Tobacco Causes Human Cancers—A Concept Founded on Epidemiology and an Insightful Experiment Now Requires Translation Worldwide

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Abstract

The recognition that tobacco smoke is carcinogenic led to the most significant and successful effort at reducing cancer incidence in human history. A major milestone of this effort was the publication in *Cancer Research* by Wynder and colleagues, which demonstrated the ability of tobacco tars to produce tumors in mice. This study provided a powerful link between the epidemiology of cancer and mechanisms of carcinogenesis. This commentary asserts that we have a moral obligation to translate our success in reducing lung cancer in the United States to the 1.25 billion smokers throughout the rest of the world. *Cancer Res; 76(4); 765–6. ©2016 AACR.*

See related article by Wynder et al., Cancer Res 1953;13:855–64.

In the early 1950s, a series of epidemiologic studies revealed a strong statistical association between lung cancer and smoking, particularly cigarettes (1). These studies additionally revealed a weaker correlation between cigarette smoking and cancers of the oral cavity, larynx, and esophagus, which constitutes the logical pathway for inhalation of cigarette smoke and the deposition of particulates. However, while many other potential human carcinogens had been shown to generate tumors in a variety of laboratory animals (2), application of cigarette smoke or tobacco tars in animal studies were inconclusive (3). Major confounding factors in these studies included the variable methodologies for extracting tobacco tars and the limited time of application feasible in animal studies. In human cancers there is a 20- to 30-year lag time between the exposure to a carcinogen and the detection of a tumor, a lag time that could not be replicated in animal studies. Thus, there was an urgent need to generate an experimentally tractable animal system to test the carcinogenic potency of cigarette smoke to provide independent support to the existing epidemiologic correlations.

The classic article by Wynder and colleagues (3) addressed this need. They designed a machine to mimic smoke inhalation by humans and collected the resultant tobacco tars; these tars were then painted onto the skins of mice at weekly intervals for up to 8 months. Wynder and colleagues observed papillomas after 8 months, and, by 2 years, 44% of the mice had histologically documented skin cancers. This study provided a working tool for the identification of carcinogenic agents in cigarette smoke. One ultimate goal of their work was to remove the carcinogens from tobacco products; another was to understand the mechanism of carcinogenesis by tobacco carcinogens.

Subsequent studies in different animal species complicated the early studies on tobacco-induced cancers. While the original results of Wynder and colleagues were confirmed in many laboratories, some additional results were unexpected. For example, there is no single carcinogen in tobacco smoke (4). Chemical carcinogens in cigarette smoke that have been shown to cause cancer in at least one animal species include 4-methylnitrosoamino-1-(3-pyridyl)-1-butapone (NNK), N-nitrosonornicotine (NNN), polycyclic aromatic hydrocarbons (PAH), radon, and formaldehyde (4, 5). Known carcinogens, including acrolein, acetaldehyde, 1,3 butadiene, and benzene are also present in cigarette smoke (5, 6), although they have not yet been conclusively shown to cause lung cancer. Of the more than 7,000 compounds inhaled during smoking, 72 have thus far been identified as carcinogenic by the International Agency for Research on Cancer (7). The original goal of removing carcinogens from cigarettes was, thus, unrealistic; cigarettes cannot be sanitized.

The variety and diversity of chemical carcinogens identified in cigarette smoke, their association with human cancers, their interaction with cellular metabolic processes, and the mutagenic adducts formed in DNA has been a major factor in driving mechanistic studies on DNA repair and mutagenesis. Most altered nucleotides in DNA are excised and the DNA sequence is restored prior to cell replication. This year, the Nobel Prize Committee recognized the importance of DNA repair by awarding the Nobel Prize in Chemistry to Drs. Lindahl, Sancar, and Modrich, who respectively pioneered the delineation of pathways for base excision repair, nucleotide excision repair, and mismatch repair. These DNA repair processes result in most tobacco-induced altered nucleotides in DNA prior to cellular replication.

Of the 72 carcinogenic compounds in cigarette smoke, NNK and PAH have been studied most extensively (5, 8). While they do not directly interact with DNA, cellular enzymes metabolize them to produce derivatives that form covalent adducts with nucleotides in DNA (8). These modified nucleotides are thought to either miscode or stall DNA replication, resulting in point mutations and chromosomal rearrangements, respectively (9). For the most part, DNA damage produces mutations randomly throughout the genome, including genes that encode proteins that maintain genetic stability. Unrepaired DNA damage can reduce the efficiency of DNA repair or the fidelity of DNA synthesis. DNA damage as a consequence of smoking cigarettes can result in a mutator

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phenotype (10); this likely accounts for the tens of thousands of mutations found in human lung cancer (11). Interestingly, nicotine, the habituating agent in cigarette smoke, has not been shown to be carcinogenic. It has, however, been shown to promote cell proliferation and cell division and to inhibit apoptosis. Thus, nicotine could act synergistically with the carcinogenic compounds in cigarette smoke to enhance mutagenesis (12).

Polymorphisms in the genes of enzymes responsible for the metabolic activation of chemical carcinogens may be responsible for some of the variations in the susceptibility of different human populations to cigarette-induced lung cancers (13). However, these variations are small compared with the overall incidence of lung cancer due to smoking, and they do not justify the stratification of resources to reduce cancer in specific populations. Advances in technology have made it feasible to quantify human exposure to cigarette smoke. Ultra-sensitive mass spectrometry is being used to measure a panel of tobacco carcinogens and toxicant metabolites including urinary cotinine and the NNK metabolite NNAL as an index of current exposure to tobacco products (14). DNA damage is being measured by digestion of cellular DNA and detection of modified nucleotides by high pressure liquid chromatography, mass spectrometry, and post-labeling (15, 16). Changes in DNA repair enzymes have been proposed as a biomarker for smoking (17). Methods to measure random mutations in DNA by ultra-accurate DNA sequencing has made it possible to quantitate mutation load (18) with the likelihood of developing lung cancer in smokers. Each of these technologies offers the possibility of determining the likelihood of developing lung cancer in smokers as well as the effectiveness of different approaches to chemoprevention.

Evidence suggests that those who decide to smoke are likely to die as a result of that decision, as tobacco-induced cancers are among the most malignant tumors—the five-year survival rate of lung cancer is 17.4% (2005–2011; ref. 2). However, the decision may not be voluntary, as the powerful advertising of the tobacco industry may greatly influence the choice of many people. The American Association for Cancer Research and other groups have made major commitments to reduce cigarette smoking in the United States (4). As a result, smoking prevalence in males is down 50% since 1960 and death from lung cancer has been reduced by 38% from 1990 to 2014. A parallel but less dramatic reduction has occurred in females. Together, these results establish the importance of smoking cessation in cancer prevention (19). However, 17% of American adults are still smoking, with 5% to 7% of young adults starting each year.

To compensate for the decline in revenue due the reduction in smoking in the United States, the tobacco industry increased its export of tobacco throughout the world. The reduction in smoking in the United States contrasts with the increase in most other countries. It is estimated that there are 1.25 billion smokers worldwide and more than one million people die of tobacco-induced lung cancer each year. This is a major worldwide epidemic that is entirely human caused. An equal number of smokers succumb to emphysema, vascular disease, and other tobacco-associated diseases each year. It is time for us to extend our success in reducing tobacco-associated diseases in the United States to other countries that lack adequate resources to combat the powerful advertising by tobacco industries.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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