NCI Monograph 23
Treating Smoking in Cancer Patients:
An Essential Component of Cancer Care

Chapter 2
Smoking in Patients With Cancer: Biological Factors

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Introduction

Enormous progress has been achieved over the past several decades in researchers' understanding of the biology that underlies cancer.[1] As a result, many cancers are now prevented or are diagnosed at an earlier stage, and fewer patients who develop cancer die from their disease. In terms of clinical care, revolutionary advances in treatment strategies, including minimally invasive surgery, highly conformal radiotherapy, targeted biologic therapeutics, and immunotherapy, have markedly improved patient outcomes.[2–4] These advances, along with successes in prevention and screening, have contributed to a 31% reduction in cancer death rates between 1991 and 2017,[5] dramatically increasing the number of patients who survive cancer.[5–7] As a result, morbidity from cancer treatment sequelae as well as noncancer-related morbidity and mortality are more important determinants of overall patient outcomes than ever before.

As described in chapter 1, a strong clinical evidence base demonstrates the adverse effects of smoking on clinical cancer outcomes. The 2014 Surgeon General's report, *The Health Consequences of Smoking—50 Years of Progress*, was the first Surgeon General's report to comprehensively review the effects of cigarette smoking on health outcomes in cancer patients and survivors. This report, which reviews more than 400 studies, concluded that quitting smoking improves the prognosis of patients with cancer, and that smoking is causally linked with adverse health outcomes, including all-cause mortality, cancer-specific mortality, and increased risk for second primary cancers caused by smoking.[8] In aggregate, among studies that included relative risks (RR), risk of all-cause mortality increased by a median of 51% among patients with cancer who smoked compared with never-smoking patients with cancer, while former smoking was associated with a median increased risk of 22% compared with never smoking. Current smoking also increased risk of cancer-specific mortality by a median of 61% while former smoking did not appear to increase risk relative to never smoking (increasing risk by only a median of 3%). Current smoking increased risk of recurrence by a median of 42% compared with never smoking, while former smoking increased median risk by 15%. Finally, there was a strong association between current smoking and the risk of developing a second primary cancer (median RR of 2.2).[8] The 2020 Surgeon General's report, *The Health Benefits of Smoking Cessation*, built on these findings by reviewing the effects of smoking cessation on risk of all-cause mortality among patients with cancer. This report reviewed 10 studies, representing 10,975 patients with cancer, which were published on this topic between 2000 and 2016. Among the 7 prospective cohort studies reviewed, continued smoking was associated with a median increased risk in all-cause mortality of 82% compared with quitting smoking.[9]

The clinical effects of smoking on cancer treatment outcomes are mirrored by biological observations that smoking increases tumor promotion and is associated with decreased efficacy of cancer treatment.[10,11] Studies of cigarette smoking and cancer contribute to the understanding of the biology of cancer and to developing treatments for cancer; they also provide a compelling

rationale for addressing tobacco use by patients with cancer. This chapter will first provide a brief discussion of the numerous mechanisms by which cigarette smoking causes cancer. It will then discuss studies of the molecular characteristics of lung cancers occurring in smokers compared with never-smokers before turning to a discussion of experimental studies of the effects of tobacco smoke exposure on cancer cells. A comprehensive review of the mechanisms by which cigarette smoking causes disease, including cancer, is available in the 2010 report of the Surgeon General, *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*.[12] This chapter will focus on the biological effects of cigarette smoking because it is the predominant form of tobacco used by adults. Additionally, there are not yet sufficient studies of the biological effects of newer forms of tobacco, such as electronic nicotine delivery systems, on cancer.

Tobacco Smoke and Tumorigenesis

Chemical Composition of Tobacco Smoke

The causal relationship between cigarette smoking and numerous cancers has been well documented.[8] Tobacco smoke contains more than 7,000 chemical compounds, of which approximately 70 cause cancer in either laboratory animals or humans.[8,12,13] This complex mixture of carcinogens causes at least 12 types of cancer in humans.[8,12] The U.S. National Toxicology Program and the International Agency for Research on Cancer (IARC) have determined that tobacco smoke is carcinogenic.[13,14] Similar to other IARC Group 1 carcinogens (known human carcinogens), tobacco smoke exhibits 1 or more of the 10 key characteristics of carcinogens shown in Table 2.1.[13,15] Although the biological effects of tobacco smoke on tumorigenesis have been well studied, some knowledge gaps remain, including whether the route of exposure to tobacco smoke influences the site-specific biology of the resultant tumors. For example, tissues that come into direct contact with tobacco smoke (e.g., lung) are exposed to the whole mixture of chemical compounds, whereas other organs are exposed only to those chemical compounds or their metabolites that reach the tissue through the circulatory system. As a result, there may be biological differences between tobacco-related tumors based on whether they receive exposure to tobacco smoke directly, through the circulatory system, or a combination of both.

Table 2.1 Key Characteristics of Carcinogens

Characteristic	Examples of relevant evidence
1. Is electrophilic or can be metabolically activated	Parent compound or metabolite with an electrophilic structure (e.g., epoxide, quinone), formation of DNA and protein adducts
2. Is genotoxic	DNA damage (DNA strand breaks, DNA–protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g., chromosome aberrations, micronuclei)
3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (e.g., topoisomerase II, base-excision, or double-strand break repair)
4. Induces epigenetic alterations	DNA methylation, histone modification, microRNA expression
5. Induces oxidative stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g., DNA, lipids)
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production

Table 2.1 (continued)

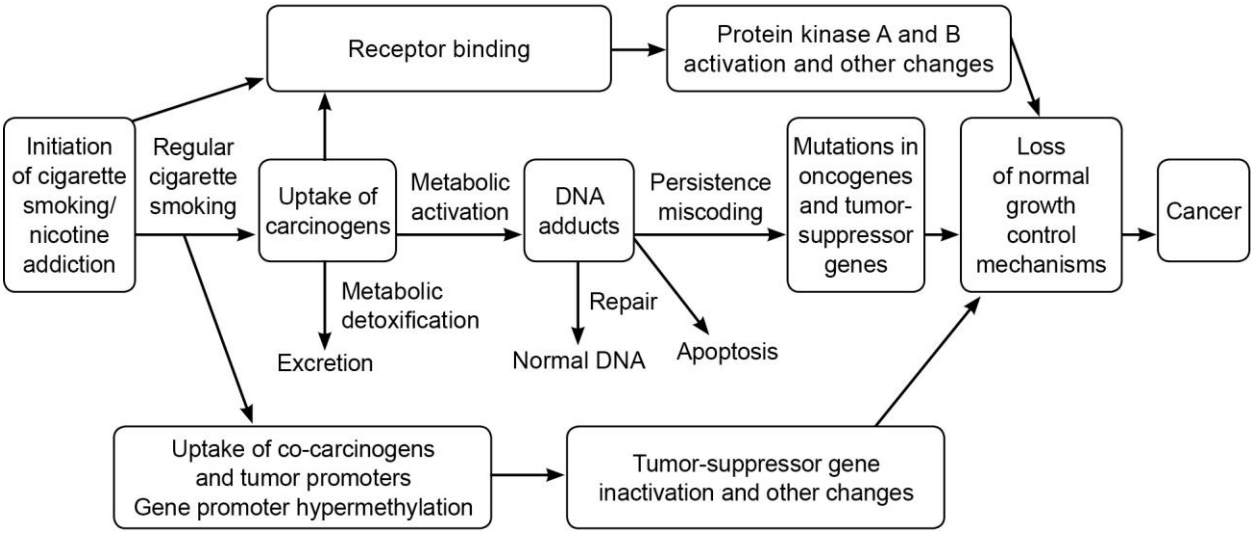
Characteristic	Examples of relevant evidence
7. Is immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor in/activation (e.g., ER, PPAR, AhR) or modulation of endogenous ligands (including hormones)
9. Causes immortalization	Inhibition of senescence, cell transformation
10. Alters cell proliferation, cell death, or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

Note: Any of the 10 characteristics in this table could interact with any other (e.g., oxidative stress, DNA damage, and chronic inflammation), which when combined provides stronger evidence for a cancer mechanism than would oxidative stress alone. DNA = deoxyribonucleic acid. RNA = ribonucleic acid. ER = estrogen receptor. PPAR = peroxisome proliferator-activated receptor. AhR = aryl hydrocarbon receptor.
Source: Smith et al. 2016.[15] Reproduced from *Environmental Health Perspectives* with permission from corresponding author, Martyn T. Smith.

Tobacco Smoke: DNA Damage

Many chemical compounds in tobacco smoke damage deoxyribonucleic acid (DNA) either directly or via their metabolic by-products.[12] This damage can lead to both small and large genetic alterations.[12,16] These alterations accumulate from prolonged exposure to tobacco smoke chemical compounds over time to increase the level of mutations within exposed tissues and can result in loss of normal function of proteins involved in the control of cell growth and DNA damage repair, thus contributing to tobacco-related tumor formation.[12] Figure 2.1 depicts the major pathways by which the carcinogens in tobacco smoke cause cancer or tumor development.[12] Former smokers are at reduced risk of many cancers relative to current smokers.[9] However, the genetic changes accrued during the time they smoked contributes to their increased cancer risk relative to never-smokers.

Figure 2.1 Major Pathways of Cancer Causation by Cigarette Smoking



Note: DNA = deoxyribonucleic acid.
Source: USDHHS 2010.[12]

Tobacco Smoke: Mutational Burden

Analyses of the genetic changes associated with tobacco smoke exposure can provide insight into molecular changes occurring in cancers among smokers. The types of genetic changes include single base substitutions (SBS), insertions or deletions (indels), or copy number variations, as well as larger chromosomal alterations.[17–20] Sequencing of tumor DNA from current and former smokers reveals significant smoking-related mutation patterns that vary by organ site.[17,20–22] The organs that come in direct contact with tobacco smoke chemical compounds have the highest number of total mutations per cancer DNA region or mutational burden.[17] Lung cancer has the highest overall mutation levels of smoking-related cancers; elevated mutation levels are also observed in head and neck, bladder, liver, and kidney tumors from smokers compared with nonsmokers.[17,20–22] In addition, the extent of mutations can be lower in former smokers relative to current smokers, depending on the organ site.[21,22]

Studies of normal bronchial cells from current, former, and never-smokers indicate that smoking causes mutations in these cells, with current smokers having the highest mutation burden; the mutational burden of former smokers is intermediate between that of current smokers and never-smokers.[23] Additionally, the fraction of cells without mutations is higher in the bronchial epithelium of former smokers than in current smokers, suggesting that following smoking cessation, the damaged cells within the bronchial epithelium are replaced by cells that avoided mutagenesis.[23]

The types of mutations associated with tobacco smoke exposure shift depending on the tumor location.[17,20,24] This may be due to the susceptibility of different tissues to the variety of chemical compounds present in tobacco smoke, to differences in tissue-specific metabolic activities that activate or inactivate mutagens, or to the extent to which different tissues are exposed to the various chemical compounds in tobacco smoke. Furthermore, there may be organ differences in how the tissues respond to tobacco smoke-related DNA damage, given that there are cancers (e.g., pancreatic or cervical cancer) for which smoking-related DNA damage has been detected but the mutational burden is not significantly different between smokers and nonsmokers.[17]

Tobacco Smoke: Mutational Signatures

Somatic mutations contribute to carcinogenesis by altering the activity of proteins involved in cell cycle control as well as other important cellular processes. Mutational signatures are distinctive patterns, or footprints, caused by specific mutagenic processes, such as exposure to individual DNA-damaging chemical compounds or defective endogenous processes like DNA repair pathways. These signatures are identified by bioinformatics analysis of genomic DNA from thousands of tumors that focuses on extracting characteristic somatic mutation patterns and, where possible, attributing them to individual mutagenic sources.[25] Researchers have compiled the mutational signatures extracted from thousands of cancer genomes in the Catalogue of Somatic Mutations in Cancer (COSMIC).[26] These patterns are based on SBS, doublet base substitutions, indels, and large-scale genomic structural alterations.[27] As numerous mutational signatures are associated with specific exposures, their presence provides evidence that a given exposure plays a role in the carcinogenic process.

Multiple signature mutations are elevated in tumors in smokers, including COSMIC mutation signatures 2, 4, 5, 13, and 16.[17] Some of these signatures are present in all tumor cells, indicating

that they likely occurred early in the tumorigenesis process. These signatures reveal valuable mechanistic information about the carcinogenic process. For example, signature 4 involves GC to TA transversion mutations in patterns similar to those produced by the tobacco smoke chemical benzo[a]pyrene in model systems.[28] This signature is mainly detected in tumors located at sites that come in direct contact with tobacco smoke chemical compounds, such as the lung, larynx, oral cavity, pharynx, and esophagus.[17] On the other hand, signature 5 is thought to derive from an endogenous mutation process.[17] Because this signature is more abundant in cancers occurring in smokers compared with never-smokers for lung, larynx, pharynx, oral cavity, esophagus, bladder, liver, and kidney tumors,[17] it is thought that indirect effects of tobacco smoke trigger an endogenous mutation process responsible for this signature. Similarly, the higher levels of signatures 2 and 13 in tobacco-related cancers are thought to be derived from indirect effects of tobacco smoke, as these signatures are associated with the APOBEC enzyme family (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like)[17]; APOBEC members can be overexpressed in some cancers and cause mutations by converting DNA cytosine bases to uracil.[29]

Tobacco Smoke: Cancer Driver Genes

Genetic analyses have shown that there are dramatic differences in somatic mutation patterns between and within cancer subtypes.[30–32] These analyses led to the identification of gene sets that drive carcinogenesis when they are mutated; the specific genes that house these mutations are defined as cancer driver genes.[33] These mutations give an advantage to the cells containing them and have been selected for during the cancer's evolution.[33,34] The combination of cancer driver genes mutated in the carcinogenic process varies with tumor subtype, stage, and the etiological factors leading to tumor formation (e.g., smoking status).[33] Identification of the specific genes mutated in a patient's tumor can inform the selection of appropriate cancer therapies and help predict patient survival, the risk of recurrence, and response to therapy.[35] Because smoking impacts the number and type of mutations, depending on the organ site, the cancers formed in ever-smokers can be biologically distinct from those in never-smokers, requiring different approaches for cancer treatment.[18,36,37]

Tobacco Smoke: Epigenetic Changes

Tobacco smoke also causes nonmutational structural changes in DNA that affect gene expression (epigenetic changes, e.g., levels of 5-methylcytosine). Consequently, the epigenetic landscape of tumors from patients with a history of smoking can differ from those of patients without a history of smoking, depending on the tumor type.[17,38–45] The most extensive effects of smoking on epigenetic markers are observed in lung tumors.[17] Similarly, smoking, particularly current smoking, has been shown to alter gene expression in some tumors.[46–55] These changes can affect the biology of the tumor, influencing tumor behavior, such as the aggressiveness of tumor growth or responsiveness to cancer therapies.

Biological Characteristics of Lung Cancers in Smokers and Never-Smokers

Lung cancers are classified as small cell lung cancers or non-small cell lung cancers (NSCLCs) by the presence or absence of neuroendocrine characteristics.[56] NSCLC, which represents approximately 85% of lung cancer in the United States,[57] is further categorized into adenocarcinoma (40% of lung cancers), squamous cell carcinoma (25% of lung cancers), and

large cell carcinoma (10% of lung cancers).[58] In the United States, the vast majority of lung cancers (~80%–90%), regardless of histologic subtype, occur in current or former smokers; lung cancers that occur in never-smokers are predominantly adenocarcinoma.[59–62] An understanding of the molecular characteristics of lung cancers contributes to the understanding of their etiology as well as to their diagnosis and treatment. To highlight how tobacco smoke exposure can influence the molecular characteristics of cancer, characteristics of lung cancer in smokers and never-smokers are discussed below.

It is important to note that studies do not always distinguish between never-smokers and former smokers, instead comparing current smokers with "nonsmokers." In addition, some studies compare never-smokers to "ever-smokers," a category that comprises both current and former smokers. The categories of current, former, and ever-smoker may include individuals with a wide range of smoking histories and patterns; in particular, the category of former smokers may include individuals who quit decades ago as well as those who quit very recently. Furthermore, it is not always possible to accurately distinguish between never-smokers, current smokers, and former smokers based on patient report or medical record. In the section below, results are reported based on the categories used in the literature cited.

Lung Cancer: Driver Genes

Studies show that lung cancers in smokers are molecularly distinct from lung cancers in never-smokers, particularly in mutations in the cancer driver genes.[62,63] The driver genes vary with histological tumor type and smoking status.[64–66] There are data indicating that the genesis of lung tumors in current smokers, former smokers, and never-smokers follow different pathways with distinct patterns of driver mutations.[67] For example, the frequency of epidermal growth factor receptor (*EGFR*) mutations is significantly higher in lung cancers in nonsmokers compared with smokers; *EGFR* is the most frequent mutation in lung adenocarcinomas in never-smokers but is relatively rare in heavy smokers.[64,68–79] The frequency of *EGFR* mutations drops with increasing pack years smoked.[69,71–73,76] In contrast, Kirsten rat sarcoma viral oncogene homolog (*KRAS*) and tumor protein p53 (*TP53*) mutations are more prevalent in adenocarcinomas in current and former smokers, compared with never-smokers.[24,64,68,69,75,80–82] Former smoker NSCLC patients had more *EGFR* mutations and fewer *KRAS* mutations than patients who currently smoke.[69,83]

Differences in driver genes are significant because they can affect the responsiveness of the tumor to different therapeutic approaches, with implications for prognosis and survival.[18,36,75] Targeted therapies have been developed to treat tumors with specific driver genes, such as *ALK*, *EGFR*, *BRAF*, *ROS1*, *RET*, and *MET*. Targeted therapies increase the life expectancy of patients with these specific mutations relative to patients who lack those mutations; this increase in survival is independent of smoking history, which emphasizes the importance of molecular genetic testing of lung adenocarcinoma specimens for targetable driver mutations regardless of smoking history.[84–86]

Lung Cancer: Mutational Burden

The mutational burden in lung tumors from smokers is higher than that in lung tumors from nonsmokers.[17,21,36,37,65] Genome-wide comparison of lung adenocarcinomas from smokers and never-smokers indicated that the average mutation frequency is more than 10 times higher in

smokers than in never-smokers.[36] This is consistent with the high mutational activity of the chemical compounds in tobacco smoke, which drives tumorigenesis.

Mutational burden includes both small and large genetic changes.[17,19,21,65] Mutated genes in lung cancers from smokers often have a different spectrum of mutations than occurs in lung cancers from never-smokers.[69,80,81,87] Genome-wide analysis of genomic aberrations in lung adenocarcinomas from smoking and nonsmoking patients indicates that these two populations have both global and regional differences in their tumor genome. Tumors from never-smokers were more likely to have gene copy number gains on chromosomes 5q, 7p, and 16p and were more likely to have a larger fraction of their genome altered. In comparison, tumors from ever-smokers were more likely to have more regions of focal DNA amplifications and deletion.[65] Another study indicated that the significant copy number gains in heavy smokers were especially frequent in 8q and 12q, whereas focal copy number losses in never-smokers or light smokers tended to occur in areas not associated with genes.[19] The overall mutational complexity of tumors in smokers may contribute to the difficulty in treating such tumors.

Lung Cancer: Epigenetic Modifications

In addition to mutations, smoking causes structural changes to DNA which, in turn, affect how the tumor grows and responds to therapy. For example, DNA methylation, an epigenetic modification, controls the expression of specific genes; there are distinct differences in the patterns of gene methylation or methylation status in lung tumor DNA from smokers compared with nonsmokers.[17,38,39,45,88–91] The methylation status of specific genes is associated with tumor aggressiveness and patient outcomes.[92,93] A meta-analysis of studies conducted in patients with lung cancer found a positive association between cigarette smoking and hypermethylation of *p16* in tumor tissues from both adenocarcinomas and squamous cell carcinomas. The meta-analysis, which included 19 studies conducted in several countries, found a stronger association between smoking and *p16* hypermethylation in studies conducted in Asian countries compared with those conducted in North America.[91] Methylation of *p16* and *MGMT* genes is elevated in NSCLC tumors in ever-smokers versus never-smokers.[39] Similarly, a meta-analysis of 97 studies of NSCLC found a significant association between cigarette smoking and hypermethylation of 7 genes (including *CDKN2A, RASSF1, MGMT, RARB, DAPK, WIF1, FHIT*).[38]

Lung Cancer: Variation in Gene Expression

Smoking-related variations in gene expression as measured by variations in ribonucleic acid (RNA) levels have also been reported for lung cancers and, in some cases, associated with patient prognosis. Smoking-associated expression networks of messenger RNA (mRNA) and a variety of noncoding RNAs have been reported.[48–50,53–55,94] In all cases, researchers observed marked differences between tumors from smoking and nonsmoking patients, with tumors from smoking patients exhibiting a more complex disease with greater dysregulation of gene expression. Studies focused on specific genes also showed differences between smokers and nonsmokers. For example, never-smokers were more likely to have down-regulation of expression of *p14*, but not *p16*, than were ever-smokers (63% vs. 35%, $p = .008$).[74] In addition, expression of a variety of receptor genes was altered in tumors as a function of smoking status. Progesterone and androgen receptor gene expression was lower in NSCLC than in normal tissues with levels being lower for smokers than for never-smokers. Aryl hydrocarbon receptor (*AHR*)

gene expression was also lower in tumors in smokers compared with never-smokers.[95] The expression patterns of genes encoding nicotinic acetylcholine receptor subunits (*CHRN*) were different depending on histological tumor type and smoking behavior. The expression of *CHRNA7* gene, which encodes a CHRN subunit, was elevated in squamous cell carcinoma in smokers relative to nonsmokers and was associated with poor survival.[96]

Therapeutic Implications of Molecular Differences in Lung Cancers

With the development of targeted therapies and immunotherapies, the molecular differences between lung cancer in smokers and never-smokers contribute to differences in treatment options, prognosis, and survival. As noted above, *EGFR* mutations are predominantly found in lung cancers in never-smokers. The presence of *EGFR* mutations strongly predicts a positive response to therapy with the *EGFR* tyrosine kinase inhibitors gefitinib, erlotinib, and osimertinib.[97,98] Lung cancers arising in never-smokers are more likely to contain *ALK* mutations than those arising in smokers; targeted therapies that improve progression-free survival, such as alectinib and crizotinib, for this subset of lung cancer are also available.[99–101] Targeted therapies now exist for several additional molecular abnormalities, including *ROS1*, *RET*, and *NTRK*, among others.[102,103]

Expression of programmed death-1 ligand (PD-L1) is a means by which cancer cells can evade normal immune surveillance. This protein is a target for immunotherapy drugs, known as immune checkpoint inhibitors, which have had a major impact on the care of patients with lung cancer; in some patients with advanced lung cancer, their use has produced long-term survival.[85,104] PD-L1 positivity is linked to checkpoint inhibitor responses and multiple studies show higher expression in patients with NSCLC who are smokers than in those who are nonsmokers.[105–107] Checkpoint inhibitors are generally not effective for cancers driven by molecular abnormalities such as *EGFR* mutations typically found in never-smokers, irrespective of PD-L1 status.[108]

The Effects of Tobacco Smoke Exposure on Cancer Cells

Tobacco smoke can have both systemic and local effects on cancer cells in experimental models. As an example of its systemic effects, tobacco smoke suppresses the immune system, which allows cancer to develop and to expand without the normal immune system checks on cell growth.[12,21,109] There are many potential local effects of tobacco smoke that may promote the continued growth and transformation of cancer cells to more advanced stages and may cause cancers to be resistant to therapeutic strategies. These may include:

1. DNA damage
2. Changes in gene expression
3. Alteration of cell cycle control
4. Promotion of epithelial-mesenchymal transition associated with metastasis
5. Promotion of angiogenesis
6. Alterations of the tumor microenvironment
7. Promotion of dedifferentiation
8. Inhibition of response to chemotherapeutic agents

This section describes studies examining the effect of tobacco smoke on cancer cells; most of the studies were performed *in vitro* with cancer cells exposed to tobacco smoke extract or individual tobacco smoke chemical compounds and may not reflect *in vivo* occurrences.

DNA Damage

Continued exposure to tobacco smoke chemical compounds may result in additional damage to cancer cell DNA.[110,111] This damage provides the opportunity for further evolution of the cancer, because of additional aberrant cellular function, such as decreased DNA repair, increased genetic instability, increased rates of cell division, as well as cellular dedifferentiation.[12] Consistent with this hypothesis, the mutations per genome in some tobacco-related cancers increased with cumulative exposure to tobacco smoke.[17]

Changes in Gene Expression

Chronic exposure of lung cancer cell lines to cigarette smoke leads to significant changes in RNA and protein levels in directions that are consistent with those observed in lung cancers and are associated with dysregulation of normal cellular function.[112,113]

Alteration of Cell Cycle Control

Tobacco smoke promotes cell proliferation (increased rate of cell division) through interaction with cell-surface receptors and activation of a variety of signaling pathways.[11] Tumor cells that express these receptors are sensitive to the cell proliferation effects of tobacco smoke chemical compounds. For example, activation of nicotinic acetylcholine receptors by tobacco smoke chemical compounds, such as nicotine and nicotine-derived nitrosamine ketone, an important tobacco-specific n-nitrosamine, increases the rate of cell proliferation by increasing the rate of cell division and blocking cell death through activation of signaling pathways; the exact signaling pathway is dependent on the cancer type.[114–116]

Promotion of Epithelial-Mesenchymal Transition Associated With Metastasis

Epithelial-mesenchymal transition (EMT) is a complex molecular process in which epithelial cells lose cell–cell adhesion and develop motility characteristics of mesenchymal cells.[117] By increasing the invasiveness and metastatic potential of tumor cells, EMT contributes to cancer progression.[118] The ability of cigarette smoke to promote EMT and increase the invasive nature of cancer cells has been explored in a wide variety of cancer cell lines.[119–129] These effects were achieved through changes in expression of metastasis-associated proteins.[123,124,127,128] In oral cancer cell lines, cigarette smoke extract increased the levels of cathepsins, protease enzymes that facilitate metastasis.[126] Mechanistic studies in lung cancer cell lines indicated that cigarette smoke extract–induced invasive activity was triggered by the increased expression of a key prometastatic gene, *SNCG (*synuclein-γ).[130] Similarly, cigarette smoke–induced EMT, migration, and invasion resulted from a series of epigenetic changes leading to reduced levels of E-cadherin, an intercellular adhesion protein, in lung cancer cells.[131] This study also found that loss of E-cadherin is an unfavorable prognostic factor in patients with lung cancer and that downregulation of this protein is associated with number of pack years of smoking.[131]

Promotion of Angiogenesis

Cigarette smoke may also increase angiogenesis, which is the ability of cancer cells to induce the formation of new blood vessels. Interaction of tobacco smoke chemical compounds with nicotinic acetylcholine receptors is linked to the increased production of vascular endothelial growth factor, a major factor in the generation of new blood vessels within tumor cells.[132] Cigarette smoke extracts trigger this production in a variety of cancer cell lines including those derived from NSCLC, pancreatic cancer, and colon cancer.[114,133,134]

Alterations Within the Tumor Microenvironment

Tumor cells alter their microenvironment, the surrounding tissue in which they reside, to inhibit antitumor processes and promote functions crucial for tumor maintenance and growth. The tumor microenvironment consists of cells and components that surround and infiltrate the tumor, which include extracellular matrix, fibroblasts, blood vessels, diverse immune cells, and other cells.[135,136] A number of studies show that tobacco smoke may enhance tumor growth and metastasis through alteration of the tumor microenvironment. For example, cigarette smoke chemical compounds alter the fibroblasts that surround the tumor, causing premature aging and mitochondrial dysfunction in these cells.[137] As a consequence, the fibroblasts secrete energy-rich compounds (e.g., L-lactate, ketone bodies) into the tumor microenvironment, which promotes tumor growth. Exposure of fibroblast cell lines to cigarette smoke leads to increased tumor growth of cancer cell lines in coculture conditions.[137,138] Cigarette smoke exposure leads to metabolic coupling between the two cell types, increases cancer cells' resistance to cell death, and causes increased cancer cell migration.[138]

Promotion of Stem Cell–Like Properties

Cancer stem cells are a subpopulation of tumor cells that have adopted stem-like properties (low in abundance, high proliferative potential, and sufficient to reconstitute all the cell types of the tumor) and are implicated in tumor formation, growth, progression, and metastasis; they also play a role in resistance to therapy, relapse, and prognosis.[139–141]

Tobacco smoke extracts or condensates have been shown to cause the development of stem cell-like subpopulations in breast and lung cancer cell lines.[121,142] Additionally, a study found that administration of nicotine to mice altered normal homeostasis of pancreatic tissue, promoted pancreatic carcinogenesis, and induced pancreatic acinar cell dedifferentiation.[143] Cigarette smoke extract–exposed renal cancer cell lines develop characteristics of cancer stem cells that are mediated through activation of the Sonic Hedgehog (SHH) pathway and express increased levels of multiple cancer stem cell markers. The observation that renal tumor tissue from smokers had higher levels of cancer stem cell markers and SHH pathway–related proteins than tumor tissue from nonsmokers suggests that this mechanism may act in renal cancers in patients.[144]

Inhibition of Response to Chemotherapeutic Agents

In vitro studies demonstrate that continued exposure to tobacco smoke reduces the ability of chemotherapeutic agents to kill cancer cells through a variety of different mechanisms. One mechanism involves the upregulation of xenobiotic transporters, which is associated with an increased removal of chemotherapeutic agents out of the cancer cell.[145,146] Mechanistic studies

suggest that the upregulation of the xenobiotic transporter ABCG2 occurs through an AhR-mediated process, and that this transporter is also important for cigarette smoke–mediated increase in malignancy.[147] Expression of this gene is correlated with chemoresistance, and the presence of cells with stem-like features in lung and esophageal cancers[148–152] and poor prognosis in these patients.[146,153,154]

Tobacco smoke may also promote chemoresistance through disruption of signal transduction pathways. In some cases, this disruption allows cancer cells to resist programmed cell death (apoptosis). For example, long-term exposure of lung cancer cell lines to cigarette smoke condensate alters apoptotic processes resulting in resistance to chemotherapy drugs, such as carboplatin.[155,156] In other cases, tobacco smoke increases the signaling pathway targeted by the therapeutic agent. For example, cigarette smoke extract reduced the sensitivity of *EGFR*-mutant cell lines to the inhibitory effects of gefitinib (an anti-EGFR tyrosine kinase inhibitor [TKI]) by increasing EGFR signaling and inducing EMT; smoking also negatively affected the progression-free survival of patients with lung cancer with mutated *EGFR* receiving EGFR-TKI treatment.[157] Nicotine may contribute to these observed effects.[158]

Summary

Tobacco smoke contains thousands of chemical compounds, including approximately 70 known carcinogens. These chemical compounds and/or their metabolic by-products may cause DNA damage, epigenetic changes, and other cellular alterations that lead to the development of cancer by altering normal cellular growth control mechanisms. Cancers in patients with and without a history of smoking can exhibit biological differences, particularly in tissues that come into direct contact with tobacco smoke. Some of these biological differences have important therapeutic consequences. For example, NSCLCs characterized by mutations of the *EGFR* gene and the *ALK* gene are highly responsive to tyrosine kinase inhibitor therapies. *In vitro* exposure of cancer cells to tobacco smoke causes them to display characteristics associated with cancer aggressiveness, metastasis, and resistance to therapy, which is consistent with clinical evidence of an association between continued smoking and reduced life expectancy and decreased response to therapies for most cancers.

Conclusions

1. Tobacco smoke contains more than 7,000 chemical compounds including approximately 70 that are carcinogenic. Continued exposure to tobacco smoke after a cancer diagnosis may promote the continued growth and transformation of tumor cells through a variety of mechanisms.
2. Tumors in smokers are often biologically distinct from tumors in nonsmokers. In the case of lung cancer, these differences have important implications for cancer treatment and prognosis.
3. Laboratory studies of cancer cells exposed to tobacco smoke or tobacco smoke constituents provide experimental evidence that continued smoking by patients with cancer increases tumor aggressiveness and reduces therapeutic response.

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