Contribution of carcinogenic compounds to lung cancer development, and the preventive role of some compounds from lung cancer

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Contents

1 Abstract

Lung cancer causes a lot of moralities each year, so this scholarly paper investigates how carcinogenic especially those found in cigarettes play a role in the development of lung cancer and how this disease can be faced, by stopping the disease spread or preventing the tumors from arising prior to it. This paper collected data from previous research and compared their findings. This has given it a wide scope and a suitable amount of information. It was found that cancer has some steps that proceed it which can be stopped, hence stopping the disease, some unfortunate findings were made as well like that som prevention agents were found to increase the prevalence of the disease and even its mortality rates and this percentage increases with increasing the rate of smoking. on the other hand, some agents were found to be really effective.

2 Introduction

2.1 Lung cancer

The multiplication of body cells is kept within control through chemical signaling maintained by the genomic information of every cell, however, this delicate system can become out of control. When this happens, the cells divide exponentially unlike usual. This produces a tumor that can become malignant carcinogenic cells that are able to spread to multiple body parts. Cancer has multiple types, yet lung cancer is the most lethal and the most common as well making 12.3% of all cancer cases. Lung cancer is one of the leading causes of mortality in developed countries. 1.3 million people (about the population of Estonia) worldwide die due to lung cancer annually [3], Despite improvements in therapy, 90% of lung cancer patients will die from their disease. In 2000 smoking resulted in 17.8 of worldwide recorded death cases[9]. lung cancer has many types however the most common type of lung cancer is non-small cell carcinoma (NSCLC), which contains multiple subcategories including adenocarcinoma which starts in the mucus cells that line the lungs. It's the most common type of lung cancer in non-smokers, but it's still more common in smokers than non-smokers and Squamous cell carcinoma starts in the flat cells inside the airways. They're less common than adenocarcinoma cancers but tend to be linked to smoking, and small cell carcinoma (SCLC) as from 80 to 85% of lung cancer patients suffer from it. NSCLC is more common and grows slowly, while SCLC is less common but often grows quickly.

2.2 Smoking and its correlation with lung cancer

Lung cancer can be caused by multiple factors including; Asbestos and other heavy metals like cadmium, selenium, etc [3], however, smoking is the factor of the greatest effect. smoking as it increases the possibility of lung cancer by 10 to 30 folds compared to non-smokers. Smoking causes 80% of the total number of lung cancer patients, however, a lot of people still smoke for instance 26% of adult Americans are smokers [5].chemical analyses of cigarette smoke reveal a multitude of known mutagens and carcinogens. Moreover, these chemicals are absorbed, metabolized, and cause demonstrable genetic changes in smokers [8]. cigarettes contain about 7000 chemicals of which 70 are known to be carcinogens. Even second-hand smoke increases the possibility of developing lung cancer in non-smokers.
E-cigarettes can also cause cancer, even though they contain a significantly lower amount of carcinogens they are still able to cause cancer. the liquid found in E-cigarettes can cause cancer as well and when it overheats, it produces carcinogens like formaldehyde. E-cigarettes can deliver some heavy metals as well such as lead Pb and tin Sn.

2.3 Chemoprevention

chemoprevention of lung cancer is the prevention of the development of tumors and carcinogenic tissues in high-risk categories. It can even stop or delay the growth of tumors in people who already suffer from cancer. These chemicals can be synthetic or naturally occurring. They inhibit cancer by inducing apoptosis, preventing cell replication, or preventing the function of carcinogens in many ways including prevention of metabolic activation of carcinogens found in cigarettes. Those preventive agents can be found in products that we consume daily like EGCG which is found in tea whether green or black, however, it is at a much higher level in green tea, or like PEITC which is found in many vegetables like cabbage and cress.

2.4 Objectives

This review aims to answer the question ”How do carcinogenic compounds contribute to lung cancer development, and how do some compounds prevent lung cancer?” and find the most effective chemical-preventing agents hence stopping, reversing, or preventing cancer in people at risk would be possible. This review seeks to gather more information about the method by which the agents perform their role, by collecting data from the previous papers and comparing data found in each paper.

3 literature review

3.1 Carcinogens

A carcinogenic is any agent that has the ability to increase tumor incidence in exposed members. carcinogenic can be physical (radiation, mineral fibers), chemical, or biological (viruses, bacteria). One important property that distinguishes carcinogens from non-carcinogens is that they can bind to proteins and DNA, but for them to bind and perform their carcinogenic effect it has to undergo metabolic activation, so the inert compounds are turned into carcinogenic by the body. the body does this as it aims to detoxify them [11]. The conversion of inert carcinogens into active intermediates involves many enzymatic and non-enzymatic steps. Usually, these active intermediates undergo further metabolism rapidly, preventing the harm of the carcinogen [5]. some of the most common carcinogens found in cigarettes and that have a role formation of lung cancer are polynuclear aromatic hydrocarbons (PAHs) which include (B[a]P) for example which form due to the incomplete combustion of tobacco in cigarettes, the other carcinogen is called NNK a nitrosamine that is formed during smoking and cigarettes processing and it is organ selective lung caecinogen mainly causing adenocarcinoma. Human lung tissues PAHs by pathways that lead to covelent modification of DNA and formation of DNA adducts in smoker's lungs. The same applies for NNK. If these adducts persist unrepaired during DNA replication, they can cause mutations in genes like RAS gene and p53 which are very important in lung cancer induction. the analysis has shown alternations G to T and G to A in those genes. blocking any of those steps can prevent lung cancer development [5].

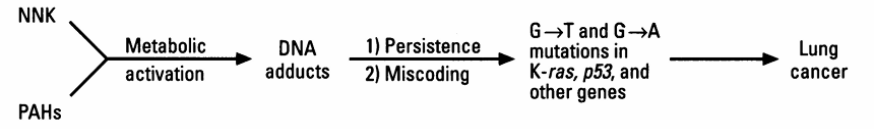

Figure 1: carcinogen activation cascade

3.2 Field cancerization

field cancerization was introduced to explain abnormal cells surrounding a carcinoma. Field cancerization which histologically normal-appearing tissue adjacent to neoplastic and pre-neoplastic lesions displays molecular abnormalities, some of which are in common with those in the tumors that happen due to a diffuse injury of an organ that results from long-term

exposure to a carcinogen, so it results in the risk of a small dysplastic lesion in airway change into cancer anywhere in airway epithelium. In the lung, it is the genetic change that happens to the cells of the respiratory epithelium as a result of exposure to smoke, radon, or any other carcinogen, causing multiple centers of premalignant and malignant cells that yield a tumor as a result of proliferation [14]. The molecular abnormalities mentioned before were detected in histologically normal epithelia adjacent to archival surgically resected tumors from patients with primary lung cancer. loss of heterozygosity and alternations in satellite cells of smokers without cancer were also detected. Moreover, and importantly, these molecular abnormalities were detected in the bronchial epithelia of cancer-free former smokers and appeared to have stayed for many years after smoking giving up. Mutations in TP53 were also described to occur in the bronchial epithelia of cancer-free smokers in a widely dispersed manner [6]. Many factors affect the probability of developing lung cancer including the genetic factor, which is why only 10 to 20% of smokers develop lung cancer. one of the most important genetic factors is the polymorphism of enzymes affecting carcinogen activation [14], however, some papers say that field cancerization is just a kind of actinic keratosis, and some researchers claim that the possibility of field cancerization is more common in males as they also claim that it is a kind of actinic keratosis which is more common in men due to the fact it is developed due to exposure to UV, and males receive a higher amount of UV [14].

3.3 Intermediate endpoints of lung cancer development

The process of carcinogenesis in the lung is well-understood that intermediate biomarkers are known to be causally linked to lung cancer can be used as surrogate endpoints in chemoprevention trials. Intermediate endpoints are useful if they can detect early, frequent carcinogenic events that are linked specifically to malignant progress .Nonspecific biomarkers, like expression of proliferative antigens and formation of micro-nuclei are not sufficiently useful as indicators of chemoprevention. Proliferative antigen can not be cured to be reversed easily, and the frequency of micronuclei is not linked to subsequent suppression of malignancy.Sputum atypia [10](intermediate between normal and abnormal cell) and metaplasia [7](the conversion of one type of cell to another type of normal adult cells) or dysplasia (a precancerous condition in which cells that are very similar to cancer cells grow in an organ but have not yet acquired the ability to invade into tissue or metastasize) of the bronchial epithelium have also been tested for their correspondence with lung cancer and their importance as surrogate endpoints. Sputum atypia, metaplasia, and dysplasia are known to happen before the occurrence of a tumor.Trials using squamous the

metaplasia as an endpoint shows that it is a dynamic process and always changing that can reverse spontaneously; more over, squamous metaplasia does not necessarily reverse with retinoid treatments known to affect the incidence of seconda1y tumors. Another problem with squamous metaplasia markers is that they vary widely and are difficult to quantitate. Another way is the detection of biochemical or genetic changes that happen before cancer. K RAS and P57 mutations have been found in cells from the sputum of lung cancer patients as early as 1 year prior to diagnosis. Accumulation of P53 mutations has been found as a dysplasia turn into invasive in the epysilium of the bronchus. Loss of alleles in the short arm of both chromosomes 3 and 9 have been reported to occur in dysplastic airway lesions. Polysomy of chromosomes 7 and 17 have been detected in premalignant lesions of the oral mucosa. Many molecular and cellular biomarkers can be used to monitor the development and progression of neoplastic cells during chemoprevention. These markers include oncofetal glycoproteins which are oncofetal which are proteins that are made within tumor cells and enter the bloodstream either by secretion from the tumor or as a breakdown product of tumor cells. Normally oncofetal proteins are present during embryogenesis and may increase with certain cancers, making them potentially useful tumor markers [12]. glycoproteins oncofetal specifically have been shown to be expressed in cells found in sputum prior to cancer development, so these proteins are levels are relatively high ratio in the blood of people at risk of lung cancer, and the level of it has a direct relation with the risk of developing the disease. certain biomarkers used for lung cancer can be also used as biomarkers for head and neck tumors, Since both these tumor types arise in epithelium derived from the aerodigestive tract and have similar risk factors, they may exhibit common genetic changes in their developmental phases.

3.4 Lung carcinogenesis

For the formation of cancer in the lung a series of events take place before the appearance of a carcinoma. This cascade can be initiated by multiple factors including genetic events, oncogenes as mentioned before, as well as growth factor imbalanc ,tumor suppressor genes, and dysregulation of other enzymes or targets including the cyclo-oxygenase pathway, telomerase activity, and the retinoic-acid pathway. Changes in one or more of those factors can lead to the change of normal cells into cancer cells or atypical cells, so the genetic changes due to the different factors previously discussed can result in dysregulation of the signal transduction pathway resulting in abnormal cellular signaling. This leads to the formation of premalignant cells that turn into cancer cells [13].

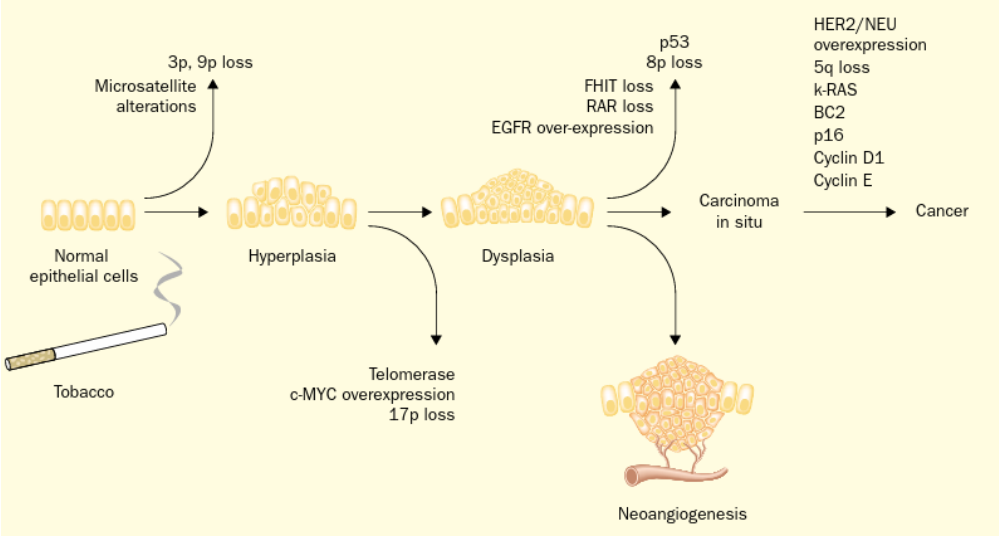

Figure 2: steps of cancer cell formation that can be used as biomarkers

3.5 Primary, secondary, and tertiary chemoprevention strategies

chemoprevention targets the development of cancer in the early phases through the prevention of one or more steps in the step-wise progress toward cancer. chemoprevention has three types, primary strategies are the strategies that aim to protect healthy people who are at risk of developing the disease like those who, smoke, are formal smokers, or have a family history. Secondary prevention is a strategy that aims to prevent cancer in people with precancerous lesions (intraepithelial neoplasia, leukoplakia, dysplasia). Tertiary prevention is the way that targets the prevention of secondary primary tumors or recurrence in people who have previous cancers. Through those ways we would be able to prevent or delay cancers.

3.6 Inhibition of cancer induced by NNk

cancer induced by NNk which is a compound found in tobacco can be prevented or even stopped if it had already started by using a compound called Phenethyl isothiocyanate which is a naturally occurring isothiocyanate (ITC) present in cruciferous vegetables(e.g. cabbage, broccoli, cress, kale) as the main bioactive compound. PEITC is released from glucosinolates by the action of the enzyme myrosinase. The enzyme myrosinase can be activated ed by cutting or chewing vegetables, but heating can destroy its activity. Furthermore, myrosinase can be released from microbial colonies in the gut as well. even though watercress and broccoli contain high levels of PEITC, cooking them reduces its level.Inastudyconducted with human volunteers, approximately 2 to 6 mg of PEITC was found to be released by the consumption of one ounce of watercresS.The preventive

effects of ITCs were evaluated in multiple clinically-induced cancer models. For example, Morse et al demonstrated that the administration of ITCs including PEITC prevented the carcinogenic effects of chemical carcinogens in rodents [4]. when PEITC was added to the diet of male rats with a concentration of 498ppm, before and during their treatment with NNK, it reduced the prevalence of adenocarcinoma of the lung by 50 percent. The treatment of A/J mice two hours before their treatment with NNk showed great results, hence the usage of PEITc for lung cancer prevention that is induced by NNk has been shown to be effective and nontoxic if used at this concentration. In laboratory animals and humans,NNK is rapidly converted to 4-(methylnitros amino)-l-(3-pyridyl)-butanol(NNAL) which another possible carcinogen by the enzyme carbonyl reductase. NNAL is partially converted to its diastereomeric glucuronide which is the detoxification of NNk.
Initial studies demonstrated that PEITC inhibited the metabolic activation of NNK to electrophiles, which is a methylation factor of pulmonary DNA in rats. further research on rats, mice, and enzymes showed clearly that the inhibitory effect of PEITC on NNK carcinogenesis is due mainly to the inhibition of NNK metabolic activation to methylating. In rats treated with PEITC by gavage or by addition to the diet, a persistent inhibition of metabolic activation of NNK is observed in lung microsomes, which results from inhibition of cytochrome P450 enzymes. Experiments in vitro have shown that PEITC is a competitive inhibitor of NNK. Chronic PEITC treatment caused significant 4- to 6-fold increases in the levels of NNAL and NNAL-gluc in urine; this most likely results from a decrease in metabolic activation of NNK since hemoglobin adducts of NNK also decreased.

3.7 Inhibition of B[a]P induced cancer

Even though PEITC was demonstrated to be a great agent for the prevention of NNk-induced cancer, it was also found to be not as effective in preventing B[a]P.In contrast, a 7.9-pmol dose of BITC given by the same protocol did result in a statistically significant 50% reduction of B[a]P-induced lung tumor multiplicity in the A/J mouse model.The contrasting effects of PEITC and BITC on lung tumorigenesis by B[a]P in A/J mice are consistent with mechanistic studies, which have shown that BITC but not PEITC significantly inhibited ethoxyresorufin O-dealkylase activity in A/J mouse lung microsomes, which is indicative of the inhibition of P4501A. P4501A may be involved in the metabolic activation of B[a]P.

3.8 Tea as a chemopreventive agent

Both green and black tea can be considered to be chemopreventive agents, however, they differ in their activity because they differ in their chemical composition even though they are made of the same leaves they are dried in two different methods. By dry weight, a cup of green tea is typically 30–40% catechins which represent approximately 70% of all polyphenols in tea, like epicatechin, epigallocatechin-3-gallate and epicatechin-3-gallate. EGCG is the main catechin in tea. Green tea is not fermented, but black tea is. The fermentation process converts many of the catechins found in green tea to the arubigins and theflavins. In contrast to green tea, by dry weight, a cup of black tea is only 3–10% catechins. EGCG is the main chemopreventive agent of tea. A cup of green contains 200 mg of EGCG.
The mechanism of tea chemoprevention of lung cancer depends on the antioxidant content of it. They perform that through induction of phase II enzymes, inhibition of TNFa, which is naturally produced by active macrophages and and which is a potent paracrine and endocrine mediator of inflammatory and immune functions and has a pleiotropic effect on both normal and tumor cells and has a wide effect on the growth and differentiation of a variety of cells, and induction of apoptosis, [1], expression and release, induction of apoptosis, and inhibition of cell proliferation. EGCG was found to inhibit protein kinase interference and More recently, EGCG was found to inhibit DNA methyltransferase. on the other hand some epidemiological papers show no positive, or negative effect, hence further research is needed.[2]

3.9 Caratonids role in chemoprevention

Is a class of over 600 compounds. They are fat-soluble plant compounds that give most vegetables the color we know, they are responsible for tomato's red color and carrot's orange color. A part from caratonids' role in giving our food color, it plays a major role in preventing many diseases including cancer, and maintaining ophthalmic health [?]. of all the carotenoids, beta-carotene is the most studied. It was found to have an antioxidant effect and the ability to boost immunity. A correlation between low beta carotene levels from the diet and lung cancer was found. Unfortunately, experiments on supplying a dose of it for smokers were negative. That can be due to the inhibition of other nutrient absorption due to large doses of beta-carotene and the auto-catalytic catalytic pro-oxidant activity of beta-carotene under high oxygen tension like in the lungs of smokers. In fac,t experiments in smokers showe a 28% increase in the incidence of cancer and a 17% increase in mortality in the groups that were given a

pharmacological dose of bta carotene. Lycopene which is found in tomatoes, is a possible antioxidant, and its consumption has been associated with a lower lung cancer risk. In vivo, animal trials assessing its chemopreventive effects in a multiorgan carcinogenesis model found pul monary adenoma and carcinoma formation were reduced with lycopene.

4 Conclusion

Smoking is the greatest factor causing lung cancer. It is one of the most common carcinogenics. The effects of smoking are long-lasting and if a person has ever smoked, the prevalence of developing cancer this person will never return to normal levels, hence creating a medication that prevents the development of cancer, stops it, or even delays it, is really crucial. As searching and analyzing literature has shown there are so many chemo-preventive agents for cancer. Those agents can be so common that they can be found in food that we consume daily, and some of them were found to have a reverse reaction in people who smoke a lot i.e. they increase the prevalence of the disease instead of diminishing it, so, for now, most chemopreventive agents has shown neutral or even negative effect, however, some positive results were found to be caused by PEITC and BITC, especially in mice.

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