Family history of bladder cancer

BC = bladder cancer; NSAID = nonsteroidal anti-inflammatory drugs.
[a] Suspected risk factors.

Figure 1

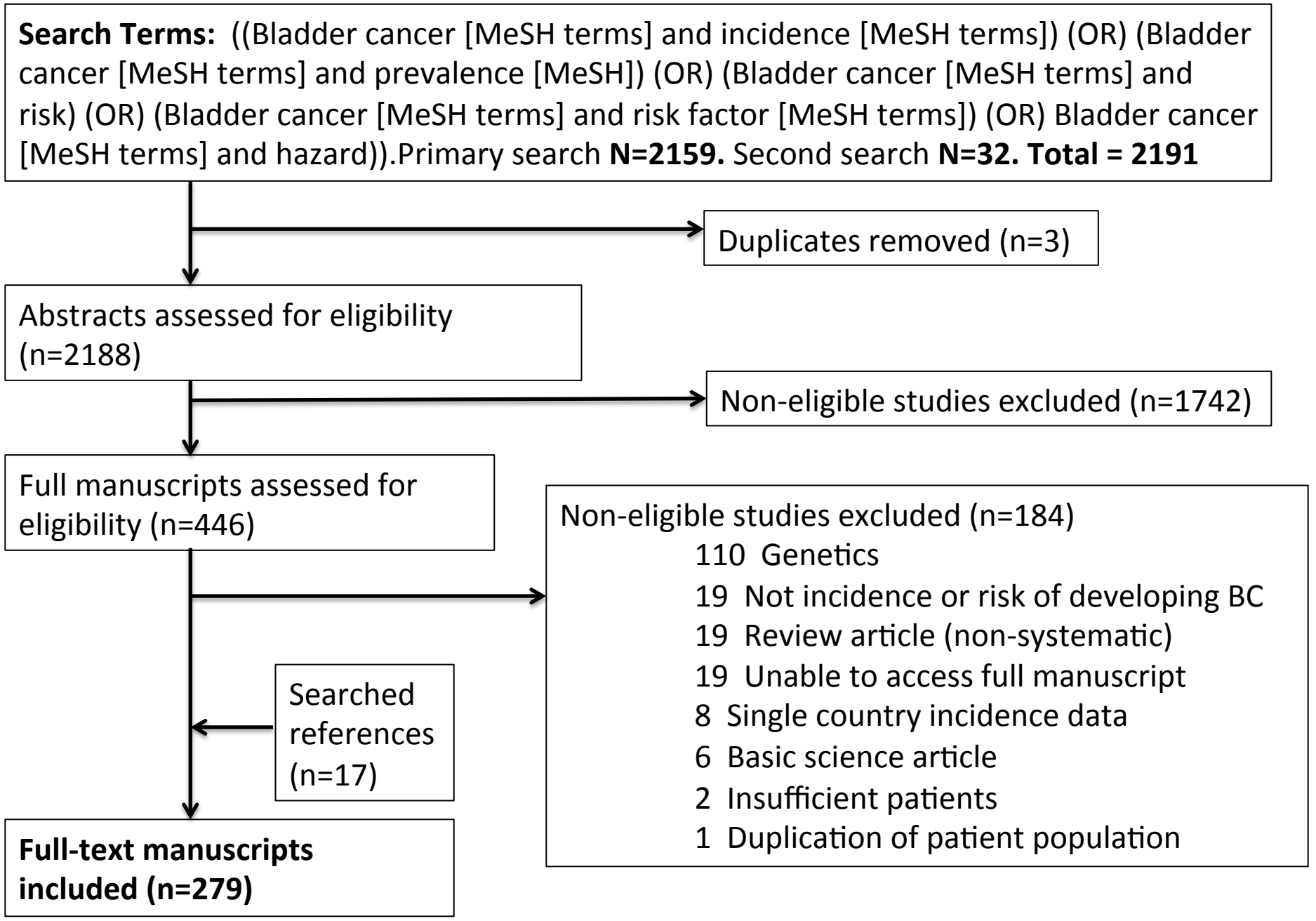

Figure 1. CONSORT. Search captured all articles from May 1st 2012 until 9th April 2018 .

Figure legends

Figure 2: International variation in estimated age-standardised bladder cancer incidence rates (a) in men; (b) in women (2). Age-standardised rates (ASR, World Standard Population) per 100,000

Figure 3: International variation in estimated age-standardised bladder cancer mortality rates (a) in men; (b) in women (2). Age-standardised rates (ASR, World Standard Population) per 100,000

Figure 4: Estimated annual percent change in age-standardised incidence (left) and mortality (right) rates of bladder cancer in men (top) and women (bottom) in selected countries (last 15 year of available data). *Reproduced from Antoni S, et al. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. Eur Urol. 2017;71(1):96-108* (1).

Regional incidence data from Gharbiah (Egypt), Blantyre (Malawi), Harare (Zimbabwe), Kampala (Uganda), Antofagasta (Chile), Villa Clara (Cuba), Cali (Colombia), Quito (Ecuador), SEER (USA), Alberta, British Columbia, Manitoba, Northwest Territories, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador, Ontario, and Saskatchewan (Canada), Miyagi, Nagasaki, and Osaka (Japan), Hong Kong and Shanghai (China), Chiang Mai (Thailand), Manila (Philippines), Chennai and Mumbai (India), Izmir (Turkey), Riyadh (Saudi Arabia), Cracow City, Kielce, and Lower Silesia (Poland), St Petersburg (Russian Federation), Granada, Murcia, Navarra, and Tarragona (Spain), City of Torino, Modena, Parma, Romagna, Ragusa, and Varese provinces (Italy), Geneva and St. Gall-Appenzell (Switzerland), Berlin, Brandenburg, Mecklenburg, Saxony, Saxony-Anhalt, Schleswig-Holstein, and Thuringia (Germany), Doubs, Isere, Haut-Rhin, Herault, and Tarn (France), Australian Capital Territory, New South Wales, Northern Territory, Queensland, South Australia, Tasmania, Victoria, and Western Australia (Australia). Data from

Cuba are presented with Central and South America.

a A change significantly different than 0.

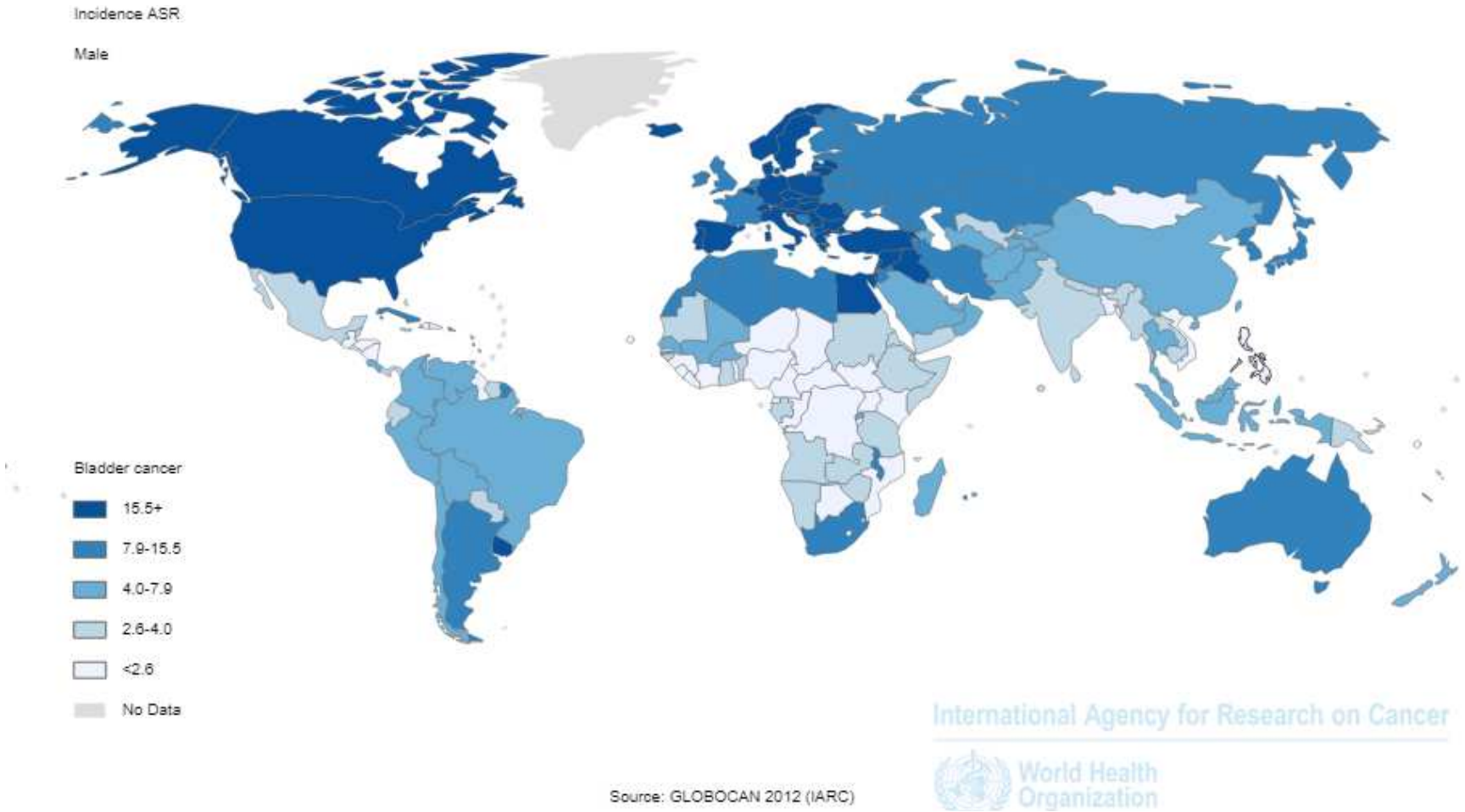
Incidence ASR
Male
Bladder cancer
15.5+
7.9-15.5
4.0-7.9
2.6-4.0
<2.6
No Data
International Agency for Research on Cancer
World Health Organization
Source: GLOBOCAN 2012 (IARC)

Figure 2a

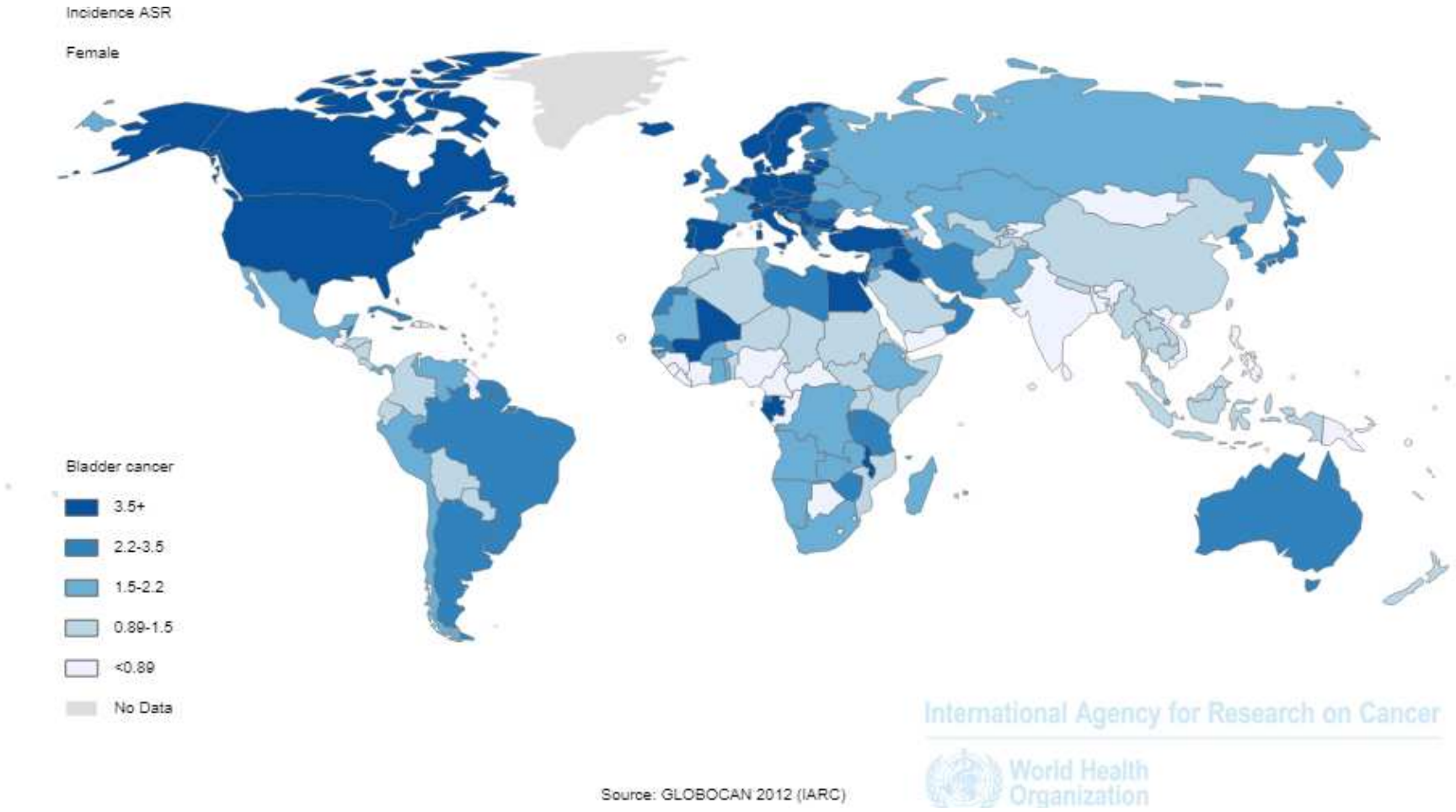
Incidence ASR
Female
Bladder cancer
3.5+
2.2-3.5
1.5-2.2
0.89-1.5
<0.89
No Data
International Agency for Research on Cancer
World Health Organization
Source: GLOBOCAN 2012 (IARC)

Figure 2b

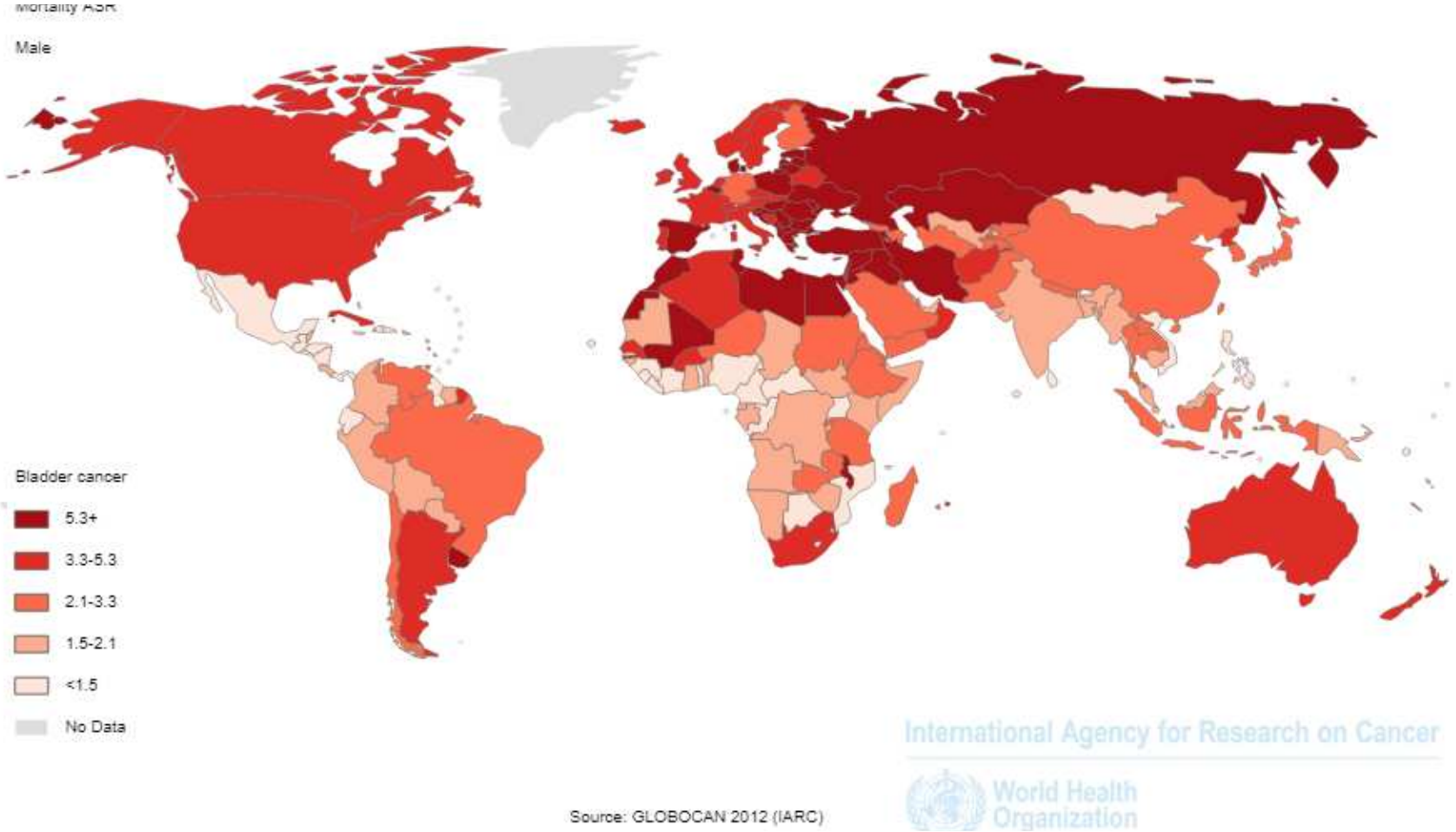
Mortality ASR
Male
Bladder cancer
5.3+
3.3-5.3
2.1-3.3
1.5-2.1
<1.5
No Data
International Agency for Research on Cancer
World Health Organization
Source: GLOBOCAN 2012 (IARC)

Figure 3a

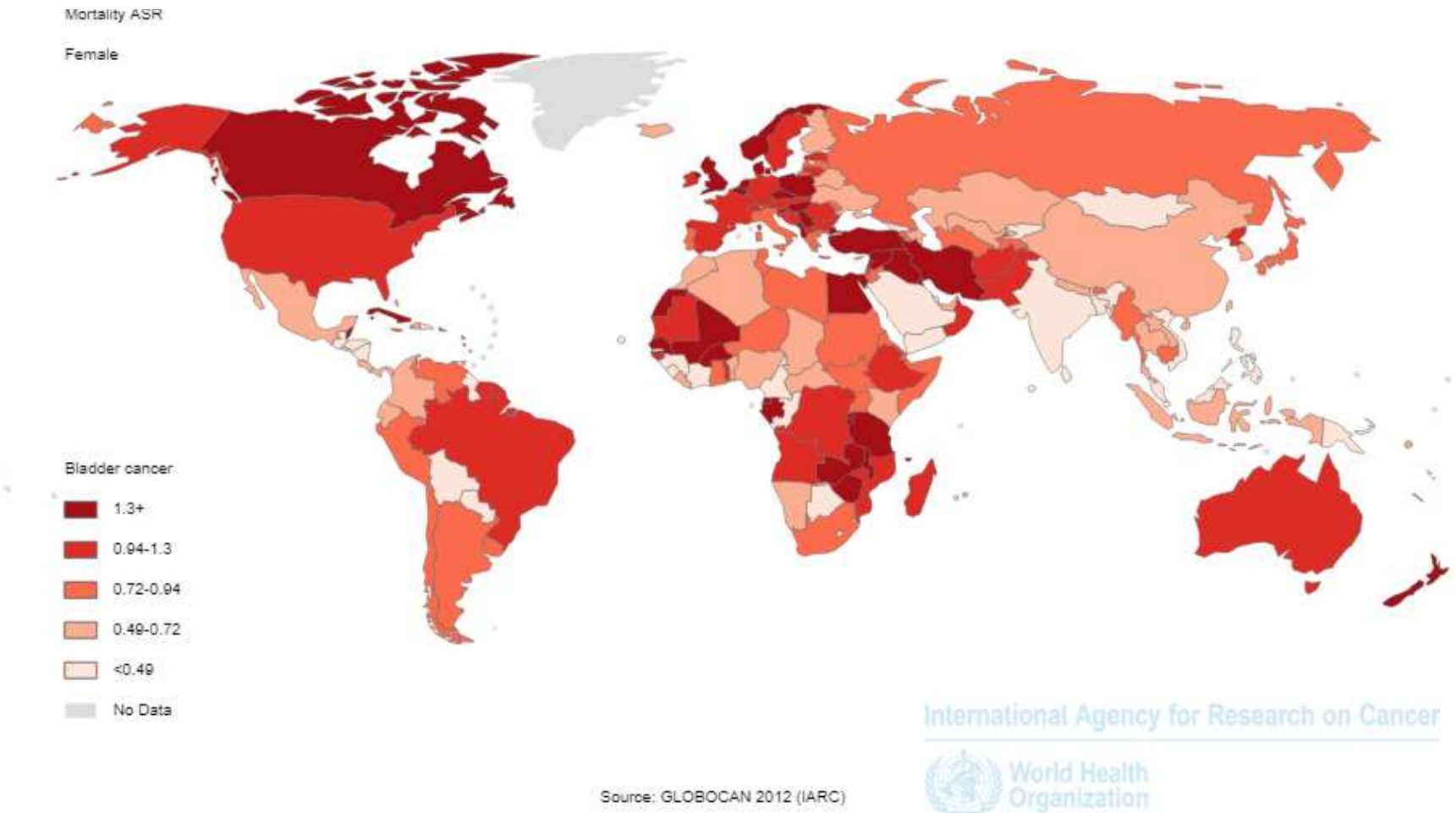
Mortality ASR
Female
Bladder cancer
1.3+
0.94-1.3
0.72-0.94
0.49-0.72
<0.49
No Data
Source: GLOBOCAN 2012 (IARC)
International Agency for Research on Cancer
World Health Organization

Figure 3b

Figure 4

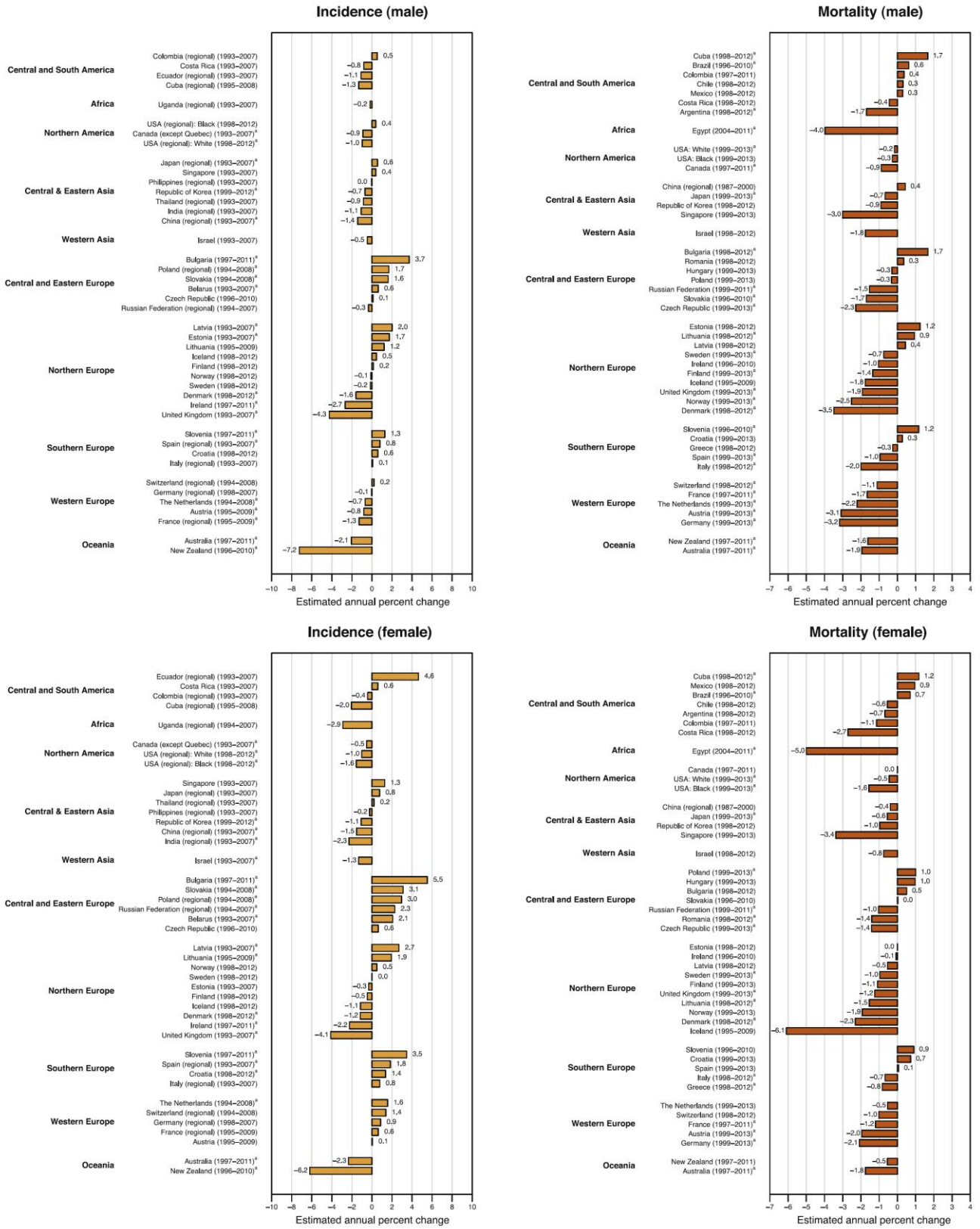

Fig. 4 – Estimated annual percent change in age-standardised incidence (left) and mortality (right) rates of bladder cancer in men (top) and women (bottom) in selected countries (last 15 yr of available data). Regional incidence data from Gharbiah (Egypt), Blantyre (Malawi), Harare (Zimbabwe), Kampala (Uganda), Antofagasta (Chile), Villa Clara (Cuba), Cali (Colombia), Quito (Ecuador), SEER (USA), Alberta, British Columbia, Manitoba, Northwest Territories, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador, Ontario, and Saskatchewan (Canada), Miyagi, Nagasaki, and Osaka (Japan), Hong Kong and Shanghai (China), Chiang Mai (Thailand), Manila (Philippines), Chennai and Mumbai (India), Izmir (Turkey), Riyadh (Saudi Arabia), Cracow City, Kielce, and Lower Silesia (Poland), St Petersburg (Russian Federation), Granada, Murcia, Navarra, and Tarragona (Spain),