

Minireview

Genetic damage in coal and uranium miners

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ABSTRACT

Mining has a direct impact on the environment and on the health of miners and is considered one of the most hazardous occupations worldwide. Miners are exposed to several occupational health risks, including genotoxic substances, which may cause adverse health effects, such as cancer. This review summarizes the relation between DNA damage and mining activities, focusing on coal and uranium miners. The search was performed using electronic databases, including original surveys reporting genetic damage in miners. Additionally, a temporal bibliometric analysis was performed using an electronic database to create a map of cooccurrence terms. The majority of studies were performed with regard to occupational exposure to coal, whereas genetic damage was assessed mainly through chromosomal aberrations (CAs), micronuclei (MNs) and comet assays. The bibliometric analysis demonstrated associations of coal exposure with silicosis and pneumoconiosis, uranium miners with lung cancer and tumors and some associated factors, such as age, smoking, working time and exposure to radiation. Significantly higher DNA damage in miners compared to nonexposed groups was observed in most of the studies. The timeline reveals that classic biomarkers (comet assay, micronucleus test and chromosomal aberrations) are still important tools to assess genotoxic/mutagenic damage in occupationally exposed miners; however, newer studies concerning genetic polymorphisms and epigenetic changes in miners are being conducted. A major challenge is to investigate further associations between miners and DNA damage and to encourage further studies with miners of other types of ores.

1. Introduction

Mining is the phase of exploration where the mineral raw material is produced. This sector is one of the most important economic activities in the world, and its activity is considered essential to the development and progress of many productive sectors due to its association with the production of essential items to daily lives [1]. Mining is an old activity that requires excessive effort and directly impacts the environment and miners' health.

Despite numerous advances over the years with the development of better technologies, safety policies and training of personnel, mining activity still presents adverse effects on miners' health and remains one of the most hazardous employment sectors [2]. The study "On the Miners' Sickness and Other Miners' Diseases" developed by Paracelsus in 1534 is one of the first recognized studies on this topic. Regardless of the date of the first studies, miners' occupational health remains a

concern as they are continuously exposed to different occupational health hazards, such as physical, biological, chemical, psychological and ergonomic hazards [3]. Miners have high rates of injury and death from underground explosions, equipment failure, mining collapse, and exposure to toxic chemical vapors and carcinogens by dust, which may cause disability and death [2,4,5]. Regarding cancer risk, although some studies have noted an association between occupational exposure in mining regions and the risk of different types of cancers (e.g., lung, nasal cavity, stomach and bladder), there is no consensus that exposure to coal increases the risk for any type of cancer [6]. On the other hand, lung cancer and, to a lesser extent, lymphoid cancers and leukemias are associated with occupational exposure to uranium [7].

The impacts of harmful effects on human DNA are not completely understood. Mining agents might present synergistic, additive and enhancing effects that can result in damage or possibly deleterious effects on DNA [8]. Numerous reports have suggested that exposure to

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extracted minerals and mining occupational environment are associated with genotoxicity biomarkers, such as chromosomal aberrations (CA), sister chromatid exchange (SCE), micronucleus (MN) formation and oxidative/DNA damage. This mini-review summarizes the scientific studies on genetic damage in miners from a systematic approach.

2. Material and methods

2.1. Search strategy

This study was registered with the open access database PROSPERO (international prospective register of systematic reviews) at its inception (registration number CRD42020185808; accessed from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020185808).

The search was conducted using electronic databases via PubMed (National Library of Medicine), Web of Science, Scientific Electronic Library (SciELO) and Google Scholar. The search was performed combining keywords: ("DNA Damage"[Mesh] OR "DNA Damages" OR "Damage, DNA" OR "Damages, DNA" OR "DNA Injury" OR "DNA Injuries" OR "Injuries, DNA" OR "Injury, DNA" OR "genotoxicity" OR "mutagenicity" OR "genotoxic" OR "mutagenic") AND ("Miners"[Mesh] OR "Miner" OR "Mine Workers" OR "Mine Worker" OR "Worker, Mine" OR "Workers, Mine" OR "Mineworkers" OR "Mineworker"). Furthermore, no language restrictions were imposed.

2.2. Eligibility criteria

To be included in this analysis, studies must have been published as an original survey reporting genetic damage in coal or uranium miners. All study designs were included, except studies using model animals and *in vitro* studies.

2.3. Data extraction process

Initially, the titles and abstracts of the articles were selected. Full-text articles were obtained when the title and abstract had insufficient information to make a clear decision. Subsequently, two reviewers individually (MS and CLF) classified those that met the inclusion criteria with approximately 95 % agreement. Differences were resolved by discussion and consultation with a third researcher as needed (FMRSJ). Two researchers completed data extraction for all studies, one review author checked text entries, and one independent checked numeric outcome data. For studies with more than one exposure group, the mean age was calculated. The quantitative data in the tables are presented only for coal miners as they are the majority group among the studies.

2.4. Bibliometric analysis

The temporal bibliometric analysis was performed using the database obtained from Web of Science (Thomson Reuters) in the review process and VOSviewer software (version 1.6.12) following criteria recommended by De Souza et al. [9]. VOSviewer uses a downloaded database to create a map of cooccurrence terms based on text data, considering words present in both title and abstract fields, which were extracted using "binary counting". This method considers the presence or absence of a term not the number of occurrences of a term. The minimum occurrence number of a term was defined as 10, as recommended by the software. The most relevant terms based on the included studies were selected, and maps were generated considering the number of times a term was cited and their connections while grouping the items into clusters according to their links. Furthermore, the normalization method selected was the "association strength". The color defines the cluster to which an item is inserted, whereas lines represent the links between the items. The distance between two items indicates the strength of the relationship, i.e., items closer to each other are more

closely related than more distant items [10].

3. Main findings

A total of 229 studies were identified using the search strategy mentioned. Thirty-two articles were included in this review, of which twenty-one focused on coal miners and eleven studied uranium miners. Fig. 1 shows a flowchart of the literature selection process. The complete characteristics of the included studies are described in a table in the supplementary material. Russia, China, Germany and Brazil are the countries with the largest number of people studied (Supplementary Material). Although all studies included in this review were developed on mineral coal and uranium occupational exposure, other ore exposures, such as copper, arsenic and other metals, were also found in the search, albeit in small numbers. Generally, genetic damage was evaluated through CA, MN and comet assays. Among the 32 studies included, 21 analyzed some associated factors. Three of eleven articles identified an association between the studied genetic outcomes and the time of work/exposure in the mine [11–13]. In addition, four of eighteen studies found an association between lifestyle (e.g., smoking, drinking, body mass index) and genetic outcomes [14–17]. Although different associated parameters have been evaluated by the studies, age was the main parameter. However, of the eleven studies that analyzed age [16, 18–27], only one [16] found it to be a factor significantly associated with the outcome.

Tables 1,2, Table 33 and 4 provide a summary of the main outcomes analyzed, average values and the results found between coal and uranium miners and the control group. The total CA observed in coal and uranium miners had an average of 4.2 (2.1–5.8) and 2.5 (2.5–2.9) aberrations in 100 counted cells, respectively. The mean MN (B) (MN in buccal mucosa cells) was 4.2 micronuclei per 1000 cells (range between 1.4–8.8 micronuclei per 1000 cells) in coal miners and 2.1 micronuclei per 1000 cell (only one study) in uranium miners. Additionally, all of the studies that evaluated this genetic outcome showed a significant difference between coal miners and the control group. The mean MN (L) (MN in lymphocytes) in coal miners was 10.4 micronuclei per 1000 cells (range between 0.6–27.1 micronuclei per 1000 cells) and in uranium miners was 15.6 micronuclei per 1000 cells (range between 10.5–20.8 micronuclei per 1000 cells), and the majority of studies found a significant difference between coal miners and controls. The studies that assessed micronuclei in uranium miners found no significant difference between exposure and control. Furthermore, all assessed micronucleus assays in lymphocytes were performed with a cytokinesis block micronucleus assay (CBMN). In buccal cells, the assays were performed with a buccal micronucleus cytome assay (BMCyt). Therefore, BMCyt seems to be a more sensitive method to assess chromosomal damage, mainly in coal miners, which can be confirmed by studies that analyze both methods in the same miner population [18,28,29]. DNA damage analyzed through comet assays presented different parameters, such as damage index, DNA damage by arbitrary units, % DNA, tail moment, damage frequency and tail length. The most common comet assay parameters were % tail DNA (mean 6.7, ranging from 2.7 to 13.1) and damage index (mean 42.5, ranging from 33.7 to 60), both in coal miners. Tail moment, Olive tail moment and tail length were also parameters reported in the studies.

Studies, such as [18,19,22,29], use parameters with some degree of subjectivity (analysis based on visual scoring). Although some important references [35,36] describe the possibility of using visual parameters to score the cells, recent guides [37,38] indicate cell measurement through an automated or semiautomated image-analysis system as a reliable method for obtaining the outcomes of the comet assay. In addition, in the case of studies performed in Latin America [18,19,22,29], it becomes interesting to standardize the nomenclature used for this type of visual measurement with other international studies in future research.

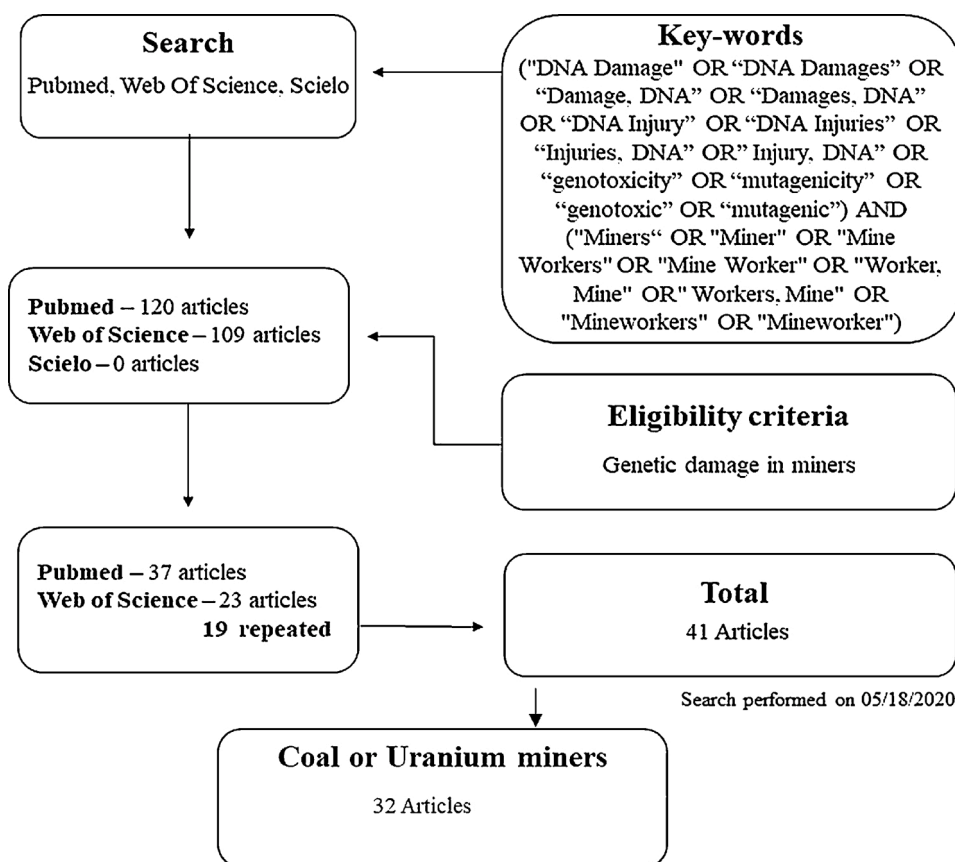


Fig. 1. Flowchart of literature selection process.

Table 1

Summary of the main methods and results of studies on micronucleus in miners.

Exposure	Exposed/control	Exposure markers	Parameter (Cell type)	Mean $\pm$ SD	Results	Fold difference vs. control	Cells scored/ subject	Ref.
Coal	158/48	–	MN (B)	1.5*	↑	2.7	1000	[28]
			MN (L)	0.6*	–	–		
Coal	69 (B) and 39 (L)/62	–	MN (B)	1.9 $\pm$ 0.3	↑	9.5	2000	[29]
			MN (L)	7.5 $\pm$ 0.7	↑	2.4		
Coal	100/100	–	MN (B)	a	↑	8.1	2000	[18]
			MN (L)	a	↔	3.0		
Coal	100/100	–	MN (L)	8.6 $\pm$ 4.8	↑	3.0	2000	[19]
Coal	39/34	Respirable coal mine dust	MN (L)	27.1 $\pm$ 1.5	↑	1.4	1000	[20]
Coal	143/127	–	MN (L)	11.1 $\pm$ 3.8	↑	1.5	1000	[21]
Coal	71/57	Trace elements in blood	MN (L)	7.5 $\pm$ 4.6	↑	2.4	2000	[22]
Coal	100/100	Trace elements in blood	MN (B)	8.8 $\pm$ 12.8	↑	8.8	2000	[23]
Coal	54/42	–	MN (B)	8.5 $\pm$ 6.8	↑	2.8	1000	[11]
Coal	41/29	Trace elements in Blood	MN (B) ^b	3.1 $\pm$ 2.2	↑	14.8	2000	[30]
Coal	97/169	–	MN (B)	1.4 $\pm$ 0.2	↑	6.2	1000	[15]
Uranium	46/52	–	MN (L)	10.5 $\pm$ 3.9	↔	0.9	1000	[31]
Uranium	85/22	Ionizing Radiation	MN (L)	20.8 $\pm$ 12.8	↔	0.9	1000	[24]
Uranium	47/52	–	MN (B) ^c	2.1 $\pm$ 0.3	↔	1.0	1000	[32]

Significant statistical difference between exposure vs. control, $p < 0.05$ according to the authors: ↔ no difference, ↑ significant increase, ↓ significant decrease.

L: Lymphocytes; B: Buccal cells. All micronucleus assays in lymphocytes were performed with cytokinesis block micronucleus assay (CBMN) and in buccal cells were performed with buccal micronucleus cytome assay (BMCyt).

^a The study did not present the values, but it presented the frequency ratio (RF). Making it possible to verify the presence of statistical difference.^b Data referring to “differentiated cells” provided by the study.^c Micronucleus in sputum.

* Mean calculated by the authors: [28], mean value between workers 1 and workers 2 groups.

3.1. Coal miner exposure

Despite all achievements of modern science and technology, working in coal mines remains one of the most dangerous occupations to human health [25]. Mineral coal consists of several solid organic compounds fossilized over millions of years. Thus, coal mining is characterized by

long-term contact with multiple harmful occupational agents, such as coal dust, polycyclic aromatic hydrocarbons and heavy metals [30]. According to Silva et al. [8], the influence of these agents increases the risk of developing several chronic diseases and genotoxic damage. Furthermore, the main mechanism reported in the literature regarding genetic damage caused by coal exposure is oxidative damage.

Table 2

Summary of the main methods and results of studies on nuclear alterations.

Exposure	Exposed/ control	Exposure markers	Parameter (Cell type)	Mean $\pm$ SD	Result	Fold difference vs. control	Cells scored/ subject	Ref.
Coal	143/127	–	NBUD (L)	7.2 $\pm$ 2.5	$\leftrightarrow$	1.2	1000	[21]
Coal	71/57	Trace elements in blood	NPB (L)	4.0 $\pm$ 2.8	$\leftrightarrow$	1.7	2000	[22]
Coal	68/46	–	NBUD (L)	6.1 $\pm$ 4.5	$\leftrightarrow$	1.2	2000	[29]
Coal	100/100	Trace elements in blood	NPB (L)	12.33 $\pm$ 7.5	$\uparrow$	2.2	2000	[23]
Coal	100/100	–	NBUD (L)	3.3 $\pm$ 0.7	$\downarrow$	0.5	2000	[18]
Coal	54/42	–	NPB (L)	12.3 $\pm$ 1.2	$\uparrow$	2.2	1000	[11]
Coal	41/29	Trace elements in Blood	KHC (B)	64.8 $\pm$ 54.9	$\uparrow$	1.8	2000	[30]
Coal	97/169	–	KYL (B)	36.1 $\pm$ 40.1	$\uparrow$	1.4	1000	[15]
			NBUD (B)	2.7 $\pm$ 4.2	$\uparrow$	2.7		
			KHC (B)	^a	$\uparrow$	1.8		
			KYL (B)	^a	$\uparrow$	1.3		
			NBUD (B)	^a	$\uparrow$	4.8		
			BN (B)	10.4 $\pm$ 7.0	$\uparrow$	2.5		
			CC (B)	5.1 $\pm$ 7.2	$\leftrightarrow$	2.2		
			KHC (B)	5.5 $\pm$ 8.2	$\uparrow$	2.3		
			KYL (B)	8.0 $\pm$ 7.5	$\leftrightarrow$	1.0		
			PYC (B)	7.5 $\pm$ 9.2	$\leftrightarrow$	1.7		
			NBUD (B)	0.8 $\pm$ 1.0	$\uparrow$	2.3		
			BN (B) ^b	13.3 $\pm$ 4.9	$\uparrow$	1.2		
			CC (B) ^b	5.7 $\pm$ 3.6	$\downarrow$	0.5		
			KHC (B) ^b	10.8 $\pm$ 5.0	$\leftrightarrow$	1.1		
			KYL (B) ^b	13.1 $\pm$ 4.5	$\leftrightarrow$	1.0		
			PYC (B) ^b	8.5 $\pm$ 3.2	$\leftrightarrow$	1.0		
			NBUD (B) ^b	7.7 $\pm$ 3.4	$\leftrightarrow$	1.1		
			BN (B)	6.3 $\pm$ 0.5	$\uparrow$	1.6		
			KHC (B)	5.0 $\pm$ 0.6	$\uparrow$	1.7		
			NBUD (B)	3.8 $\pm$ 0.3	$\uparrow$	2.1		

Significant statistical difference between exposure vs. control, $p < 0.05$ according to the authors: $\leftrightarrow$ no difference, $\uparrow$ significant increase, $\downarrow$ significant decrease.

(L): Lymphocytes; (B): Buccal cells.

APOP: Apoptotic bodies; BN: Binucleated cells; BEGG: Broken egg; CC: Condensed chromatin; KHC: Karyorrhectic; KLC: Karyolysis; MN: Micronuclei; NBUD: Nuclear buds; NPB: Nucleoplasmic bridges; PYC: Pyknotic.

^a The study did not present the values, but it presented the frequency ratio (RF). Making it possible to verify the presence of statistical difference.^b Data referring to “differentiated cells” provided by the study.

The majority of studies are concentrated in coal miners mainly due to the high number of coal mines around the globe. Coal is one of the most commonly ore extracted in the world due to its multiple needs, especially its use in power generation plants [1]. This review included studies in miners from eight different countries and sought to assess genetic damage and DNA alterations through different genotoxicity biomarkers. This review highlights the use of traditional biomarkers, such as CA, SCE, and MN formation and DNA damage, evaluated through comet assays [11,14,18–23,25,26,28,29,33], and some more recently used biomarkers, such as telomere length, % methylation in DNA and mitochondrial DNA copy number among coal miners [16,29,39]. In addition, some authors also evaluated the presence of polymorphisms in metabolism genes and DNA repair genes [18,21,29,33,40,41]. It is important to emphasize the quality of the studies developed by the different research groups and the pattern of biomarkers used to assess genetic damage, which made the comparison between the studies possible. Only two studies did not present parameters of traditional biomarkers and did not report having used data from previous studies available in the literature [16,41].

The major finding regarding coal miners is that all studies that evaluated outcomes with traditional biomarkers found statistically significant differences when comparing the exposed group with the nonexposed group. These data are extremely important and raise concern because coal dust continues to be classified as non-carcinogenic to humans by the International Cancer Research Agency (IARC) [22,30].

It is interesting to mention that the studies that compared different activities performed by miners, seeking to relate the degree of exposure and DNA damage [18,28], found a significant increase in genetic damage in workers with activities linked to greater exposure. It is also important to highlight the studies that evaluated polymorphisms of metabolic genes and DNA repair, indicating advances in the knowledge of how malfunction of DNA repair machinery can lead to cell death and genetic damage and how polymorphisms may indicate evidence of early

DNA damage [18,29,33,40]. Finally, we highlight the importance of evaluating miners' lifestyle, which can be associated with genetic damage [14–17]. As mentioned by Qiu et al. [42], it is important to understand the intrinsic relationship between occupational and lifestyle factors and, finally, how this relationship may influence genetic damage and occupational health.

3.2. Uranium miner exposure

The second group of miners studied were uranium miners. The attention to the possibility of damage to genetic material of these workers is intrinsically related to the fact that ionizing radiation was the first recognized factor with mutagenic properties [43]. Ionizing radiation cause numerous of genetic damage including oxidation of DNA bases, generation of single-strand breaks and double-strand breaks, base modifications and protein-DNA crosslinks [44,45]. Concerns regarding the exposure of uranium miners to ionizing radiation is not only due to uranium itself, but also to its decay products, mainly radon and radon progeny, which are well-known human lung carcinogens according to IARC [46].

Radon is a radioactive noble gas released by the uranium decay chain [44]. The risk of lung cancer is associated with radon and its progeny due to cumulative radon exposure, exposure rate, duration of exposure, time since exposure and attained age of miners [47,48]. The literature showed a dose-dependent increase in mortality from lung cancer in uranium miners due their exposure to radon and its progeny [46,48]. Thus, it is comprehensible why most of the included studies about uranium miners focus on possible genetic outcomes caused by exposure to Radon.

There are two major research lines being developed among uranium miners and genetic damage. The first seeks to find and evaluate potential new genetic biomarkers that contribute to early detection of genetic damage and its possible relationship with high cancer risk [13,27,49].

Table 3

Summary of the main methods and results of studies on chromosomal aberrations.

Exposure	Exposed/ control	Exposure markers	Parameter (Cell type)	Mean $\pm$ SD	Results	Fold difference vs. control	Cells scored/ subject	Ref.
Coal	39/34	Respirable coal mine dust	AT (L)	5.8 $\pm$ 0.4	↑	5.5	100	[20]
			AT (L)	4.7 $\pm$ 0.3	↑	2.2	100	
Coal	116/169	–	CTB (L)	2.7 $\pm$ 0.2	↑	1.8	200	[15]
			CHB (L)	2.0 $\pm$ 0.1	↑	3.1		
			DIC (L)	0.2 $\pm$ 0.0	↑	5.5		
Coal	58/24	–	AT (L)	2.8*	↑	1.9	100	[14]
			CTB (L)	1.8*	↑	2.0		
			CHB (L)	0.8*	↑	1.7		
			DIC (L)	0.2*	↑	–		
			AT (L)	5.6*	↑	1.5		
Coal	132/124	–	CTB (L)	3.9*	↑	1.5	100	[25]
			CHB (L)	1.6*	↑	5.3		
			DIC (L)	0.2*	↑	4.3		
			AT (L)	5.5	↑	1.5		
Coal	48/42	–	CTB (L)	3.7	↑	1.5	–	[33]
			CHB (L)	1.8	↔	1.5		
			DIC (L)	0.3	↑	3.1		
			AT (L)	2.1	↑	1.6		
Coal	27/23	Ionizing radiation	CTB (L)	11.5	↑	1.4	1000	[12]
			CHB (L)	11.1	↑	2.4		
			DIC (L)	3.6	↑	2.8		
Uranium	73/23	Ionizing radiation	AT (L)	2.9 $\pm$ 2.6	↑	1.8	100	[24]
			DIC (L)	0.1 $\pm$ 0.3	↔	2.0		
			AT (L)	2.2	↑	1.6		
Uranium	60/23	Ionizing radiation	CTB (L)	11.7	↑	1.4	1000	[12]
			CHB (L)	12.4	↑	2.7		
			DIC (L)	3.2	↑	2.5		
			AT (L)	2.5**	–	–		
Uranium	238/0	–	CTB (L)	1.2**	↔	–	100	[34]
			CHB (L)	1.0**	↔	–		

Significant statistical difference between exposure vs. control, $p < 0.05$ according to the authors: ↔ no difference, ↑ significant increase, ↓ significant decrease.

(L): Lymphocytes; (B): Buccal cells.

AT: Aberrations Total (%); CHB: Chromosomal breaks; CTB: Chromatid-type breaks; DIC: Dicentric chromosomes.

* Mean calculated by the authors: [14], mean value between Mine I and Mine II groups, both in the period of March (beginning of the study); [25], mean value between Study group (coal miners with diseases) and Control 2 (Healthy coal miners).

** Median.

Table 4

Summary of the main methods and results of studies on DNA damage (comet assay).

Exposure	Exposed/ control	Exposure markers	Parameter	Mean $\pm$ SD	Results	Fold difference vs. control	Cells scored/ subject	Ref.
Coal	68/46	–	Damage Index ^a	33.7 $\pm$ 3.5	↑	2.2	100	[29]
Coal	158/-	–	Tail Moment	9.5	–	–	100	[17]
			% tail DNA	4.3 $\pm$ 0.4	↑	2		
Coal	94/169	–	Tail Moment	1.4 $\pm$ 0.2	↑	2.7	100	[15]
			Olive Tail Moment	1.9 $\pm$ 0.2	↑	2.5		
Coal	71/57	Trace elements in blood	Damage Index ^a	33.7 $\pm$ 28.7	↑	2.2	100	[22]
			Damage frequency	27.4 $\pm$ 23.7	↑	2.2		
			% tail DNA	2.7*	↔	1.2		
Coal	158/48	–	Tail Moment	9.7*	↔	1.1	100	[28]
			Tail length	2.9*	↔	0.8		
Coal	100/100	–	% tail DNA	^b	↑	4.1	100	[18]
			Damage Index ^a	^b	↑	4.8		
			Damage Index ^a	60 $\pm$ 39.5	↑	6.7		
Coal	100/100	–	% tail DNA	13.1 $\pm$ 7.9	↑	4.5	100	[19]
			Tail length	23.4 $\pm$ 6.5	↑	1.6		
Uranium	106/23	Ionizing radiation	Damage frequency	4.4 $\pm$ 11.0	↔	1.8	60	[24]

Significant statistical difference between exposure vs. control, $p < 0.05$ according to the authors: ↔ no difference, ↑ significant increase, ↓ significant decrease.^a The authors mention for the calculation of the "damage index" that the values for the damage index could range from 0 (100 cells class 0) up to 400 (100 cells class 4).^b The study did not present the values, but it presented the frequency ratio (RF). Making it possible to verify the presence of statistical difference.

* Mean calculated by the authors: [28], mean value between workers 1 and workers 2 groups.

While, the second investigates genetic damage with well-established traditional biomarkers, such as MN, CA and comet assay [12,24,33,34].

There were many different techniques that allow the identification of cancer risk among uranium miners. Among these techniques the most common analyzed were mutations in the p53 gene [45], inactivation of p163 tumor suppressor gene, O⁶-methylguanine-DNA methyltransferase repair gene by aberrant promoter methylation [27,49] and modified

nucleosides through urine [13]. Recently, Rosemberguer et al. [44], explained a genome-wide significant interaction of the marker rs12440014 within the gene CHRN4.

Some trends can be observed in studies that evaluated traditional genetic damage biomarkers. All of them found a significant increase in the frequency of CA, compared to the control group [12,24,34], highlighting the effect of ionizing radiation on DNA. Studies that evaluated

the number of MN in former uranium miners did not observe an increase in this outcome in lymphocytes [31] and in epithelial cells from sputum [32]. According to Zölzer et al. [31], this can be explained because unstable CA and MN are short-lived and usually considered unsuitable biomarkers of radiation exposure after more than a few years. However, there are cases in which elevated frequencies of such genetic damage have been reported in individuals many years after they had been in contact with radiation [50].

Several considerations should be highlighted regarding studies that have evaluated damaging endpoints to DNA in uranium miners. Popp et al. [24] attributed their findings of enhanced aberration rates connected with alterations of other biomarkers in former miners as a symptom of genomic instability and repair deficiency, which is also observed by Kryscio et al. [50]. Zölzer et al. [31], from his results with individuals who worked as uranium processors, indicate the possibility that uranium miners received a greater percentage of their effective dose from the inhalation of Radon and its progeny, so their genetic damage is possibly higher. Finally, based on Wolf findings [12], we highlight the importance of assessing associated factors such as age, lifestyle, illnesses, medications and diagnostic irradiations, which can represent higher importance to genetic damage than the exposure obtained during mining.

4. Bibliometric analysis and timeline

The bibliometric analysis performed identified the main aspects related to the genetic damage of miners regardless of the ores being extracted. The network view map is presented in Fig. 2. The software divided and classified the terms into two clusters. The red cluster comprised terms related to uranium miners and exposure to radioactive substances during mining, whereas the green cluster grouped terms related to coal exposure. Bibliometric mapping also demonstrated the association of coal miners with silicosis and pneumoconiosis and uranium miners with lung cancer and tumors. Some terms are commonly considered associated with the presence of damage to genetic material, such as age, smoking, time of work and exposure to radiation and their proximity to DNA damage in miners. Diesel exhaust by equipment and machinery in underground mines is an important topic that might be considered genetic damage in miners as recognized by bibliographic mapping. Finally, bibliometrics related the main techniques used to measure damage to genetic material, highlighting comet assays and chromosomal aberrations.

Temporally, studies investigating genetic damage in miners started in the 1960s based on the evaluation of chromosomal aberrations in uranium miners. Concerns about genetic damage resulting from occupational activity in coal mines began in the 1980s with the use of chromosomal aberration tests. In the following decades, other types of miners were investigated, but a large volume of study remained among uranium and coal miners. On the other hand, the number of genetic and cytogenetic techniques used has expanded and, more recently, has evolved to molecular and epigenetic assessments with the aim of investigating mechanisms of individual susceptibility (Fig. 3).

5. Summary and concluding remarks

In general, the collection of studies included in this review points to an increase in genetic damage in miners. The major focus of this investigation between exposure to ore and genetic damage in miners has been coal miners and, to a lesser extent, uranium miners. The relationship between occupational exposure in non-coal and non-uranium activities remains almost unknown. In addition, studies have concentrated on a small number of countries, which is an important point to be explored, given that socioeconomic conditions, eating habits and lifestyle are associated with genotoxic outcomes.

In general, studies have been conducted with populations over the age of 40 years and predominantly male, obviously reflecting the type of occupation in mining areas. Although age is a factor commonly associated with increased mutagenic damage, an important number of studies have shown no association between age and genetic damage. Perhaps in an aggressive occupational scenario, age loses importance compared to studies with unexposed (healthy) populations. In addition, as the studies are performed with older individuals, it is possible that other cumulative associated factors mask this hypothetically linear association.

Moreover, in addition to occupational exposure (primary factor), exposure time, smoking and alcohol consumption were the most investigated variables but still exhibited no clear association with increased genetic risk in this population. In this field, there are still countless questions to be answered given that many studies minimally addressed lifestyle, eating habits and health conditions. Another limitation is the lack of details on occupations and service stations. Most studies have grouped all miners into a single group and compared them to an unexposed group. In addition, few studies use exposure biomarkers (e.g., measurements of metals in biological matrices), reducing the clarity between exposure and effect. Finally, it was observed that there is

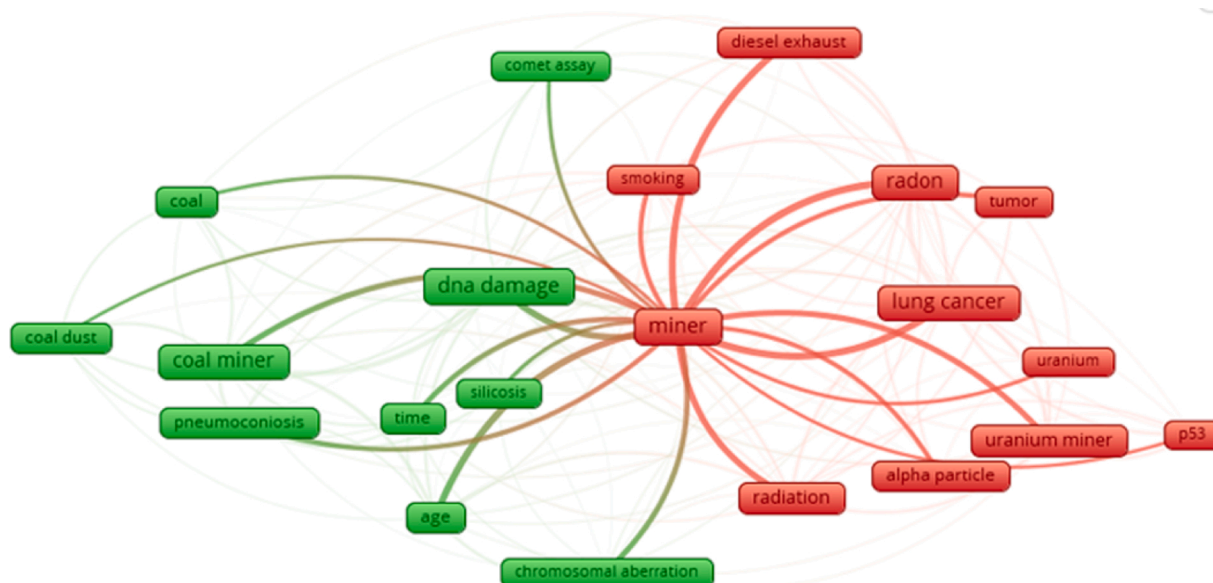


Fig. 2. Network view map generated in VOSviewer Web of Science database.

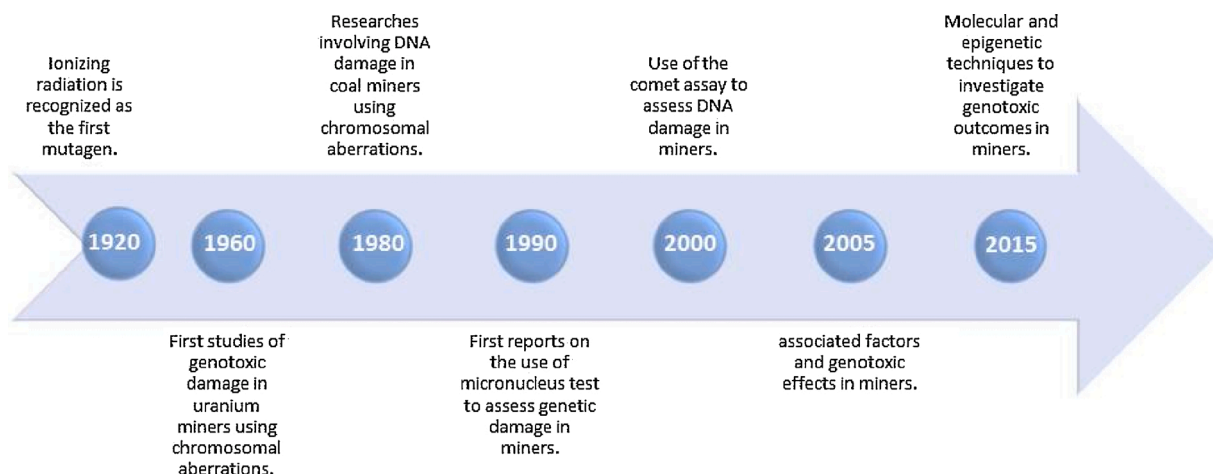


Fig. 3. Timeline of genetic damage studies among miners.

a small number of studies investigating miners of other types of ores and genetic damage. Thus, we highlight the need to encourage studies that fill these knowledge gaps.

Regarding the biomarkers and bioassays used, classic methods have been shown to be sensitive when detecting the damage resulting from occupational exposure with an average increase of 2 to 4-fold in relation to the unexposed groups. On the other hand, a vast field of more recent markers directly or indirectly associated with genotoxicity and mutagenicity (polymorphisms, genes involved in DNA repair, methylation) emerges as an alternative to elucidate cellular mechanisms and individual susceptibility.

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Author Declaration

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from f.m.r.silvajunior@gmail.com

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.mrgentox.2021.503348>.

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