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REVIEW PAPER

GENE-OCCUPATION INTERACTIONS: A REVIEW OF THE LITERATURE ON BLADDER AND PROSTATE CANCER

Edyta Wieczorek[1], Anna Wolniakowska[1], Joanna Roszak[1], Robim M. Rodrigues[2], Tamara Vanhaecke[2], Edyta Reszka[1]

[1] Nofer Institute of Occupational Medicine, Łódź, Poland
Department of Translational Research

[2] Vrije Universiteit Brussel, Brussels, Belgium
Faculty of Medicine and Pharmacy, Department of In Vitro Toxicology and Dermato-Cosmetology

Abstract

Bladder cancer (BCa) and prostate cancer (PCa) are genitourinary cancers which constitute significant health problems in men and in which environmental factors play an important role. Understanding the genetic susceptibility to BCa or PCa and occupational exposure is paramount to improving cancer prevention and early detection. The aim of this review article was to address the scientific evidence on the genetic risk factors and occupational exposure associated with the occurrence of BCa and PCa. The authors identified relevant original articles that have been published between 1994 and 2023. Variations of the following search terms: "gene" and "occupational" combined with one of the following terms: "bladder cancer" or "prostate cancer" were applied for the search purpose. The authors found 342 publications of which 50 population studies met their requirements for gene-occupation interactions. In total, 34 full-text manuscripts were about BCa and 16 about PCa. These research examines the genes involved in detoxification processes of xenobiotics (glutathione S-transferase, N-acetyltransferase, cytochrome P450, UDP-glucuronosyltransferase), oxidative stress (glutathione peroxidase 1, manganese superoxide dismutase, catalase), altering DNA repair capacity (X-ray repair cross-complementing 1, base excision repair, nucleotide excision repair), tumour suppression (*TP53* gene), and vitamin D pathway (vitamin D receptor gene). The role of genetic factors in the occupational exposure has not been conclusively established, but it appears the possibility of genetic involvement. Determination of environmentally responsive genes provides important mechanistic implications for the etiology of occupational cancers, and valuable input in occupational exposure limits set by taking genetic susceptibility into account. More genetic research is needed to corroborate these findings and assess their significance in the workplace.
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Key words: bladder cancer, gene, genetic susceptibility, occupational exposure, prostate cancer, workplace

Corresponding author: Edyta Wieczorek, Nofer Institute of Occupational Medicine, Department of Translational Research, św. Teresy 8, 91-348 Łódź, Poland, e-mail: Edyta.Wieczorek@imp.lodz.pl
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INTRODUCTION

Bladder cancer (BCa) and prostate cancer (PCa) are genitourinary cancers, which are among the most commonly diagnosed cancers in men. The BCa was the ninth most common cancer in 2020 in the world and the one with the highest recurrence rates among all cancers. The authors observed male predominance all over the world (Figure 1). The BCa is the fourth in Europe and fifth in the world most common cancer in men. The highest worldwide incidence rates are observed in Southern Europe, Western Europe, Northern America, Central and Eastern Europe, Northern Africa, and Western Asia. In turn, mortality rates are greater, especially in Northern Africa, Central and Eastern Europe, as well as Western Asia [1]. The PCa is a heterogeneous disease with variable clinical outcomes. The PCa affects only men and ranks first and second among cancer incidence in Europe and the world, respectively (Figure 2).

The BCa and PCa were respectively the tenth and the fourth most common causes of cancer-related mortality among men worldwide in 2020 [2]. There are

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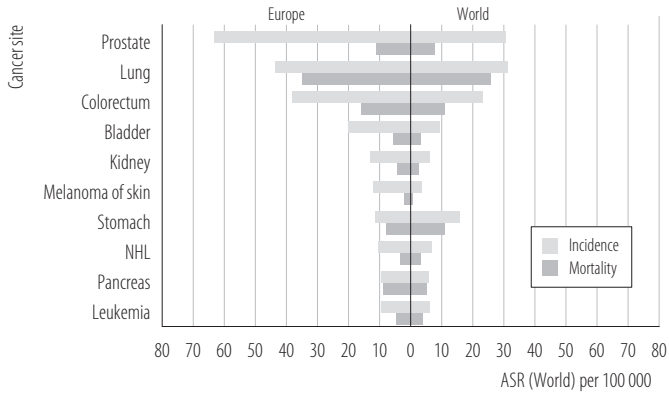
ASR – age-standardized rate.
Data source: Globocan 2020 Graph production: Global Cancer Observatory [78].

Figure 1. Estimated age-standardized incidence rates (World) in 2020, bladder, all of ages



ASR – age-standardized rate, NHL – non-Hodgkin lymphoma.
Data source: Globocan 2020 Graph production: Global Cancer Observatory [79].

Figure 2. Estimated age-standardized incidence and mortality rates (World) in 2020, males, all of ages (excluding nonmelanoma skin cancer)

2 common types of BCa. The first, which is called non–muscle-invasive BCa occurs in approx. 75% of patients. It is characterized by non-aggressive natural history, has good prognosis, and can be treated locally. The second one, called muscle-invasive BCa, occurs in approx. 25% of patients and is often treated with cystectomy. The PCa has symptoms ranging from small indolent low-grade tumours, to large aggressive life-threatening tumours [3]. To estimate the prognosis and decide on the treatment of PCa, clinical factors such as tumour stage, diagnostic prostate-specific antigen (PSA) levels and biopsy Gleason score [4] are used.

The primary risk factors for BCa include male gender, advanced age, tobacco smoking and chemical carcinogens from occupational exposure and general environment [5]. For BCa the attributable risk for occupational carcinogen exposure history alone is 5–8% [6,7]. In the case of PCa, the major known risk factors include advanced age, ethnicity, family history and lifestyle (diet, physical activity, cigarette smoking) [8]. For many years researchers have been investigating the association between occupational exposure and the risk of developing cancers. Multiple studies show evidence of an association between the development of BCa and PCa and occupational exposure to carcinogens classified as Group 1 by the International Agency for Research on Cancer (IARC) such as trichloroethylene and benzidine. A potential association has also been described for exposure to carcinogenic agents classified as Group 2A – perchloroethylene, and other industrial chemicals such as aromatic hydrocarbon solvents, arylamines, aromatic amines, polycyclic aromatic hydrocarbons, diesel exhaust, chlorinated hydrocarbons and toluene [9,10]. Due to the differences between the incidence of the disease in individual employees with the same exposure, other factors, including their genetic background, might also influence the risk of developing BCa or PCa. Therefore, genetic testing of the workers constituted the next step of the evaluation of the risk of BCa and PCa among exposed workers. There is evidence that the kind and rate of enzyme metabolism participating in the detoxification processes of xenobiotics are determined by genetic polymorphisms. Genetic susceptibility to occupational exposure may be one of the potential mechanisms of BCa and PCa risks among exposed workers. Despite the described associations between the genotype, exposure and the occurrence of the disease, the results are considered controversial and require further investigation. This review summarizes the current evidence of a genetic role in the BCa or PCa incidence among exposed workers.

METHODS

A comprehensive literature review was performed using PubMed/Medline databases to find articles published until January 2023. The articles considered in the review were obtained by performing a search using the keywords: (gene [Text Word]) AND (occupational [Text Word]) AND (bladder cancer [Text Word]) – 191 manuscripts were found and additionally (gene [Text Word]) AND (occupational [Text Word]) AND (prostate cancer [Text Word]) – 151 manuscripts were found. The authors used the following exclusion criteria: manuscripts not written in English, not about humans, conference abstracts, systematic reviews and meta-analyses. The researchers (E.W. and E.R.) reviewed the abstracts using the exclusion and inclusion criteria

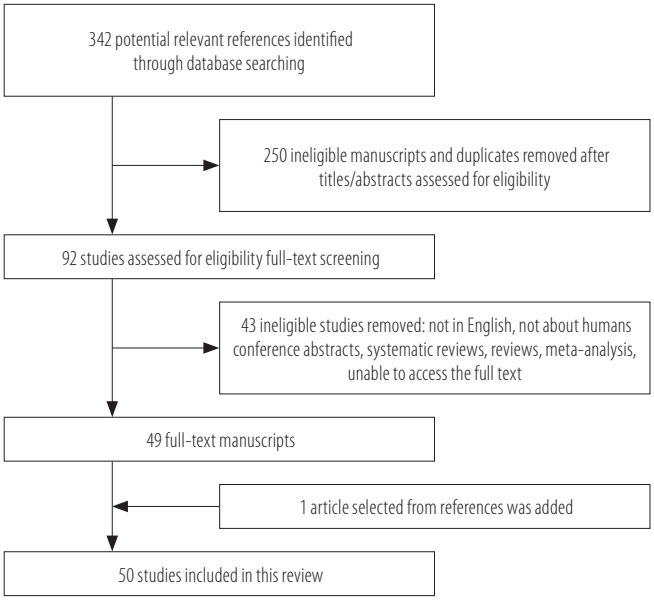


Figure 3. Search diagram for selection of studies included in a critical review of literature from 1994–2023

applied in the review. Finally, the reference lists of the included manuscripts were also searched. The search process has been outlined on Figure 3.

RESULTS

The literature search resulted in the identification of 342 articles, of which 34 full-text manuscripts about BCa and 16 about PCa were included in the review. The collected publications include research conducted using biological material, i.e., genomic DNA isolated from blood (N = 37), buccal cells (N = 7) or tissue samples (formalin-fixed, paraffin-embedded tumors, N = 6) in which genetic polymorphism, copy number variation (CNV), mutations, DNA methylation (DNAm), DNA adducts and telomere length (TL) were examined, determined by the use of methods such as the single strand conformation polymorphism (SSCP) analysis, restriction fragment length polymorphism (RFLP), reverse transcription-polymerase chain reaction (RT-PCR), and genome-wide association studies (GWAS) analyses. The DNA was extracted from buccal cells only in the case of PCa studies and from tissue samples only in the BCa studies.

The first paper on gene-occupational interaction and BCa was published in 1994. The study was conducted among workers from metal and electronic industries and painters exposed to industrial chemicals [11]. Whereas the first PCa case-only study was published in 2001. It was conducted among outdoor workers exposed to ultraviolet (UV) [12]. Publications on BCa were published more often and over a longer period of time (from 1994–2022) than those on PCa. The final number of manuscripts and their publication dates for BCa and PCa, which were selected for this literature review are presented in Figure 4.

The main types of studies were case-control studies, where the study group consisted of employees who were occupationally exposed to toxic or carcinogenic substances. In turn, the control group consisted of healthy people who were not exposed, who could work in similar conditions as the study group, or of people with other occupations. There were also studies in which the control groups were partially exposed to xenobiotics. Among the studies, there was also a case-only study, where all the employees who had been surveyed developed cancer. The group was divided into people who were exposed or the relationship between genetic tests and the type of cancer was examined. The cancer free study concerned healthy employees, where the group of employees was divided into exposed and unexposed employees, in whom genetic polymorphism of genes that could predispose to a selected type of cancer was tested [13–15]. Due to the significant differences in the occurrence of individual genotypes in populations, all the studies took into account differences in population, race or ethnicity so that the study group was homogeneous.

Table 1 summarizes the studies on the gene-occupation interactions and the BCa incidence. In the publications where the BCa incidence was studied, the surveyed

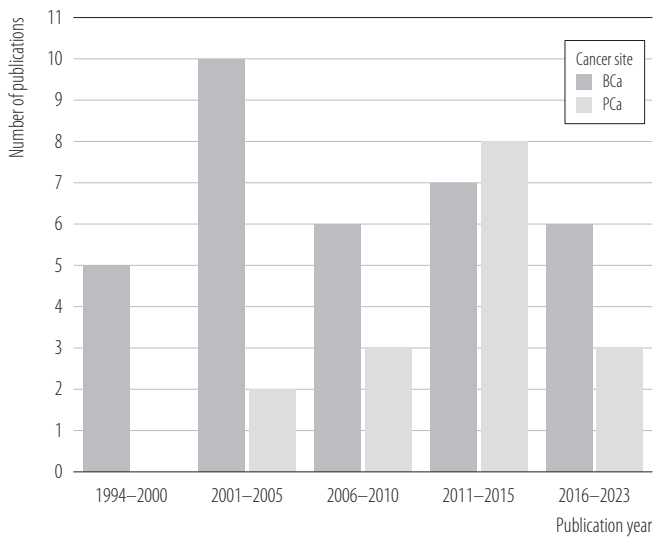


Figure 4. Number of publications on interaction between genes and occupational exposures in bladder cancer (BCa) and prostate cancer (PCa)

employee groups were occupationally exposed to aromatic amines (AAs), azo dyes (AD), asbestos, arylamines including, benzidine and β-naphthylamine, benzidine, combustion fumes, metalworking fluids, organic solvents, pesticides, polycyclic aromatic hydrocarbons (PAHs), chemical carcinogens and hazardous compounds. The group of workers who were exposed mainly to these industrial chemicals included metal/plastic-processing machine operators, fabricators, assemblers, painter, hairdressers, textile workers, leather workers and others working in dyestuff industry, paint industry, printing ink industry, rubber and cable manufacture, vehicle maintenance, repair, plumbing and road transportation. Among these employees the genetic research mainly involved genes important in tumour suppression, xenobiotics metabolism altered DNA repair capacity and BCa-related genes. Gender was considered as one of the risk factors for the incidence of BCa. As many as 7 of 28 publications concerned groups of male employees [16–22] and only 1 study concerned women [13]. The remaining studies were conducted taking into account both genders. Exposure to pesticides, PAHs, Pb, Cd, UV, asbestos and hazardous chemicals predominated in the PCa studies. The main role in the research was played by the nested case-control and Agricultural Health Study (AHS) cohorts of farmers and agricultural workers, which were used for the research several times over the years by various groups of researchers. The cohorts consisted entirely of Caucasian race (Table 1).

Multiple carcinogenic agents with sufficient evidence or limited evidence in human cancers have been described by IARC. These agents also appeared as occupational carcinogens in the production of aluminium, auramine, magenta, firefighting, painting, rubber manufacturing, and sufficient evidence for association with BCa could be shown. The agents with limited evidence of BCa in humans included: 4-chloro-ortho-toluidine, 2-mercaptobenzothiazole, pioglitazone, tetrachloroethylene. In the case of PCa, limited evidence for arsenic and inorganic arsenic compounds, cadmium and cadmium compounds, thorium-232 and its decay products, X- and γ-radiation was indicated.

Occupational exposure in dry cleaning, exposure to engine exhaust, diesel, in the professions of hairdresser or barber, in printing processes, occupational exposure of chimney sweepers to soot and the textile manufacturing industry showed limited evidence of BCa, whereas working as a firefighter, working in a rubber manufacturing industry of PCa [23].

Farming entails a way of life with occupational exposure to various agents which it is difficult to separate into individual components. Different observations between excess risks among American farmers may reflect lifestyle or farming practices. There is some evidence that fat consumption and chemical contaminants in fat, especially organochlorines from pesticides and herbicides, may modulate the androgenic hormones action [24]. Nested case-control and AHS cohorts exposed to various pesticides have been particularly well studied in terms of genetic susceptibility to PCa [13–19]. The most diverse number of types of pesticides was included in the analyses by Koutros et al. [25]. They collected data on up to 49 pesticides such as organophosphate insecticides (coumaphos, terbufos, fonofos and phorate), and pyrethroid insecticide (permethrin).

Schroeder et al. [26], in the group of occupations carrying a risk of cancer included a gasoline station attendant, automobile mechanic, gasoline station attendant, farmer, truck, bus, and taxi drivers. These occupational groups are exposed to, among others, cutting or lubricating oils, paint thinner or stripper, organic solvents, welding or soldering materials, soot, pesticides or insecticides. In another study, Nasr et al. [27], as risk occupations included frame works such as hairdressers, truck or bus drivers, roofers, chimney sweepers, truck drivers, tar and asphalt workers, brickyard workers, blacksmiths as well as work in various types of industry: paint, printing ink industries, rubber and cable manufacture, textile and leather works, aluminum industry, gas industry [27]. Ben Fradj et al. [28] took into account the effect of working in construction, painting, vehicles maintenance, repair, plumbing, road transportation as well as air-conditioning, farming or gardening and mining on occupational disease risk.

Some works used general terms related to the type of hazard that existed in the working environment, i.e., carcinogenic substances, chemical carcinogens or hazardous compounds. Therefore, it can be suspected that some of the study groups included workers with a wide range of exposure.

Depending on the research hypothesis, the importance of different genes was assessed. The studies were linked in particular to genetic polymorphisms of genes involved in 1) detoxification processes of xenobiotics, 2) oxidative stress, 3) altering DNA repair capacity, 4) tumour suppression, and 5) vitamin D pathway genes.

Table 1. Gene-occupation interactions and bladder (BCa) or prostate cancer (PCa) in a population study – a critical review of literature from 1994–2023

Occupational exposure	Workplace/Worker	Gene function	Type of molecular marker/ Gene name	Cohort/ Population/Race/ Ethnicity[a]	Study type/ Number of samples	Association result	Reference
Bladder cancer							
AAs	risk occupations	tumor suppression	mutations: *PTEN* gene exons 1,2,4,5	Iranian males (100%)	case-control 55/66	association with increased BCa risk and occupational exposure	Mashhadi et al., 2014 [16]
	hairdressers, paint industry, printing ink industry, rubber and cable manufacture, textile and leather works or other	xenobiotics metabolism	10 SNPs: *NAT2 C282T, G191A, A434C, C481T, T111C, G590A, C759T, G857A, T341C, A803G*	Lebanese (100%)	case-control 115/306	association with increased BCa risk and AAs exposure; no direct relationship between BCa risk and genes	Nasr et al., 2017 [27]
AAs, hair dye	hairdressers	xenobiotics metabolism, BCa-related genes	9 DNAm, TL: *APC, DAPK1, GSTP1, MGMT, TWIST1, CDKN2A, RASSF1A, POU4F2, RUNX3*	Southern Sweden females (100%)	cancer-free 295/92[c]	association with exposure and *CDKN2A* DNAm and shorter telomeres	Li et al., 2016 [13]
AAs, PAHs	occupationally exposed to chemicals	DNA repair genes	Genotypes: *XRCC1 Arg399Gln, XRCC3 Thr241Met, XPD Lys751Gln*	Italian males (100%)	case-control 201/214	association with reduced BCa risk and *XRCC3* codon 241; no direct relationship between BCa risk and genes and exposure	Shen et al., 2003 [17]
	risk occupations	xenobiotics metabolism	2 SNPs: *CYP1A2 -2467T/delT rs35694136, -163C/Ars762551*	Caucasian males (100%)	case-control 185/180	no direct relationship between BCa risk, gene and exposure	Pavanello et al., 2010 [18]
		xenobiotics metabolism, oxidative stress	Genotypes: *GSTM1, GSTT1, GSTP1, NAT1, NAT2, SULT1A1, XRCC1-3, XPD, CYP1A2, MPO, COMT, MnSOD, NQO1*, DNA adducts		case-control 199/213	association with BCa risk and DNA adducts; DNA adducts and exposure; BCa risk and DNA adducts and exposure	Porru et al., 2014 [29]
	occupationally exposed to BCa carcinogens	xenobiotics metabolism	SNP: *UGT1A* rs11892031	IfADo: Caucasian majority (85%)	case-control 1805/2141	association with BCa risk and *rs11892031*; BCa risk, AAs, PAHs and *rs11892031*	Selinski et al., 2012 [44]
AAs, PAHs, AD	occupationally exposed to BCa carcinogens	pathogenesis of cancer	SNPs: *IGFBP3 rs2854744*		case-control 1450/1725	no direct relationship between BCa risk, gene and exposure	Selinski et al., 2012 [69]
asbestos	construction, shipyard or other	tumor suppression	mutation: *TP53*	Finland (100%)	case-control 28/28[b]	association with increased BCa risk and exposure; no direct relationship between BCa risk, genes and exposure	Kannio et al., 1996 [56]
arylamines: benzidine, β-naphthylamine	risk occupations	tumor suppression	mutations: *p53* exons 4-8	white males (100%)	case-only 34/30[c]	no direct relationship between gene and exposure	Taylor et al., 1996 [19]

Table 1. Gene-occupation interactions and bladder (BCa) or prostate cancer (PCa) in a population study – a critical review of literature from 1994–2023 – cont.

Occupational exposure	Workplace/Worker	Gene function	Type of molecular marker/ Gene name	Cohort/ Population/Race/ Ethnicity[a]	Study type/ Number of samples	Association result	Reference
Bladder cancer – cont.							
benzidine	dyestuff industry	xenobiotics metabolism	genotypes: *GSTM1, GSTT1*	Chinese majority (93%)	case-only 317	no direct relationship between BCa grade, genes and exposure	Lin et al., 2001 [30]
		xenobiotics metabolism	genotypes: *GSTT1, GSTM1, GSTP1-A1578G, -C2293T*		case-control 61/499	no direct relationship between BCa risk, genes and exposure	Ma et al., 2002 [31]
		xenobiotics metabolism	SNP: *UGT2B7*		case-control 36/469	association with increased BCa risk, *UGT2B7 C802T* and exposure	Lin et al., 2005 [45]
		xenobiotics metabolism	genotypes: *NAT1 T1088A, C1095A, G560A*	Chinese (100%)	case-control 38/214	no direct relationship between BCa risk, gene and exposure	Guo et al., 2004 [39]
		xenobiotics metabolism	genotypes: *NAT2 G191A, C282T, T341C, C481T, G590A, A803G, G857A*		case-control 61/112	no direct relationship between BCa risk, gene and exposure	Ma et al., 2004 [40]
chemical carcinogens	building, painting, vehicles maintenance, repair, plumbing, road transportation and other	vitamin D pathway	SNP: *VDR FokI rs10735810*	Tunisian (100%)	case-control 200/200	association with increased BCa risk, chemical carcinogens and *VDR FokI ff*	Ben Fradj et al., 2016 [28]
	rubber and plastics industry, laboratories, printing, paints, dyes or diesel fumes	DNA repair capacity	genotypes: *XPC-PAT, Lys939Gln, IVS11-6*	white majority (98%)	case-control 547/579	no direct relationship between BCa risk, genes and exposure	Sak et al., 2005 [49]
	risk occupations	xenobiotics metabolism	genotypes: *GSTT1, GSTM1*	Spanish (100%)	case-control 208/208	association with increased BCa risk and *GSTM1* null or both null; no direct relationship with genes and exposure	Salinas-Sánchez et al., 2011 [32]
combustion fumes	risk occupations	xenobiotics metabolism	9 SNPs: *NAT1*	Lebanese males (100%)	case-control 54/105	association with increased BCa risk, occupational exposure to combustion fumes and *NAT1*	Yassine et al., 2012 [20]
hazardous compounds	rubber, plastics, labs, printing, dyes, diesel	DNA double strand break signaling	24 SNPs: *MRE11, NBS1, RAD50, H2AX, ATM*	Caucasian majority (92%)	case-control 771/800[c]	association with increased BCa risk, dye exposure; increased BCA risk, dye exposure and *MRE11* rs2155209	Choudhury et al., 2008 [70]

	risk occupations	xenobiotics metabolism	11 SNPs: *NAT1, NAT2*	Caucasian (100%)	case-control 425/343	association with decreased BCa risk, occupational exposure, *NAT1* and *NAT2*	Cascorbi et al., 2001 [42]
	risk occupations	xenobiotics metabolism	13 genotypes: *NAT2, mEH, GSTM1, GSTT1, CYP1A1, CYP2C19, CYP2D6, CYP2E1*		case-control 374/373	association with increased BCa risk, occupational exposure, *NAT2* and *GSTM1*	Brockmöller et al., 1996 [33]
	metal/plastic-processing machine operators, fabricators, assemblers and other	tumor suppression	mutation: *TP53*	white (100%)	case-only 330	association with occupations and *TP53* mutation in men	Kelsey et al., 2005 [57]
industrial chemicals	metal and electronic industry worker, painter or other	xenobiotics metabolism	10 SNPs: *GSTM1*	German (100%)	case-control 296/400	association with increased BCa risk and *GSTM1*; BCA risk and occupational exposure; no direct relationship with gene and exposure	Brockmöller et al., 1994 [11]
	rubber/plastics industries, laboratories, printing, paints, dyes, or diesel fumes	DNA repair capacity	22 SNPs: *XPC*	Caucasian majority (98%)	case-control 547/579	association with increased BCa risk and Ala499Val, Ex15-184, Ex15-177; no direct relationship with gene and exposure	Sak et al., 2006 [50]
		DNA repair capacity	14 SNPs: *XRCC1*			no direct relationship between BCa risk, gene and exposure	Sak et al., 2007 [51]
	several patterns of industrial/ occupational classifications	BCa development	GWAS: 6 GWAS patterns for BCa development	East Asian (100%)	case-control 352/434	association with *GLDN*	Takeuchi et al., 2022 [71]
	risk occupations	xenobiotics metabolism	genotypes: *NAT2*	Japanese (100%)	case-control 85/146	association with increased BCa risk and *NAT2*; no direct relationship with gene and exposure	Inatomi et al., 1999 [41]
	occupationally exposed to cutting or lubricating oils, paint thinner, organic solvents, pesticides or other	xenobiotics metabolism	mutations, genotypes: *TP53, GSTM1, NAT1, NAT2*	white majority (92%)	case-control 245/215	association with tumors grade and *p53*-positive; no direct relationship with genes and exposure	Schroeder et al., 2003 [26]
	high-risk occupations	BCa-related genes	SNVs, somatic mutations, mutational signatures: COSMIC signature 1, APOBEC signature 2 and 13 motifs, ERCC2 signature mutation	NEBCAS: white majority (91%)	case-only 241/63[c]	association with high-risk occupation and mutations in cell-cycle pathway genes, *TP53* mutations	Koutros et al., 2021 [58]

Table 1. Gene-occupation interactions and bladder (BCa) or prostate cancer (PCa) in a population study – a critical review of literature from 1994–2023 – cont.

Occupational exposure	Workplace/Worker	Gene function	Type of molecular marker/ Gene name	Cohort/ Population/Race/ Ethnicity[a]	Study type/ Number of samples	Association result	Reference
Bladder cancer – cont.							
metalworking fluids	risk occupations	xenobiotics metabolism	16 SNPs: *UGT1A, TP63, TMEM129-TACC3-FGFR3, TERT-CLPTML, NAT2, PSCA, CCNE1, CBX6-APOBEC3A, SLC14A2, GSTM1, TERC, LSP1- miRNA-4298, CDKAL1*	NEBCAS, SBCAS (100%)	case-control 2258/2410	association with increased BCa risk, occupational exposure and *GSTM1* deletion, *UGT1A rs11892031, TMEM129-TACC3-FGFR3 rs798766*	Figueroa et al., 2015 [34]
organic solvents, pesticides	risk occupations	xenobiotics metabolism	4 SNPs: *GSTA1, GSTM1, GSTP1, GSTT1*	Serbia males (100%)	case-control 143/114	association with increased BCa risk and *GSTM1*; BCa risk and exposure; BCa risk and occupational exposure to solvents and *GSTA1, GSTM1, GSTT1;* occupational exposure and *GSTP1* interaction	Matic et al., 2014 [21]
organophosphates in pesticides	risk occupations	critical DNA target for chemical carcinogens	mutations: K-ras	Egypt (100%)	case-control 100/200	association with increased BCa risk and exposure; BCa risk and K-ras mutation; pesticide exposure and K-ras mutation	Hameed et al., 2018 [72]
PAHs	risk occupations	tumor suppression	mutations: *FGFR3 R248C, S249C, G372C, Y375C, A393E, K652E, K652Q, K652M, K652T*	Caucasian males (100%)	case-only 104/66[c]	association with tumors stage and *FGFR3*; no direct relationship between gene and exposure	Bakkar et al., 2010 [22]
Prostate cancer							
asbestos	asbestos-exposed workers	oxidative stress	SNPs: *MnSOD*, *CAT*, *GPX1*	nested case-control, CARET: Caucasian majority (90%)	case-control 533/1470	PCa risk and *MnSOD Ala16Val, CAT-262 C>T, GPX1 Pro200Leu* and exposure	Choiet al., 2007 [47]
hazardous chemicals	agriculture, livestock, construction, chemical industry	xenobiotics metabolism	CNV: *GSTM1* (xenobiotics metabolism)	Spanish Caucasian (100%)	case-control 158/159	no direct relationship between PCa risk and exposure	Gómez-Martín et al., 2019 [35]
PAHs	occupationally exposed to wood, petroleum, coal or other sources PAHs	xenobiotics metabolism	genotypes: *GSTP1* Ile105Val (xenobiotics metabolism)	white (57%), African-American (43%)	case-control 637/244	association with highest quartile exposure of occupational respiratory PAHs and *GSTP1 Val105*; no direct relationship between PCa risk and *GSTP1 Ile105Val*	Rybicki et al., 2006 [36]
	firefighters	xenobiotics metabolism	DNAm: *GSTP1, IFN-γ, RAD21, DUSP22* (xenobiotics metabolism)	Ohio: white majority (90%)	cancer-free 18/20[c]	association with exposure and *DUSP22* promoter hypomethylation	Ouyang et al., 2012 [14]

Pb	risk occupations	the second step of heme biosynthesis and endogenous inhibitor of the 26S proteasome	11 tag SNPs: *ALAD*	white (57%), black (43%)	case-only 603	association with increased PCa risk and Pb exposure and *ALAD rs818684, rs818689, rs2761016*	Neslund-Dudas et al., 2014 [73]
Pb and Cd	heavy metals-exposed workers and household	physical interaction with heavy metals	SNP: *JAZF1*	African-American (100%)	case-control 228/82	association with increased PCa risk and Pb exposure and *JAZF1 rs10486567 CC*	Neslund-Dudas et al., 2014 [74]
pesticides	farmers, agricultural workers	risk factors for PCa	211 SNPs: 8q24 region variants	nested case-control, AHS: white (100%)	case-control 776/1444	association with increased PCa risk, insecticide exposure and 8q24 *rs4242382, rs7837328*	Koutros et al., 2010 [25]
		xenobiotic metabolizing enzyme pathway	1913 SNPs			association with increased PCa risk and petroleum oil/petroleum distillate or terbufos use and *GCLC rs1883633, TXNRD2 rs4485648, EPHX1 rs17309872, MPO rs11079344*	Koutros et al., 2011 [75]
		repair oxidative damage	394 tag SNPs: 31 *BER*			association with increased PCa risk and fonofos use and *NEIL3 rs1983132 CT/TT*	Barry et al., 2011 [53]
		repair a broad range of DNA damage	324 tag SNPs: 27 *NER*			association with increased PCa risk and fonofos use and *ERCC1 rs2298881 A*, carbofuran use and *CDK7 rs11744596 TT, rs2932778 TT*	Barry et al., 2012 [54]
		PCa susceptibility loci	32 SNPs			association with increased PCa risk and malathion use and *EHBP1 rs2710647 TT*, aldrin use and *TET2 rs7679673 AA*	Koutros et al., 2013 [76]
		vitamin D pathway, xenobiotics metabolism	152 SNPs: *GC, VDR, RXRA, RXRB, CYP24A1, CYP27A1, CYP27B1, MED24, MED16*			association with increased PCa risk and parathion and terbufos use and *VDR, RXRB, GC rs7041 CC*	Karami et al., 2013 [43]
		hormone synthesis, metabolism or regulation, circulating sex steroid concentrations	1117 SNPs			association with reduced PCa risk and dicamba and *SRD5A1 rs8192166 CC*	Christensen et al., 2016 [77]
		tumor and invasion suppressor, DNA protection from electrophilic metabolites of carcinogens and reactive oxygen species, chromosomal instability	DNAm: *CDH1*, *GSTP1*, *MGMT, LINE-1*	AHS: white majority (98%)	cancer-free 142/454[c]	association with exposure and DNAm in *GSTP1* (increased), and in *MGMT* and *LINE-1* (reduced)	Rusiecki et al., 2017 [15]

Table 1. Gene-occupation interactions and bladder (BCa) or prostate cancer (PCa) in a population study – a critical review of literature from 1994–2023 – cont.

Occupational exposure	Workplace/Worker	Gene function	Type of molecular marker/ Gene name	Cohort/ Population/Race/ Ethnicity[a]	Study type/ Number of samples	Association result	Reference
Prostate cancer – cont.							
UV	outdoor working	vitamin D pathway, melanin synthesis	genotypes: *MC1R, VDR, TYR*	northern European Caucasian (100%)	case-only 210	association with increased PCa risk of metastases and *MC1R* Val92/ Val92, *VDR ff*	Luscombe et al., 2001 [12]
		vitamin D pathway	4 SNPs: *VDR* regulatory region: *Cdx-2, FokI, TaqI, BglI*	non-Hispanic White (100%)	case-control 450/455	association with reduced PCa risk, sun exposure and *FokI rs10735810 FF or Ff, TaqI rs731236 tt, BglI BB*	John et al., 2005 [62]

AAs – aromatic amines, AChE – acetylcholinesterase, AD – azo dyes, AHR – aryl hydrocarbon receptor, ALAD – delta-aminolevulinic acid dehydratase, AHS – Agricultural Health Study, BCa – bladder cancer, BER – base excision repair, CARET – β-Carotene and Retinol Efficacy Trial, CDH1 – E-cadherin, CNV – copy number variation, COSMIC – Catalogue Of Somatic Mutations In Cancer, CYP – cytochrome P-450 enzymes, DNAm – DNA methylation, DUSP22 – dual specificity phosphatase 22, EHBP1 – EH domain binding protein 1, EPHX1 – microsomal epoxide hydrolase 1, FGFR3 – fibroblast growth factor receptor 3, GC – group specific component, GCLC – oxidative stress gene glutamate–cysteine ligase, GLDN – gliomedin, GSTs – glutathione S-transferases, GWAS – genome-wide association study, HPEEs – high pesticide exposure events, IfADo – Leibniz Research Centre for Working Environment and Human Factors, IGFBP3 – insulin-like growth factor-binding protein-3, JAZF1 – gene juxtaposed with another zinc finger protein 1, K-ras – Kristen ras, LINE-1 – long interspersed nucleotide element, MED – mediator complex subunit, MGMT – O6-alkylguanine-DNA alkyltransferase, MPO – myeloperoxidase, MTNR1B – melatonin receptor 1B gene, NAT – N-acetyltransferase, NEBCAS – New England Bladder Cancer Study, NER – nucleotide excision repair, PAHs – polycyclic aromatic hydrocarbons, PCa – prostate cancer, Pb – lead, SNP – single-nucleotide polymorphism, SBCAS – Spanish Bladder Cancer Study, SNV – single-nucleotide variants, SRD5A1 – hormone-associated gene Steroid Reductase 5-alpha-1, TL – telomere length, TXNRD2 – thioredoxin reductase 2, VDR – vitamin D receptor, UGT – UDP-glucuronyltransferase, XPC – xeroderma pigmentosum complementation group C, VDR – vitamin D receptor.
[a] In bladder cancer studies both sexes if not indicated, [b] All group exposed, [c] Number of exposed/unexposed.

Genes responsible for detoxification processes of xenobiotics

Both in the BCa and PCa studies, genes encoding enzymes involved in the metabolism of xenobiotics were most often examined. Table 1 shows 18 studies which focused on genes related to xenobiotics metabolism in BCa, while 5 such studies in PCa. Occupational exposure in these studies was related to workers' exposure to various industrial chemicals or chemical carcinogens such as AAs, hair dye, benzidine, combustion fumes, hazardous compounds, organic solvents, PAHs and pesticides.

Glutathione S-transferase

Glutathione S-transferase (GST) is one of the major xenobiotic detoxifying enzymes and one of the most frequently studied genes. The *GST* genes are divided according to similarities between enzymes of amino acid sequences into 7 different families. The GST mu (GST M), pi (GST P), theta (GST T), and alpha (GST A) are particularly important. Homozygous deletion in *GSTM1* or *GSTT1* genes (null genotype) is related to the loss of enzymatic activity. The presence of at least one gene copy of *GSTM1* or *GSTT1* leads to enzymatic activity. The *GSTT1* and *GSTM1* deletion polymorphisms have been associated with numerous diseases including cancers. The *GSTM1* genotype is well documented to be associated with the risk of BCa. Some studies did not show the relationship between occupational exposure to AAs, PAHs or benzidine and the *GSTM1* genotype and the incidence of cancer in different populations [11,26,29–32]. However, the relationship between an increased BCa risk, *GSTM1* genotype and occupational exposure to hazardous compounds [33] or metalworking fluids [34] in Caucasian population, or occupational exposure and exposure to solvents in Serbia men [21] was shown. Four studies examined the genotypes *GSTP1* such as *-A1578G, -C2293T* in different populations [13,21,29,31]. Only 1 of them indicated a significant interaction with the *GSTP1* genotype and occupational exposure [21]. The *GSTT1* studies were conducted in employees such as workers of dye stuff industry and other risk occupations where AAs, PAHs, benzidine, organic solvents, pesticides, hazardous compounds and other chemical carcinogens are used. Regardless of the tested population or occupational exposure of workers, no direct relationship with the BCa risk, genes and exposurewas shown [29–33]. Only 1 study indicated a significant relationship with the BCa risk and *GSTT1* genotype

and solvents exposure but not with pesticides exposure [21]. Only 1 study reported results related to *GSTA1* genotype. The result showed an association between this gene, the BCa risk and occupational exposure [21]. Among the cases of PCa, an association with genetic polymorphism in genes *GSTM1*, *GSTP1* and occupational exposure to hazardous chemicals or PAHs was observed [35,36]. The DNA methylation (DNAm) in gene *GSTP1* was examined in cancer-free studies. The DNAm in *GSTP1* gene was not related to PAHs exposure among firefighters [14] but it was related to the pesticides exposure [15].

N-acetyltransferase

The coding gene N-acetyltransferase (*NAT*) was the second most frequently studied gene. The NAT enzymes detoxify a large group of industrial chemicals. Its role is known in the metabolism of numerous aromatic amines [37]. Its enzymes can catalyse both N-acetylation and O-acetylation reactions and are implicated in the activation and detoxification of well-known carcinogens [38]. The *NAT2* is a carcinogen detoxification gene and several different allelic variants exist that determine the acetylator phenotype. Links with NAT2 acetylation status was well documented to be associated with the risk of BCa. The 2 expressed genes encoding NAT activity, *NAT1* and *NAT2* were screened for genotype in 10 studies. The authors reported that genetic polymorphism in *NAT1* enzyme involved in biotransformation of benzidine and its metabolite, did not show a direct relationship with the BCa risk, genotypes in *NAT1 T1088A, C1095A, G560A* and exposure to benzidine in Chinese population [39]. Other studies conducted on Chinese population showed that *NAT2 G191A, C282T, T341C, C481T, G590A, A803G, G857A* genotypes have no impact on genetic susceptibility to occupational benzidine exposure and the BCa risk [40]. Also in Lebanese population, studies showed the lack of a direct relationship with gene encoding enzyme involved in carcinogens and their metabolites inactivation. The researcher showed that *NAT2* genotypes *C282T, G191A, A434C, C481T, T111C, G590A, C759T, G857A, T341C, A803G* were not associated with BCa and exposure to AAs [27]. The studies conducted among Caucasian population [29,34], Japanese population [41], White race [26] also did not indicate genetic susceptibility to occupational exposure and the BCa risk. They included groups of workers exposed to AAs, PAHs, metalworking fluids or industrial chemicals, respectively. Three studies suggested a significant relationship with an increased BCa risk, occupational exposure to combustion fumes and *NAT1* in Lebanese population [20] or *NAT2* in Caucasian population [33], and a significant relationship with a decreased BCa risk, occupational exposure to hazardous compounds, *NAT1* and *NAT2* in Caucasian population [42].

Cytochrome P450

Cytochrome P450 (CYP) is a key enzyme for activation of bladder carcinogens, i.e., AAs and PAHs, which require formation of reactive metabolites with damaging effects. Three studies investigated the relationship between *CYP* genetic polymorphisms, occupational exposure and the BCa risk [11,18,29]. The researchers focused on the following genotypes: *CYP1A2* (*-2467T/delT rs35694136, -163C/Ars762551*), *CYP1A1, CYP2C19, CYP2D6* and *CYP2E1*. In these studies no significant relationship between the gene, exposure to AAs, PAHs or hazardous compounds and the BCa risk was observed. In the PCa risk study, genotypes of the gene such as *CYP24A1, CYP27A1, CYP27B1* were also not related to pesticides exposure [43]. Even though in the last several years, studies showed that CYPs activity may be a modulating factor along the continuum from the occupational exposure and certain cancers, no molecular epidemiology study has shown the role of genetic polymorphisms of *CYPs* in the interaction between occupational exposure and the risk of BCa or PCa.

UDP-glucuronosyltransferase

Metabolism and clearance of endogenous and exogenous carcinogenic compounds is primarily catalyzed by the UDP-glucuronosyltransferase (UGT) 1A and UGT2B enzymes. They conjugate and detoxify aromatic amines, and play a role in benzidine metabolism. Studies show that *UGT* gene promoter activity or enzymatic activity is modulated by genetic polymorphisms at the *UGT1A* and *UGT2B*. On the basis of these data, it was hypothesized that *UGT* gene polymorphisms reduce the capacity to glucuronidate carcinogens and other types of cancer-promoting factors (e.g., sex hormones), and may be associated with cancer risk. Studies by Selinski et al. [44] and Figueroa et al. [34] showed an association between the BCa risk, *UGT1A rs11892031* genotype and AAs, PAHs or metalworking fluids exposure. Moreover, Lin et al. [45] reported a relationship between an increased BCa risk, dye exposure and genotype in *UGT2B7 C802T* [45].

Genes responsible for oxidative stress

Glutathione peroxidase 1

Glutathione peroxidase 1 (GPX1) is a ubiquitously expressed selenium-dependent enzyme. The GPX1 is one of the key antioxidant enzymes. It protects cells against peroxidative damage by reducing hydrogen peroxide and a wide range of organic peroxides. The most common functional genetic polymorphism of *GPX1* is called *Pro198Leu (rs1050450 C>T)*. Numerous case-control studies have assessed the association between *GPX1 Pro198Leu* genotype and cancer risk in different populations [46]. However, only 1 molecular epidemiology study has been conducted but has not shown the role of *GPX1 Pro200Leu* genetic polymorphisms in the interaction between occupational exposure and the risk of PCa [47].

Manganese superoxide dismutase

Manganese superoxide dismutase (MnSOD) is one of the most important antioxidant enzymes in the defense system against reactive oxygen species and the only mitochondrial enzyme that dismutates O_2 – into H_2O_2. The human *MnSOD* gene has a gene polymorphism at the *Ala16Val*. The genotype has an influence on the MnSOD enzyme structure and activity. The *Ala* variant generates a high mitochondrial activity, while *Val* variant results in a low activity [48]. In a BCa and PCa molecular epidemiology study, Choi et al. [47] and Porru et al. [29] reported no direct relationship with this gene and occupational exposure to AAs, PAHs or asbestos.

Catalase

Catalase (CAT) is a critical endogenous antioxidant enzyme that detoxifies H_2O_2 into water and oxygen in our body. Based on the results of Choi et al. [47], no statistically significant relationship was found between *CAT-262 C>T* gene polymorphism, asbestos exposure and PCa risk.

Genes responsible for altering DNA repair capacity

X-ray repair cross-complementing 1

X-ray repair cross-complementing 1 (XRCC1) acts as an indispensable factor in base excision repair (BER). Genetic polymorphisms in the DNA repair genes *XRCC1 Arg399Gln, XRCC3 Thr241Met, XPD Lys751Gln* were studied by Shen et al. [17]. The molecular epidemiology study showed a relationship with a reduced BCa risk and genotype at the XRCC3 codon 241. Despite this, no direct relationship with the BCa risk and genes and exposure to AAs, PAHs was found. The xeroderma pigmentosum group C (XPC) is essential for repair of bulky adducts from carcinogens. Sak et al. [49] showed the lack of an association between the BCa risk, genotypes in *XPC-PAT, Lys939Gln, IVS11-6* and exposure to chemical carcinogens in rubber and plastics industry, laboratories, printing, paints, dyes or diesel fumes. Two other studies by Sak et al. [50,51] related to the association between 22 single nucleotide polymorphisms (SNPs) in the *XPC* gene, and 14 SNPs in the *XRCC1*, industrial chemicals exposure and the BCa risk showed only a relationship with an increased cancer risk and *Ala499Val, Ex15-184, Ex15-177* genotypes. No significant association between the genes and exposure was found.

Base excision repair and nucleotide excision repair

The BER and nucleotide excision repair (NER) are highly versatile and sophisticated single-strand DNA damage removal pathways. The BER and NER counteract the deleterious effects of a multitude of DNA lesions, including damage induced by environmental sources [52]. Association molecular epidemiology studies by Barry et al. investigated 394 tag SNPs at the 31 *BER* and 324 tag SNPs at the 27 *NER*, genes responsible for repair of a broad range of DNA damage. The results showed a relationship between an increased PCa risk and fonofos use and *NEIL3 rs1983132 CT/TT* [53]; fonofos use and *ERCC1 rs2298881 A*; carbofuran use and *CDK7 rs11744596 TT, rs2932778 TT* genotypes [54].

Genes responsible for tumour suppression

Human tumour suppressor gene *TP53*

The human tumour suppressor gene *TP53* is the most commonly mutated gene in cancer. Mutations in this gene are found in over half of human cancers. The human *TP53* locus, encodes a tumour suppressor protein whose functions initiate transcription of genes involved in the processes such as cell cycle arrest, apoptosis, metabolism, DNA repair, autophagy, and cellular senescence in response to stressors. The wild type *TP53* gene was classified as tumour suppressor [55]. Kannio et al. [56] in their case-control study and Taylor et al. [19] in their case-only study presented no direct relationship with *TP53* mutation and exposure to asbestos or arylamines, respectively. In the case-only study by Kelsey et al. [57] a relationship with occupations (metal/plastic-processing machine operators, fabricators, assemblers) and *TP53* mutation in men was

shown. Koutros et al. [58] in the results of their case-only study documented a relationship between high-risk occupations (workers occupationally exposed to cutting or lubricating oils, paint thinner, organic solvents, pesticides) and mutations in *TP53* and cell-cycle pathway genes.

Genes responsible for vitamin D pathway

One of hypotheses advanced that vitamin D as antitumour agent might be responsible for the occurrence of PCa. Researchers observed an association between the PCa risk and 2 factors affecting decreased synthesis of vitamin D – the first increasing age and the second increasing rates in African-American population. Epidemiologic studies suggest that PCa development is influenced by environmental factors, including UV radiation from the sun exposure [59]. Ultraviolet B-rich sunlight stimulates synthesis of vitamin D in the skin and has been hypothesized to reduce the risk of PCa. Vitamin D is involved in a wide range of pharmacological and physiological functions. It modulates numerous genes encoding proteins that regulate cell proliferation, differentiation and apoptosis. Therefore, it is now established that vitamin D also influences the processes of cell proliferation, differentiation, adhesion and apoptosis potentially leading to cancer [60]. Moreover, several studies investigated if vitamin D supplementation reduced circulating androgens (testosterone and dihydrotestosterone), reduced PSA secretion and inhibited cell growth of the hormone-sensitive PCa cell line [61]. The action of vitamin D is mediated by the vitamin D receptor gene (VDR). Hence, genetic variations in the VDR as a PCa-related gene, may be important in determining disease susceptibility. However, the findings from analytic studies have been inconsistent on the role of vitamin D in the PCa development. Two studies of the relationships between gene polymorphisms and PCa in outdoor workers analysed steroid hormone receptor gene polymorphisms such as *VDR*. One of the studies was a case-only study and showed a significant relationship between an increased PCa risk of metastases and *VDR ff* andmelanocortin-1 receptor (*MC1R*) *Val92/Val92* [12]. The case-control study investigating 4 SNPs in *VDR* regulatory regions such as *Cdx-2, FokI, TaqI, BglI* showed a significant relationship with a reduced PCa risk, sun exposure and the following genotypes: *FokI rs10735810 FF or Ff, TaqI rs731236 tt, BglI BB* [62].

CONCLUSIONS

Many studies indicate that the genotypes presented in this review exhibit a significant association with the risk of developing cancer. Therefore, gene polymorphisms represent a potential biomarker also for BCa and PCa. The genetic basis of BCa and PCa is gaining increased attention and more and more evidence especially in gene-environment interaction studies. The attention paid to the role of genetic polymorphisms in increasing BCa and PCa susceptibility in workers exposed to industrial chemicals and chemical carcinogens constitutes the scope of this review. The objectives of this literature review were to investigate the state of genetic diversity as additional risk factors and enhancers for the main occupational exposure attributable factors. So far, research has mainly been conducted among employees on low-penetrance genes involved in xenobiotics metabolism that contribute to the BCa and PCa risks by augmenting the effects of chemicals and carcinogen exposures.

The role of genetic factors in the occupational exposure has not been conclusively established, but it appears the possibility of genetic involvement. Determination of environmentally responsive genes provides important mechanistic implications for the etiology of occupational cancers, and valuable input in occupational exposure limit setting by taking genetic susceptibility into account. On the other hand, even if polymorphisms for genetic susceptibility have a clear role in identifying cancer risk, the value of wide scale genetic screening in occupational settings remains limited due to primarily ethical and social concerns. Thus, the large scale genetic screening in the workplace is not currently recommended. However, the possibility of using genetic polymorphisms as an important factor for limitation dose and cancer prevention should not be forgotten in future interpretations. More genetic research is needed to corroborate these findings and assess their significance in the workplace.

In conclusion, there is a considerable number of studies that indicate a significant association between the increased BCa and PCa risks and susceptibility genes in the general population [63–66]. Moreover, examples of various occupational carcinogens exposure that have an association with the risk of BCa or PCa have been shown [67,68]. However, when considering genetic susceptibility in exposure

to chemicals as cancer risk factors, statistically insignificant results have been often obtained. This confirms that the development of cancers presented here is influenced by several risk factors present in the general population, which probably vary significantly between individual employees. The importance of chemical exposure at work as a risk factor for the BCa and PCa incidence is directly related to tobacco smoke, gender differences, age, schistosomiasis and other lifestyle and nutritional modifiable factors. The importance of exposure to cancer risk factors is not limited to the workplace. Therefore, the inseparable non-occupational risk factors should not be overlooked.

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