BREATHS OF DEATH:
HOW SMOKING LEADS TO LUNG CANCER

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According to the CDC, around 40 million adults in the US smoke cigarettes, and around half a million Americans die each year from smoking-related causes.[1] The numbers are even more concerning worldwide, especially in lower income countries. According to the World Health Organization (WHO), tobacco use kills around 8 million people each year, with 80% of smokers being from low- or middle-income countries. WHO has gone so far as to call this "the tobacco epidemic."[2]

The bulk of smoking-related deaths are caused by lung cancer, one of the most common and deadly cancers. According to the NIH (National Cancer Institute), 8 to 9 out of 10 lung cancer cases are caused by tobacco use in some form—whether it be smoking cigarettes or e-cigarettes or simply being exposed to second-hand smoke.[3] Tobacco has been proven to be the biggest risk factor in lung cancer for many years. In fact, the correlation is so strong that smokers are at a 20 times higher risk of developing lung cancer than non-smokers.

It is curious that, despite the dangers of smoking being known for decades, many smokers do not quit, and many non-smokers still get into the habit of smoking. "Every day, about 1,600 U.S. youth younger than 18 years smoke their first cigarette," reports the CDC. The persistence of smoking as a habit in our society is equal parts concerning and counter-intuitive; considering how many deaths cigarettes cause each year, we should all be horrified even at the sight of one. So why aren't we? Scientists believe that the answer lies in our evolution—or, rather, the lack of it. Many of our human emotions and responses to the environment stem from our evolutionary past, explains evolutionary biologist Gordon H. Orians in his book Snakes, Sunrises and Shakespeare. Among the most common human fears include snakes, spiders, or heights, all of which were common causes of death for our ancestors but not at all in the modern day.[4] With the rapid advance of technology and modernization, our environment and lifestyles have changed rapidly without giving our emotions and fears time to match pace. While we may scream at the sight of a harmless spider in our homes, millions of people poison themselves with deadly tobacco smoke everyday.

The lack of fear surrounding tobacco use and lung cancer also partially lies in a lack of scientific education about the subject. Though the sentence, "Smoking causes lung cancer," is repeated everywhere, many people do not fully grasp the grim consequences smoking has on one's lungs and the pathology underlying this deadly disease. Understanding the science behind smoking is an essential step in the process of quitting.

WHAT IS LUNG CANCER?

Cancer is a disease where cells grow

uncontrollably and spread to nearby tissues. Lung cancer is a type of cancer that develops in the lungs. It includes many different types, each of which grow and are treated differently. Cancer that begins in the lungs can potentially spread to the lymph nodes or other organs in the body in a process called metastasis, which is often incredibly dangerous and occurs in the later, more severe stages of cancer progression.

Unlike diseases that are caused by infections with a specific pathogen resulting in similar symptoms or requiring similar treatments across patients, cancer is a broad term that refers to a variety of abnormal growths in the body. Lung cancers also exhibit substantial variability between individuals and have many different genetic origins. However, almost all cancers are caused by alterations in the genetic material of a single cell; whether it is a mutation that deletes an important regulatory/inhibitory gene in the cell or a genetic alteration that leads to higher expression of a cancer-causing gene, some genetic alteration causes a single cell to grow uncontrollably, eventually developing into cancer.

HOW DOES SMOKING CAUSE LUNG CANCER?

These abnormalities in DNA can be caused by mutagens, which are substances that can mutate or alter the genetic material. Substances that specifically cause cancer by altering the DNA are called "carcinogens." This is the main mechanism through which smoking leads to cancer. There are about 7000 chemicals in cigarette smoke, and more than a tenth of them are known carcinogens. Every time somebody inhales cigarette smoke, they are introducing these chemicals into their body, where these carcinogens can potentially attack their DNA. Every breath of smoke is a gamble on one's life.

One of the carcinogens known to be present in tobacco smoke is called benzo(a)pyrene (BP). Although BP is one of the many carcinogens that can lead to lung cancer in smokers, it is unique because of its discovery and role in the history of cancer research. Sources of BP other than cigarette smoke include car exhaust, burned meat, and, most importantly, soot, which is commonly found inside chimneys.

In 1775, Dr. Percivall Pott in London published a report noting a curious observation: the incidence of scrotum cancer seemed to be strongly linked with chimney sweeps who, at the time, were mostly young boys.[5] During that time, it was common for these boys to enter chimneys with their thighs naked. A by-product of combustion in the chimney, soot is a dangerous carcinogen which, after Pott's observation, was found to be sticking to the chimney sweep's sweaty skin at the scrotum region, getting stuck in between the wrinkles, and being rubbed against the layers of skin.[6] These unsafe working conditions, together with improper hygiene that kept soot from being washed away, contributed to the development of scrotum cancer in these boys.

But how does BP cause cancer? Although not active in its natural form, once BP enters the body, an enzyme called cytochrome p450 reacts with it, transforming it into its active form.[7] The active BP is incredibly reactive and quickly attacks the DNA in the cell, leading to mutations. Due to its high reactivity, BP has a short half-life, meaning that it is quickly degraded in the cell. The short half-life of BP implies that its damage will largely be limited to the cell it first encounters; in the case of smoking, this is lung cells. Although smoking can lead to other types of cancers as well, the quick reactivity and short half-life of carcinogens like BP explain the strong correlation it has with lung cancer specifically.

The "active" form of BP refers to its water soluble form called an epoxide, which is particularly good at binding DNA. DNA-bound epoxides look like bulky attachments that are also called DNA adducts, that bend the DNA and change its shape. The presence of DNA adducts not only causes the DNA to change its shape, but also leads to mistakes in DNA replication, which can have severe consequences. Smokers show elevated levels of DNA adducts in lung and other tissues compared to non-smokers, explaining their increased risk of cancer.[8] Research has also shown that in people who have quit smoking, DNA adduct levels decrease in proportion to the time they have been smoke-free.[9]

There is not one single mutation that causes cancer; different patients have different mutational burdens in different genes, so it is difficult to find a single cure that will work in every cancer case — a problem that has pushed the field towards more personalized approaches that are patient specific. However, some genes are mutated in cancer more often than others, and not every mutation has the same effect on tumor progression.

Mutations that "drive" cancer progression are known as driver mutations. Some of the important driver mutations for non-small cell lung cancer (NSCLC) affect the Epidermal Growth Factor Receptor (EGFR) gene, which encodes a receptor that binds growth factors in response to growth signals, leading the cell to grow.[10] An overactive EGFR could lead to cells growing abnormally and uncontrollably — a feature important for cancer progression. Many current therapies target these known driver mutations. For instance, many lung cancer patients with EGFR mutations are treated by a class of drugs called tyrosine kinase inhibitors (TKIs) which slow tumor growth by preventing the activation of EGFR. However, many tumors develop resistance against these therapies, which is a huge challenge in cancer treatment today.

THE ALTERNATIVE

In recent years, the use of electronic cigarettes has increased as an alternative to smoking, especially among young populations. Many e-cigarette companies particularly target teens and young adults, leading to the so-called "vaping epidemic" where more than 2.5 million youth use e-cigarettes, as reported by the CDC. There has been many discussions around the safety of e-cigarettes and their damaging effects on the young individuals who use them. However, a lot is still unknown about these devices.[11]

E-cigarettes are electronic devices that come in various shapes and sizes, that work by heating and vaporizing a liquid to produce air droplets, or "aerosols," that the consumer inhales. Most e-cigarettes contain nicotine, although in different amounts, as well as other chemicals that give it a taste or flavor. In addition to the highly carcinogenic nicotine and the many flavoring chemicals that could be toxic, e-cigarettes contain many other harmful substances that could damage the lungs, airways and even the heart.[12] It is important to realize that although they seem and are even marketed

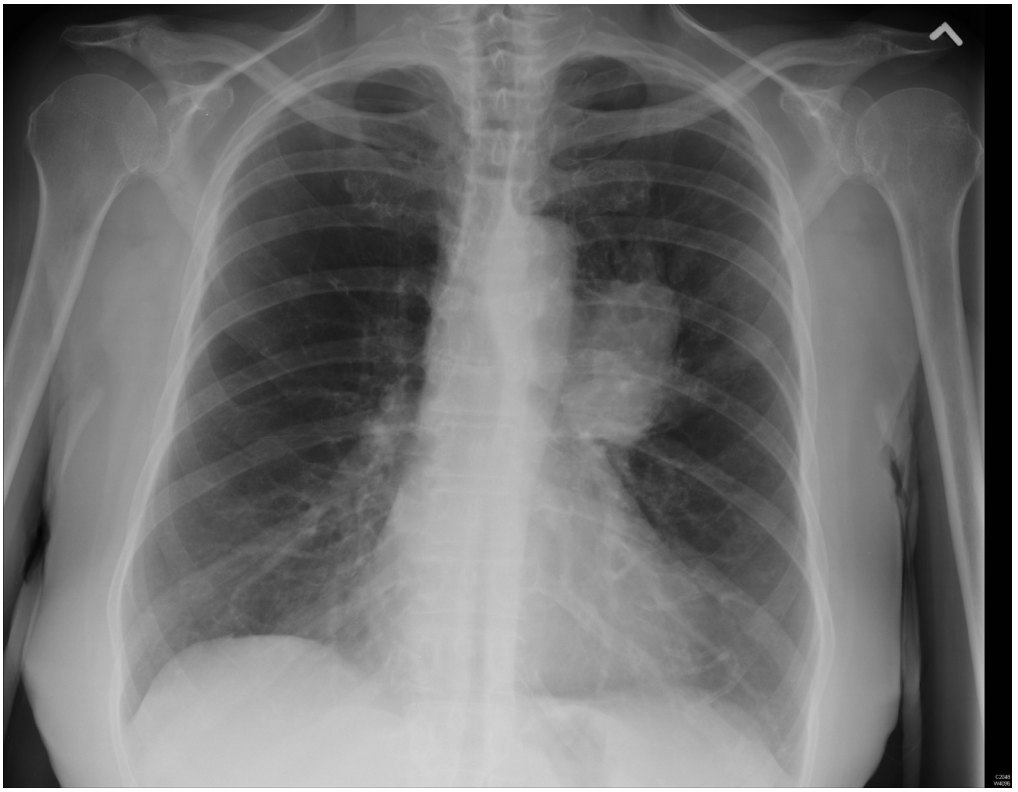

Figure 1: Imaging of the lungs of a patient with cancer.

as harmless, e-cigarettes are devices whose long-term effects have not yet been studied, and have already been shown to cause multiple detrimental effects on the human body. At the end of the day, the best — and perhaps only — way to prevent cancer and other smoking-related diseases, is to quit smoking altogether.

LOOKING AHEAD

Reducing the use of cigarettes and vapes can lead to a future where the incidence of cancer is lower. Though it is generally known that smoking is dangerous, the science behind it is not always discussed. Access to information and a scientific education is key to making people understand the biology of cancer and the role smoking plays in it.

REFERENCES

1. *CDC Newsroom*. (2016, January 1). CDC. https://www.cdc.gov/media/releases/2022/p1007-e-cigarette-use.html
2. *Tobacco*. (n.d.). Retrieved December 15, 2022, from https://www.who.int/news-room/fact-sheets/detail/tobacco
3. *Lung Cancer Prevention* (PDQ®)–Patient Version—NCI (nciglobal,ncienterprise). (2022, September 30). [PdqCancerInfoSummary]. https://www.cancer.gov/types/lung/patient/lung-prevention-pdq
4. Orians, G. H. (2014). *Snakes, Sunrises, and Shakespeare: How Evolution Shapes Our Loves and Fears.* University of Chicago Press.
5. Waldron, H. A. (1983). A brief history of scrotal cancer. *British Journal of Industrial Medicine*, 40(4), 390–401.
6. Hogstedt, C., Jansson, C., Hugosson, M., Tinnerberg, H., & Gustavsson, P. (2013). Cancer Incidence in a Cohort of Swedish Chimney Sweeps, 1958–2006. *American Journal of Public Health*, 103(9), 1708–1714. https://doi.org/10.2105/AJPH.2012.300860
7. Prevention (US), C. for D. C. and, Promotion (US), N. C. for C. D. P. and H., & Health (US), O. on S. and. (2010). Cancer. In *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Centers for Disease Control and Prevention (US). https://www.ncbi.nlm.nih.gov/books/NBK53010/
8. Alexandrov, L. B., Ju, Y. S., Haase, K., Van Loo, P., Martincorena, I., Nik-Zainal, S., Totoki, Y., Fujimoto, A., Nakagawa, H., Shibata, T., Campbell, P. J., Vineis, P., Phillips, D. H., & Stratton, M. R. (2016). Mutational signatures associated with tobacco smoking in human cancer. *Science (New York, N.Y.), 354*(6312), 618–622. https://doi.org/10.1126/science.aag0299
9. Phillips, D. H., Hewer, A., Martin, C. N., Garner, R. C., & King, M. M. (1988). Correlation of DNA adduct levels in human lung with cigarette smoking. *Nature, 336*(6201), Article 6201. https://doi.org/10.1038/336790a0
10. *Targeting mutations that drive lung cancer.* (n.d.). Retrieved December 15, 2022, from https://www.nature.com/articles/d42473-020-00479-0
11. Canistro, D., Vivarelli, F., Cirillo, S., Babot Marquillas, C., Buschini, A., Lazzaretti, M., Marchi, L., Cardenia,

1. V., Rodriguez-Estrada, M. T., Lodovici, M., Cipriani, C., Lorenzini, A., Croco, E., Marchionni, S., Franchi, P., Lucarini, M., Longo, V., Della Croce, C. M., Vornoli, A., … Paolini, M. (2017). E-cigarettes induce toxicological effects that can raise the cancer risk. *Scientific Reports, 7*(1), Article 1. https://doi.org/10.1038/s41598-017-02317-8
2. Jones, K., & Salzman, G. A. (2020). The Vaping Epidemic in Adolescents. *Missouri Medicine, 117*(1), 56–58.

IMAGE REFERENCES

1. Banner: https://www.pexels.com/photo/unrecognizable-person-smoking-cigarette-in-darkness-on-black-background-4538421/
2. Figure 1: https://www.flickr.com/photos/pulmonary_pathology/6327961394