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Genes involved in lung cancer in non-smokers associated with radon exposure

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Abstract
Tobacco exposure is the main risk factor for the development of lung cancer, however, it is known that at least 10% and 20% of diagnosed men and women, respectively, are never-smokers. In these individuals, lung cancer has distinct genetic mechanisms compared to smokers and comprise, in most cases, driver mutations in tumor promoting genes capable of triggering carcinogenic activity. The main genes affected in this group of individuals are EGFR, ALK and ROS1. Currently, the main risk factor for the appearance of lung cancer in never-smokers is the exposure to radon gas, a radioactive gas present in atmospheric air, soils, vegetation, dwellings, and other buildings. The risk of radon is that when inhaled, it deposits directly on the lung tissue. This element and its decay products emit alpha particles that may cause severe DNA damage and eventually lung cancer through years of exposure. This systematic review aims to synthesize the knowledge about genetic mechanisms linked to lung cancer in never-smokers and to gather the most recent studies on the association of radon gas with this neoplasm.

Keywords: *lung cancer, radon gas, carcinogenesis, mutation.*

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I. Introduction

Lung cancer is the leading cause of cancer incidence and mortality worldwide. The malignancy is characterized as a pathology causally related to the degree of economic development, social factors, and the lifestyle of the population of a country [1]. In Brazil, lung cancer stands as the second most commonly diagnosed cancer in men and women, and is also the second leading cause of death [2].

Tobacco is the main risk factor for lung cancer development [3]. However, estimates indicate that 10% and 20% of diagnosed men and women, respectively, were never-smokers [4]. Interestingly, the external variable that has the highest isolated risk value for the occurrence of this neoplasm is the existence of an early-diagnosed first-degree relative (< 60 years old), observed by lung cancer screening models. The existence of previous pathologies, including pneumonia, chronic obstructive pulmonary disease, passive smoking and exposure to asbestos and radon gas are additional factors that may increase lung cancer incidence, independently of the use of tobacco [3,5].

Lung cancer can be divided into two histological types: Small-Cell Lung Cancer (SCLC) and Non-Small-Cell Lung Cancer (NSCLC) [6]. NSCLC can also be classified as Large-Cell Carcinoma, Squamous Cell and Adenocarcinoma. Importantly, about 65% of non-smokers with lung cancer are diagnosed with adenocarcinoma [7]. Several genes are proven to be associated with this type of cancer, such as EGFR, KRAS, ALK, ROS1, BRAF, TP53, genes in 15q25 locus, among others, being the mutations in EGFR, ALK and ROS1 the most found in non-smokers [7,8].

Exposure to ionizing radiation (alpha and beta particles, and gamma-ray) is one of the most documented factors in clinical literature that can induce severe mutations in DNA, thus triggering the surge of tumors [9]. About 55% of the natural radiation received by humans comes from radon, a noble and radioactive gas formed by radioactive decay of uranium and thorium in soil and rocks [9,10][7,11]. In fact, radon exposure is known to be the second most important cause of lung cancer after smoking in the general population [11]. Prior studies have shown that the possible biological mechanisms related to radon emission and lung cancer in non-smokers comprise chromosomal aberrations, generation of reactive oxygen species (ROS), positive and negative regulation of cytokines and protein synthesis associated with cell cycle regulation [12].

Thereby, this work thoroughly reviews the recently published scientific data that correlates radon gas exposure, genetic modifications and lung cancer in non-smokers.

II. Methods

The present study is a bibliographic review proposed after a thorough research of the literature addressing the topic of lung cancer in non-smokers and its relation to radon exposure. The search was limited to studies published from 2000 to 2020, and the articles were retrieved through the Pubmed database. Our choice of descriptors combined terms related to lung cancer ("lung cancer", "lung neoplasms"), non-smoking ("non-smokers", "never smokers"), and also related to the main genes involved in this pathology ("EGFR", "KRAS", "ALK", "BRAF", "ROS1", "TP53"), using the connective "AND" between the descriptors. In the search of radon-related studies, we applied exclusively the keyword "radon exposure" with the two first descriptors, excluding the genetic factors. Additional articles were used from the reference list of other reviews. Regarding the studies restricted to radon exposure and lung cancer, 10 papers were included into the discussion based on the flowchart shown in Figure 3.

III. Genes involved in Lung Cancer

3.1. EGFR

The EGFR is a membrane receptor tyrosine kinase (RTK) that belongs to the ErbB receptor's family, which hosts human epidermal growth factor receptors (HERs) [13]. Firstly described in 1965 by Cohen, the EGFR's structure has an extracellular (N-terminal) domain, a transmembrane domain and an intracellular (C-terminal) domain. The tyrosine kinase activity occurs in the C-terminal part, while the N-terminal domain confers ligand specificity to the ligands EGF (HERs), TGF-α (transforming growth factor α), amphiregulin and betacellulin [14].

According to Figure 1, two main pathways related to EGFR are those guided by MAPK (mitogen-activated protein kinase) and by PI3K (phosphatidylinositol 3-kinase) [15-17]. The MAPK proteins undergo a phosphorylation cascade and will activate gene expression of regulatory factors for division, motility and cell adhesion [16]. The PI3K activates serine/threonine kinase (AKT), which plays a role in metabolic regulation of glycolytic apoptosis, cell proliferation and angiogenesis.

The EGRF's tyrosine-kinase function may be unregulated due to oncogenic mechanisms associated with activating mutations in EGFR gene and with overexpression of EGFR molecules in the tumor cell membranes [18]. There are more than 200 mutations already identified in the EGFR gene. Nevertheless, exon 19 deletion and exon 21 point mutations are the most detected. These alterations induce an activated receptor state. Such mutations were found in samples of patients with NSCLC, especially in adenocarcinomas, hence highlighting a continuous activity of the pathways associated with this receptor [19-21].

3.2. ALK

Anaplastic lymphoma kinase (ALK) is a transmembrane tyrosine-kinase receptor belonging to the insulin receptor family [22]. Heparin-binding growth factors, such as Pleiotrophin (PTN) and Midkine (MK), were previously reported as ALK's ligand activators related to neuronal development and carcinogenesis [23,24]. Nevertheless, other studies pointed to controversial outcomes regarding these ligands. Indeed, the exact physiological function of ALK is still poorly understood [25].

The fusion of ALK with other genes is strongly associated with the development of adenocarcinoma in non-smokers [26,27,28]. These structural alterations occur in the short arm of chromosome 2 and generate the fusion of exon 20 of the ALK gene with other genes, being EML4 (echinoderm microtubule-associated protein-like 4) the most frequent one, especially in NSCLC. This restructuration creates a fusion protein, which dimerizes to provide constant tyrosine-kinase activity. Hence, the activity of pathways related to cell proliferation will increase, thus triggering tumor formation [28]. The main signal transduction pathways activated due to ALK action comprise phospholipase Cy (PLCy), JAK/STAT (Janus kinase-signal transducer and activator of transcription), PI3K/AKT, and MAPK and GTPases signaling cascades, as shown in Figure 1. Accordingly, it is well known that the mechanisms of action by which they operate are associated with growth, transformation and anti-apoptotic cell signaling [29,30,31,32].

3.3. KRAS

KRAS is a proto-oncogene located downstream of the EGFR signaling pathway, which belongs to the RAS gene family that encodes G-proteins with intrinsic GTPase activity [33]. The GTPase belongs to the hydrolase enzyme group, whose function is to bind and hydrolyze GTP (guanosine triphosphate). In the resting cell, RAS proteins are bound to GDP (guanosine diphosphate) and remain in their inactive state [34]. The activation of these proteins is regulated by guanine nucleotide exchange factors (GEFs), thus allowing the conversion of GDP to GTP [35]. Activated GTPase transmits signals from EGFR receptor activation to various pathways that will regulate cell proliferation, growth and motility. As shown in Figure 1, the KRAS protein linked to GTP, that is, activated, has an intrinsic activity catalyzed by GAPs (GTPase-activating proteins) that hydrolyzes GTP into GDP, and then it returns to its inactive state. Thus, mutations in RAS proteins prevent the occurrence of

this hydrolysis, keeping them constantly activated [36,37]. Therefore, under these conditions, there will be a continuous stimulation of factors involved in cell proliferation, differentiation and apoptosis. Loss of intrinsic activity and deregulation of cell proliferation signals are due to point mutations and tumors [33,38,39].

Mutant KRAS is present in about 30% of lung adenocarcinomas and is particularly affected by missense mutations in codons 12, 13 and 61. The oncogene plays a crucial role in the growth of cancer cells and resistance to therapy, driving the activation of signaling pathways without stimulating EGFR gene and/or HER receptors [35,40-42].

Mutations in the KRAS oncogene are more frequently seen in adenocarcinomas in smokers (19%) than in non-smokers (3.6%), and occur in a mutually exclusive way in relation to mutations in the EGFR gene [43].

3.4. ROS1

Similar to ALK gene, the proto-oncogene ROS1 is also a tyrosine-kinase receptor in the insulin receptor family [44]. The protein synthesized from this gene acts as a factor of cell growth and differentiation because it activates several signaling pathways related to cell proliferation. Among these pathways, the ones mediated by STAT3 (Signal Transducers and Activators of Transcription), activated after phosphorylation by ROS1, and the PI3K/AKT pathway, stand out (Figure 2) [45,46,47]. Both are also identified in the mechanisms of action of EGFR.

The transmembrane portion of the ROS1 receptor is generally lost in cases of rearrangements. Consequently, the synthesized fusion protein is translocated from the plasma membrane to the cytoplasm. This abnormal condition allows it to interact with different substrates and signaling pathways that will directly influence cellular changes. However, some other fusion proteins still remain with the transmembrane part of ROS1, indicating that different rearrangements can result in different cell interactions and, thus, in different signal transductions [48,49,50].

ROS1 rearrangements are found in about 2% of NSCLC, being even more frequent in young non-smokers with adenocarcinoma and who do not have other driver mutations in their tumors. Because of that, the fusion of ROS1 in NSCLC tends to occur in a mutually exclusive way in relation to mutations in EGFR and rearrangements of ALK [51,52].

3.5. BRAF

The proto-oncogene BRAF encodes a RAS-regulated kinase (rapidly accelerated fibrosarcoma) and acts as an intercessor in the pathways of MAPK, which in turn interferes with cell proliferation and differentiation, angiogenesis, senescence and apoptosis [53-55]. The BRAF protein has 3 domains, CR1, CR2 and CR3. The CR1 portion acts as an auto-inhibitor of the CR3 domain and has a binding region for a RAS-GTP protein. CR2 is rich in serine and threonine residues, thereby conferring flexibility to the protein. CR3 is the domain that provides the kinase activity and the binding of the ATP molecule and other substrates. CR3 has also a P-loop region (handle), which is important for maintaining BRAF's inactive conformation. In the activated state, a RAS-GTP protein interacts with the CR1 region and the BRAF is phosphorylated. Then, the proto-oncogene undergoes a dimerization of its structure and the kinase domain is activated, leading to phosphorylation of MEK1 and MEK2, proteins of the MAPK pathway [56-60].

Mutations in the BRAF oncogene are found in approximately 2-5% of NSCLC and can be classified into V600E and non-V600E mutations [61]. Non-V600E mutations correspond to 50-80% of BRAF mutations and are more frequent in NSCLC than V600 mutations [61,62,63]. Such mutations occur in exons 11 and 15, and demonstrate low to moderate kinase activity when compared to V600E mutations [61,64,65]. According to the study conducted by Cardarella et al. (2013), mutations in the BRAF gene occur more commonly in smokers than in non-smokers, however, both V600E and non-V600E mutations can also be observed in non-smokers [66]. The BRAF proto-oncogene mechanism is described in Figure 2.

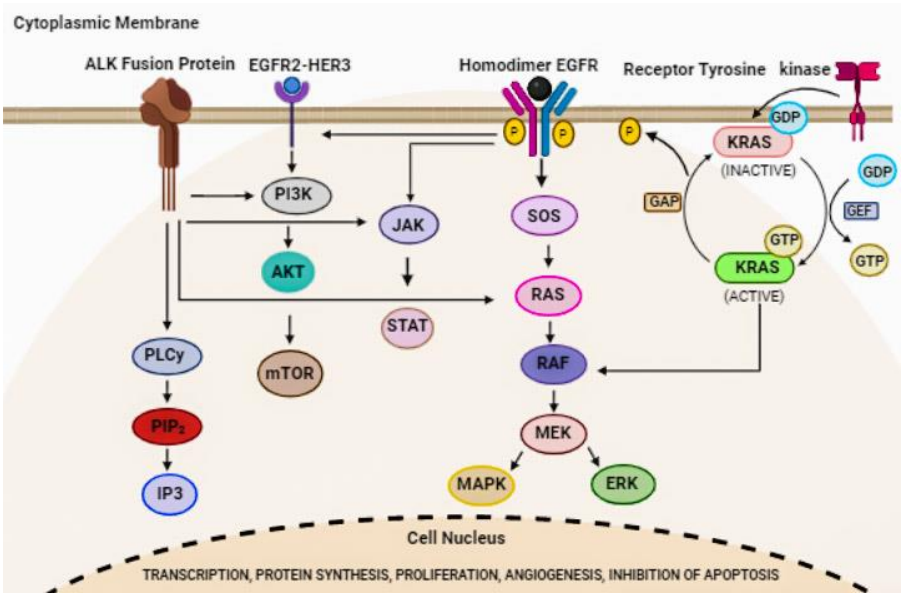
3.6. TP53

TP53 is a gene that encodes the tumor suppressor p53, a protein capable of activating DNA repair, interrupting the progression of the cell cycle and inducing apoptosis through transcriptional activation of the tumor suppressor gene p21 [67-70]. The suppressor p53 plays a key role in both cell cycle and transcription factor, and regulates several genes in response to cell injuries, such as DNA damage and activation of oncogenes [71,72].

TP53 mutations are present in approximately 50% of NSCLC. Such mutations occur from genomic instabilities of aneuploidies, presence of missense mutations, in addition to massive amount of somatic mutations. As the tumor advances, these somatic mutations are accompanied by loss of heterozygosity (LOH) [71,73-75]. When there is loss of cellular programming, the mutations can result in uncontrolled cell proliferation and carcinogenesis [76,77]. Most of these mutations occur in the DNA-binding domain (DBD) and promote loss of protein activity [78].

Interestingly, p53 tumor suppressor can be stabilized by three pathways (Figure 2). The first one comprises the response to DNA damage caused by ionizing or ultraviolet radiation involving both ATM kinases (ataxia-telangiectasia mutated) and Chk2 (checkpoint kinase 2). ATM kinases are essential for cell replication, being activated in the S phase of the cell cycle. Chk2, a stable protein expressed throughout the cell cycle, is activated through phosphorylation mechanisms by the ATM axis [79-82]. The second pathway comprehends the p14ARF protein, which consolidates the p53 through the HDM2 binding, keeping it in the nucleoli. Within it, p53 is fostered by modified growth signals [83,84]. The third pathway is conducted by ultraviolet light, chemotherapeutic drugs and protein kinase inhibitors, including a serine/threonine-protein kinase (ATR) [85].

P53 degradation occurs from ubiquitin-mediated proteolysis. Ubiquitin acts as a marker that promotes the detection of p53 by protein degradation machinery, which is controlled by the MDM2 oncogene, whose function is to modulate the p53 tumor suppressor activity. The binding between the protein and p53 promotes the addition of ubiquitin groups, hence inducing the degradation of p53 [86].



Figre 1 – Scheme representing the mechanism of ALK, EGFR and KRAS pathways.

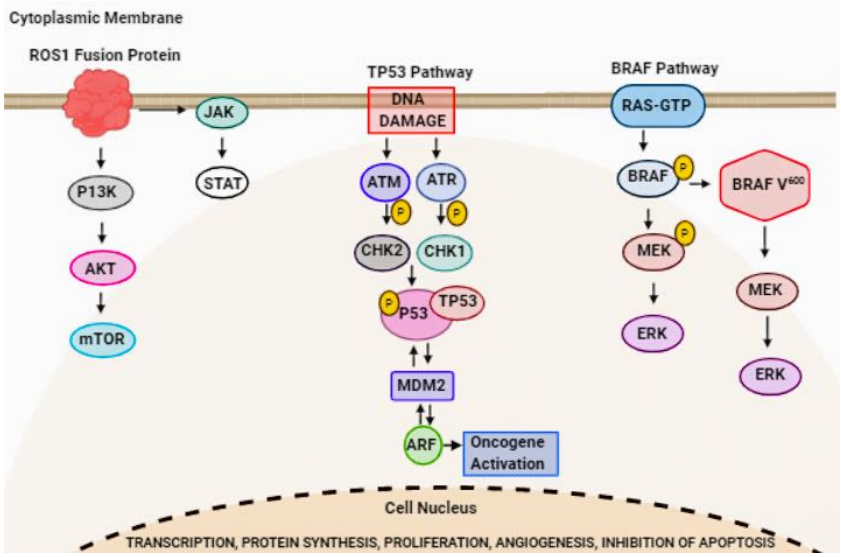


Figure 2 - Scheme representing the mechanism of ROS1, TP53 and BRAF pathways.

IV. Radon

Smoking is the main risk factor for lung cancer. However, studies revealed that exposure to radon gas can be considered one of the major threats to the increased incidence of this cancer among non-smokers [87-90].

There is still no clear evidence on the health effects caused by radon exposure in the short term, but at longer periods, there is strong evidence of its relation with lung cancer [9,91].

Radon is a noble, radioactive, colorless, and odorless gas. As a naturally occurring material, radon is originated from the decay of uranium and thorium, and is found in soil and rocks, from which it diffuses into nature through porous and fractures. Being denser than air, radon is easily found in the lower layers of the atmosphere, and is deposited on vegetation, plantations, soils, buildings and natural watercourses [9,10,92]. According to the International Commission on Radiological Protection (ICRP), approximately 55% of the incidence of radiation during human lifetime comes from radon and its decay products. Further, the International Agency for Research on Cancer (IARC) recognizes radon as a Class I carcinogen for humans [9].

The radiation from this compound emits alpha particles, the ones with less ability to penetrate skin among ionizing radiation. However, if the radiation-emitting material is inside the body, similar to an inhalation process, its lack of penetration will also be active, thus preventing it from leaving the body [9,92].

Biological mechanisms related to radon exposure may increase the risk of genetic mutations, chromosomal changes and deregulation of proteins associated with the maintenance of the cell cycle [93,94]. The ionizing radiation emitted by alpha particles induces the oxidation of DNA bases and generates single-strand (SSBs) and double-strand (DSBs) breaks. Evidences suggest that the injuries caused by these particles are mediated by reactive oxygen species (ROS) that can increase oxidative stress and, consequently, induce inflammatory processes and directly reach the cell nucleus [95-97].

The exposure of an individual to radon is closely related to the concentration levels found within the residences and buildings where they live or frequent. Such concentrations are dependent on the possible amount of uranium in the soil around the establishment, the presence of cracks in the walls and floors and the way the residence is ventilated. Although the World Health Organization (WHO) recommends a maximum concentration of radon of 100 Bq/m³ in air, findings reveal that an increased risk of developing lung cancer cannot be rule out, even at concentrations below those established [9,11].

V. Results and Discussion

As shown in Figure 3, from 64 studies that integrated the variables "lung cancer", "exposure to radon" and "non-smokers", only 10 had similar objectives to the present study, and were selected for discussion (Table 1).

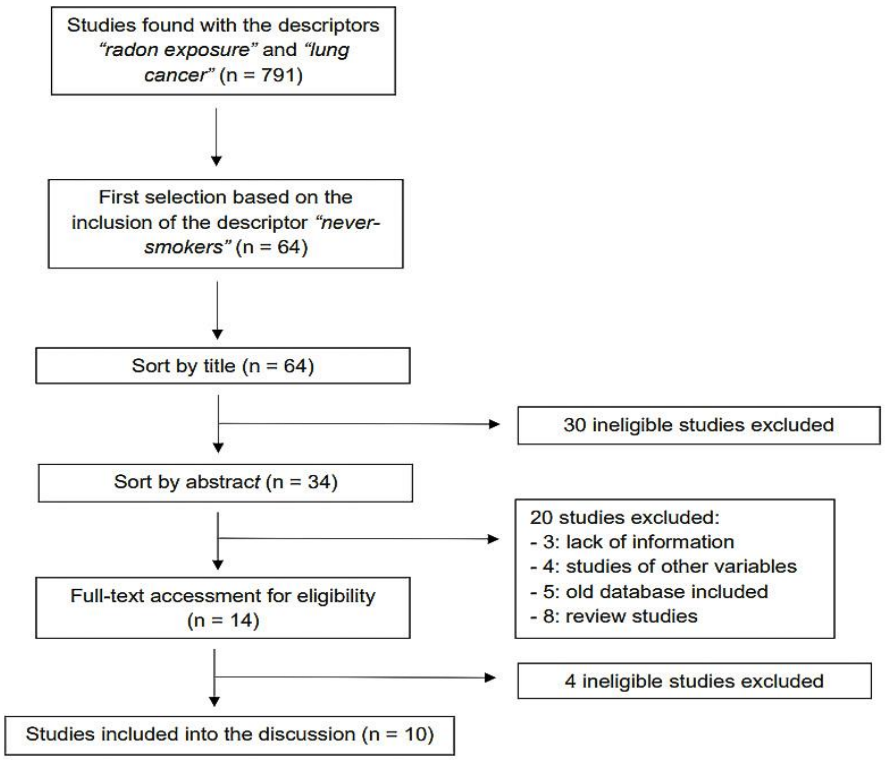


Figure 3 – Flowchart summarizing the bibliographic research and the study selection method

Table 1 – Studies selected for discussion.

Authors,Year [reference]	Locality	Type of Study	Lung cancer population studied	Range or average of Radon Concentration (Bq/m³)

Thompson et al., 2008 [98]	Massachusetts (USA)	Case-control	Smokers, non-smokers and former smokers	61.6 to 176.8	
Taga et al., 2012 [108]	Missouri (USA)	Case-control	Non-smokers and former smokers	-Mutations Median 63.7 IQR 30.5-94.1	+Mutations Median 46.5 IQR 37.0-57.4
Grundy et al., 2017 [99]	Alberta (Canada)	Cohort	Smokers and non-smokers	Avrg 71.0	
(1)Torres-Dúran et al., 2014 [100]	Galicia, Asturias (Spain)	Case-control	Non-smokers		NI 114,7 GM
Torres-Dúran et al., 2015 [102]	Galicia (Spain)	Case-control	Non-smokers	Cases: Median 187 Range 11 to 2350	Controls: Median 149 Range 18 to 1084
Ruano-Ravina et al., 2016 [107]	Galicia (Spain)	Case-control	Non-smokers	Median 182 Range 11-2350 IQR 103.5-333	
Lorenzo-Gonzalez et al., 2019 [101]	Spain	Case-control	Non-smokers		NI 114,7 GM
Casal-Mouriño et al., 2020 [103]	Spain	Case-control	Non-smokers	186 (available for 306 patients)	
Choi et al., 2017 [109]	South Korea	Analytic	Non-smokers	Median 61 Range 22.8-163.6	Nation-wide GM 43,3
Lim et al., 2019 [106]	South Korea	Analytic	Non-smokers	Median 48	Nation-wide GM 43,3

NI: not informed; avrg: average; GM: geometric mean; IQR: interquartile range; "-Mutations", means no mutations in EGFR receptor; "+Mutations" means mutations in EGFR receptor.

(1) The author did not inform the range neither average but presented 4 classes of study: ≤ 100; 101-147; 148-199; ≥ 200 Bq/m³. GM value retrieved from the webpage of Galician Radon Laboratory (http://radon.gal/radon-en-galicia/tablas-de-medicions/).

The study carried out by Thompson et al. (2008) aimed to establish the chances of developing lung cancer associated with exposure to radon. The authors divided the cases (n = 200) and controls (n = 397) into 3 groups according to the smoking history: non-smokers, smokers and ex-smokers, with only 15 of the cases of non-smokers. The average concentrations of residential radon varied between 61.6 and 176.8 Bq/m³. The statistical data analysis revealed that as the radon concentration increases up to 150 Bq/m³, the chances of lung cancer decrease significantly with adjusted odds ratio (AOR) ranging from 0.75 to 0.36 (95% CI), from the concentration "≤ 25 Bq/m³" to "≤ 250 Bq/m³", all statistically significant ($p < 0.1$). Thus, these findings confirmed that there was a reduction in the probability of occurrence of this neoplasm after the exposure to radon. Notwithstanding that, as the authors themselves reported, these results differed considerably from previously published studies, in addition to not having independently exposed AORs of non-smokers [98].

In contrast, Grundy et al. (2017) evaluated the attributable risk of lung cancer for the population of Alberta, Canada, after residential exposure to radon. The authors considered populations of smokers and non-smokers, and obtained an average residential radon concentration of 71.0 Bq/m³. Considering 1,952 studied cases, the attributable risk reached an average of 16.6% when not related to smoking. However, when the smoking history was examined, a higher estimate was obtained for non-smokers (24.8%, n = 195) when compared to smokers (15.6%, n = 1,757). Proportionally, more non-smoking patients developed lung cancer due to radon exposure than smokers. Yet, in absolute numbers, of the 324 cases attributed to radon exposure, 48 were non-smokers and 274 were smokers. Thus, the authors stated that the discrepancy between both groups is because approximately only 10% of lung cancer cases occur in non-smokers, making it impossible for the number of cases between these categories to be equal [99].

The case-control study performed by Torres-Dúran et al. (2014) evaluated the influence on non-smokers and a possible interference of secondhand smoke in the effects of residential radon exposure. All cases included (n = 192) were non-smoking individuals. According to the results, the risk of developing lung cancer in non-smokers increased when they were exposed to concentrations ≥ 200 Bq/m³ (OR of 2.42, at 95% CI 1.45-4.06). This result corroborates with the hypothesis that the radon concentration needed to promote lung cancer in non-smokers must be higher than that in smokers, since smoking and radon have additive effects, therefore creating conditions that, even in lower concentrations, this neoplasm can occur. Furthermore, lung cancer risk increases for non-smokers exposed to tobacco smoke through cohabitation with smokers for more than 20 years when radon concentrations are higher than 200 Bq/m³ (OR of 1.83, 95% CI 1.01-3.30). In conclusion, the association of secondhand smoke with exposure to radon is capable of further intensifying the risk of developing lung cancer in non-smokers [100].

Lorenzo-González et al. (2019) conducted a similar study as Torres-Durán et al. (2014) [101] about lung cancer in non-smokers, but with a considerably higher number of cases (n = 489). The authors demonstrated that concentrations higher than 200 Bq/m³ increase the risk for lung cancer development (OR of 1.73, 95% CI, 1.27-2.35). Further, adenocarcinoma was the most frequent histological type (73.9%), and the residences of the individuals with this type of cancer had an average radon concentration of 160 Bq/m³. Comparatively, concentrations of 150 and 109 Bq/m³ were associated with residences of patients that developed squamous cell carcinoma and large cell carcinoma, respectively. The categories "small cell carcinoma" and "other unusual histological types" obtained average concentrations even higher than that of adenocarcinoma, equivalent to 187 and 207 Bq/m³, respectively, which is, however, of little relevance, as they correspond to only 7.1% and 6.7% of the cases. This research not only demonstrated a strong association between exposure to radon and lung cancer, but also specified adenocarcinoma as the most frequently diagnosed histological type related to the neoplasm [101].

Moreover, a previous study performed by Torres-Durán et al. (2015) exhibited the prevalence of adenocarcinoma in dwellings with higher radon concentrations. The average residential radon concentration of 189 Bq/m³ was calculated in households of individuals with adenocarcinoma, against 173 Bq/m³ in the residences of individuals with small cell carcinoma and 109 Bq/m³ for those with large cell carcinoma. These findings are similar to that found by González et al. (2019) [101]. However, the category "squamous cell carcinoma" had an average radon concentration of 223 Bq/m³, higher than that observed in adenocarcinoma. Despite that, the only statistical significance refers to dwellings of individuals with adenocarcinoma, with an OR of 2.19 (95% CI 1.44-3.33) at a concentration equal or higher than 200 Bq/m³ [102], which is in accordance with González et al. (2019) [101].

Torres-Durán et al. (2015) also investigated the association of exposure to high radon concentrations with the advent of lung cancer at younger ages. Individuals with cancer under 50 years had an average exposure to the gas of 346 Bq/m³ versus 164 Bq/m³ in patients aged 61-70 years old. Remarkably, these results suggest a cumulative effect of exposure to high radon concentrations over time, being a factor responsible for the early appearance of cancer [102].

Recently, Casal-Mouriño et al. (2020) developed a multicentric case-control study with 369 cases of lung cancer in non-smokers. 79% of them were women with an average age of 72 years. Adenocarcinoma was the most frequent histological type, representing 80% of the total cases, which corroborates with the results already described [101,102]. The research aimed to assess the survival rates of lung cancer in non-smokers considering several variables, including the effect of exposure to residential radon. From a univariate descriptive analysis, the authors obtained an average survival considering three situations: one, three and five years from the diagnosis. The average concentration of residential radon was 186 Bq/m³, being part of the range of 100-299 Bq/m³, which had an average survival of 18.8 months. In the interval of 300-599 Bq/m³, they observed a survival of 14.6 months. However, for exposures greater than 600 Bq/m³, the survival was 21.6 months. Despite the result was not discussed, the authors demonstrated that patients exposed to concentrations between 300 and 599 Bq/m³ have lower survival rates for 3 and 5 years after diagnosis, being 23 and 14%, respectively. The presence of specific mutations in the tumor of 152 patients was also evaluated, of whom 130 (85.5%) expressed EGFR mutations, 21 (13.8%) ALK mutations, and 1 (0.7%) had detectable BRAF mutations. The study concluded that the presence of these mutations is associated with a higher survival rate when compared to individuals who do not have them, a hypothesis supported by similar results obtained by Viñolas et al. (2017) and Liu et al. (2017) [103-105].

Lim et al. (2019) investigated the mutational pattern of tumors in 41 non-smokers with adenocarcinoma exposed to residential radon. The average concentration of radon was 48 Bq/m³, therefore, two groups were separated according to this value: those exposed to concentrations higher than 48 Bq/m³ and less than 48 Bq/m³. The tumor mutation burden (TMB) was measured based on the number of somatic missense mutations per megabase in the target region. It was observed that the patients exposed to concentrations greater than 48 Bq/m³ obtained a TMB value significantly higher than individuals in the group exposed to less than 48 Bq/m³ (4.94 Mb vs 2.62 Mb). No difference was found in radon concentration among patients with EGFR mutations. Meanwhile, TP53 mutations were more common in the group exposed to higher concentrations. Lastly, the authors reported that the cumulative effect of radon over time may contribute to an increase in TMB in non-smokers with lung cancer [106].

Ravina et al. (2016) also sought to relate residential exposure to radon to mutational patterns in non-smokers, especially in the EGFR and ALK genes. The study comprised 323 cases, of which 209 were selected for EGFR sequencing and 80 for ALK analysis by FISH (Fluorescence *in situ* hybridisation). The EGFR was mutated in 42% of the patients, in which deletion of exon 19 was the most frequent mutation, with 56.3% of the cases against 39.1% of point mutations in exon 21. Patients who presented mutation in exon 19 were exposed to residential radon concentrations almost twice as high as those with mutations in exon 21 (216 Bq/m³ versus 118 Bq/m³). Despite this, the mean radon concentration found in individuals with EGFR mutations was 160 Bq/m³

versus 174 Bq/m³ in those who did not have this mutation. Additionally, the residential radon concentrations between these two groups were 100-306 Bq/m³ and 95-295 Bq/m³, respectively [107].

Thus, it was not observed an association between the level of residential radon and alterations in the EGFR gene. Then, the study suggested that residential radon may induce molecular changes in driver genes of non-smoking patients, precisely because of the action of alpha radiation from this gas. In turn, higher exposures to radon will not necessarily be related to mutations in the EGFR gene. Regarding ALK, only 15% of the analyzed individuals had rearrangements on this gene, and a much higher radon concentration was detected in the residences of these patients, in comparison to others who did not have this translocation (290 Bq/m³ vs 165 Bq/m³). However, the authors claimed that the small cohort might have played a role in the low frequency of ALK rearrangements (only 12), therefore making it more difficult to find any significant associations [107].

Taga et al. (2012) evaluated the existence of a potential association between exposure to radon, secondhand smoking and the presence of EGFR mutations in non-smokers and ex-smokers with lung cancer. In terms of changes in exons within EGFR mutations, the results were similar to those of Ravina et al. (2016) [107]. Among 105 analyzed cases, the frequency of the EGFR mutation was 41%, with alterations in exons 19 and 21. However, the hypothesis of the relationship between high exposures to radon and the increased probability of mutations in the EGFR gene was not confirmed. Moreover, the research demonstrated that the frequency of these mutations may be higher in individuals exposed to lower concentrations of radon (23% between 4.8-33.3 Bq/m³) when compared to those exposed to higher concentrations (9% in > 82.7 Bq/m³) [108].

The main limitations of the study are the relatively small sample size and the low concentrations of radon attributed to the research (4.8 to > 82.7 Bq/m³) [108]. Conversely, Ravina et al. (2016) [107] reported a much higher exposure in never-smokers (100 - 306 Bq/m³) and showed a relatively equal frequency of patients with EGFR mutations (42%) when compared to Taga et. al (2013) (41%) [108]. However, this divergence can be explained based on the different geographical location in which each work was performed. As shown in Table 1, Ravina et al. (2016) [107] evaluated a region already known for being a radon prone area, which is evident in their measurements.

For the last selected paper, Choi et al. (2017) developed an exploratory research to identify the genetic changes induced by radon exposure and its potential risk of causing cancer in non-smokers. They analyzed tumor tissue, normal tissue and blood samples from 19 patients with non-small cell lung cancer. Adenocarcinoma was the most common histological type in the group. The study sought to sequence mutations of both somatic and germ lines, and 760 single nucleotide variants (SNVs) were detected in exon sequences in the germ line. In addition, 68 somatic mutations were identified in 38 genes, being EGFR (37%) and TP53 (21%) the most frequent ones, which corroborates with Lim et al. (2019) [106]. Regarding the residential radon concentration, the measures ranged from 22.75 to 163.6 Bq/m³ in the individuals analyzed. Nevertheless, no influence of radon concentration with the different patterns of genetic changes was observed in these patients. Finally, the authors reported the inadequacy of the small sample size and confirmed the need for further studies to prove or not this influence [109].

VI. Conclusions

The findings provide strong evidence for increased lung cancer risk after residential exposure to radon in non-smokers. The most common genetic mutations found in non-smokers are in the EGFR, ALK and TP53 genes. Although present in non-smokers, the BRAF and KRAS genes are more frequent in smokers. Besides, exposure to radon may have a cumulative effect over time, thus constant exposure to high concentrations of this gas can lead to the early appearance of cancer. Adenocarcinoma was the most common histological type found in the studies. Lastly, we understand that three core measures are imperative to make national and regional health policies more effective regarding prevention and awareness of the population about residential radon: mapping of radon-prone areas; calculation of lung cancer incidence caused by radon; and mitigation acts. These measures are able to point out where attention should be given and would help to improve clinical and infrastructure of oncology treatment centers.

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References

[1]. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424. doi: 10.3322/caac.21492.

[2]. Brasil. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA) [*web page*]. Rio de Janeiro: INCA; Tipos de Câncer: Câncer de Pulmão [Types of Cancer: Lung Cancer]. Portuguese. Available in: <http/inca.gov.br>. Accessed: 02 Oct., 2020;

[3]. Bravo-Iñiguez CE, Fox SW, De Leon LE, Tarascio JN, Jaklitsch MT, Jacobson FL. Cumulative nonsmoking risk factors increase the probability of developing lung cancer. J Thorac Cardiovasc Surg. 2019 Oct;158(4):1248-1254.e1. doi: 10.1016/j.jtcvs.2019.04.098. Epub 2019 May 18.

[4]. Scagliotti GV, Longo M, Novello S. Non Small cell lung cancer in never smokers. Curr Opin Oncol. 2009 Mar;21(2):99-104. doi: 10.1097/CCO.0b013e328321049e.

[5]. Pallis AG, Syrigos KN. Lung cancer in never smokers: disease characteristics and risk factors. Crit Rev Oncol Hematol. 2013 Dec;88(3):494-503. doi: 10.1016/j.critrevonc.2013.06.011.

[6]. Yang IA, Holloway JW, Fong KM. Genetic susceptibility to lung cancer and comorbidities. J Thorac Dis. 2013 Oct;5 Suppl 5(Suppl 5):S454-62. doi: 10.3978/j.issn.2072-1439.2013.08.06.

[7]. Okazaki I, Ishikawa S, Sohara Y. Genes associated with susceptibility to lung adenocarcinoma among never smokers suggest the mechanism of disease. Anticancer Res. 2014 Oct;34(10):5229-40.

[8]. Govindan R, Ding L, Griffith M, Subramanian J, Dees ND, Kanchi KL, Maher CA, Fulton R, Fulton L, Wallis J, Chen K, Walker J, McDonald S, Bose R, Ornitz D, Xiong D, You M, Dooling DJ, Watson M, Mardis ER, Wilson RK. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell. 2012 Sep 14;150(6):1121-34. doi: 10.1016/j.cell.2012.08.024.

[9]. Petta RA, Campos TCF. O gás radônio e suas implicações para a saúde pública. [Radon gas and its implications on public health]. Revista de Geologia, 2013, 26(2). Portuguese.

[10]. Jobbágy V, Altzitzoglou T, Malo P, Tanner V, Hult M. A brief overview on radon measurements in drinking water. J Environ Radioact. 2017 Jul; 173:18-24. doi: 10.1016/j.jenvrad.2016.09.019.

[11]. WHO - WHO handbook on indoor radon: a public health perspective. WHO Library Cataloguing-in-Publication Data/edited by Hajo Zeeb, and Ferid Shannoun. 2009. Available in: <http://whqlibdoc.who.int/publications/2009/9789241547673_ eng.pdf>. Accessed: Oct. 26, 2020.

[12]. Choi H, Mazzone P. Radon and lung cancer: assessing and mitigating the risk. Cleve Clin J Med. 2014 Sep;81(9):567-75. doi: 10.3949/ccjm.81a.14046.

[13]. Lopes GL, Vattimo EFQ, Castro Junior G. Identifying activating mutations in the EGFR gene: prognostic and therapeutic implications in non-small cell lung cancer. J Bras Pneumol. 2015;41(4):365-375.

[14]. Cohen S. The stimulation of epidermal proliferation by a specific protein (EGF). Dev Biol. 1965 Dec;12(3):394-407. doi: 10.1016/0012-1606(65)90005-9.

[15]. Seger R, Krebs EG. The MAPK signaling cascade. FASEB J. 1995;9(9):726-35. Doi: 10.1096/fasebj.9.9.7601337.

[16]. Buday L, Downward J. Epidermal growth factor regulates p21ras through the formation of a complex of receptor, Grb2 adapter protein, and Sos nucleotide exchange factor. Cell. 1993 May 7;73(3):611-20. doi: 10.1016/0092-8674(93)90146-h

[17]. Fresno Vara JA, Casado E, de Castro J, Cejas P, Belda-Iniesta C, González-Barón M. PI3K/Akt signalling pathway and cancer. Cancer Treat Rev. 2004 Apr;30(2):193-204. doi: 10.1016/j.ctrv.2003.07.007.

[18]. Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. N Engl J Med. 2008 Mar 13;358(11):1160-74. doi: 10.1056/NEJMra0707704. Erratum in: N Engl J Med. 2009 Apr 9;360(15):1579.

[19]. An SJ, Chen ZH, Su J, Zhang XC, Zhong WZ, Yang JJ, Zhou Q, Yang XN, Huang L, Guan JL, Nie Q, Yan HH, Mok TS, Wu YL. Identification of enriched driver gene alterations in subgroups of non-small cell lung cancer patients based on histology and smoking status. PLoS One. 2012;7(6):e40109. doi: 10.1371/journal.pone.0040109.

[20]. da Cunha Santos G, Shepherd FA, Tsao MS. EGFR mutations and lung cancer. Annu Rev Pathol. 2011;6:49-69. doi: 10.1146/annurev-pathol-011110-130206.

[21]. Okabe T, Okamoto I, Tamura K, Terashima M, Yoshida T, Satoh T, Takada M, Fukuoka M, Nakagawa K. Differential constitutive activation of the epidermal growth factor receptor in non-small cell lung cancer cells bearing EGFR gene mutation and amplification. Cancer Res. 2007 Mar 1;67(5):2046-53. doi: 10.1158/0008-5472.CAN-06-3339.

[22]. Morris SW, Kirstein MN, Valentine MB, Dittmer KG, Shapiro DN, Saltman DL, Look AT. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science. 1994 Mar 4;263(5151):1281-4. doi: 10.1126/science.8122112.

[23]. Stoica GE, Kuo A, Aigner A, Sunitha I, Souttou B, Malerczyk C, Caughey DJ, Wen D, Karavanov A, Riegel AT, Wellstein A. Identification of anaplastic lymphoma kinase as a receptor for the growth factor pleiotrophin. J Biol Chem. 2001 May 18;276(20):16772-9. doi: 10.1074/jbc.M010660200.

[24]. Stoica GE, Kuo A, Powers C, Bowden ET, Sale EB, Riegel AT, Wellstein A. Midkine binds to anaplastic lymphoma kinase (ALK) and acts as a growth factor for different cell types. J Biol Chem. 2002 Sep 27;277(39):35990-8. doi: 10.1074/jbc.M205749200.

[25]. Hallberg B, Palmer RH. Mechanistic insight into ALK receptor tyrosine kinase in human cancer biology. Nat Rev Cancer. 2013 Oct;13(10):685-700. doi: 10.1038/nrc3580.

[26]. Kim H, Shim HS, Kim L, Kim TJ, Kwon KY, Lee GK, Chung JH; Korean Cardiopulmonary Pathology Study Group. Guideline Recommendations for Testing of ALK Gene Rearrangement in Lung Cancer: A Proposal of the Korean Cardiopulmonary Pathology Study Group. Korean J Pathol. 2014 Feb;48(1):1-9. doi: 10.4132/KoreanJPathol.2014.48.1.1.

[27]. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, Chirieac LR, Dacic S, Duhig E, Flieder DB, Geisinger K, Hirsch FR, Ishikawa Y, Kerr KM, Noguchi M, Pelosi G, Powell CA, Tsao MS, Wistuba I; WHO Panel. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol. 2015 Sep;10(9):1243-1260. doi: 10.1097/JTO.0000000000000630.

[28]. Sabir SR, Yeoh S, Jackson G, Bayliss R. EML4-ALK Variants: Biological and Molecular Properties, and the Implications for Patients. Cancers (Basel). 2017 Sep 5;9(9):118. doi: 10.3390/cancers9090118.

[29]. Mossé YP, Wood A, Maris JM. Inhibition of ALK signaling for cancer therapy. Clin Cancer Res. 2009 Sep 15;15(18):5609-14. doi: 10.1158/1078-0432.CCR-08-2762.

[30]. Palmer RH, Vernersson E, Grabbe C, Hallberg B. Anaplastic lymphoma kinase: signalling in development and disease. Biochem J. 2009 May 27;420(3):345-61. doi: 10.1042/BJ20090387.

[31]. Barreca A, Lasorsa E, Riera L, Machiorlatti R, Piva R, Ponzoni M, Kwee I, Bertoni F, Piccaluga PP, Pileri SA, Inghirami G; European T-Cell Lymphoma Study Group. Anaplastic lymphoma kinase in human cancer. J Mol Endocrinol. 2011 Jul 4;47(1): R11-23. doi: 10.1530/JME-11-0004.

[32]. Chiarle R, Voena C, Ambrogio C, Piva R, Inghirami G. The anaplastic lymphoma kinase in the pathogenesis of cancer. Nat Rev Cancer. 2008 Jan;8(1):11-23. doi: 10.1038/nrc2291.

[33]. Inamura K. Clinicopathological Characteristics and Mutations Driving Development of Early Lung Adenocarcinoma: Tumor Initiation and Progression. Int J Mol Sci. 2018 Apr 23;19(4):1259. doi: 10.3390/ijms19041259. PMID: 29690599; PMCID: PMC5979290.

[34]. Roberts PJ, Der CJ. Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. Oncogene. 2007 May 14;26(22):3291-310. doi: 10.1038/sj.onc.1210422.

[35]. Pylayeva-Gupta Y, Grabocka E, Bar-Sagi D. RAS oncogenes: weaving a tumorigenic web. Nat Rev Cancer. 2011 Oct 13;11(11):761-74. doi: 10.1038/nrc3106.

[36]. Vigil D, Cherfils J, Rossman KL, Der CJ. Ras superfamily GEFs and GAPs: validated and tractable targets for cancer therapy? Nat Rev Cancer. 2010 Dec;10(12):842-57. doi: 10.1038/nrc2960.

[37]. Karnoub AE, Weinberg RA. Ras oncogenes: split personalities. Nat Rev Mol Cell Biol. 2008 Jul;9(7):517-31. doi: 10.1038/nrm2438.

[38]. Martin P, Leighl NB, Tsao MS, Shepherd FA. KRAS mutations as prognostic and predictive markers in non-small cell lung cancer. J Thorac Oncol. 2013 May;8(5):530-42. doi: 10.1097/JTO.0b013e318283d958.

[39]. Pylayeva-Gupta Y, Grabocka E, Bar-Sagi D. RAS oncogenes: weaving a tumorigenic web. Nat Rev Cancer. 2011 Oct 13;11(11):761-74. doi: 10.1038/nrc3106.

[40]. Kranenburg O. The KRAS oncogene: past, present, and future. Biochim Biophys Acta. 2005 Nov 25;1756(2):81-2. doi: 10.1016/j.bbcan.2005.10.001. Epub 2005 Oct 25.

[41]. Zenker M, Lehmann K, Schulz AL, Barth H, Hansmann D, Koenig R, Korinthenberg R, Kreiss-Nachtsheim M, Meinecke P, Morlot S, Mundlos S, Quante AS, Raskin S, Schnabel D, Wehner LE, Kratz CP, Horn D, Kutsche K. Expansion of the genotypic and phenotypic spectrum in patients with KRAS germline mutations. J Med Genet. 2007 Feb;44(2):131-5. doi: 10.1136/jmg.2006.046300. Epub 2006 Oct 20.

[42]. Piva S, Ganzinelli M, Garassino MC, Caiola E, Farina G, Broggini M, Marabese M. Across the universe of K-RAS mutations in non-small-cell-lung cancer. Curr Pharm Des. 2014;20(24):3933-43. doi: 10.2174/13816128113196660761.

[43]. Tam IY, Chung LP, Suen WS, Wang E, Wong MC, Ho KK, Lam WK, Chiu SW, Girard L, Minna JD, Gazdar AF, Wong MP. Distinct epidermal growth factor receptor and KRAS mutation patterns in non-small cell lung cancer patients with different tobacco exposure and clinicopathologic features. Clin Cancer Res. 2006 Mar 1;12(5):1647-53. doi: 10.1158/1078-0432.CCR-05-1981.

[44]. Savic S, Rothschild S, Bubendorf L. Lonely Driver ROS1. J Thorac Oncol. 2017 May;12(5):776-777. doi: 10.1016/j.jtho.2017.02.019.

[45]. Zong CS, Zeng L, Jiang Y, Sadowski HB, Wang LH. Stat3 plays an important role in oncogenic Ros- and insulin-like growth factor I receptor-induced anchorage-independent growth. J Biol Chem. 1998 Oct 23;273(43):28065-72. doi: 10.1074/jbc.273.43.28065.

[46]. Zeng L, Sachdev P, Yan L, Chan JL, Trenkle T, McClelland M, Welsh J, Wang LH. Vav3 mediates receptor protein tyrosine kinase signaling, regulates GTPase activity, modulates cell morphology, and induces cell transformation. Mol Cell Biol. 2000 Dec;20(24):9212-24. doi: 10.1128/mcb.20.24.9212-9224.2000.

[47]. Nguyen KT, Zong CS, Uttamsingh S, Sachdev P, Bhanot M, Le MT, Chan JL, Wang LH. The role of phosphatidylinositol 3-kinase, rho family GTPases, and STAT3 in Ros-induced cell transformation. J Biol Chem. 2002 Mar 29;277(13):11107-15. doi: 10.1074/jbc.M108166200. Epub 2002 Jan 17.

[48]. Uguen A, De Braekeleer M. ROS1 fusions in cancer: a review. Future Oncol. 2016 Aug;12(16):1911-28. doi: 10.2217/fon-2016-0050. Epub 2016 Jun 3.

[49]. Gu TL, Deng X, Huang F, Tucker M, Crosby K, Rimkunas V, Wang Y, Deng G, Zhu L, Tan Z, Hu Y, Wu C, Nardone J, MacNeill J, Ren J, Reeves C, Innocenti G, Norris B, Yuan J, Yu J, Haack H, Shen B, Peng C, Li H, Zhou X, Liu X, Rush J, Comb MJ. Survey of tyrosine kinase signaling reveals ROS kinase fusions in human cholangiocarcinoma. PLoS One. 2011 Jan 6;6(1):e15640. doi: 10.1371/journal.pone.0015640.

[50]. Jun HJ, Johnson H, Bronson RT, de Feraudy S, White F, Charest A. The oncogenic lung cancer fusion kinase CD74-ROS activates a novel invasiveness pathway through E-Syt1 phosphorylation. Cancer Res. 2012 Aug 1;72(15):3764-74. doi: 10.1158/0008-5472.CAN-11-3990. Epub 2012 Jun 1.

[51]. De Braekeleer M, De Braekeleer E, Douet-Guilbert N. Geographic/ethnic variability of chromosomal and molecular abnormalities in leukemia. Expert Rev Anticancer Ther. 2015;15(9):1093-102. doi: 10.1586/14737140.2015.1068123. Epub 2015 Jul 27.

[52]. Duffy MJ, O'Byrne K. Tissue and Blood Biomarkers in Lung Cancer: A Review. Adv Clin Chem. 2018; 86:1-21. doi: 10.1016/bs.acc.2018.05.001. Epub 2018 May 30.

[53]. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Wilson R, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JW, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, Paterson H, Marais R, Marshall CJ, Wooster R, Stratton MR, Futreal PA. Mutations of the BRAF gene in human cancer. Nature. 2002 Jun 27;417(6892):949-54. doi: 10.1038/nature00766. Epub 2002 Jun 9.

[54]. Pritchard C, Carragher L, Aldridge V, Giblett S, Jin H, Foster C, Andreadi C, Kamata T. Mouse models for BRAF-induced cancers. Biochem Soc Trans. 2007 Nov;35(Pt 5):1329-33. doi: 10.1042/BST0351329.

[55]. Brose MS, Volpe P, Feldman M, Kumar M, Rishi I, Gerrero R, Einhorn E, Herlyn M, Minna J, Nicholson A, Roth JA, Albelda SM, Davies H, Cox C, Brignell G, Stephens P, Futreal PA, Wooster R, Stratton MR, Weber BL. BRAF and RAS mutations in human lung cancer and melanoma. Cancer Res. 2002 Dec 1;62(23):6997-7000.

[56]. Cutler RE Jr, Stephens RM, Saracino MR, Morrison DK. Autoregulation of the Raf-1 serine/threonine kinase. Proc Natl Acad Sci U S A. 1998 Aug 4;95(16):9214-9. doi: 10.1073/pnas.95.16.9214.

[57]. Lavoie H, Therrien M. Regulation of RAF protein kinases in ERK signalling. Nat Rev Mol Cell Biol. 2015 May;16(5):281-98. doi: 10.1038/nrm3979.

[58]. Tran NH, Frost JA. Phosphorylation of Raf-1 by p21-activated kinase 1 and Src regulates Raf-1 autoinhibition. J Biol Chem. 2003 Mar 28;278(13):11221-6. doi: 10.1074/jbc.M210318200.

[59]. Chong H, Guan KL. Regulation of Raf through phosphorylation and N terminus-C terminus interaction. J Biol Chem. 2003 Sep 19;278(38):36269-76. doi: 10.1074/jbc.M212803200.

[60]. Kyriakis JM, App H, Zhang XF, Banerjee P, Brautigan DL, Rapp UR, Avruch J. Raf-1 activates MAP kinase-kinase. Nature. 1992 Jul 30;358(6385):417-21. doi: 10.1038/358417a0.

[61]. Paik PK, Arcila ME, Fara M, Sima CS, Miller VA, Kris MG, Ladanyi M, Riely GJ. Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. J Clin Oncol. 2011 May 20;29(15):2046-51. doi: 10.1200/JCO.2010.33.1280.

[62]. Litvak AM, Paik PK, Woo KM, Sima CS, Hellmann MD, Arcila ME, Ladanyi M, Rudin CM, Kris MG, Riely GJ. Clinical characteristics and course of 63 patients with BRAF mutant lung cancers. J Thorac Oncol. 2014 Nov;9(11):1669-74. doi: 10.1097/JTO.0000000000000344.

[63]. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385.

[64]. Marchetti A, Felicioni L, Malatesta S, Grazia Sciarrotta M, Guetti L, Chella A, Viola P, Pullara C, Mucilli F, Buttitta F. Clinical features and outcome of patients with non-small-cell lung cancer harboring BRAF mutations. J Clin Oncol. 2011 Sep 10;29(26):3574-9. doi: 10.1200/JCO.2011.35.9638.

[65]. Pratilas CA, Hanrahan AJ, Halilovic E, Persaud Y, Soh J, Chitale D, Shigematsu H, Yamamoto H, Sawai A, Janakiraman M, Taylor BS, Pao W, Toyooka S, Ladanyi M, Gazdar A, Rosen N, Solit DB. Genetic predictors of MEK dependence in non-small cell lung cancer. Cancer Res. 2008 Nov 15;68(22):9375-83. doi: 10.1158/0008-5472.CAN-08-2223.

[66]. Cardarella S, Ogino A, Nishino M, Butaney M, Shen J, Lydon C, Yeap BY, Sholl LM, Johnson BE, Jänne PA. Clinical, pathologic, and biologic features associated with BRAF mutations in non-small cell lung cancer. Clin Cancer Res. 2013 Aug 15;19(16):4532-40. doi: 10.1158/1078-0432.CCR-13-0657. Epub 2013 Jul 5.

[67]. Robles AI, Harris CC. Clinical outcomes and correlates of TP53 mutations and cancer. Cold Spring Harb Perspect Biol. 2010 Mar;2(3):a001016. doi: 10.1101/ cshperspect. a001016.

[68]. Vogelstein B, Lane D, Levine AJ. Surfing the p53 network. Nature. 2000 Nov 16;408(6810):307-10. doi: 10.1038/35042675.

[69]. Woods DB, Vousden KH. Regulation of p53 function. Exp Cell Res. 2001 Mar 10;264(1):56-66. doi: 10.1006/excr.2000.5141.

[70]. Harada K, Ogden GR. An overview of the cell cycle arrest protein, p21(WAF1). Oral Oncol. 2000 Jan;36(1):3-7. doi: 10.1016/s1368-8375(99)00049-4.

[71]. Bullock AN, Fersht AR. Rescuing the function of mutant p53. Nat Rev Cancer. 2001 Oct;1(1):68-76. doi: 10.1038/35094077.

[72]. Maslon MM, Hupp TR. Drug discovery and mutant p53. Trends Cell Biol. 2010 Sep;20(9):542-55. doi: 10.1016/j.tcb.2010.06.005.

[73]. Nahar R, Zhai W, Zhang T, Takano A, Khng AJ, Lee YY, Liu X, Lim CH, Koh TPT, Aung ZW, Lim TKH, Veeravalli L, Yuan J, Teo ASM, Chan CX, Poh HM, Chua IML, Liew AA, Lau DPX, Kwang XL, Toh CK, Lim WT, Lim B, Tam WL, Tan EH, Hillmer AM, Tan DSW. Elucidating the genomic architecture of Asian EGFR-mutant lung adenocarcinoma through multi-region exome sequencing. Nat Commun. 2018 Jan 15;9(1):216. doi: 10.1038/s41467-017-02584-z.

[74]. Oren M, Rotter V. Mutant p53 gain-of-function in cancer. Cold Spring Harb Perspect Biol. 2010 Feb;2(2): a001107. doi: 10.1101/cshperspect.a001107.

[75]. Toyooka S, Tsuda T, Gazdar AF. The TP53 gene, tobacco exposure, and lung cancer. Hum Mutat. 2003 Mar;21(3):229-39. doi: 10.1002/humu.10177.

[76]. Olivier M, Hollstein M, Hainaut P. TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol. 2010 Jan;2(1): a001008. doi: 10.1101/ cshperspect.a001008.

[77]. Halvorsen AR, Silwal-Pandit L, Meza-Zepeda LA, Vodak D, Vu P, Sagerup C, Hovig E, Myklebost O, Børresen-Dale AL, Brustugun OT, Helland Å. TP53 Mutation Spectrum in Smokers and Never Smoking Lung Cancer Patients. Front Genet. 2016 May 11;7:85. doi: 10.3389/fgene.2016.00085.

[78]. Lehmann BD, Pietenpol JA. Targeting mutant p53 in human tumors. J Clin Oncol. 2012 Oct 10;30(29):3648-50. doi: 10.1200/JCO.2012.44.0412. Epub 2012 Sep 10.

[79]. Ferreira CG, da Rocha JCC. Oncologia Molecular [Molecular Oncology]. 2nd ed. [place unknown]: Atheneu; 2010. 700 p. ISBN: 8538801643.

[80]. Ribeiro-Silva A, Moutinho MA, Moura HB, Vale FR, Zucoloto S. Expression of checkpoint kinase 2 in breast carcinomas: correlation with key regulators of tumor cell proliferation, angiogenesis, and survival. Histol Histopathol. 2006 Apr;21(4):373-82. doi: 10.14670/HH-21.373.

[81]. Wang H, Wang S, Shen L, Chen Y, Zhang X, Zhou J, Wang Z, Hu C, Yue W, Wang H. Chk2 down-regulation by promoter hypermethylation in human bulk gliomas. Life Sci. 2010 Jan 30;86(5-6):185-91. doi: 10.1016/j.lfs.2009.11.023. Epub 2009 Dec 5.

[82]. Vogelstein B, Lane D, Levine AJ. Surfing the p53 network. Nature. 2000 Nov 16;408(6810):307-10. doi: 10.1038/35042675.

[83]. Weber JD, Kuo ML, Bothner B, DiGiammarino EL, Kriwacki RW, Roussel MF, Sherr CJ. Cooperative signals governing ARF-mdm2 interaction and nucleolar localization of the complex. Mol Cell Biol. 2000 Apr;20(7):2517-28. doi: 10.1128/mcb.20.7.2517-2528.2000.

[84]. Lowe SW, Lin AW. Apoptosis in cancer. Carcinogenesis. 2000 Mar;21(3): 485-495. doi: 10.1093/carcin/21.3.485.

[85]. Meek DW. Mechanisms of switching on p53: a role for covalent modification? Oncogene. 1999 Dec 13;18(53):7666-75. doi: 10.1038/sj.onc.1202951.

[86]. Momand J, Wu HH, Dasgupta G. MDM2--master regulator of the p53 tumor suppressor protein. Gene. 2000 Jan 25;242(1-2):15-29. doi: 10.1016/s0378-1119(99)00487-4.

[87]. National Research Council. Health Effects of Exposure to Radon: BEIR VI. Washington, DC: The National Academies Press; 1999. 592 p. ISBN: 978-0-309-05645-8. doi: 10.17226/5499.

[88]. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and Effects of Ionizing Radiation. UNSCEAR 2000 Report. New York; 2000.1 vol. ISBN: 92-1-142238-8.

[89]. International Agency for Research on Cancer. Man-made Mineral Fibres and Radon. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon; 1988. 43 vol. ISBN: 978-92-832-1243-0.

[90]. International Agency for Research on Cancer. Ionizing Radiation, part 2: Some Internally Deposited Radionuclides. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon; 2001. 78 vol. ISBN: 978-92-832-1578-3.

[91]. Gaskin J, Coyle D, Whyte J, Krewksi D. Global Estimate of Lung Cancer Mortality Attributable to Residential Radon. Environ Health Perspect. 2018 May 31;126(5):057009. doi: 10.1289/EHP2503.

[92]. Afonso JC. Elemento Químico Radônio [Radon Chemical Element]. Química Nova na Escola. 2009 Nov; 32(4).

[93]. Choi JR, Park SY, Noh OK, Koh YW, Kang DR. Gene mutation discovery research of non-smoking lung cancer patients due to indoor radon exposure. Ann Occup Environ Med. 2016 Mar 16;28:13. doi: 10.1186/s40557-016-0095-2.

[94]. Baysson H, Tirmarche M. Exposition domestique au radon et risque de cancer du poumon: bilan des études cas-témoins [Indoor radon exposure and lung cancer risk: a review of case-control studies]. Rev Epidemiol Sante Publique. 2004 Apr;52(2):161-71. French. doi: 10.1016/s0398-7620(04)99037-2.

[95]. Narayanan PK, Goodwin EH, Lehnert BE. Alpha particles initiate biological production of superoxide anions and hydrogen peroxide in human cells. Cancer Res. 1997 Sep 15;57(18):3963-71.

[96]. American Cancer Society. Lung Cancer (Non-Small Cell). Updated on Sep 2011. Available in: <http://www.cancer.org/Cancer/LungCancer-Non-SmallCell/Detailed Guide/non-small-cell-lung-cancer-what-is-non-small-cell-lung-cancer>. Accessed: Oct. 12, 2020.

[97]. Azad N, Rojanasakul Y, Vallyathan V. Inflammation and lung cancer: roles of reactive oxygen/nitrogen species. J Toxicol Environ Health B Crit Rev. 2008 Jan;11(1):1-15. doi: 10.1080/10937400701436460.
[98]. Thompson RE, Nelson DF, Popkin JH, Popkin Z. Case-control study of lung cancer risk from residential radon exposure in Worcester county, Massachusetts. Health Phys. 2008 Mar;94(3):228-41. doi: 10.1097/01.HP.0000288561.53790.5f.
[99]. Grundy A, Brand K, Khandwala F, Poirier A, Tamminen S, Friedenreich CM, Brenner DR. Lung cancer incidence attributable to residential radon exposure in Alberta in 2012. CMAJ Open. 2017 Jun 28;5(2):E529-E534. doi: 10.9778/cmajo.20160053.
[100]. Torres-Durán M, Ruano-Ravina A, Parente-Lamelas I, Leiro-Fernández V, Abal-Arca J, Montero-Martínez C, Pena-Álvarez C, González-Barcala FJ, Castro-Añón O, Golpe-Gómez A, Martínez C, Mejuto-Martí MJ, Fernández-Villar A, Barros-Dios JM. Lung cancer in never-smokers: a case-control study in a radon-prone area (Galicia, Spain). Eur Respir J. 2014 Oct;44(4):994-1001. doi: 10.1183/09031936.00017114.
[101]. Lorenzo-González M, Ruano-Ravina A, Torres-Durán M, Kelsey KT, Provencio M, Parente-Lamelas I, Leiro-Fernández V, Vidal-García I, Castro-Añón O, Martínez C, Golpe-Gómez A, Zapata-Cachafeiro M, Piñeiro-Lamas M, Pérez-Ríos M, Abal-Arca J, Montero-Martínez C, Fernández-Villar A, Barros-Dios JM. Lung cancer and residential radon in never-smokers: A pooling study in the Northwest of Spain. Environ Res. 2019 May;172:713-718. doi: 10.1016/j.envres.2019.03.011. Epub 2019 Mar 6.
[102]. Torres-Durán M, Ruano-Ravina A, Parente-Lamelas I, Leiro-Fernández V, Abal-Arca J, Montero-Martínez C, Pena-Álvarez C, Castro-Añón O, Golpe-Gómez A, Martínez C, Guzmán-Taveras R, Mejuto-Martí MJ, Provencio M, Fernández-Villar A, Barros-Dios JM. Residential radon and lung cancer characteristics in never smokers. Int J Radiat Biol. 2015 Aug;91(8):605-10. doi: 10.3109/09553002.2015.1047985. Epub 2015 Jun 17.
[103]. Casal-Mouriño A, Ruano-Ravina A, Torres-Durán M, Parente-Lamelas I, Provencio-Pulla M, Castro-Añón O, Vidal-García I, Pena-Álvarez C, Abal-Arca J, Piñeiro-Lamas M, Fuente-Merino I, Fernández-Villar A, Abdulkader I, Valdés-Cuadrado L, Barros-Dios JM, Pérez-Ríos M. Lung cancer survival in never-smokers and exposure to residential radon: Results of the LCRINS study. Cancer Lett. 2020 Sep 1;487:21-26. doi: 10.1016/j.canlet.2020.05.022. Epub 2020 May 24. Erratum in: Cancer Lett. 2020 Nov 28;493:10.
[104]. Viñolas N, Garrido P, Isla D, Provencio M, Majem M, Artal A, Carcereny E, Garcia Campelo R, Lianes P, De La Peñas R, Felip E. Lung Cancer in Never-Smoking Women: A Sub-Analysis of the Spanish Female-Specific Database WORLD07. Cancer Invest. 2017 May 28;35(5):358-365. doi: 10.1080/07357907.2017.1295461.
[105]. Liu X, Wang P, Zhang C, Ma Z. Epidermal growth factor receptor (EGFR): A rising star in the era of precision medicine of lung cancer. Oncotarget. 2017 Jul 25;8(30):50209-50220. doi: 10.18632/oncotarget.16854.
[106]. Lim SM, Choi JW, Hong MH, Jung D, Lee CY, Park SY, Shim HS, Sheen S, Kwak KI, Kang DR, Cho BC, Kim HR. Indoor radon exposure increases tumor mutation burden in never-smoker patients with lung adenocarcinoma. Lung Cancer. 2019 May;131:139-146. doi: 10.1016/j.lungcan.2019.04.002.
[107]. Ruano-Ravina A, Torres-Durán M, Kelsey KT, Parente-Lamelas I, Leiro-Fernández V, Abdulkader I, Abal-Arca J, Montero-Martínez C, Vidal-García I, Amenedo M, Castro-Añón O, Golpe-Gómez A, González-Barcala J, Martínez C, Guzmán-Taveras R, Provencio M, Mejuto-Martí MJ, Fernández-Villar A, Barros-Dios JM. Residential radon, EGFR mutations and ALK alterations in never-smoking lung cancer cases. Eur Respir J. 2016 Nov;48(5):1462-1470. doi: 10.1183/13993003.00407-2016. Epub 2016 Oct 6.
[108]. Taga M, Mechanic LE, Hagiwara N, Vähäkangas KH, Bennett WP, Alavanja MC, Welsh JA, Khan MA, Lee A, Diasio R, Edell E, Bungum A, Jang JS, Yang P, Jen J, Harris CC. EGFR somatic mutations in lung tumors: radon exposure and passive smoking in former- and never-smoking U.S. women. Cancer Epidemiol Biomarkers Prev. 2012 Jun;21(6):988-92. doi: 10.1158/1055-9965.EPI-12-0166. Epub 2012 Apr 20.
[109]. Choi JR, Koh SB, Park SY, Kim HR, Lee H, Kang DR. Novel Genetic Associations Between Lung Cancer and Indoor Radon Exposure. J Cancer Prev. 2017 Dec;22(4):234-240. doi: 10.15430/JCP.2017.22.4.234. Epub 2017 Dec 30. Erratum in: J Cancer Prev. 2018 Mar;23 (1):61. Erratum in: J Cancer Prev. 2018 Dec;23(4):197.

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