

## REVIEW PAPER

**ENVIRONMENT AND URINARY BLADDER CANCER.  
A HISTORICAL PERSPECTIVE**GABRIELLA NESI<sup>1</sup>, ILARIA C. GALLI<sup>1</sup>, ANDREA AMOROSI<sup>2</sup>, RAFFAELLA SANTI<sup>3</sup><sup>1</sup>University of Florence, Florence, Italy<sup>2</sup>University of Magna Graecia, Catanzaro, Italy<sup>3</sup>Careggi University Hospital, Florence, Italy

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Our understanding of aetiological factors associated with urinary bladder cancer has radically improved over the last decades. Cigarette smoking is considered the most important risk factor, even in the industrialised world, while various occupational and environmental exposures to chemicals are also held responsible. The link between bladder cancer and schistosomiasis, highly prevalent in sub-Saharan Africa, Sudan, Egypt, and Yemen, provides input for investigating and potentially preventing bladder carcinogenesis. Growing concern regarding environmental diseases prompts investigation into the historical milestones that have helped disentangle the relationships between health and environment.

**Key words:** bladder cancer, environment, risk factors, aetiology.

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**Introduction**

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Bladder cancer ranks tenth among the most common cancers worldwide, with high rates reported in Europe, North America, and Australia, but relatively low in Far Eastern countries [1]. It affects males more often than females and its incidence increases notably after the age of 65 years. Most cases of bladder cancer have been found to be urothelial carcinomas (90%), 70% of which are papillary and non-muscle invasive tumours. Less common histotypes are squamous cell carcinoma (< 3%), adenocarcinoma (0.5-2%), and small cell carcinoma (< 1%). Rare neoplasms comprise sarcoma, paraganglioma, malignant melanoma, and lymphoma [2].

The pathogenesis of human bladder cancer has been thoroughly investigated for several decades. Early studies involved descriptions of development of these neoplasms in workers exposed to occupational arylamines, while more recent studies have employed animal models and have extended to tissue, cellular, and molecular analyses. Each of these levels

of activity has provided opportunities for mechanistic studies, yet we still do not have a complete categorisation of the processes behind bladder carcinogenesis [3].

**The natural environment**

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Until the twentieth century, in the wild and windy moorlands of Devonshire, fields of bracken were set ablaze to encourage rainfall [4]. Perhaps not even a drop was generated, but due to this popular belief, a potential carcinogen-promoting agent for urinary bladder carcinoma was inadvertently incinerated. Many important carcinogens of bladder cancer aetiology can be found in nature and may have been present on this planet as long as man [3]. Bracken fern (*Pteridium aquilinum*) is one of the most abundant plant species. It was used by several Pacific Northwestern Indian tribes as a dietary staple as long ago as 14,000 BC, and in more modern times as food for both humans and animals in many parts of the world [5]. Bracken fern has been implicated

in human oesophageal carcinogenesis and has been reported to be associated with several diseases and tumour types in animals [4]. Chemical carcinogenic compounds (e.g. ptaquiloside or ptaquiloside analogues) have been isolated in various ferns, including bracken, which is now recognised as a potent experimental plant to induce urinary bladder carcinoma [6].

Odourless, tasteless, and lethal, arsenic gained notoriety over the ages as a powerful homicidal and suicidal poison. It is well documented that arsenic, often referred to as the “king of poisons” and the “poison of kings”, was used by the Medici and Borgia families to eliminate enemies and has been suspected as the deadly agent in several high-profile murders. Yet, it is a natural environmental contaminant, found in water, soil, and air, to which humans are constantly exposed [7].

On the one hand, arsenic has been used as a pesticide, on the other in therapies and as a component of consumer products. Although exposure to arsenic is not generally a health hazard, high concentrations have been found in ground water and surface soil in several countries, including China, Bangladesh, India, and Hungary [7].

In 1822, arsenic was first suspected of being a carcinogen when cutaneous neoplasms were observed in the hips of cattle grazing close to foundries, and they were attributed to arsenic-containing expelled gases [8]. Later, in 1885, James C. White (1833-1916), Professor of Dermatology at Harvard University, described psoriasis-verruca-epitheliomas in two patients who had used arsenic as a treatment for skin diseases, but did not realise its carcinogenic role [9]. In 1888, Sir Jonathan Hutchinson (1828-1913), reported six cases of skin cancer in patients given arsenic as a medication for dermatologic conditions. It was not until 1922 that cancer was induced by applying an alcoholic solution of potassium arsenite on rats, the first squamous cell carcinoma appearing after 86 days [10]. Evidence suggests a strong link between bladder cancer and arsenic content in drinking water over 300-500  $\mu\text{g/l}$ , whereas even concentrations below 200  $\mu\text{g/l}$  may pose a risk to smokers [1].

The mechanism behind arsenic-induced bladder cancer is poorly known. While arsenic indirectly impedes sulphhydryl-containing enzymes and hampers cellular metabolism (e.g. cytotoxicity, genotoxicity, and inhibition of enzymes with antioxidant function), the p53 protein may also be involved in the development of arsenic-induced bladder cancer [7]. In addition, genetic differences in DNA repair are likely to modulate the process of arsenic carcinogenesis [1].

## Infective agents

Infectious agents are believed to cause over 20% of malignancies worldwide [11]. *Schistosoma haematobium* is a trematode parasite endemic in Africa and the Middle East; where many individuals suffer from repeated infestations from an early age [3, 12]. The parasite invades the system venules and capillaries of the human urinary bladder and other pelvic organs (Fig. 1).

Theodor Bilharz (1825-1862) first identified this blood fluke during an autopsy at the Kasr El Ainy Hospital (Cairo) in 1851 [13], while Robert Leiper (1881-1969) described the life cycle of the Schistosome parasite in 1915 [14]. An association between schistosomiasis and urinary bladder cancer was first theorised by the German surgeon Carl Goebel in 1905 [15]. Some years later, after investigating 40 autopsy cases, Alexander Robert Ferguson (1870-1920), Professor of Pathology and Microbiology at the Faculty of Medicine in Cairo, reported that urinary bladder carcinoma could be linked to granulomas caused by *Schistosoma haematobium* [15, 16], a hypothesis validated only in 1994 by the International Agency for Research on Cancer (IARC) [17]. Several paleoparasitological studies have shown that *Schistosoma haematobium* was already endemic in Ancient Egypt [18]. Sir Marc Armand Ruffer (1859-1917) started this intriguing journey through time in 1910, when he discovered calcified schistosome eggs in two Egyptian mummies of the 20<sup>th</sup> dynasty [19]. Conventional radiology on two other mummies revealed calcified urinary bladders likely to result from *Schistosoma haematobium* infection [20]. An Egyptian adolescent who lived 5000 years ago would never have imagined being the earliest documented case of human schistosomiasis, a diagnosis carried out using the enzyme-linked immunosorbent assay (ELISA) [21]. This technique

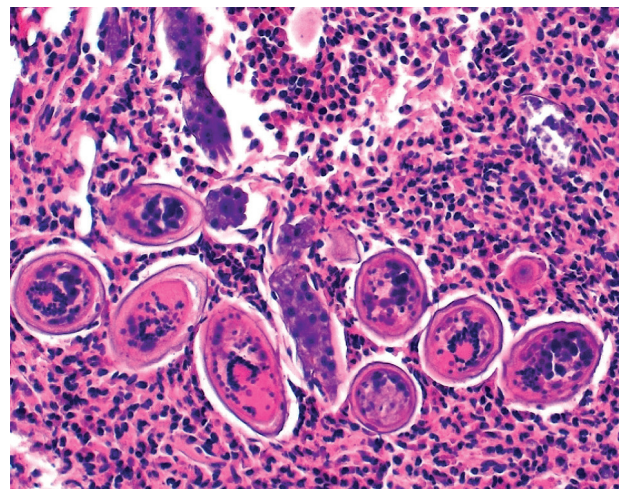


Fig. 1. Schistosomiasis. Numerous eggs are present in the lamina propria of the bladder with prominent chronic inflammation (HE, 20 $\times$ )

allowed the diagnosis of *Schistosoma haematobium* infection in two other mummies aged 3000 and 4000 years, respectively [22]. The first contact of Europeans with *Schistosoma* occurred in 1779 during the three-year French invasion of Egypt. Many soldiers are believed to have been infected as well as Napoleon himself [23]. Increased travel for business, education, and tourism has led to unusual schistosomiasis cases in non-endemic countries.

The close relationship between schistosomiasis and bladder cancer, particularly squamous cell carcinoma, almost always invasive, was reported by Mostafa *et al.* [24]. Deposition of schistosomes can induce chronic inflammation and irritation of urothelium, which Rosin *et al.* found to be associated with cancer initiation [25]. Activated inflammatory cells, e.g. macrophages and neutrophils, can lead to endogenous synthesis of N-nitrosamines as well as production of oxygen radicals. Levels of DNA damage in host cells are high and correlate with the intensity of the inflammatory reaction. It has been hypothesised that *Schistosoma haematobium* may be oncogenic by inducing *K-RAS* mutations [26].

### Tobacco smoking

Throughout the centuries, human exposure to natural agents posing urinary bladder carcinogenic hazards has been deliberate, with varying degrees of awareness of potential risks. Following the expeditions by Christopher Columbus (1451-1506) at the turn of the 15<sup>th</sup> to 16<sup>th</sup> century, shipments of gold, silver, and precious stones arrived in Europe from the “New World”. Just as important, from the economic point of view, plants of the *Solanaceae* family, such as potatoes, tomatoes, eggplants, and peppers, also reached Europe. Besides these widely used food plants, other species of the *Solanaceae* family, i.e. Mandragora, Datura, Atropa, and Belladonna, were well known for their psychotropic effects, or for being poisonous. Last but not least, another plant of the same family was introduced: tobacco [3]. Tobacco was used for many centuries in tribal ceremonies by North American Indians. The tobacco smoking culture was introduced into Europe in 1519 by Spanish explorers, and its use spread rapidly to Asia and Africa (Fig. 2). John Hill (1716-1775), the English physician and botanist, reported a link between tobacco use and cancer in 1761 [27]. However, evidence that cigarette smoking was aetiological for human urinary bladder cancer only came to light in the 1950s. It is now widely acknowledged that cigarette smoke contains a huge number of carcinogens,



Fig. 2. *Gentlemen Smoking and Playing Backgammon in an Interior* by Dirck Hals, 1627

some of which are reported to induce urinary bladder cancer [4]. Smoking is the main contributor to this disease in most populations and is estimated to cause as many as half of such cases [28].

### Occupational carcinogens

In his famous *De morbis artificum* (1700), Bernardino Ramazzini (1633-1714) recommended that physicians add the question “*et quam artem exercent*” to the Hippocratic anamnestic interview in order to accurately evaluate their patients [29]. Several neoplastic diseases may occur as a result of professional or occupational activities. Indeed, urinary bladder cancer was one of the first diseases for which specific industrial chemicals were identified as causative agents of human cancer [3]. In 1895, the German surgeon Ludwig Rehn (1849-1930) described three cases of occupational-related bladder cancer in 45 labourers working with fuchsine dye in Frankfurt, Germany [30]. The following 50 years saw many other reports regarding workers in several countries. All shared the same characteristics of clusters of industrial exposure to aromatic amines and development of urinary bladder cancer [3].

Products from chemical, dye, and rubber industries as well as hair dyes, cigarette smoke, fungicides, paints, plastics, metal, and motor vehicle exhaust and pollutant emissions from industrial processes, all contain the compounds 2-naphthylamine, 4-aminobiphenyl, and benzidine [1]. Evaluating British workers exposed to 2-naphthylamine in 1954, Case *et al.* found a 200-fold increased bladder cancer risk in that cohort [31]. An increased risk of bladder cancer development was documented a year later, as the result of a study involving 171 workers in the rubber industry exposed to 4-aminobiphenyl [32]. The most important carcinogenic





**Fig. 3.** In 1856 William Henry Perkin (1838-1907), a chemistry student, produced fortuitously the first aniline dye, subsequently called “mauvine”. In the picture a silk skirt and a blouse dyed with Sir Perkin’s purple colour

aromatic amine causing human bladder damage is benzidine. Of 331 workers at an industrial establishment in Leverkusen, Germany, who had been exposed to the production of benzidine-1967, 92 were diagnosed with bladder cancer [33].

Based on these findings, procedures were put into place by several industrialised countries to reduce or abolish the production of these chemicals. The belief at that time was that up to 1% of human urothelial neoplasms were aetiologically related to exposure to at least one of these chemicals. Important information was therefore provided for future researchers by clinicians concerned about cases of bladder cancer in their patients [3].

The second major advance in urinary bladder cancer causation studies came in 1938 when the pathologist Wilhelm C. Hueper (1894-1978) demonstrated that the application of 2-naphthylamine to dogs could trigger the growth of urinary bladder cancers [34]. This major achievement led to the development of laboratory methods to investigate known or suspected chemical carcinogens under controlled conditions. It also provided opportunities to examine the cellular and molecular mechanisms in the pathogenesis of urinary bladder cancer in order to elucidate these phenomena and create a rational approach for their inhibition or reversal.

## Conclusions

Cancer is not a recently discovered disease and has afflicted people since ancient times. Besides ageing and inherited predisposing conditions, environmental exposure to carcinogens plays a major role in cancer promotion. Known carcinogens include lifestyle habits (e.g. cigarette smoking), natural elements (e.g. ultraviolet light), infective agents, drugs, and pollution. Prevention of exposure to toxins is one of the main goals in the fight against cancer.

Multiple environmental factors are considered causative of urinary bladder cancer. A historical perspective of this disease highlights how unveiling the potentially involved environmental factors in carcinogenesis has led to the development of preventive measures, the application of which is still beneficial.

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