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Minireview

Gene–environment interactions in heavy metal and pesticide carcinogenesis

Shams Tabrez[a,*], Medha Priyadarshini[b], Shubha Priyamvada[c], Mohd Shahnawaz Khan[d], Arivarasu NA[c], Syed Kashif Zaidi[e]

[a] King Fahd Medical Research Center, King Abdulaziz University, Jeddah 21589, Saudi Arabia
[b] Division of Endocrinology, Department of Medicine, Feinberg School of Medicine Northwestern University, Chicago, USA
[c] Section of Digestive Diseases and Nutrition, Department of Medicine, University of Illinois, Chicago, USA
[d] Protein Research Chair, Department of Biochemistry, College of Science, King Saud University, Saudi Arabia
[e] Center of Excellence in Genomic Medicine Research, King Abdulaziz University, Jeddah, Saudi Arabia

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ABSTRACT

Cancer is a complex disease involving a sequence of gene–environment interactions. Lifestyle, genetics, dietary factors, and environmental pollutants can increase the risk of cancer. Gene–environment interactions have been studied by a candidate-gene approach focusing on metabolism, DNA repair, and apoptosis. Here, we review the influence of gene–environment interactions in carcinogenesis, with emphasis on heavy metal and pesticide exposures.

Contents

* Corresponding author. Tel.: +966 640 1000,
fax: +966 640 1000x25185/2695 2076.
E-mail address: shamstabrez1@gmail.com (S. Tabrez).

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1. Introduction

Humans are exposed to many environmental carcinogens. The increasing incidence of cancer is at least partly attributable to carcinogenic agents in the occupational and general environment [1]. How and when these agents become critical for carcinogenesis is not well understood.

Carcinogenesis is a complex, multistep, multifactorial process involving genetic alterations, immune suppression, and malignant transformation [2]. Cancers are thought to arise from a single cell, initiated by mutation of a few crucial genes caused by errors in DNA replication or exposure of DNA to free radicals or carcinogens [3]. Initiated cells undergo further genetic/epigenetic changes that provide survival advantages and ultimately lead to the conversion of normal cells to malignant cancer cells. These processes can be activated by environmental factors such as cigarette smoke, industrial pollutants, oxidative and inflammatory agents. Gene–environment interactions (GEI), broadly defined as interactions between environmental exposures and specific (risk) genotypes, are known to act in a plethora of diseases [4,5], including cancer development.

In this review, we summarize the pathways leading to cancer, GEIs, and two classes of carcinogenic environmental pollutants: heavy metals and pesticides. (Carcinogenesis induced by other agents, such as polycyclic aromatic hydrocarbons, is not within the scope of this article).

2. Multistep process of carcinogenesis:

Cancer development includes initiation, proliferation, and progression phases. The multistage process of transformation and tumorigenesis includes evasion of apoptosis, self-sufficiency in growth signals, insensitivity to antigrowth signals, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis [6,7]. Epigenetic disruption of gene expression also occurs during cancer development [8]; diet- and environment-mediated epigenetic perturbations play a crucial role in cancer progression in humans [9,10].

Accumulation of mutations seems to be necessary for tumor development [2] and one expects a higher rate of mutations with exposure to carcinogens. These mutations can affect genes encoding xenobiotic-metabolizing enzymes, produce polymorphisms leading to altered ligand affinity and activity, or influence the expression of downstream target genes, resulting in differential susceptibility to environmental toxicants [11].

Oxidative and inflammatory stresses are involved in the initiation and progression of carcinogenesis. Biomarkers of oxidative stress have been reported in cancer, due to factors such as elevated metabolism, mitochondrial mutations, cytokines, and inflammation [12]. Oxidative stress arises from increased production of reactive oxygen species (ROS) associated with decreased antioxidant capacity. ROS are constantly generated in aerobic cells by the incomplete reduction of molecular O_2 to H_2O during mitochondrial oxidative phosphorylation, as well as during processes such as inflammation, infection, mechanical or chemical stress, and exposure to ultraviolet or ionizing radiation [13]. The effect of ROS on cell depends on the level at which they are present. Low levels may be beneficial, but, at high levels, ROS can oxidatively damage macromolecules and cause detrimental effects that can lead to cell death. ROS can induce genotoxic damage, including DNA single- and double-strand breaks, DNA–protein cross-links, abasic sites, and modified bases [14–17].

Cells counteract oxidative stress by the use of several defense mechanisms, ranging from free radical scavengers and antioxidant molecules/enzymes to DNA repair mechanisms to reduce levels of ROS and prevent irreversible cellular damage [18,19]. Oxidative stress is also closely associated with carcinogenesis [20]. Increased ROS production occurs in highly proliferative cancer cells, owing to the presence of oncogenic mutations. Increased oxidative stress is well documented in transformed cells [21] and ROS regulation is crucial for transformed cells that counteract ROS accumulation by upregulating antioxidant systems [22].

Blood oxidative stress-related markers such as 8-isoprostane and 8-hydroxy-2′-deoxyguanosine (8-OHdG) are reported to be significantly increased in patients with breast cancer [23]. Over time, DNA damage can lead to an increased incidence of cancer [24]. Under normal circumstances, damaged DNA is repaired, but excess oxidative stress may result in non-repairable DNA damage, which may lead to mutations in critical genes involved in the control of cell growth. ROS act as signaling molecules to initiate inflammatory responses, which can affect cell proliferation and apoptosis. Oxidative modification of cell signal transduction by ROS may result in dysfunctional cell growth, differentiation and cell death, which can ultimately lead to the development of inflammation and cancer [16].

The effects of ROS on p53, cell proliferation, invasiveness, and metastasis are important in cancer biology. ROS are major activators of the NF-κB and AP-1 transcription factors involved in innate immune or inflammation responses [25,26]. Activation of NF-κB upregulates the expression of many inflammation-related genes, including tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-8 and vascular endothelial growth factor. TNF-α and IL-1 in turn bind to tumor necrosis factor receptors and IL-1 receptors, thereby further activating the NF-κB pathway and repeating the cycle. Inflammatory chemokines act on inflammatory cells to increase their pro-tumorigenic properties and act directly on tumor cells through specific receptors expressed by those cells [27].

Investigations of oxidative stress have primarily focused on genotoxicity [14,15,19,28], but ROS also play a significant role in promotion of carcinogenesis. Many tumor promoters generate ROS [29,30].

3. Gene–environment interactions and cancer

The term Gene–environment interaction (GEI) refers to the joint influences of genetic and environmental factors on health and disease. Environmental exposures affect gene regulation and/or act as additive risk factors in conjunction with a particular allelic form of a gene (genetic polymorphism), influencing disease initiation and progression. GEI also entails the different effects of a given environmental exposure on individuals and the different effects of a genotype in people with different histories of environmental

exposure [31]. Such interactions may be important determinants in cancer [32].

3.1. Environment affects gene regulatory mechanisms

Environmentally induced changes in gene regulatory mechanisms correlate strongly with cancer etiology [33,34]. These mechanisms include gene translocation, histone modification, DNA methylation, DNA repair, gene copy number, transposon activation and RNA stability, alternative splicing, retrotransposons, and transcription factor induction [33]. One of the most prominent examples of cancer characterized by specific translocation and positive association with pesticide exposure is follicular non-Hodgkin lymphoma (NHL). In NHL, the anti-apoptotic *BCL-2* (B cell leukemia/lymphoma 2) translocates from chromosome 18 to chromosome 14 (immunoglobulin heavy chain locus). Epidemiologic studies show that the t(14;18) translocation frequency correlates positively with exposure to pesticides (including dieldrin, toxaphene, lindane, etc.) and fungicides [35]. This suggests a role for environmentally induced genetic instability in cancer.

Transposon/retrotransposon activation by environmental contaminants has also been documented. Exposure to benzo[*a*]pyrene, pyrene, organochlorine pesticides, and certain heavy metals, such as nickel, activates the transposon/L1 retrotransposon/promoter of L1Hs retrotransposon in HeLa cells, fish liver cells, and human choriocarcinoma cells [36–38].

DNA methylation and histone modifications, the first epigenetic control elements identified [39,40], are susceptible to modulation by environmental factors. Epigenetic alteration in DNA methylation patterns is trans-generational, increasing disease (cancer) risk in the offspring [41]. Increased risk for tumor development was reported in the offspring of mice exposed to a chemical carcinogen ($CrCl_3$) prior to conception [42]. The observed tumors included thyroid follicular cell and Harderian gland tumors, ovarian cysts, lung tumors, reproductive gland tumors, and other abnormalities. Most of these tumors were gender specific. Subsequent studies showed that the sperm of Cr-exposed mice had increased copies of hypomethylated 45S ribosomal RNA gene [43,44]. This modification might have caused an increase in the number of ribosomes in the cell, deregulation of protein synthesis, progression of tissue growth, and proliferation [44,45].

During embryonic development, the remethylation of DNA can also be modified environmentally and has been implicated in tumor development. 2,3,7,8-Tetrachlorodibenzo- *p*-dioxin (TCDD) is a persistent environmental contaminant produced during paper, polyvinyl chloride plastics and chlorinated pesticides manufacture. Dietary exposure to TCDD in humans [CDC, 2005] has been correlated to aberrant methylation and expression of the H19/Insulin growth factor 2 (*Igf2*) gene, leading to the development of Wilms tumors [46], testicular germ cell [47], ovarian [48], and adrenocortical tumors [49]. Aberrant methylation of oncogenes (demethylation) and tumor suppressor genes (methylation) accompanies aging [50,51]. These incorrect methylation events may be mediated by deregulated DNA methyltransferase enzyme, as found in gastric cancer [52] or by altered dietary folate intake [53]. Folate deficiency is associated with overmethylation of the *p16INK4A* gene in human head and neck squamous cell carcinoma (HNSCC) [53]. This may be further modified by functional polymorphism in methylene tetrahydrofolate reductase (*MTHFR*) gene (discussed later). Diethylstilbestrol (DES) exposure-induced abnormal methylation is also transgenerational. The F1 and F2 generations of humans exposed to DES in utero showed enhanced rates of uterine sarcomas and adenocarcinomas, lymphomas, malignant reproductive tract tumors, and benign ovarian tumors [54,55].

Environmental factors may also affect RNA stability and tumor development. For instance, in rat hepatocellular carcinoma, TCDD promotes carcinogenesis by stabilizing the mRNA of urokinase plasminogen activator, a protein controlling the matrix turnover and tumor cell growth [56].

3.2. Environment and gene polymorphism intercommunication

Environmental factors also affect cancer progression via cancer susceptibility gene polymorphisms.

4. Carcinogenesis and genetic susceptibility

Carcinogens may interact with host-related gene polymorphisms [57]. Highly penetrant inherited cancer susceptibility genes account for only a small proportion of cancer cases [58]. Common sporadic cancers are associated with polymorphic low-penetrance cancer susceptibility genes [32,59]. Analyses of single nucleotide polymorphisms (SNPs) along the entire human genome suggest that combined effects of polymorphic allelic variants (polygenic mechanisms) account for the overall susceptibility of individuals to exogenous chemical carcinogens [60]. Genetic polymorphisms, however, act only secondarily to exposure to exogenous chemicals and the effects depend on the quality of allelic variation (heterozygous being low risk compared to homozygous) and the quantity (and frequency) of the chemical exposure [61]. Polymorphisms are frequent in genes encoding xenobiotic-metabolizing enzymes (such as P450 enzymes and enzymes catalyzing conjugation reactions), DNA repair proteins, and cell cycle control proteins, and roles in carcinogenesis have been indicated [57]. Any single form of cancer may be influenced by multiple polymorphic genes [62]; thus, gene–gene interactions may also affect cancer risk.

4.1. Polymorphisms affecting enzymes that catalyze oxidative metabolism of xenobiotics

Interactions between cytochrome P450 (*CYP*) gene polymorphisms and cancer risk have been noted. *CYP2E1* polymorphisms may interact with factors such as smoking and diet to influence gastric cancer susceptibility [63–65]. Interplay of environmental factors and/or ethnicity and *CYP2E1* polymorphisms has also been implicated in the incidences of esophageal cancer [64], hepatocellular carcinoma [66], nasopharyngeal cancer [67], and other cancer types [68,69]. *CYP* and *GST* (glutathione-S-transferase) polymorphisms have often been shown to co-influence the cancer risk. Significant associations of *CYP1A1* variant genotypes and *GSTM1*-null genotypes separately with lung and head-and-neck cancer risk have been revealed. The combined genotype of a *CYP1A1* specific variant (*CYP1A1*2A*) and *GSTM1* null increases cancer risk several-fold. The risk may be potentiated by alcohol consumption, tobacco chewing, or cigarette smoking [70,71]. Combinations of *CYP2E1*, *GSTM1*, and *XRCC1* (X-ray Repair Cross Complementing Group I) variant genotypes along with tobacco/alcohol use increases risk for head and neck squamous cell carcinoma [72]. Variants of *CYP2D6*, *CYP3A1*, *CYP3A4*, *CYP2A6* have also been associated with increased risk of lung, head and neck, esophageal and gastric cancers and this is influenced by tobacco usage and nitrosamine exposure [73–75]. An increased risk of breast cancer is correlated with *CYP1A1* and *CYP1B1* gene variants in women exposed to polyhalogenated aromatic hydrocarbons (PHAHs) and organochlorine pesticides [76]. Polymorphisms affecting other xenobiotic metabolizing enzymes, including EPHX1 (epoxide hydrolase) and MPO (myeloperoxidase), also correlate with cancer risk. Increased lung cancer risk is associated with *EPHX1* gene variants and the effects may be independent of or additive to the arylamine N-acetyltransferase (*NAT2*) gene polymorphism [77–80]. The risk conferred by combined genotypes depends on cumulative smoking exposure [78]. Contrasting data

exists on polymorphisms in the *MPO* gene for its possible protective role in lung cancer [81,82]. SNPs of *MPO* and *paraoxonase* (rs11079344 (*MPO*), rs8178406 (*MPO*), rs2243828 (*MPO*), rs662 (*PON1*), rs705379 (*PON1*), and PON1 (304A/G) may serve as predictors/biomarkers of cancers [83].

A cyclooxygenase-2 (COX2, another oxidative enzyme involved in xenobiotic metabolism) promoter region polymorphism is correlated to oral squamous cell carcinoma risk and the effect may be enhanced by use of alcohol, betel quid, and cigarettes [84].

4.2. Gene polymorphisms affecting xenobiotic conjugation enzymes

GSTT1, *GSTM1*, and *GSTP1* genotypes may influence risk for (i) breast cancer [85], which may be affected by coincident alcohol consumption and menopausal state of women or exposure to organochlorine pesticides [86]; (ii) hepatocellular carcinoma [87], additively with aflatoxin in the presence of chronic hepatitis B; (iii) esophageal cancer [88]; (iv) head and neck squamous cell carcinoma [89] independently of or in association with NAD(P)H:quinone oxidoreductase-1 (NQO1) [90]; prostate cancer [91]; and bladder and colon cancers [57,92]. NAT has also been suggested to be associated with cancer risk. Recently, the NAT2 'ultra-slow' acetylator genotype has been reported to be associated with bladder cancer caused by occupational exposure to aromatic amines [79,80]. The rapid acetylator genotype correlates with the incidence of colon cancer associated with dietary consumption of heterocyclic aromatic amines [93]. Very few studies have associated SULT variants with cancer [94]. One such study correlated the homozygous *SULT1A1* genotype with increased risk for esophageal squamous cell carcinoma among smokers and observed that this risk increases in combination with the *CYP3A5* heterozygous genotype, again in smokers as compared to non-smokers [95].

4.3. Gene polymorphisms in DNA repair/metabolism enzymes

SNPs in DNA repair genes may influence susceptibility to oral, breast, gastric, prostate, and colorectal cancers [96–99]. Polymorphisms in *ERCC2* (Excision Repair Cross Complementing Group 2) and *XRCC1* tend to be risk factors for lung cancer, especially in non- and moderate smokers [100]. Polymorphisms in *XRCC1* and *NQO1* together with smoking additively influence the risk for gastric cancer [101]. RAD51L1 (a member of RAD51 protein family) plays a central role in homologous recombination DNA repair [102] and may be involved in nasopharyngeal carcinoma [103]. RAD51 and its variants are implicated in risk for breast, ovarian and nasopharyngeal carcinomas [103]. Exo1 is an important nuclease involved in the mismatch repair system and is crucial to the cell cycle and DNA recombination. Polymorphisms in *Exo1* may influence risk of several cancer types. A specific *Exo1 K589E* genotype in combination with smoking raises the risk for gastric cancer and has been proposed as a novel marker in gastric oncology [104]. Specific combinations of polymorphic allelic variants of DNA repair genes, such as those involved in base excision repair (*XRCC1*), nucleotide excision repair (*xeroderma pigmentosum D*, *XPD* and *XPA*), and double-strand break repair (*XRCC3*), markedly increase the cancer risk [105,106].

5,10-Methylene-tetrahydrofolate reductase (MTHFR) activity is critical for proper folate metabolism. De novo purine and thymidylate synthesis is dependent upon adequate concentrations of 5,10-methylenetetrahydrofolate. Hence, the activity of MTHFR may influence susceptibility to cancer. *MTHFR* 677TT homozygous genotypes are associated with cervical intraepithelial neoplasia [107], esophageal [108], endometrial [109], laryngeal squamous cell carcinoma [110] and certain forms of breast cancer [111,112]. *MTHFR* C677T and A1298C polymorphisms may have protective effects on childhood acute lymphoblastic leukemia and folate levels influence the protection efficiency, suggesting a *MTHFR* Gene–environment interaction [113].

4.4. Polymorphisms in apoptotic pathway and cell cycle enzyme genes

Apoptosis is prerequisite for maintenance of cell number and elimination of damaged cells. Polymorphisms/mutations in apoptotic pathway genes may influence a cell's ability to undergo apoptosis, allowing transformed cells to accumulate and induce cancer [114]. Polymorphisms in apoptotic pathway genes through gene–gene or Gene–environment (smoking or presence of certain diseases) interactions may play a role in etiology of esophageal adenocarcinoma, hepatocellular carcinoma, etc. [115–117].

Cell cycle gene polymorphisms may modify cancer risk [73,118,119]. These polymorphisms (such as those in the *CCND1* gene) may influence gene–gene and gene–environment interactions, such as smoking and polymorphisms in *BCL2* or *FAS* [120,121].

4.5. Polymorphisms in cytokine genes

Inflammation may play a role in cancer pathogenesis [122,123]. Polymorphisms in the interleukin 1β (*IL1B*) gene are associated with risk of cancers: gastric [124,125], lung [126], breast [127], liver [128], colorectal [129], endometrial [130], and ovarian [131]. Polymorphisms in the *IL8* gene also modify cancers risk in the presence of infections such as *Helicobacter pylori* [132,133].

4.6. Other gene polymorphisms

Other candidate genes include those involved in the insulin pathway *IGF-1* [134], adipokines and receptors (adiponectin) [135], alcohol metabolism (alcohol dehydrogenase and acetaldehyde dehydrogenase) [136].

5. Carcinogenic environmental pollutants and GEI

5.1. Heavy metals

Several metals and metalloids have been rated as proven or probable carcinogens by the International Agency for Research on Cancer (IARC). For instance, exposure to Cr or Ni is associated with nasopharyngeal carcinoma, exposure to Pb or Hg with brain tumors, exposure to Pb or Cd with kidney cancer and exposure to Cd with prostate cancer [2,137]. Metals modulate gene expression by interfering with signal transduction pathways that play important roles in cell growth and development [138,139]. The underlying mechanism involves formation of the superoxide radical, hydroxyl radical, and finally the production of mutagenic and carcinogenic malondialdehyde (MDA), 4-hydroxynonenal (HNE), and exocyclic DNA adducts [138]. Carcinogenic metals and metalloids, such as As, Cd, Ni, and Co can also inhibit zinc finger-containing DNA repair proteins [140]. The effects of some of the highly potent cancer causing heavy metals are briefly explained.

5.2. Chromium

The toxicity/carcinogenicity of Cr is primarily related to its oxidation state. Certain forms such as hexavalent Cr [Cr(VI)] compounds, primarily generated from industrial processes, are well-established environmental contaminants and human occupational respiratory carcinogens [141]. Workers exposed to specific forms of Cr(VI) exhibit a significant increase in lung cancer risk. In vivo and cell culture studies have also demonstrated an increased

incidence of neoplastic transformation and tumor formation as a result of Cr (VI) exposure [141,142].

Cr(VI) carcinogenesis is site specific, targeted mainly to the lung [143], and may be initiated or promoted through several mechanisms, including intracellular metabolic reduction of Cr(VI), producing Cr species capable of interacting with DNA to yield genotoxic and mutagenic effects, and Cr(VI)-induced inflammatory/immunological responses and alteration of survival signaling pathways. Epidemiological studies carried out in U.K., Europe, Japan and U.S. have consistently shown that workers in occupations where particulate chromates are generated or used have an elevated risk of lung cancer [144].

The National Institute of Occupational Safety and Health (NIOSH) has listed chromate compounds as one of the major causes of occupational lung cancer, and the U.S. Environmental Protection Agency (U.S. EPA) and the IARC have also classified chromium as a human carcinogen. The final product of chromate reduction, Cr(III), is biologically stable and has a greater DNA-binding efficiency than Cr(VI), resulting in high levels of chromium-DNA adducts and producing mutations inducing DNA damage [144,145].

Genomic instability, which can be caused by aberrant cell cycle checkpoints and dysregulated DNA repair mechanisms via microsatellite instability (MIN), plays an important role in Cr(VI) carcinogenesis [146]. A recent in vitro study showed that chronic exposure to Cr(VI) induced malignant transformation of human bronchial epithelial cells [147]. Holmes et al. [146] reported that the mutagenic capacity of Cr(VI) is insufficient to induce levels of mutations to critical tumor suppressor and oncogenes, such as p53 and ras, that could lead to Cr(VI)-induced multistage carcinogenesis. Moreover, they supported the hypothesis that genomic instability could potentiate Cr(VI) carcinogenesis [146,148].

Ye and Shi [149] reported altered expression of genes involved in redox stress mechanisms, energy metabolism, protein synthesis, cell cycle, and carcinogenesis as a result of Cr(VI) exposure. The process by which chromium is able to induce neoplastic progression is complex and elusive. Signaling pathways that could be affected by Cr(VI) exposure include mitogen activated protein kinase (MAPK) family, Src family proto-oncogenic tyrosine kinases and Akt family protein kinases.

5.3. Iron

The role of free radicals in the etiology of cancer via hydroxyl radical-induced DNA damage has been well established [21]. Intestinal exposure to ingested iron and induced oxidative stress may be key determinants of human colorectal cancer [138]. A significant increase in levels of 8-OH-G, 2-hydroxy-adenine and 8-hydroxy-adenine adducts has been reported in DNA from colon and rectum biopsies, suggesting hydroxyl radical damage [150].

5.4. Cadmium

The excretion of Cd from the human body is slow; hence, it accumulates in tissues such as the kidneys, liver, pancreas, and lungs [151].

Cd participates in indirect formation of ROS and RNS [137,152]. Cd is a potent human carcinogen preferentially causing prostate, lung and gastro-intestinal cancers. Researchers have also reported a synergistic increase in the carcinogenic potential of Cd in smokers [153,154].

5.5. Arsenic and cobalt

Arsenic is a well-documented carcinogen [155,156]. Inhalation of arsenic oxides is associated with common cancers, including lung, kidney, and liver [157]. The molecular mechanism of As toxicity and carcinogenesis is not known. Arsenic induces toxicity through genetic changes, oxidative stress, enhanced cell proliferation, and altered gene expression. The toxicity of Co is lower than that of many other metals [158]. Co can interfere with DNA repair processes and can also cause direct induction of DNA damage, DNA–protein crosslinking and sister-chromatid exchanges, which contributes to its toxicity and carcinogenicity.

6. Pesticides

Pesticides are used extensively for pest control and weed destruction. Pesticide exposure is associated with blood, prostate, pancreas, brain, liver and other cancer types. Risk of cancer in children is associated with parental exposure to occupational or non-occupational pesticides [159,160]. A positive link between pesticide exposure and breast or prostate cancers has also been suggested [161,162]. A strong association between pesticides and relative risk of Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) has been reported for DDT, chlorophenols, and phenoxyherbicides [163,164]. Underlying mechanisms of pesticide-induced cancer may include DNA damage and oxidative stress. The principal classes of pesticides that are still used in developing and/or developed countries are organochlorines, organophosphates, carbamates and pyrethroids.

6.1. Organochlorines

Dioxins, hexachlorobenzene (HCB), and polychlorinated biphenyls (PCB) are the main representatives of this category. These chemicals are endocrine disruptors, interfere with developmental processes and can cause cancer through promoting or co-carcinogenic effects [165,166]. PCBs may cause mutations in *p53* and *K-ras* oncogenes and represent risk factors for colorectal and pancreatic cancers [167]. Exposure to organochlorines is also a risk factor for breast cancer because of their potential estrogenic activity [2] and immunosuppressive and tumor-promoting properties [168]. Aldrin and dieldrin induce hepatocarcinogenesis in mice [2,169].

6.2. Organophosphates and carbamates

Organophosphates are generally the most toxic of all pesticides. Since the withdrawal of organochlorine insecticides from use, organophosphate insecticides (diazinon, chlorpyrifos, disulfoton, azinphos-methyl and fonofos) have been widely used in agricultural and household applications. In a case-control study, Soldin et al. [170] reported an association of acute lymphoblastic leukemia with organophosphate exposure. Another study highlighted the genotoxic/carcinogenic potential of glyphosate [171]. Carbamates, esters of N-methyl carbamic acid, act by inhibition of acetylcholinesterases. Some carbamates contain ethylene thiourea (ETU), which produces tumors in the thyroid and at other sites in rodent bioassays [172]. Carbamate derivatives such as carbaryl and N-nitrosocarbaryl are linked with NHL in humans [173] and are also carcinogens in mice [174].

6.3. Pyrethroids

Pyrethroids are the most commonly used pesticides, due to their high insecticidal potency and comparatively low mammalian toxicity [175]. However, certain pyrethroids are suspected to have genotoxic/carcinogenic potential [176]. Canistro et al. [177] reported that exposure to piperonyl butoxide (PBO) increases expression of P450 1A1, which catalyzes procarcinogen activation. It also promotes liver tumors via ROS formation [178]. The increase in ROS is due to PBO-induced regulation of glutathione reductase

(GRx), NQO1, and other antioxidant enzymes. NQO1 is elevated in tumors of the breast, ovary, lung, colon, thyroid, and adrenal gland [179].

7. Conclusions

Additional genetic susceptibility loci for cancer risk and outcome may be identified through genome-wide association studies. Priorities include identifying the biological mechanisms underlying associations between gene variants and cancer risk; detecting GEIs; and incorporating genetic knowledge into clinically applicable risk-prediction models that can benefit patients and public health [180]. Challenges include difficulties in proper assessment of effects, due to variations in ethnicity, limited sample size, and uncertain xenobiotic/pathogen exposures. GEI studies are expected to influence genetic toxicology and oncology in the future.

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