



Lung Cancer Screening—Why Do It? Tobacco, the History of Screening, and Future Challenges

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The US National Lung Cancer Screening Trial (NLST) begun in 2002 was halted early in October 2010 owing to clear evidence that annual screening with low-dose computed tomography (LDCT) scans led to decreased mortality in the screened population. The NLST posted a 20% reduction in deaths due to lung cancer and a 7% decrease in all-cause mortality.¹ Building on decades of research and previous trials, it was the first randomized controlled clinical trial to incontrovertibly validate a mortality benefit from lung cancer screening. The results have given hope of making inroads into reducing the burden of lung carcinoma, the most deadly cancer in the United States and in the world, for which an abysmal overall 5-year survival rate of 15% has not changed in decades.

Perhaps, the most persuasive argument for lung cancer screening is the ubiquity of tobacco use. Smoking is implicated in more than 90% of lung cancers. Although complete cessation of tobacco abuse would be ideal and would achieve staggering reductions in incidence and mortality from lung cancer as well as other smoking-related diseases over time, the fact remains that in the United States alone, 42.1 million adults 18 years of age and older were current smokers in 2012; this figure does not include former smokers or adolescents.² According to the World Health Organization (WHO), there are more than 1 billion tobacco users worldwide.³ Lung cancer most often manifests 2 or more decades after smoking initiation, and the current youngest smoking cohorts will remain at risk through the end of the 21st century. And although the tobacco epidemic is considered to have peaked in the Western world, it is only just beginning in countries

like China, where 65% of men are now smoking by their mid-20s.⁴

There are a number of challenges and controversies involved in screening for lung cancer. These include, among other things, recruitment of the appropriate screening population, the price, and the cost, relationship to tobacco cessation programs and barriers to screening.

The Tobacco Epidemic

History of Smoking

The history of modern tobacco use began in the 16th century. Tobacco had been used in the Americas for millennia by native populations in a limited fashion for medicinal and ritual purposes.⁴⁻⁶ Explorers to the New World brought tobacco back to Spain, and from there its use spread throughout Europe. It was considered a panacea for all manner of physical ailments and was chewed, sniffed, or applied as a poultice for diseases as diverse as headache, asthma, and open wounds.⁴⁻⁶ Although originally discouraged, tobacco was also consumed for pleasure. Early pipe smoking gave way to the use of snuff in the 17th century, followed by cigar smoking in the 18th century. Cigarettes, which at the time were hand-rolled, became fashionable in the latter half of the 19th century following the Crimean War.⁴

Some technological developments in the late 1800s promoted the rise of cigarette smoking in the general population. A cigarette-rolling machine was first patented in 1880 by a Virginian, John Bonsack; commercial use by the Duke family-owned American Tobacco Company followed soon thereafter.^{4,7} Mass production led to decrease in prices and wide availability. A second change was the new method of flue-curing tobacco, which made tobacco smoke smoother and easier to inhale.⁴ It also produces nicotine in nonionized form, which requires exposure to a larger surface area through inhalation into the lungs to be absorbed in sufficient quantities.⁸ The invention of the safety match in the late 19th century offered greater convenience and ease in lighting up.⁸

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Smoking also became more socially acceptable in the early 20th century. Manuals on etiquette in the mid-19th century advised against smoking in the company of women, public places, or closed confines. If one had to smoke, it was done privately, and subsequent oral hygiene and a change of clothing were required.⁹ By 1897, it was noted that “At one time it was considered a sign of infamously bad taste to smoke in the presence of women in any circumstances. But it is now no longer so.”¹⁰

The number of cigarette smokers, at first primarily men, climbed dramatically through the mid-20th century in the United States and Europe.⁴ During both World Wars, free cigarettes were supplied to military personnel, who brought the habit back home with them. Women began smoking in greater numbers during and after World War II, as they began to work outside the home and had more disposable income. Other groups were also targeted by the tobacco industry. Tobacco advertisements were put in medical journals, and doctors were used in many cigarette ads. Free cigarettes were made available at medical conferences.¹¹ In the early 1950s, nursing school residences in Winston Salem, NC, had weekly deliveries of cigarette 4-packs, which were left in the common lounge area.¹²

This free-sample marketing strategy by the tobacco industry has also been practiced much more recently. In the 1980s and early 1990s, directed marketing of menthol cigarettes to African Americans involved free distribution in urban neighborhoods by mobile vans.¹³ Despite military tobacco control policies, complimentary cigarettes were still being provided to deployed US soldiers in the Middle East in 1990 and 1991, sometimes shipped at the taxpayers' expense.¹⁴ Tobacco companies also engaged in more subtle marketing ploys to generate publicity and good will during the first Gulf War, such as the Marlboro voice card campaign, in which military families recorded voice messages that were delivered to soldiers abroad.¹⁴

The prevalence of smoking in the general US population has halved since the first Surgeon General's Report on smoking in 1964, to 18.1% in 2012.² However, the burden of smoking is not evenly applied across socio-economic, educational, or occupational groups.¹⁵ In the military, for instance, smoking prevalence was 32.2% in 2005.¹⁴ Further, the decrease in overall prevalence is in large measure owing to the growth of the population: the actual number of active US adult smokers was 48.1 million in 1970¹⁶ and 42.1 million in 2012,² only a 12.5% decrease. Tobacco use among adolescents is also substantial and represents a continuation of the tobacco problem.¹⁷ Up to 23.3% of high-school students and 6.7% of middle-school students reported currently using tobacco in 2012.¹⁸

Smoking and Addiction

Nicotine, a natural alkaloid, is the addictive component of tobacco.¹⁹ It mimics acetylcholine and acts by binding to nicotinic acetylcholine receptors, which are cell membrane ion channels found throughout the central nervous system.^{19,20}

Activation of these channels allows entry of calcium and to a lesser extent sodium ions and enables the release of neurotransmitters, including dopamine, serotonin, glutamate, gamma-aminobutyric acid, norepinephrine, endorphins, and others.¹⁹ Long-term nicotine exposure upregulates the number of nicotinic receptors. Neuroadaptation from smoking also produces alterations in gene expression and creation of new synaptic links. These factors set up a cycle of dependence and addiction.^{19,20}

Genetic variations from single-nucleotide polymorphisms confer increased susceptibility to nicotine dependence and increased difficulty in smoking cessation.²¹ Several of these variants are clustered on chromosome 15 (15q25.1), related to the expression of nicotinic receptor subunit genes, including *CHRNA5-CHRNA3-CHRNA4*.²² One of the strongest links is related to *CHRNA5*, the $\alpha 5$ nicotinic receptor subunit gene; individuals with this variant have twice the risk of nicotine dependence if they start smoking.²⁰

Nicotine levels in manufactured cigarettes have decreased over the years. The nicotine yield in the average cigarette in the 1950s was 2.7 mg, whereas modern cigarettes have a yield of only 0.8-0.9 mg per cigarette. This is likely responsible for adaptive smoking behaviors such as deeper inhalations, longer smoking of each cigarette, and most of all, increased number of cigarettes smoked, in efforts to satisfy individual levels of nicotine dependence.^{23,24}

Menthol as a cigarette additive has come under increased scrutiny; other candy, fruit, and spice additives to cigarettes were banned in 2009 under the Family Smoking Prevention and Tobacco Control Act.^{25,26} The recommendation to the US Food and Drug Administration from the Tobacco Products Scientific Advisory Committee in March 2011 was the “removal of menthol cigarettes from the marketplace” to benefit public health,²⁷ but this has not yet been adopted. Menthol is a monocyclic terpine alcohol derived from the peppermint plant and has been an additive to cigarettes since 1926; currently it is present in 90% of tobacco products, even those not labeled as “menthol.”^{13,26}

The ability of menthol to alter smoking behavior has been recognized through tobacco company research for years and has been verified by independent studies.²⁶ Menthol blunts the irritation of smoke inhalation and provides an icy sensory experience in the mouth and nasal passages, and is associated with easier initiation and continuation of cigarette smoking.^{13,26} Menthol acts by noncompetitive binding to attenuate nicotine activation of nicotinic acetylcholine receptors. The metabolism of nicotine and its primary product, cotinine, is slowed down by menthol, resulting in prolonged systemic nicotine exposure.¹³ Menthol also upregulates nicotinic cholinergic receptor expression.^{13,28} As a result, menthol appears to potentiate the addictive properties of nicotine in addition to making cigarettes, especially low-tar varieties, more palatable.¹³ Menthol cigarette smoking is prevalent among youth, women, and the African American community, to all of whom it has been aggressively marketed.^{13,26}

Age and racial differences constitute other factors in nicotine addiction. Smoking initiation at younger ages is associated with more severe dependency. In some studies, African Americans

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