Chapter 5
Smoking Cessation in a Lung Cancer Screening Program

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Background

Tobacco use is the leading preventable cause of disease and all-cause mortality in the United States [1, 2]. Cigarettes are responsible for over seven million deaths worldwide and 480,000 deaths in the United States yearly [3, 4]. In 1964, the United States Surgeon General released a landmark report on the harmful effects of smoking. Since then, there have been worldwide initiatives to end tobacco use [1]. Research dedicated to better understanding tobacco use has significantly contributed to the improvement of smoking cessation initiatives and treatment options. Nicotine addiction and dependence is the main reason smokers continue to smoke. Smoking cessation must be approached as an addiction, with comprehensive interventions addressing the psychological and physiological aspects of addiction. Smoking cessation within a LCS program could broaden the impact of LCS, further reducing mortality and risk of smoking-related diseases. This chapter will examine nicotine addiction and dependence, review pharmacologic and behavioral strategies to address nicotine addiction, and the importance of smoking cessation within a LCS program.

Nicotine and Tobacco

Nicotine is a highly addictive chemical substance, naturally found in the tobacco plant. It has been shown to be more addictive than heroin, cocaine, marijuana, and other illicit drugs [5].

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Nicotine is present in all forms of tobacco products, along with thousands of other chemicals and toxins that are created and released by the combustion of tobacco. These toxins are inhaled when tobacco is burned and used in the form of a cigarette. Surprisingly, nicotine itself does not have the same risks as other chemicals in tobacco and tobacco smoke. Despite what many think, many diseases and deaths in smokers are related to the mix of these chemicals, not the nicotine itself [6]. However, nicotine is the primary inducer of tobacco dependence and may result in compulsive behavior or an addiction. The paramount driver of continued tobacco use is nicotine addiction [6]. Not all smokers are diagnosed as nicotine dependent; however, the incidence of diagnosis is higher than any other substance use disorder [7].

The tobacco industry has been working for decades to continually improve and intensify the rapid delivery of nicotine without regard for the downstream health impact. Tobacco companies discovered that adding the corrosive substance ammonia increased nicotine absorption, making cigarettes even more addictive than prior iterations of cigarettes [1, 2, 8].

Chemicals in Cigarettes

One cigarette, when lit and activated, contains a mix of over 7000 chemicals, including toxic metals, poisonous gases, and carcinogens. There are at least 70 known carcinogens in cigarettes, such as formaldehyde, which is used to embalm bodies, and vinyl chloride, which is used to make pipes [2].

Not all chemicals found in a cigarette are added in the manufacturing process. Some substances, like nicotine, are naturally occurring in the plant itself. Other potentially harmful chemicals, such as cadmium, lead, and nitrates, are absorbed from the soil and fertilizer as the tobacco plant grows and remains in the tobacco leaves when they are processed and turned into cigarettes [5]. Additional chemical compounds form due to combustion during the burning of a cigarette. As a result, harmful chemicals may develop throughout the lifecycle of a cigarette; growing, manufacturing, or burning [5].

Over the years, the tobacco industry has redesigned the cigarette to help increase sales and improve profit margins. The "light" or "ultralight" cigarettes were designed after the link between tar and cancer risk was identified [5, 8, 9]. Features of these light cigarettes include cellulose acetate filters to trap tar and reduce intake, highly porous cigarette paper to allow toxic chemicals to escape, ventilation holes in the filter tip to dilute smoke with air, and different tobacco blends thought to decrease smoke yield of polynuclear aromatic hydrocarbons (PAHs) [9]. When all these features were combined and machine measured, they produced a lower yield of tar than the smoke from a regular cigarette [9].

Light cigarettes were marketed as containing fewer chemicals and less tar, as well as carrying a reduced risk of disease. However, individuals smoking light cigarettes are at the same risk of developing smoking-related cancers and diseases as their regular cigarette-smoking counterparts [9]. Studies indicate that the same

features that reduce tar yield also lessen nicotine yield. To compensate for the lower nicotine yield, smokers must take deeper, larger, and more frequent puffs or increase their cigarette intake to achieve a comparable nicotine level [9]. Despite features of light cigarettes appearing less harmful due to decreased tar levels, machine-measuring does not take overcompensation due to lesser nicotine levels into consideration; therefore, smokers of light cigarettes inhale more tar, nicotine, and chemicals than machine-based numbers indicate [9].

Chemicals in Other Tobacco Products

The cigarette is not the only tobacco product with potentially harmful chemicals, other products include hookah, smokeless tobacco, and e-cigarettes. Hookah smoke has been found to contain carbon monoxide, metals, and carcinogens [10]. Additionally, hookah smokers may be at a higher risk of absorption of these toxic chemicals than cigarette smokers. This risk is associated with the length of time for a "hookah session" [10, 11]. A 1-h hookah session produces as much smoke as several packs of cigarettes, inhaling 100–200 times the amount of smoke in a single cigarette [5, 10, 11].

Smokeless tobacco has been found to contain at least 4000 chemicals, with as many as 30 linked to cancer [5, 12]. Heavy metals including cadmium, lead, and nickel, in addition to other harmful substances such as formaldehyde, and N-Nitrosonornicotine (NNN) have all been found in smokeless tobacco [5, 10]. NNN is a known carcinogen in animals and may be linked to increased cancer risk in humans [5, 13, 14]. Furthermore, smokeless tobacco is proven to cause esophageal, pancreatic, and oral cancer [5, 15].

E-cigarettes are the most recent "tobacco product" with a variety of models released in the last decade. Marketed as a "safer" alternative to smoking, yet containing many of the same chemicals and toxins as cigarettes. While not all, most contain nicotine and have also been found to contain formaldehyde, acrolein, and acetaldehyde [1, 5]. The combination of these chemicals is linked to irreversible lung damage [5]. Additionally, e-cigarettes are often flavored with chemical compounds such as diacetyl and acetoin. While these chemicals are safe to ingest, inhaling these compounds is associated with interstitial lung disease [5, 16].

Biological Basis of Nicotine Dependence

Nicotine acts on the brain and nervous system, easily crossing the blood-brain barrier and then diffusing into brain tissue. Nicotine is a selective binder to nicotinic cholinergic receptors (nAChRs) in the brain and other tissues [17]. It imitates the action of the natural neurotransmitter acetylcholine by binding to those "nicotine receptors." This results in a release of neurotransmitters, predominately dopamine,

norepinephrine, acetylcholine, serotonin (5-HT), GABA, glutamate, and endorphins [17], stimulating various responses and behaviors after intake.

The most crucial reward pathway in the brain is the mesolimbic dopamine system, composed of the ventral tegmental area (VTA) and nucleus accumbens (NAc) [18]. The VTA-NAc pathway involves reward and mediating the reinforcing actions of drug abuse. Dopamine is the neurotransmitter responsible for emotion, motivation, feelings of pleasure, and VTA-NAc pathway activation [17, 18].

When nicotine receptors located in the VTA and NAc are stimulated, they release large quantities of dopamine, activating the mesolimbic dopamine system [18]. Addictive substances and behaviors provide shortcuts to the brain's reward system by flooding it with dopamine. This process is critical for drug-induced rewards and is responsible for reinforcing behaviors similar to other dependence-producing drugs [18]. Nicotine use alters the brain structure and function of neurotransmitters, including dopamine, norepinephrine, serotonin (5-HT), glutamate, gamma-aminobutyric acid (GABA), and endogenous opioid peptides, which are associated with the development of psychiatric disorders [18]. Habitual nicotine use results in an increase in active nicotine receptor sites, resulting in nicotine tolerance and dependence [18].

Cognitive Management of Dependence

The majority of cigarette smokers (68%) want to quit smoking entirely [1]. However, quitting smoking successfully is exceedingly difficult. Nicotine addiction is a mental and physical disease with compulsive behaviors. Prior to the twentieth century, smoking cessation was approached as a habit, not an addiction [2, 18]. The pharmacologic and behavioral process changes that determine nicotine addiction are like those seen with heroin and cocaine addiction. Cigarettes are designed for addiction, delivering more nicotine faster than seen in previous eras [2]. The simple design of the cigarette allows nicotine in toxic substances inhaled into the pulmonary alveolar sacs to rapidly enter blood capillaries via simple diffusion, travel via the pulmonary veins to the left atrium, enter the left ventricle and be pumped immediately through the aortic arch to the central nervous system. Nicotine alters brain structure and function, resulting in cravings that intensify with prolonged use [2, 7]. Smokers become dependent on the physical action of smoking, in addition to the physiological dependence, and continue to smoke despite knowing the negative health effects and wanting to quit. Smokers feel intense compulsions to continue to smoke, in addition to feeling trapped in a pattern of repetitive and senseless thinking.

When initiating smoking cessation treatment, it is important to evaluate what level of nicotine dependence may be present in the smoker. High levels of nicotine dependence are associated with an increased risk of difficulty quitting, distress, and relapse [1, 19]. Additionally, smokers with high nicotine dependence have a greater success rate with nicotine replacement therapy (NRT) [1, 20]. Therefore, nicotine dependence levels should be evaluated, allowing for treatment options and tailoring

of recommendations based on the level of dependence. Several questionnaires can be utilized to measure nicotine dependence, including the Fagerstrom Test for Nicotine Dependence, Wisconsin Inventory of Smoking Dependence and Motives, and Smokeless Tobacco Dependence Scale [17].

Nicotine dependence must be treated as an addiction, with counseling and behavioral approaches, as well as medications for withdrawal symptoms. A comprehensive approach to tobacco-cessation must address pharmacology, conditioned factors, personality, and social settings [18]. A publication by Jiloha et al. states that pharmacological treatment for smoking cessation should both block the positive reinforcing effects of nicotine as well as prevent or reduce the development of withdrawal symptoms. Pharmacotherapy should also target the receptor subtypes involved in nicotine addiction without affecting the receptors that, if activated, would produce unwanted adverse effects.

In the United States, it is common to browse for smoking cessation treatments and receive infinite results. However, the Food and Drug Administration (FDA) currently has only approved a handful of treatment modalities for smoking cessation; including nicotine replacement therapy (NRT) (transdermal patch, gum, nasal spray, inhaler, and lozenges); bupropion (Zyban, Wellbutrin), varenicline (Chantix) [20].

Nicotine Replacement Therapies

At least half of adult smokers (55.1%) attempt to quit smoking each year, with thousands struggling with quitting daily [7]. Evidence-based cessation counseling, in conjunction with medications, is the most efficacious intervention and is proven to increase rates of long-term cessation. Although both cessation counseling and medication can be effective, the dual modality methodology is superior [1, 7]. Despite this evidence, less than one-third of smokers of those attempting to quit report using medications or counseling when quitting smoking [1, 7].

Nicotine dependence is what makes quitting so tricky and leads to most smokers having multiple quit attempts [21]. Many smokers may have at least 30 or more quit attempts before successfully quitting [22]. Because all smoking cessation treatment strategies should approach nicotine as an addiction, a dual-tack approach is best, which addresses both the physical (urges, withdrawal) and psychological (mental, emotional) aspects of dependence. NRTs work to address physical aspects of addiction [15], while behavioral programs, such as 1–800-QUIT-NOW or smoking cessation counseling programs, aim to address the psychological aspects of addiction [23].

NRTs work directly and indirectly by enhancing natural gratification signals, thereby helping to manage chronic withdrawal and sudden compulsions. The main mechanism of action of an NRT is the stimulation of nicotinic receptors in the ventral tegmental area of the brain and the consequent release of dopamine in the nucleus accumben [24]. NRTs deliver lower plasma concentrations that rise more slowly than conventional cigarettes, decreasing the behaviorally reinforcing effects

of smoking [1]. Additionally, NRTs work to satisfy the physiological need for a reward [1, 18].

NRTs have shown to be effective and may double one's chances at smoking cessation [15]. There are six different forms of NRT products: transdermal patches, lozenges, gums, nasal sprays, inhalers, and sublingual tablets [1, 25]. The nicotine patch, also known as "the controller medication," delivers a steady dose of nicotine over 16–24 h to maintain a continuous nicotine level in the blood and prevent cravings from peaking [1, 26]. All other NRT products are "short-acting" and achieve lower levels of nicotine in the blood than nicotine patches. Therefore, they are mainly prescribed for "breakthrough cravings" and are used every 1–2 h as needed for withdrawal symptoms [1, 26]. When used in combination with patches, short-acting NRTs act to provide an additional spike in nicotine levels in the blood, like that of a cigarette.

There are only two prescription medications approved by the FDA to treat nicotine addiction, varenicline and bupropion. Varenicline is a selective $alpha_4$-$beta_2$ neuronal nicotinic acetylcholine receptor partial agonist and antagonist, which works to block the effects of nicotine on the brain while also providing some receptor stimulation [27]. Its mechanism of action inhibits dopaminergic activation produced through smoking, decreases cravings, reduces withdrawal symptoms, and prevents nicotine stimulation of the mesolimbic dopamine system which is associated with nicotine addiction [27]. The American Thoracic Society (ATS) clinical practice guidelines strongly recommend varenicline for smoking cessation over the nicotine patch and bupropion [28]. Additionally, there are recommendations to initiate varenicline even in adults not ready to quit [28].

Bupropion is an atypical antidepressant that was initially developed to treat depression and later found to be effective in smoking cessation [25]. Bupropion is a norepinephrine/dopamine reuptake inhibitor and can decrease the function of nAChRs by acting as an antagonist of the receptors [1]. As an nAChR antagonist, it alters nicotine-mediated dopamine responses, which likely causes antismoking activity [18].

Lung Cancer and Smoking

The risks of disease and death related to tobacco use have been well documented for more than a century. Smoking is the number one cause of lung cancer. However, despite this knowledge, lung cancer is still the most common tobacco-related cause of cancer mortality in the United States [2]. Cigarettes contain notorious carcinogens, toxins, and chemicals. Repeated exposure to these chemicals through tobacco smoke stresses healthy cells, causing damage and altering their normal growth and function, thus starting a path toward cancer formation [2]. Typically, the immune system protects individuals from cancer by sending out tumor fighters to attack cancer cells. However, the same toxins within the cigarette that stress healthy cells weaken tumor-fighting cells. Without tumor fighters, these abnormal cancer cells

continue to grow and spread. Therefore, not only does tobacco smoke causes cancer, but then it inhibits the body from fighting the cancer with its own immune system [2].

Even after a cancer diagnosis, 64% of patients continue to smoke [29]. Smoking cessation is critical amongst this population as poorer outcomes in cancer patients have been linked to tobacco use. It directly impacts the overall effectiveness of treatment, quality of life, and long-term survival [29]. In addition to promoting tumor growth, tobacco smoke may decrease chemotherapy benefits [2]. Therefore, smoking after cancer diagnosis increases the failure of treatment across all types of cancer [30]. Smokers with cancer have a lower quality of life, as well as an increase in symptoms during and following chemotherapy infusions compared to nonsmokers with cancer [31]. There is also an increased chance of second primary cancer with continued tobacco use.

Smoking Cessation Within a Lung Cancer Screening Program

Lung cancer screening with low-dose computed tomography (LDCT) has been demonstrated to decrease lung cancer mortality and overall mortality in high-risk individuals [32]. Individuals who qualify for screening are not only at an increased risk for lung cancer, but also at risk for other cancers and diseases. Furthermore, those undergoing screening and continuing to smoke are at even higher risk.

Smoking cessation counseling along with SDM, are CMS requirements for all current smokers in order to receive reimbursement for screening. LCS programs have an opportunity to further improve the impact of LCS by integrating smoking cessation within their programs as many individuals who undergo screening are current smokers. Studies indicate an increase in smoking cessation following a screen-detected abnormality on LDCT [33]. The SDM process and screening results review process are opportunities to encourage smoking cessation [33]. Integrating smoking cessation within LCS further improves smoking-related morbidity and mortality [33].

Thomas Jefferson University Hospital, a major urban, academic medical center, has a nursing-driven centralized lung cancer screening program. The program relies heavily on a multidisciplinary model to provide the best possible patient care; however, our core team is comprised of an advanced practice provider, two master tobacco treatment specialist-certified nurse navigators, and a dedicated coordinator. After referral to the program, an eligibility assessment including an extensive smoking history is conducted by the program coordinator. After patients sit down with our highly trained specialized nurse navigators for a shared decision-making session with smoking cessation counseling when applicable. If a patient agrees to undergo screening with a LDCT, the program offers an extensive result review, as well as concierge scheduling of follow-up tests, procedures, and appointments, if applicable. In addition to our high-quality, evidence-based workflow, our LCS program has worked diligently to develop a more comprehensive and standardized approach to smoking cessation. Along with tobacco cessation counseling during SDM, our tobacco treatment protocol includes follow-up counseling at the time of LCS results review, additional

support at an optional 2-week appointment, and/or ongoing telephone counseling as requested by patients. Furthermore, we provide all patients who are interested in a prescription for tobacco cessation medication and other treatment options.

An effective smoking cessation program must have a comprehensive approach to treating nicotine addiction at both the psychological and physiological root of the dependence. Often, healthcare professionals feel they do not have time to address all aspects of patient care in addition to tobacco cessation with their patients. LCS programs have a unique opportunity to provide one-to-one tobacco counseling with patients who are at increased risk for negative health outcomes associated with tobacco use.

Conclusion

Smoking cessation is known to decrease the risk of lung cancer mortality, all-cause mortality, as well as reduce the incidence of diseases including chronic obstructive pulmonary disease (COPD), heart disease, and cerebrovascular disease. Smoking cessation at any age has short-term and long-term benefits including increasing life expectancy. Even among individuals considered senior citizens (≥65 years), cessation can increase the life expectancy by years [2]. Additionally, even just decreasing one's daily cigarette consumption is linked to increased health benefits, such as decreases in COPD and asthma symptoms, and reduced progression of peripheral vascular disease [34]. All healthcare providers should initiate smoking cessation discussions with smokers at each point of contact, regardless of specialty. Unfortunately, the increasing complexity of patient care and time constraints for office appointments provide barriers for the proper initiation of smoking cessation. LCS programs are not only dedicated to early detection but also prevention of lung cancer. Therefore, programs have been well-positioned to be the champions of smoking cessation. Furthermore, CMS requires smoking cessation counseling of all current smokers undergoing SDM for LCS. Smoking cessation is multifaceted process and requires a comprehensive approach that addresses the physiological and psychological aspects of addiction, while providing support and nonjudgmental space to discuss the challenges of quitting smoking. The integration of evidence-based smoking cessation counseling and treatment in LCS programs would amplify the benefits of LCS, further improving long-term patient outcomes.

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