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REVIEW

Epidemiology of urinary bladder cancer: from tumor development to patient's death

Cristiane Murta-Nascimento · Bernd J. Schmitz-Dräger · Maurice P. Zeegers · Gunnar Steineck · Manolis Kogevinas · Francisco X. Real · Núria Malats

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Abstract Urinary bladder cancer (UBC) ranks ninth in worldwide cancer incidence. It is more frequent in men than in women. We review the main established/proposed factors, both environmental and genetic, associated with bladder cancer etiology and prognosis. Data were extracted from previous reviews and original articles identified from PubMed searches, reference lists, and book chapters dealing with the reviewed topics. Evaluation and consensus of both the contribution of each factor in bladder cancer burden and the appropriateness of the available evidences was done during an ad hoc meeting held during the 18th Congress of the European Society for Urological Research. Cigarette smoking and specific occupational exposures are the main known causes of UBC. Phenacetin, chlornaphazine and cyclophosphamide also increase the risk of bladder cancer. Chronic infection by *Schistosoma haematobium* is a cause of squamous cell carcinoma of the bladder. NAT2 slow acetylator and GSTM1 null genotypes are associated with an increased risk of this cancer. Vegetables and fresh fruits protect against this tumor. Regarding prognosis, there is little knowledge on the predictive role of environmental exposures and genetic polymorphisms on tumor recurrence and progression and patient's death. Although active tobacco smoking is the most commonly studied factor, no definitive conclusion can be drawn from the literature. More research is needed regarding the effect of complex etiological factors in bladder carcinogenesis. Subgroup analysis according to stage, grade, and molecular features may help in identifying specific etiological and prognostic factors involved in different bladder cancer progression pathways.

Keywords Urinary bladder cancer · Review · Epidemiology · Risk factors · Prognosis · Survival

C. Murta-Nascimento · M. Kogevinas · F. X. Real · N. Malats (✉)
Centre de Recerca en Epidemiologia Ambiental (CREAL),
Institut Municipal d'Investigació Medica (IMIM),
Carrer del Dr. Aiguader 88, 08003 Barcelona, Spain
e-mail: nuria@imim.es

B. J. Schmitz-Dräger (✉)
Urologie, EuromedClinic, Fürth, Germany
e-mail: bsd@euromed.de

M. P. Zeegers
Unit of genetic epidemiology,
Department of Public Health and Epidemiology,
School of Medicine, University of Birmingham, Birmingham, UK

G. Steineck
Division of Clinical Cancer Epidemiology,
Karolinska Institutet, Stockholm, Sweden

F. X. Real
Universitat Pompeu Fabra, Barcelona, Spain

Introduction

Approximately 357,000 new cases of urinary bladder cancer (UBC) occurred worldwide in 2002 [1]. UBC is the 7th most common cancer worldwide in men (10.1 new cases per 100,000 person-years) and the 17th in women (2.5 per 100,000 person-years). These differences in incidence rates between genders have been attributed in part to differences in smoking habits.

High incidence rates are observed in developed countries (Fig. 1) [1]. The highest incidence rate in men was in Egypt (37.1 per 100,000 person-years), Spain (33.0 per 100,000 person-years), and The Netherlands (32.6 per 100,000 person-years). In women, the highest incidence rate was recorded in Zambia (13.8 per 100,000 person-years),

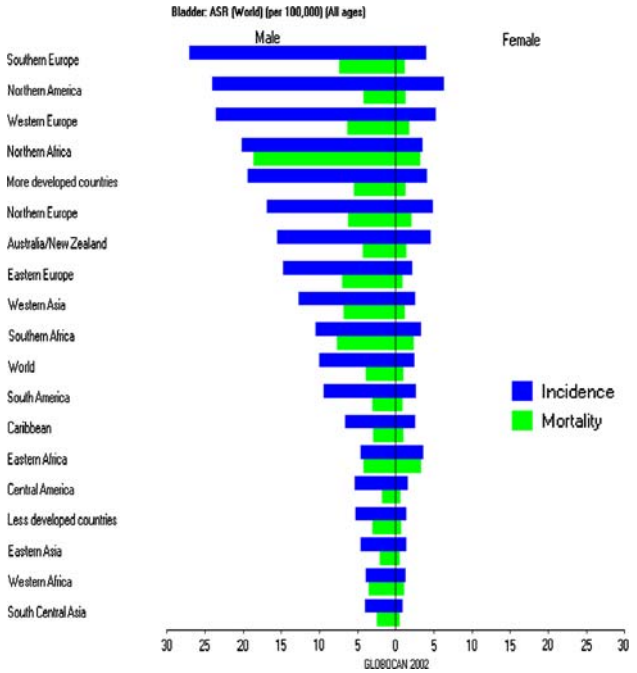

Fig. 1 Worldwide age standardized incidence and mortality rates (per 100,000 habitants) for men and women

Mozambique (13.0 per 100,000 person-years), and Zimbabwe (8.0 per 100,000 person-years). A similar pattern is observed for mortality rates (Fig. 1) that tended to increase in men in the majority of European countries between 1960 and 1990, with a subsequent decline in many countries [2].

The difference between incidence and mortality rates suggests that UBC has a long progression period. In USA, the 5-year relative survival rate ranges from 97% for those diagnosed with stage I to 22% for those with stage IV according to the TNM classification [3]. In Europe, the overall rate was 71%, varying widely across countries [4].

Chronic diseases, such as UBC, can be considered as a continuum, from initiation of the disease at the subclinical level to patient's cure/death. This standpoint contrasts with the common view of disease as a two-stage process, i.e. before and after diagnosis, leading to the search for "risk/protective" factors and "prognostic" factors. Actually, both types of factors could play a role throughout the disease process. While this paradigm is not commonly applied to cancer—possibly due to the often-devastating effects of the disease—there are evidences from other clinical situations and there is enough progress in cancer management that warrants its consideration. For example, patients having suffered a myocardial infarction who continue smoking have an increased risk of death compared to those who quit smoking [5]. Risk factors for disease development are candidate factors to be avoided also after the diagnosis is made. Remarkably, little is known in this area for UBC.

Here, we first review the main established or proposed factors associated with UBC development ("risk" factors) and then summarize the evidence available in the literature on the role of the same group of factors in "tumor prognosis".

Risk factors

Life-style factors

Tobacco

Cigarette smoking is the most important risk factor for UBC, accounting for 50% of cases in men and 35% in women [6]. A meta-analysis reported that current cigarette smokers have a risk of 2.57 (95%CI 2.20–3.00) compared with non-smokers [6]. A positive dose-response relationship was found with both number of cigarettes smoked daily and number of years of smoking [7]. The risk for non-transitional cell carcinoma is also increased in smokers [8]. Upon cessation of cigarette smoking, the excess risk for UBC falls over 30% after 1–4 years and over 60% after 25 years of cessation [7, 9]. People who exclusively smoke unfiltered cigarettes have a 30–70% higher risk than those who smoke only filtered cigarettes [10, 11]. Inhalation of tobacco smoke moderately increases the risk compared with no inhalation [12]. Black tobacco consumption is associated with a higher increase in risk compared with blond tobacco [13–16]. Some studies have reported an increased risk of UBC among pipe smokers [17–19].

Alcohol drinking

Many studies have evaluated the role of alcoholic beverage consumption on UBC risk and have provided inconsistent results. A recent meta-analysis indicated no effect for alcohol consumption with odds ratio (OR) for alcohol consumption being 1.3 (95%CI 0.9–2.0) for men and 1.0 (95%CI 0.6–1.7) for women [20].

Coffee drinking

The role of coffee in UBC is not clear in spite of several epidemiological studies. In 1991, an IARC working group concluded that coffee is possibly carcinogenic to the human urinary bladder, though the possibilities of a bias or an influence of confounding factors could not be excluded [21]. A meta-analysis found an OR for current coffee consumption of 1.26 (95%CI 1.09–1.46) for men, 1.08 (95%CI 0.79, 1.46) for women and 1.18 (95%CI 1.01–1.38) for men and women combined [22].

One major problem in evaluating the independent effect of coffee consumption in UBC is its relationship with tobacco smoking. A pooled analysis of studies in Europe exclusively on non-smokers was performed to avoid a residual confounding effect of cigarette smoking [23]. Although a misclassification between non-smokers and smokers could not been ruled out, the authors observed an excess risk only for subjects consuming ten or more cups per day (OR = 1.8, 95%CI 1.0–3.3).

Tea drinking

The results of the studies evaluating the effect of tea consumption on UBC are also inconsistent [21]. A recent meta-analysis has not found any association between tea consumption and UBC [22].

Total fluid intake

Case-control and cohort studies evaluating the effect of total fluid consumption and UBC risk have also shown contradictory results. Some of them reported positive significant associations [24–26]. On the other hand, others have found that high fluid consumption is a protective factor [27, 28]. Other studies have failed to find significant associations [22, 29–32].

Artificial sweeteners

Most epidemiological studies failed to show any evidence of bladder carcinogenicity for saccharin and other sweeteners [13, 33–40]. In 1999, the IARC evaluated the effect of saccharin and its salts on UBC and the working group's conclusion was that these substances were not classifiable as carcinogenic in humans despite the evidence for sodium saccharin producing urothelial bladder tumors in experimental animals [41].

Diet

Most observational studies that investigated the consumption of fresh fruits and vegetables have shown a protective effect against development of UBC [42]. A meta-analysis reported an increased risk associated with diets with low fruit content (RR = 1.40, 95%CI 1.08–1.83) [43]. Regarding vegetable consumption, the same authors provided a meta-OR of 1.16 (95%CI 1.01–1.34) associated with diets low in vegetable content.

The effects of fat and meat intake were also summarized in the same meta-analysis [43]. Elevated risks were identified for diets with a high fat content (RR = 1.37, 95%CI 1.16–1.62) but not for diets with a high meat content (RR = 1.08, 95%CI 0.82–1.42). Whether energy intake mostly accounts for this excess risk has not been elucidated. Only one case-control study has investigated the effect of heterocyclic amines—carcinogens arising from the cooking of meat and fish at high temperatures—and failed to find a relationship with UBC [44].

There is less evidence for an effect of vitamins and antioxidants on bladder carcinogenesis. A meta-analysis did not find increased risks for diets low in retinol (RR = 1.01, 95%CI 0.83–1.23) or beta-carotene (RR = 1.10, 95%CI 0.93–1.30) [43]. Some studies have reported a protective effect of other antioxidants such as vitamin E [45, 46] and selenium [47–49] but the evidence remains insufficient. There is no evidence that dietary or supplement intake of potassium, sodium, calcium, magnesium, phosphorus, iron, vitamin B1, B2, B6 and B12, niacin or folic acid affect UBC risk based on the results of the prospective Health Professionals Follow-Up Study in USA [46].

Physical activity

The effect of physical activity was investigated in a cohort study including 37,459 women followed for 13 years in USA [50]. Women who reported regular physical activity presented a decreased risk of UBC compared with more sedentary individuals (RR = 0.66, 95%CI 0.43–1.01). On the other hand, a cohort study including 7,588 men found an increased risk of UBC among men reporting vigorous physical activity (RR = 2.06, 95%CI 1.08–3.95) compared with those reporting none to moderate [51].

Hair dyes

Almost all cohort [52, 53] and case-control [17, 54–58] studies examining the association between personal use of hair dyes and bladder cancer risk found no significant effect, though a population based case-control study in Los Angeles reported an elevated risk for women with frequent and long-term permanent dye use [59]. The results of the Spanish Bladder Cancer Study did not support these findings [58].

Medications

The use of phenacetin-containing analgesics has been associated with an increased risk of renal pelvis tumors. An association with UBC has been found in most, but not all, published case-control studies [60–62]. The IARC included the analgesic mixtures containing phenacetin in Group 1 but phenacetin, in Group 2A [63].

In contrast, acetaminophen (paracetamol), the major metabolite of phenacetin, has generally not been found to increase the risk of UBC [60, 64, 65]. Only one case-control

study found a significant increased risk of transitional cell cancer among users of paracetamol (OR = 1.6, 95%CI 1.1–2.3) [66]. However, analyses by duration and quantity of paracetamol use did not support this association. In 1999, the IARC concluded that there was inadequate evidence for both humans and experimental animals as to the carcinogenicity of paracetamol [41]. Subsequent publications have also failed to demonstrate an association with UBC risk [61, 62, 67, 68].

Regarding the use of non-steroidal anti-inflammatory drugs (NSAIDs), the intake of any class of NSAIDs, except for pyrazolone derivatives, was inversely associated with UBC [61]. The protective effect was strongest among regular users of acetic acid compounds (OR = 0.54, 95%CI 0.31–0.94) and weaker for users of aspirin and other salicylic acids and oxicams. Nevertheless, other studies did not find any significant effect of NSAIDs [62, 67, 69–71].

Phenobarbital use has been observed to be inversely associated with UBC development in a few studies [72–74]. On the other hand, a population case-control study did not support these findings and suggested that phenobarbital use may even increase UBC risk [75].

Regarding isoniazid, IARC considers that there is inadequate evidence for its carcinogenicity in humans [63]. Three case-control studies including UBC [76, 77] or bladder and renal cancer [78] failed to provide conclusive evidence.

Chlornaphazine, a chloroethyl-derivative of 2-naphthylamine, is included in IARC Group 1 [63]. Among 61 patients with polycythemia vera treated with chlornaphazine, 13 developed UBC and 8 had an abnormal urinary cytology, suggesting a carcinogenic effect of this compound.

Cyclophosphamide use has been found to be associated with an increased risk of bladder neoplasms [79–81] and it is also included in the group of human carcinogens [63].

Occupational exposures

Exposure to specific chemical carcinogens is another well-established risk factor for UBC. Exposure to aromatic amines, in chemical industry workplaces involving use of these chemical substances and in the rubber industry, is associated with UBC [63]. An excess risk was also reported for dyers in textile industries, painters, varnishers and hairdressers [82]. Other agents having been associated with UBC are polycyclic aromatic hydrocarbons (PAHs), used in aluminum production, coal gasification, coal tars, roofing and carbon black manufacture [83]. An excess risk of UBC was reported among workers exposed to diesel-engine exhaust, such as drivers. In a meta-analysis, the relative risk among truck drivers was 1.17 (95%CI 1.06–1.29) and among bus drivers, it was 1.33 (95%CI 1.22–1.45) [84]. High-risk occupations may account for 5–10% of UBC cases in European men [85].

The pattern of UBC risk among women is similar to that in men. A pooled analysis observed an excess risk among women working in the manufacturing industries, particularly those involving tobacco (OR: 3.0, 95%CI 1.2–7.4), wood products (OR: 3.5, 95%CI 1.0–12.1) and other non-metallic mineral products (OR: 3.6, 95%CI 1.2–10.7) [86].

Environmental exposures

Contaminants in drinking water

Several studies have found a positive association between chlorination by-products in drinking water and UBC [31, 87–90]. A pooled analysis supported these findings [91]. An increased risk was observed among men exposed to an average of more than 1 μg/L (ppb) trihalomethanes (OR = 1.24, 95%CI 1.09–1.41).

Increased UBC risks associated with exposure to high-levels of arsenic in drinking water have been consistently reported [92–95]. An IARC working group has evaluated and classified arsenic in drinking water (primarily inorganic) as carcinogenic to humans [96].

The data on exposure to nitrate in drinking water is limited. A cohort study of 21,977 Iowa women found a positive association between nitrate in drinking water and UBC [97]. In contrast, two case-control studies did not observe a significant effect [89, 98].

Radiation

Chronic low-dose radiation could affect bladder urothelium through oxidative stress and impairment of DNA repair. Therapeutic pelvic radiation, used for dysfunctional uterine bleeding, ovarian, cervical and prostate cancer, is associated with an increase in UBC risk [99–102].

Radioiodine (iodine-131), used for treating hyperthyroidism, was reported as being associated with UBC in some [103, 104], but not all, publications [105].

Passive smoking

At present, there is no evidence that environmental tobacco smoking increases UBC risk [106–108].

Previous medical conditions and endogenous factors

Urinary tract infections

A chronic urinary infection caused by *Schistosoma haematobium* is associated with UBC [109]. The evidence linking this infection with UBC came from studies in Africa, showing

higher incidence of squamous cell carcinoma in areas with high prevalence of *S. haematobium* infection compared with areas with low prevalence. Several case-control studies have shown significant positive associations, with risks ranging from 2 to 14 [109].

The evidence on the effect of other urinary tract infections is inconclusive [17, 25, 103, 110–114]. Similarly, the evidence supporting the role of Human papillomavirus (HPV) in UBC is conflicting [115].

Urinary tract stones

The role of urinary tract stones on UBC risk is controversial. Several case-control [111, 114] and cohort [116] studies have found an increased risk in patients with a history of urinary stones. However, other case-control studies could not show a significant effect [112, 113].

Urine pH

Rothman et al. [117] found that low urine pH was associated with elevated levels of free urinary benzidine and *N*-acetylbenzidine and tenfold higher DNA adduct levels in exfoliated urothelial cells. However, a recent case-control study did not detect any association between urine pH and UBC [118].

Menstrual, reproductive, and hormonal factors

Hormonal factors have been proposed as one explanation for the excessive incidence of UBC in men [119]. Nevertheless, data on hormonal, menstrual, and reproductive factors and UBC risk are scarce. A case-control study reported a decreased risk for ever-parous women who never-smoked (OR = 0.51, 95%CI 0.30–0.88) [120]. A more recent case-control study has not confirmed this association and also has not found significant results for other menstrual and reproductive factors [121]. However, an elevated risk of UBC for ever users of menopause hormone replacement therapy was observed (OR = 3.29, 95%CI 1.49–7.25).

Hereditary factors

Familial history of bladder cancer

Familial clustering of UBC has been described in several case-reports [122–125], although the results of case-control studies are controversial [25, 33, 76, 103, 126–129]. Other than that, Goldgar et al. [130] reported an increased risk of lymphocytic leukemia and cervical cancer among first-degree relatives of early-onset bladder cancer probands. The largest population case-control study of 2,982 bladder cancer patients and 5,782 controls conducted in USA found a risk of 1.45 (95%CI 1.2–1.8) for those with a first-degree relative with cancer of the genitourinary tract [127]. In a population-based family case-control study including patients with urothelial cell carcinoma of the bladder, ureter, renal pelvis or urethra, the risk of bladder cancer among case-relatives was 1.8 (95%CI 1.3–2.7) compared with control-relatives [131]. In a cohort study of twins from Sweden, Denmark, and Finland, it was estimated that 31% of the risk of bladder cancer might be explained by heritable factors, although the estimation was not statistically significant [132]. Altogether, it seems that a slightly increased risk of bladder cancer is associated with individuals with a family history of cancer.

Genetic susceptibility

Genetic polymorphisms in genes coding for enzymes involved in the metabolism of urothelial carcinogens, such as aromatic amines and PAHs, might contribute to the inter-individual susceptibility to UBC. *N*-acetyltransferases (NATs) are involved in the bioactivation and detoxification of aromatic amines. The lack of two functional NAT2 alleles leads to a slow acetylation phenotype. NAT2 status has been extensively studied as a risk factor. García-Closas et al. [133] combined data from 31 case-control studies and reported a statistically significant OR for UBC in NAT2 slow acetylators (OR = 1.4, 95%CI 1.2–1.6). A likely interaction between smoking and the NAT2 genetic variants is one of the few examples of consistent gene-environment interactions shown to date [133, 134]. Only limited data have been reported on the role of polymorphisms of NAT1 gene in the etiology of UBC [135, 136].

The glutathione-*S*-transferases (GST), a large family of enzymes involved in the detoxification of electrophiles by glutathione conjugation, have a wide variety of substrates, including PAH epoxides and by-products of oxidative stress. GSTM1 deletion, a common polymorphism in humans, leads to loss of enzyme activity and was associated with UBC in several studies. A meta-analysis estimated an OR of 1.5 (95%CI 1.3–1.6) for GSTM1-null individuals [133]. Few studies investigated the effect of GSTT1 and GSTP1 and UBC risk, the results being inconclusive [135, 137–143].

Sulfotransferases (SULT) and cytochrome P450 enzymes (CYP) are also involved in the metabolism of aromatic amines and PAHs. The SULT1A1 Arg213His polymorphism seems to decrease the risk of UBC [135, 144, 145], but this finding needs to be confirmed by larger studies. There is only limited evidence regarding polymorphisms in CYP1A1, CYP1A2, CYP1B1, CYP2C19, CYP2D6, and CYP2E1 [135, 137, 146–148].

Among the DNA repair pathways, nucleotide excision repair (NER) is the most positively associated one with

bladder cancer risk, both considering individual SNPs in candidate genes (i.e., ERCC1, ERCC2, ERCC5, and RAD23B) and the global effect of the pathway [149–152]. Furthermore, an interaction between NER pathway and tobacco is observed [150–152]. However, only a small fraction of the 37 potential genes involved in this pathway have been considered in the studies [153].

Prognosis

Much research has been done on the prognostic factors in UBC focusing especially in histopathologic characteristics and in biological markers. Little attention has been paid to exposures that are usually investigated as risk/protector factors for this cancer. Since the majority of UBC are superficial and treated with bladder preservation, factors contributing to the development of UBC may affect the risk of recurrence, progression or death.

The exposure most extensively investigated regarding prognosis is tobacco smoking [154–165]. All studies found an increased risk of recurrence in current or ever smokers, although in only one study it was statistically significant [158]. With regard to progression and mortality, none of the studies found statistically significant effects. A recent systematic review concluded that cigarette smoking may be a weak factor influencing the prognosis of UBC, but the results are inconclusive [166].

Regarding chemical exposure in the workplace, a prospective cohort study including 334 patients with non-muscle invasive UBC did not find any statistically significant effect of this exposure on recurrence [167]. The paper did not provide details about the chemical exposures that had been evaluated.

Recently, a prospective study including 267 non-muscle invasive UBC cases has investigated the effect of fluid intake on recurrence [168] and no relationship was observed. One of the four studies that investigated the effect of alcohol consumption on UBC prognosis found a significant risk reduction for males who ever used alcoholic beverages compared with those who never used [160, 162, 164, 169]. Regarding other beverages such as coffee, black and green tea, none of the reviewed studies found significant effects on UBC prognosis [162, 167].

A recent cohort study found a significantly reduced risk of UBC mortality among long-term vitamin E supplement users [170]. No effect of dietary vitamin A on recurrence was reported by a cohort study including 102 patients with localized disease [171]. Similarly, no effect of artificial sweeteners on UBC prognosis was described [162, 167].

Recently a great deal of interest has been generated regarding the effect of NSAIDs on UBC prognosis. A significant reduction in recurrence for those using selective cyclooxygenase (COX) 2 inhibitors or other NSAIDs has been presented [172], while no effect was observed among acetaminophen users. A randomized clinical trial is being conducted in the USA to evaluate the effectiveness of Celecoxib in preventing the UBC recurrence (http://www.clinicaltrials.gov/ct/gui/show/NCT00006124).

Schistosoma haematobium, HPV and non-specific urinary tract infections seem to have no effect on the prognosis of this cancer [164, 173, 174]. Personal use of hair dyes and prognosis was evaluated in one study, which did not find any effect [162]. Having family history of cancer does not to confer a worse prognosis [160]. Regarding genetic susceptibility, ten studies assessed the association of several polymorphisms with established prognostic factors (i.e., stage and grade) [175–184]. A study investigated the effect of NAT2, SULT1A1 and CYP1A2 polymorphisms in recurrence and has not observed significant effect of these polymorphisms [183]. Another study has not found any effect of NAD(P)H:quinone oxidoreductase (NQO1) and NADPH cytochrome P450 reductase (P450R) protein expression in clinical response of patients with non-muscle invasive UBC treated with mitomicin C [185]. One study reported an elevated risk of recurrence among patients with high CYP2D6 activity [186]. Marsh et al. [180] investigated the effect of tumor necrosis factor (TNF) polymorphisms in progression and found no effect. Finally, Sakano et al. [187] reported a significantly shorter tumor-specific survival for patients with polymorphisms in the cyclin-dependent kinase inhibitor 2A (CDKN2A) gene compared with those carrying wild-type sequences.

Overall, no established associations between environmental exposures, lifestyle habits, and genetic susceptibility factors and the prognosis of UBC have been identified up to now.

Conclusions

Urinary bladder cancer ranks ninth in worldwide cancer incidence. It is more frequent in men than in women. Cigarette smoking and occupational exposure to aromatic amines are the main known causes of UBC. Phenacetin, chlornaphazine and cyclophosphamide also increase UBC risk. Chronic infection by *S. haematobium* is a cause of squamous cell carcinoma. NAT2 slow acetylator and GSTM1 null genotypes, alone and in interaction with tobacco, are associated with an increased risk. Consumption of vegetables and fresh fruits protects against this tumor.

These risk factors have been mainly investigated in Caucasians and it is uncertain whether they play the same role in individuals of different ethnicity. Further research is needed to disentangle whether established risks/protective

and susceptibility factors have a different effect on different UBC subgroups according to pathological or molecular characteristics. Similarly, an in-depth study of endogenous factors such as inflammation, oxidative stress, and hormonal status may help in identifying further causes of UBC as well as to elucidate the reasons for sex differences in incidence.

Regarding prognosis, the knowledge on the role of environmental exposures and genetic polymorphisms in predicting tumor recurrence and progression and death is scarce, active tobacco smoking being the most commonly studied factor. Unfortunately, no definitive conclusion can be drawn from the published studies. Again, subgroup analysis according to stage and grade may help in identifying prognostic factors involved in different UBC progression pathways, TaG1 and Ta/1G2 tumors providing a more suitable setting to conduct these analyses. A better understanding of the genetic basis of UBC may also provide clues in order to determine how information on factors affecting the development of UBC can be used to improve patient's prognosis. Future studies should follow a strict methodology, considering, among others, well defined outcomes (recurrence and progression), appropriate follow-up, and multivariable survival analysis adjusted for established prognostic factors.

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