Published in final edited form as:

Actas Urol Esp. 2013 September ; 37(8): 513–522. doi:10.1016/j.acuro.2013.01.001.

Constitutional and occupational risk factors associated with bladder cancer

J. Ferrís^{a,*}, J. Garcia^b, O. Berbel^c, and J.A. Ortega^d

^aUnitat de Salut Mediambiental Pediàtrica, Unitat d'Oncologia Pediàtrica, Hospital Universitari i Politècnic La Fe, València, Spain

^bSecció d'Anatomia Patològica, Hospital de Sagunt, València, Spain

^cFacultad de Medicina, Universidad Católica de Valencia, Centro de Salud de Chella, Chella, Valencia, Spain

^dUnidad de Salud Medioambiental Pediátrica, Hospital Materno-Infantil Universitario Virgen de la Arrixaca, Murcia, Spain

Abstract

Objective—Bladder carcinoma (BC) is the fourth most common type of cancer in males from Western countries, with primary prevention an important healthcare challenge. We review the associated constitutional and occupational risk factors (RF), with greater or lesser scientific evidence, in the etiology of BC.

Material and methods—Literature review of the last 25 years of the constitutional and occupational RF associated with BC, conducted on MedLine, CancerLit, Science Citation Index and Embase. The search profiles were Risk factors/Genetic factors/Genetic polymorphisms/Epidemiology/Occupational factors and Bladder cancer.

Results—The main RF were (a) age and gender (diagnosed at age 65 and over, with a 4:1 ratio of males to females); (b) race, ethnicity and geographic location (predominantly in Caucasians and in Southern European countries); (c) genetic (N-acetyltransferase-2 and glutathione s-transferase M1 gene mutations, which significantly increase the risk for BC); (d) occupational, which represent 5–10% of BC RF; and (f) occupations with high BC risk, such as aluminum production, the manufacture of dyes, paints and colourings, the rubber industry and the extraction and industrial use of fossil fuels.

Conclusions—BC is the end result of the variable combination of constitutional and environmental RF, the majority of which are unknown. The most significant constitutional RF are related to age, gender, race, ethnicity geographic location and genetic polymorphisms. The main occupational RF are those related to aromatic amines and polycyclic aromatic hydrocarbons.

*Corresponding author. ferris_jos@gva.es (J. Ferrís).

Conflict of interest

The authors declare that they have no conflict of interest.

Resumen

En los países occidentales el carcinoma vesical (CV) es el 4.º cáncer más frecuente en varones, siendo la prevención primaria un reto sanitario importante. Se revisan los factores de riesgo (FR) constitucionales y ocupacionales implicados, con mayor o menor evidencia científica, en la etiopatogenia del CV.

Revisión bibliográfica de los últimos 25 años de los FR constitucionales y ocupacionales asociados al CP, obtenida de MedLine, CancerLit, Science Citation Index y Embase. Los perfiles de búsqueda han sido *Risk factors/Genetic factors/Genetic polymorphisms/Epidemiology/Occupational factors* y *Bladder cancer*.

Los principales FR son: a) edad y sexo (se diagnostica en mayores de 65 años con una relación hombre/mujer de 4/1); b) étnico- raciales y geográficos (predominio en caucásicos y los países del Sur de Europa); c) genéticos (las mutaciones del gen N-acetil-transferasa 2 y el Glutation-S-transferasa-M1, incrementan significativamente el riesgo de CV); d) los FR ocupacionales representan el 5–10%; y f) las profesiones con mayores riesgos de CV son la producción de aluminio, manufactura de tintes, pinturas y colorantes, industria del caucho y la extracción y usos industriales de combustibles fósiles.

El CV es el resultado final de la combinación variable de los FR constitucionales y ambientales. Desconocemos la mayoría de FR implicados en los CV. Los FR constitucionales más decisivos son la edad y el sexo, los étnico- raciales-geográficos y los polimorfismos genéticos. Los principales FR ocupacionales corresponden a exposiciones a aminas aromáticas e hidrocarburos policíclicos aromáticos.

Keywords

Bladder cancer; Genetic risk factors; Epidemiology; Occupational exposure; Aromatic amines; Polycyclic aromatic hydrocarbons

PALABRAS CLAVE

Cáncer vesical; Factores de riesgo genéticos; Epidemiología; Exposiciones ocupacionales; Aminas aromáticas; Hidrocarburos policíclicos aromáticos

Introduction

With a worldwide, European and Spanish prevalence of 294,345, 112,819 and 11,227 new cases annually, bladder carcinoma (BC) is the fourth most common type of cancer in males from Western countries and the second urological malignancy after prostate cancer. In women with 88,315, 30,736 and 1781 new cases respectively, the prevalence is much lower (Figs. 1 and 2 and Table 1).^{1,2}

In industrialized countries, transitional cell carcinoma is the predominant histological variety of bladder carcinoma accounting for 93–95% cases. Generally, 75–80% of cases are diagnosed as superficial BC, the remainder being muscle-invasive BC. These histological

features, together with diagnostic and therapeutic interventions, determine a good survival.^{3–5}

However, its diagnosis carries enormous human and economic burden, because: (a) it is a serious and potentially fatal disease; (b) it needs lifelong surveillance; (c) high rate of local recurrences; and (d) sequels of treatments. Therefore, the advance in the knowledge of risk factors (RF) associated with BC in order to improve its prevention is a priority. The involvement of urologists is essential, especially when BC incidence in our country is among the highest in the world (Fig. 3).^{1,2}

BC has been one of the first neoplasias with evidence for a causal association with occupational exposures and the subsequent demonstration of its interactions with genetic FR, especially polymorphisms.^{4–6} For this reason, our working group will review and update the constitutional RF, with more or less scientific evidence, as we did in the articles on prostate cancer.^{7–9} Remaining environmental RF will be reviewed in a later article.

Constitutional risk factors

Generals factors (age, sex, ethnic and geographic)

The BC is typical of old-age, the vast majority of cases are diagnosed after the age 65, rarely before age 50 years, and exceptionally in patients aged 10 years or younger.^{10–12} This feature highlights the innate biological resistance of the cells of the bladder mucosa to urinary and plasmatic carcinogens, with latencies of several decades.

The incidence is 3–5 times lower in women than men, although in some Southern European countries the differences are greater.^{1,2} In USA, 6% of all cancers in men are BC and only 2% in women, with a mortality rate of 3 and 1% respectively.^{1,4,5} Moreover, the incidence of BC in non-Hispanic white population is 50% higher than in Hispanic whites and African Americans. The rates are even lower in Asians, and especially low in native Indians and Eskimos. Interestingly, differences between whites and African Americans are observed in BC localized, being similar in the invasive BC. Both superficial and infiltrating carcinomas, are more frequent in African American women than in Caucasian. The mechanisms responsible for these ethnic and sex differences remain unknown.^{4,5}

With regard to the geographical distribution, large differences are observed. Southern European countries have the highest population-based incidence rates in the world (30–40 cases per 100,000 inhabitants/year), followed by North America, Western and Northern Europe, Israel and North Africa. The lowest incidences are found in the countries of East Africa, Melanesia and Central Africa (Fig. 4).^{1–3} Regarding men, Spain stands out for two reasons. Firstly, it is the country with the highest incidence of the world (51 cases/10⁵/year), and secondly for being 8 times higher than the incidence in women. The reasons for such large differences are unknown. This disproportion between Spanish male and female is partially attributed to the differences between black and blond tobacco consumption.^{4–6}

Genetics factors

BC is the final result of the variable combination of two determinants: endogenous or constitutional factors and exogenous or environmental factors. Each determinant is composed of multiple RF, most unknown. Bladder carcinogenesis process or transformation of a normal urothelial into malignant cells is caused by mutations in specific tumor genes associated with repetitive exposure to biological, physical and chemical carcinogens. Their degree of biological aggressiveness and response to treatment will be conditioned by these oncogenes.^{13,14} Within the scope of the current review, only the constitutional genes present in all somatic cells will be examined.

High-penetrance genes^{15–20}—The relative risks (RR) among first-degree relatives of a patient with BC are 1.2–4.0 compared to expected population-based.¹⁵ Also relative risk in dizygotic twins reaches RR = 1.7 (95% CI: 0.4–6.9) and in monozygotic ones RR = 6.6 (95% CI: 2.6–16.9).¹⁶ However, familial cancer syndromes with a high risk of BC are rare and constitute 1% of all BC. They are characterized by diagnosis at 50 years of age and being carriers of high penetrance genes. BC takes a secondary place in these hereditary cancer syndromes, predominating neoplasms of the other locations. We briefly describe the most important.^{15–20}

Hereditary nonpolyposis colorectal cancer syndrome: Caused by germline mutations in MLH1, MSH2, MSH6 and PMS2 mismatch repair genes. The predominant locations of urothelial cancers are renal pelvis and ureter; the vesical locations are less common.

Lynch syndrome is a hereditary nonpolyposis colorectal cancer caused by germline mutation MSH2 mismatch repair gene located on the short arm of chromosome 2 (bands p22–p21). In males, the likelihood of developing BC before the age of 70 years is 4.2 times higher than in females. Furthermore, first-degree relative carriers of this mutation have a risk 7 times higher than expected, having or not having BC.^{15,16}

Hereditary retinoblastoma¹⁹: Caused by mutations in gene encoding RB, which is located in the long arm of chromosome 13 (band q14). The most common varieties are: bilateral and multifocal retinoblastoma in early childhood. Among the second tumors, multiple osteosarcomas and soft tissue sarcomas are the most common. BC development is more frequent in this syndrome than in hereditary nonpolyposis colorectal cancer syndrome. Initially, the development of second tumors was related to radiotherapy (and/or chemotherapy) treatment for BC. However, risk of BC mortality in patients only undergoing enucleation is higher than expected (OR = 26.3; 95% CI: 8.5–61.4).

Costello syndrome²⁰: Caused by germline mutations in HRAS gene, located in the short arm of chromosome 11 (band p13.3). HRAS gene encodes small GTP-binding proteins superfamily. It is a rare autosomal dominant disorder characterized by multiple congenital anomalies. Patients with Costello syndrome have greater predisposition to rhabdomyosarcoma, neuroblastoma and BC.

Apert syndrome¹⁸: Caused by germline mutations in FGFR2 gene, which is located in the long arm of chromosome 10 (band q25–26). Apert syndrome, one of eight craniosynostosis

syndromes and it is associated with multiple congenital anomalies greater predisposition to develop BC.

Germline mutations in CDC91L1^{15,18}: This gene is located in long arm of chromosome 20 (band q11.22), that encodes and regulates expression of phosphatidylinositol glycan class U, that is critical in cell cycle regulation and synchronization. This mutation has also been identified in tumor cells from patients without somatic germline mutation.

Genetic polymorphism in the metabolism of carcinogens^{4,5,10,11,21–26}

Acetylator genes^{4,10,21–23}: N-acetylation is the major metabolic pathway in the human body involved in neutralizing and detoxifying carcinogenic chemicals. Acetylated metabolites are rapidly excreted in urine before being N-oxidized in reactive forms. In human, genes encoding N-acetyltransferase (NAT) are polymorphics. Patients homozygous for the mutated NAT2 gene, located on the short arm of chromosome 8 (band p22), have reduced ability to neutralize and remove carcinogens. NAT2 gene is mutated in 50% of Caucasian, 30% of African Americans and Africans and 15% of Asians. NAT2 carriers have 40% higher risk to develop BC. In smokers, the risk increases due to 4-aminobiphenyls and 2-naftalamina exposure. Both are carcinogens present in cigarette smoke and are detoxified via NAT. Similarly, the risk for developing BC in NAT2 carriers occupationally exposed to aromatic amines (AA) and benzidine is higher than that for non-carriers workers.^{4,5,21}

Glutathione-S-transferase genes^{5,22–24}: GSTM-1 gene, located in the short arm of chromosome 1 (band p13.3), encodes the enzyme Glutathione S-transferases-M1. This enzyme is involved in the detoxification of carcinogens, including polycyclic aromatic hydrocarbons (PAHs) and reactive oxygen species, by conjugation with glutathione. 50% of caucasian population have homozygous deletion of the GSTM-1 gene (GSTM1 null genotype) which is a polymorphism associated with loss of enzyme activity. Several meta-analysis have proposed that GSTM1 null genotypes are associated with BC elevated incidences.^{4,5,21} In a study conducted in Spain on GSTM1 null genotypes it was demonstrated that BC risk between smokers and non-smokers is similar, suggesting that the GSTM1 activity protects equally against tobacco-related and non-tobacco-related BC.²² Probably, different detoxification mechanisms might come into play to protect against cigarette smoke PAHs.^{22,23} Another way of action of GSTM1 is the oxidative damage protection against oxygen free radicals. Other genes of GST family, GSTT1 and GSTP1, have been evaluated with inconsistent results.^{4,5,23,24}

Cytochrome P-450 group genes^{4,5,23}: Cytochrome P-450-1A2 gene (CYP1A2), located in the long arm of chromosome 15, q24.1, plays an important role in activation of numerous AA metabolic pathways, N-oxidation and N-hydroxylation. BC induced by exposure to AA compounds shows variable susceptibility, depending on the individual levels of CYP1A2. However, the influence of CYP1A2 population polymorphism in the risk of BC is unclear. Likewise, other CYP polymorphisms (CYP1A1, CYP1B1, CYP2C19, CYP2D6 and CYP2E1) have shown inconsistent results regarding the risk with BC, although theoretically they are involved in the enzymatic activation of AA.

Cyclooxygenase-2 gene: Evidences for involvement of Cyclooxygenase-2 gene (COX2) polymorphisms in some forms of bladder carcinogenesis associated with chronic inflammations have been recently published.²⁶ Underlying mechanism resides in COX 2 gene (chromosome 1, bands q25.2–q25.3) intervention in the synthesis of prostaglandins, which regulate and modulate acute and chronic inflammatory responses.

DNA repair genes^{4,25}: The major repair pathway is the excision repair of nucleotides that efficiently repair the adducts caused by environmental PAHs and AA. Epidemiological studies suggest that DNA repair polymorphisms affect the risk of BC.

Excision repair of secondary bases caused by alkylating and oxidants agents exposure is another pathway in which genetic polymorphisms may modify the risk of BC. In addition, the repair of double helix breaks is an important pathway for the maintenance of genetic stability and integrity. The relationship between them and BC associated risk have been evaluated with promising results; however, this result requires the higher statistical confirmation.

Other genetic susceptibility factors^{4,5}—The DNA damage is higher in lymphocyte cultures from patients with BC exposed to carcinogens than in control healthy lymphocyte cultures, after exposure to different PAHs and AA compounds.⁴

Telomerase length as example of genetic stability has also been studied. Some studies suggest that shorter telomerase carriers have increased risk of BC than longer ones.^{4,5}

Occupational factors^{4,5,10,11,21,27–40}

Occupational exposures were up-to 20–25% of the total BC cases in some industrialized countries, at the end of XXth century, but thanks to the new labor legislation developed in last decades the percentage has been reduced to 5–10%.^{27,28} Unfortunately, production transfer to underdeveloped countries will increase BC cases in them.

Occupational carcinogens identification potentially associated to BC is difficult for: (a) multiple exposures to complex mixtures of toxic, mutagenic and carcinogenic compounds; (b) long latency periods; and (c) genetic polymorphisms influence in BCs. Although many carcinogens associated with an increase risk of BC have been identified, professions associated with high risk of BC in which carcinogens identification has not been possible still remains. In Table 2, human carcinogens associated to BC and BC-related occupational exposures are listed according to documented scientific evidence.^{5,27–31} AA are the major group of carcinogens associated to BC from occupational exposure to them.³²

Aromatic amines exposure^{4,10,21,27,32}

The link between AA and increased risk of BC was first described in 1895 by Ludwig Rehn, a German physician who reported numerous cases of bladder cancer with workers of dye factories, relating it with aniline compounds. In 1954, Case et al. documented for workers in dye industry of England and Wales BC mortality rates from 10 to 50 times higher than expected, discarding aniline and identifying as responsible for this mortality rate 2AA: 2-

naphthylamine and benzidine. Subsequently, other AA have been identified: 4-aminobiphenyl, 4-chloro-o-toluidine and 4,4'-methylenebis (2-chloroaniline). AA exposure is ubiquitous in many industrial and agricultural activities, as well as in cigarette smoke. AA are used as antioxidants in the rubber production, industrial oils, manufacturing of azo dyes (magenta or Fuchsin, auramine) and pesticides. AA may be found in many professional environments including chemical, metallurgical, mechanical, textile, petrochemical industries, etc.

Numerous epidemiological studies convincingly demonstrate the relationship between occupational exposures and increased risk of BC, and document the following findings: (a) direct relationship between tumor mortality and long-term occupational exposure; (b) risk reduction after the ban of using 2-naphthylamine and benzidine; (c) estimated mean of the exposure-to-death time is 25 years (with limits between 12 and 41 years); (d) inverse relationship between exposure and observed risk, being higher for workers who started work before age 15 years than later; (e) negative trend in risk with increasing years since last exposure; (f) the pathways of penetration are transdermal and respiratory route; (g) increased risk in carriers of vulnerable polymorphisms; and (h) higher risk in smokers associated with the presence of AA and other carcinogens in cigarette smoke.

Besides chemical industries of dyes, paints and colorings, other occupations with exposure to AA have been described. Among them are the following.

Aluminum production—In aluminum refineries, volatile organic compounds (VOCs) are emitted as by-product of electrolytic reduction processes, highlighting the presence of 2-naphthylamine, 4-aminobiphenyl and nitro-PAHs. Relative risk increases in proportion to the time worked (RR = 1.2:1 year; 1.9:1–9 years; 3.0:10–19 years; 3.2:20–29 years and 4.5: 30 years of job experience).³³

Rubber industry—Risk is associated with the use of 2-naphthylamine as an anti-oxidant, both in rubber and electric cables manufacturing. BC incidence has decreased dramatically with the prohibition and substitution of 2-naphthylamine as antioxidant.^{29,31}

Leather workers—Although not unanimous, most epidemiological studies document increased risks of BC in workers exposed to leather dust (RR between 1.4 and 1.6). Although their relationship to toxic exposure is unknown, risk of BC is significantly related to prior exposure to leather dust. Exposure takes place in leather production, cutting and assembly processes, including fur trade, leather industry, shoe manufacturing and repair. Leather workers are also exposed to dyes, glues, solvents and intermediate reactants.^{27,28}

Painters—Most authors found risk rates 20–50% higher than expected. In workers with more than 20 years exposure the RR reaches up to 4.1. Benzidine, polychlorinated biphenyls, dioxane and methylene chloride are some of carcinogens associated with this occupation.³⁴

Hairdressers and barbers—In 1994, the International Agency for Research on Cancer classified occupational exposure for hairdressers and barbers as “carcinogenic to humans”

(2A). Hair dyes contain AA, aromatic nitrous compounds, high molecular weight complexes, minerals and other chemicals. A meta-analysis including 42 studies reported a relative risk statistically significant (1.25–1.70 for hairdressers in jobs held 10 years). Because of the long latency times of bladder cancer it remains an open question whether hairdressers working after 1980, when some AA were banned as hair dye ingredients, have the same risk for bladder cancer.⁴⁰

Exposure to polycyclic aromatic hydrocarbons^{5,27,35–37}

PAHs are produced as byproducts of biomass incomplete burning or pyrolysis and of fossil fuels extraction, processing and consumption. Among the 15 PAH compounds classified as probable human carcinogens, benzo[a]anthracene, benzo[a]pyrene and dibenzo[a,h]anthracene have shown strong evidence of association to BC. Occupational exposures to high, medium and low concentrations are associated with increased risks of BC. In aluminum manufacturing, workers are exposed to aggregate emissions of PAHs and AA. In addition to the PAHs, workers in the metallurgical industry are exposed to very large number of chemical pollutants by inhalation, dermal and mucosal route as: various mixtures of oils, lubricants, coolants, heavy metal particles, numerous combustion gases, etc. Exposures levels are dependent on the type of industry, the specific type of work performed there, the duration of employment, collective and individual safety requirements regulated by law in each country. Routes of exposure are inhalation and skin absorption. In some industries, benzo[a]pyrene concentrations reach up to 100 g/m³, while in the ambient air they are about ng/m³. The coal mining, the conversion of coal to gas, coke and coal tar, the tar distillation, paving, the use of creosote as a wood preservative, the calcium carbide production, the soot workers, petroleum refineries and thermoelectric plants are other occupations with exposures to PAHs. The risk of BC is increased for exposures to tar (including production and use) and is dependent on the application temperature and the duration of employment. Professional activities related to diesel engines have low levels of exposure to PAHs; the more hazardous among them are: truck, bus and taxi drivers and diesel engine mechanics.

Other occupational exposures^{4,27,31,39}

Environmental smoke and snuff manufacturing—A epidemiological study covering 15 million of people in Nordic countries and during a follow-up period of 45 years, analyzed cancer incidence data regarding occupational category.³⁹ The highest incidences among men were observed in waiters (RR = 1.50, 95% CI: 1.32–1.69), while among women they were found in tobacco workers (RR = 2.01, 95% CI: 1.49–2.65). Environmental cigarette smoke contains more than 4000 different chemicals of which 69 have been classified as carcinogenic to humans, including AA and PAHs.

Other occupations^{27,30,31}—Increased risks for developing BC for workers exposed to chlorinated hydrocarbons (perchloroethylene, trichloroethylene and tetrachloroethylene) in dry cleaners and laundries have been reported.

This increased risk has also been observed in explosives manufacturers, firefighters, carpenters, railwaymen, clergy, butchers, cooks, food processors, gas stations employees,

health workers, welders, glassmakers, night watchmen, sailors, plumbers, and in drink, asbestos and automotive industries workers.

Protective occupations

Finally, the study conducted in Nordic countries revealed significantly lower risks of BC among farmers, foresters and gardeners, in males; and farmers and gardeners, in females.³⁹

Final remarks

The multifactorial character, the current lack of knowledge and the long latency periods in bladder carcinogenesis may explain the conflicting results and the limited statistical consistency in the majority of epidemiological studies reviewed. Future progress in molecular biology, in genetic and epigenetic aspects (morphological and functional) will reveal the underlying mechanisms in ethnic, general and geographical differences observed in BC. Occupational legislation and industrial technology, which have reduced the incidence of BC in Western countries, must be transferred to developing countries. Finally, the urologists should recommend changes to safer jobs to patients diagnosed of BC working in jobs with high-risk exposures.

Acknowledgments

The authors acknowledge Dña. Pilar Martín Lozano, National Library of Health Sciences, Institute of Health Carlos III of Madrid, for her collaboration in obtaining bibliography.

Financing

This review has been made possible by funding and assistance from: (a) Scientific Foundation of the AECC (Macape Research Project) and (b) Mount Sinai International Exchange Program for Minority Students (MD001452, National Center on Minority Health and Health Disparities, National Institutes of Health).

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Figure 1.
Estimated incidence and mortality: men and women in the WHO European Region.
(GLOBOCAN).

Source: WHO Europe Region. Available at: <http://globocan.iarc.fr>.

Figure 2.

Estimated incidence, age and mortality-standardized: men and women in Spain. (GLOBOCAN).

Source: GLOBOCAN. Spain. Available at: <http://globocan.iarc.fr>.

Figure 3.

Age-Standardized Bladder Urothelium Cancer Estimated Incidence Rates per 100,000 men and World countries.

Source: GLOBOCAN. World Area for Countries. Available at: <http://globocan.iarc.fr>.

Figure 4.

Standardized Bladder Cancer Estimated Incidence Rates by sex and World countries.

Source: GLOBOCAN. World Area for Regions. Available at: <http://globocan.iarc.fr>.

Table 1

Estimated incidence, mortality and prevalence at 5 years, men and women.

Cancer	Incidence		Mortality		5-year prevalence	
	Number	(%) ASR (W)	Number	(%) ASR (W)	Number	(%) Prop.
<i>WHO Europe region: male</i>						
Bladder	112,819	6.2	16.5	42,323	4.1	5.7
						364,851
						8.3
						104.2
<i>WHO Europe region: female</i>						
Bladder	30,736	1.9	3.1	13,266	1.6	1.1
						98,587
						2.2
						25.7
<i>Spain: male</i>						
Bladder	11,227	9.4	27.7	3969	6.0	8.3
						38,597
						12.7
						208.0
<i>Spain: female</i>						
Bladder	1781	2.3	3.2	851	2.2	1.1
						5978
						2.6
						30.8

Source: GLOBOCAN. WHO European Region and Spain. Available at: <http://globocan.iarc.fr>.

Incidence and mortality data for all ages. Prevalence at 5 years for adults only. Age-standardized rate and ratios per 100,000.

Table 2

List of human carcinogens and occupational exposures associated with bladder cancer associated with varying degrees of scientific evidence.

<i>Exposures and agents with sufficient evidence</i>	
Aluminum industry	Coal gasification
4-aminobiphenyl	Production of auramine
Arsenic and organic compounds	Benzidine
Chlornaphazine	Cyclophosphamide
Magenta production	2-Naphthylamine
Industrial production of rubber	Schistosoma haematobium
Cigarette consumption	Ortho-toluidine
Production and professional use of paints	Ionizing radiation
Cyclophosphamide	Ifosfamide
<i>Agents and exposures with limited evidence</i>	
4-Chloro-ortho-toluidine	Benzo[a]anthracene
Coal-tar pitch	Benzo[a]pyrene
Coffee	Dibenzo[a,h]anthracene
Dry-cleaning	Benzidine derivatives
Emissions from diesel engines	Coke production
Hairdressers and barbers	Metilene 4,4'-bis (2-chloroaniline)
Typography and printing processes	Mineral oils
Soot handling	Oil refineries
Textile industry	Tetrachloroethylene
Shoes manufacturing and repair	

Source: Kogevinas et al.,⁵ International Agency for Research on Cancer,²⁷ Weiderpass et al.,²⁸ Siemiatycki et al.,²⁹ Kiriluk et al.,³⁰ and Golka et al.³¹