Lung Cancer Epidemiology, Risk Factors, and Prevention

Patricia de Groot, MD*, Reginald F. Munden, MD, DMD, MBA

KEYWORDS

• Lung cancer • Epidemiology • Risk factors • Prevention

KEY POINTS

- All types of lung cancer are directly correlated with cigarette smoking. Adenocarcinoma rates have increased significantly over the last 30 years.
- Environmental tobacco smoke is a major contributor to morbidity and mortality worldwide. There is no safe level of second-hand smoke.
- Pollution, occupational exposures, and environmental radon are additional risk factors for developing lung cancer.
- Genetic factors contribute to development of lung cancer. Future progress in understanding and treating lung cancer will be based on genetic analysis.

EPIDEMIOLOGY

Carcinoma of the lung is currently the leading cause worldwide of death due to cancer. The disease has become an epidemic as incidence rates and lung cancer deaths have risen dramatically over the last century, correlating with an increase in cigarette consumption. The magnitude of the impact on mortality is indicated by comparing changes over time. More than 1.5 million new cases of lung cancer are now diagnosed annually worldwide,[1,2] with incidence in the United States projected to be 221,130 cases in 2011,[3] compared with 1974, when new cases of lung cancer were estimated at 83,000 worldwide, with an expected 75,400 deaths that year.[4] Even more dramatically, in 1927 cancers of the lungs and pleura were implicated in just 2012 deaths in the United States[5] and before the turn of the twentieth century, lung cancer was considered an extremely rare malignancy.[6]

Trends in Incidence and Mortality

In 2011 in the United States there were 115,060 new cases of lung cancer in men and 106,070 new cases in women. The number of deaths in 2011 caused by lung and bronchus cancers was an estimated 156,940: 84,600 in men and 71,340 in women. In men, this represents a continuing decline in incidence and mortality after a peak in the 1980s. Between 1990 and 2007, male mortality from lung cancer in the United States decreased by almost 28%.[3] In women, however, lung cancer rates began to increase in 1965, and only in the last few years since 2000 has there been a slight decline of about 2%. Overall, female lung cancer mortality is increased by 6.31% in comparison with 1990.[3]

Within the United States there is geographic diversity in cases of lung cancer, with Kentucky having the highest number at a rate 3 times that of Utah, the state with the lowest incidence. California, Florida, and Texas lead the nation in age-standardized death rates from lung cancer, whereas Alaska, Wyoming, and North Dakota have some of the lowest annual death rates.[3]

Age, racial and ethnic, and socioeconomic disparities also exist. Cancer is a disease of aging, with 60% of cancers diagnosed in persons older than 65 years and 70% of cancer deaths belonging

Division of Diagnostic Imaging, Department of Diagnostic Radiology, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1478, Houston, TX 77030, USA
* Corresponding author.
E-mail address: pdegroot@mdanderson.org

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to the same age cohort.[7] The incidence and death rates from lung cancer are higher for Caucasian and African American populations in the United States than for other ethnic and racial groups, including Asian Americans and Pacific Islanders, Native Americans, and Hispanic people. Education levels, as a proxy for socioeconomic status, show a striking inverse correlation with death rates from lung cancer.[3] Survival rates for lung cancer remain abysmal, with a 5-year survival of approximately 15%, unchanged for decades despite advances in medical knowledge.[3]

Incidence of and mortality from lung cancer are higher in Caucasians and African Americans than in other ethnic groups in the United States. Age and geographic location also are important.

Histopathology of Lung Cancer

The major cell types of cancer are small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC), with the latter category comprising several histologic subtypes, the major ones being squamous cell cancer, adenocarcinoma, and large cell cancer. The cell types with the strongest association to cigarette smoking are SCLC and squamous cell lung cancer, but there is growing evidence that adenocarcinoma also is strongly associated with smoking.[8] In 1979, squamous cell lung carcinoma was significantly more common than adenocarcinoma, at a ratio of approximately 17:1. In the last 30 years, there has been a relative increase in the number of lung adenocarcinomas, bringing that ratio to 1.4:1.[9,10] Adenocarcinoma is the most common type of lung cancer in North America, whereas squamous cell carcinoma remains more prevalent in Europe and Australia.[11]

In recent years new techniques in immunohistochemistry have allowed for more accurate identification of cell type, and testing is available for detecting specific genetic mutations that have prognostic and treatment implications, such as epidermal growth factor receptor (EGFR) mutations in adenocarcinomas of nonsmokers.

All subtypes of lung cancer are related to cigarette smoking. Adenocarcinoma rates have increased significantly over the last 30 years.

Lung Cancer in Never-Smokers

A growing number of incident lung carcinomas are occurring in never-smokers, defined by many as individuals who have smoked fewer than 100 cigarettes in a lifetime. This group comprises 15% to 25% of the lung cancer population, with 300,000 deaths resulting annually.[12,13] This subset of patients with lung cancer is more likely to be female, and the cancer cell type is more likely to be adenocarcinoma.[14] Although lung cancer in nonsmokers occurs worldwide, geographic variation is striking, with 30% to 40% of Asian patients with lung cancer being never-smokers, compared with 10% to 20% of Caucasians.[12,13] In the United States, nonsmoking African Americans have greater incidence and mortality rates of lung cancer compared with nonsmoking whites.[12]

Lung cancer in never-smokers (LCINS) is linked with environmental factors, including secondhand tobacco smoke, outdoor and indoor air pollution, and radon. In addition, human papillomavirus infection is seen frequently in nonsmoking Chinese women with lung cancer.[13] However, no single risk factor appears to be dominant.

Specific genetic mutations associated with LCINS are not common in the lung cancers of smokers, suggesting a different biological disease, with implications for chemotherapeutic response. For instance, EGFR gene mutation and the EML4-ALK fusion gene are more common in never-smokers, whereas epigenetic changes such as promoter gene methylation are less common in nonsmokers.[13] Although women are disproportionately affected by LCINS, as a group their survival is better than that of nonsmoking men who develop lung cancer.[12,14]

RISK FACTORS

The hallmarks of tumorigenesis are acquired capabilities of individual cells or groups of cells that enable transformation to a malignant entity. These requisite acquired abilities of cells have been described by Hanahan and Weinberg[15] as (1) self-sufficiency in growth signals; (2) insensitivity to antigrowth signals; (3) evasion of apoptosis; (4) limitless replication potential; (5) sustained angiogenesis; and (6) tissue invasion and metastasis. The underlying mechanism that allows these changes to occur is instability of the genome; in particular, breakdown of DNA repair capacity.[15] This process is influenced by a complex interplay of genetic, behavioral, and environmental factors, which can increase the risk of an individual developing lung cancer.

Genetic Factors

Individual organisms respond to environmental challenges in different ways. For instance, although

the vast majority of lung cancers (up to 90%) occur in smokers, only 15% of smokers will develop lung cancer.[16] Variation in genetic makeup is an important survival mechanism in the face of disease.

Heredity and genetic susceptibility

Certain families possess an inherited susceptibility to malignancies, primarily in the context of uncommon germ-line mutations in tumor suppressor genes p53 and RB or RB1 (retinoblastoma),[17] and in other unusual autosomal recessive disorders such as Bloom syndrome and Werner syndrome.[18] In the absence of a genetic syndrome, the published literature on risk of lung cancer within families suggests a twofold increased risk in smoking individuals with a positive family history of cancer, and this risk is additionally elevated if a family member was diagnosed at an early age and/or if multiple relatives have been affected.[19] In nonsmoking families, a positive family history for lung cancer is associated with a 1.5-fold increased odds ratio of developing the disease.[12]

Variant alleles of several genes are associated with increased susceptibility to lung cancer. Some of these genes encode proteins that are involved in the metabolism of tobacco carcinogens, such as the cytochrome P450 enzyme (CYP1A1 gene) and the glutathione-*S*-transferases (GSTM1, GSTT1). Other genes are those responsible for DNA damage repair, including XRCC1, XPA, XPC, and XPD, which encode nucleotide excision repair proteins.[20]

Genome-wide association (GWA) studies have attempted to identify other polymorphisms that engender susceptibility or predisposition to lung cancer. Several chromosomal regions have been proposed, including 5p15.33, 6q21, and a locus on the long arm of chromosome 15, 15q24-25.[17] The 5p15.33 region encodes the gene for telomerase reverse transcriptase (TERT), which is involved in cell replication and is linked with a wide variety of cancers. In lung cancer it is associated with adenocarcinomas, including in never-smokers, but not with squamous cell carcinoma or SCLC.[20,21] 6q21 encodes a regulator of the G-protein signaling family. Never-smokers with this variant have a 4.7-fold greater risk of lung cancer than those without the haplotype.[20]

The 15q24-25 region of chromosome 15 contains the genes for several cholinergic nicotinic receptor subunits, CHRNA5, CHRNA3, and CHRNB4. Studies have shown an increased risk of lung cancer independent of smoking status associated with this variant.[20,22,23] In addition, it confers greater susceptibility to nicotine dependence.[24] Among smokers, carriers of this polymorphism smoke more and may find it harder to quit.[24] This risk haplotype is found more frequently in people of European descent; it is less common in Asians and is not present in Africans.[22,25]

Genomic instability Tumors also exhibit acquired genetic mutations and amplifications, which require the breakdown of multiple regulatory steps and safeguards in the cellular processes of replication, repair, and apoptosis. Most of the best studied driver mutations in lung cancer involve signaling pathways within the cell. The ErbB family (EGFR/HER1, HER2, HER3, and HER4) and the c-MET gene (a proto-oncogene encoding the Hepatocyte Growth Factor Receptor [HGFR] protein) code for tyrosine kinase receptors in cell membranes; mutations or amplifications of these receptors can constitutively activate intracellular signaling cascades involved in cell division and proliferation.[17,26] Other oncogenic mutations, such as that of GTPase K-Ras, activate proteins downstream in the signaling pathways. Still other mutations, deletions, or epigenetic changes are responsible for inactivation of tumor suppressor genes p53, p16, and PTEN. Some mutations are more associated with adenocarcinomas, such as EGFR mutation, LKB1 mutation, and the EML4-ALK fusion gene.[17] Others are linked with squamous cell carcinomas, including phosphatidylinositol-3-kinase (PI3K), PTEN, focal fibroblast growth factor receptor 1 (FGFR1) amplification,[27] and discoidin domain receptor family, member 2 (DDR2) mutation.[28] Mutations in the same signaling pathway appear to be mutually exclusive, including HER2, EGFR, and K-Ras.[26]

The mechanisms of genome instability include both genetic and epigenetic changes to DNA. Genetic variation is normal and occurs constantly throughout the genome. However, changes that are positionally or functionally clustered in critical regions of the genome are associated with malignancy, including lung cancer. Single nucleotide polymorphisms (SNPs) are substitutions of one nucleotide for another in a DNA sequence, and depending on their location can cause functional changes in the gene product. Copy number alterations (CNAs) indicate either repetition or deletion of segments of DNA, which can result in multiple copies of a gene or its absence. Normally, CNAs are much more likely to occur outside gene-encoding regions. In lung-tumor tissue, CNAs tend to be gains rather than losses, are more frequent in later-stage tumors, and have an equal chance of being located within a gene sequence.[29] The formation of DNA adducts from tobacco-specific and other carcinogens that covalently bind to sections of DNA can result in miscoding and permanent mutations. Methylation is an

example of an epigenetic mechanism that may cause constitutive activation or deactivation of a gene without an actual change in the encoded DNA.

Age

Lung cancer is partly a disease of senescence, with continual shortening of telomeres during repeated cell replication cycles, and greater chances of DNA damage as a factor of time.[4] Although lung cancer does manifest in persons younger than 55 years, it continues to be uncommon in that age group.[3] At present the median age at diagnosis is older than 70 years.[30] In 2006, 14% of all patients with lung cancer and 24% of all deaths attributable to lung cancer were in persons older than 80 years. The number of patients older than 85 years with lung cancer is expected to quadruple by the middle of this century,[30] at least in part because of the aging of the population in the Western world. There is decreased survival from lung cancer in the octogenarian group compared with the 70- to 79-year-old and the younger than 70-year age groups.[30,31]

Gender

Although men historically have had a much higher incidence of lung cancer than women, rates in men declined fairly dramatically in the late twentieth century in tandem with a proportional decrease in the male smoking population. Conversely, rates of lung cancer in women have been increasing since 1965, with a very modest reduction beginning only in the year 2000.[3] Cigarette smoking remains prevalent, especially in younger women.[32] In addition, nonsmoking women are more likely than men to be subject to second-hand smoke from a smoking spouse (**Figs. 1** and **2**).

Multiple large cohort studies have found no association between sex and risk of lung cancer.[32] Nonetheless, lung cancer may be a biologically different disease in women. Women are more likely to develop adenocarcinoma than squamous cell cancer; in particular, adenocarcinoma with lepidic predominant features is 2 to 4 times more common in women than in men. In addition, women with lung cancer have improved survival compared with male counterparts.[32,33]

These differences may be explained by some genetic variations between the sexes. For instance, the CYP1A1 gene has increased expression in the lungs of women smokers in comparison with men, possibly induced by estrogen. The CYP1A1 enzyme metabolizes tobacco carcinogens such as polycyclic aromatic hydrocarbons (PAHs), with the resulting products able to form DNA adducts. Other potential sex-related differences in genotype or phenotype may involve the detoxification enzyme glutathione-*S*-transferase M1 (GSTM1), and the X-linked gene for gastrin-releasing peptide receptor (GRPR), which stimulates bronchial epithelial cell growth.[32]

On a molecular level, tobacco-related mutations in the p53 tumor suppressor gene are more common in women than in men. EGFR, and possibly K-Ras, mutations are more common in the resected NSCLC of women.[33] DNA repair capacity has been reported to be lower in women than in men.[32] Evidence suggests that endogenous and exogenous estrogens affect lung carcinogenesis. Estrogens can activate cellular proliferation pathways through estrogen receptors

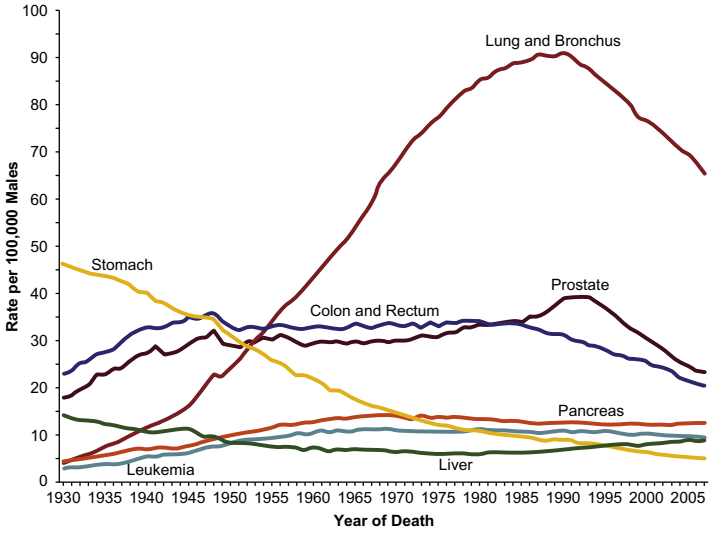

Fig. 1. Annual age-adjusted cancer death rates among males for selected cancers, United States, 1930 to 2007. Rates are age-adjusted to the 2000 US standard population. Because of changes in International Classification of Diseases (ICD) coding, numerator information has changed over time. Rates for cancers of the lung and bronchus, colon and rectum, and liver are affected by these changes. Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2007, National Center for Health Statistics, Centers for Disease Control and Prevention. (*Reprinted from* Siegel R, Ward E, Brawley O, et al. Cancer statistics, 2011. CA Cancer J Clin 2011;61:212–36; with permission.)

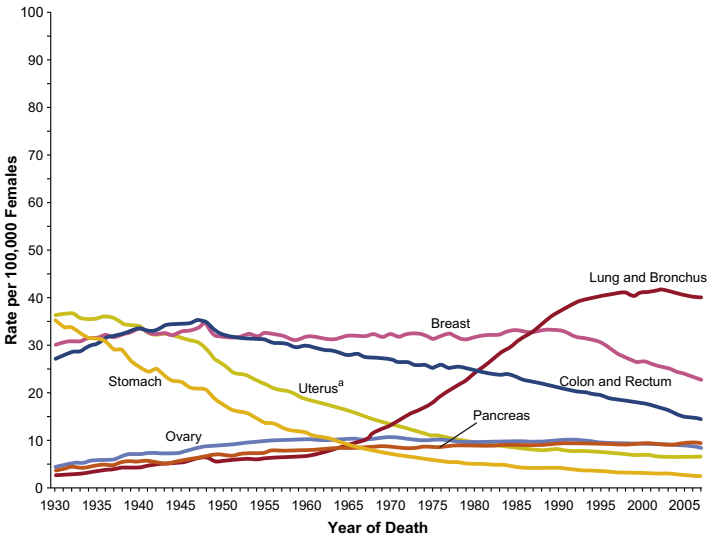

Fig. 2. Annual age-adjusted cancer death rates among females for selected cancers, United States, 1930 to 2007. Rates are age-adjusted to the 2000 US standard population. [a]Uterus indicates uterine cervix and uterine corpus. Because of changes in ICD coding, numerator information has changed over time. Rates for cancers of the uterus, ovary, lung and bronchus, and colon and rectum are affected by these changes. Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2007, National Center for Health Statistics, Centers for Disease Control and Prevention. (*Reprinted from* Siegel R, Ward E, Brawley O, et al. Cancer statistics, 2011. CA Cancer J Clin 2011;61:212–36; with permission.)

(ER), and the EGFR and ER pathways may have interactive elements.[33] Estrogen and its derivatives can also be metabolized to reactive intermediates that bind to DNA, producing adducts, or may cause oxidative damage.[32]

Race

Both incidence rates and mortality rates of lung cancer differ by racial and ethnic groups in the United States. African American men have markedly higher rates of lung cancer than non-Hispanic Caucasian white men, while both of those groups have a higher risk than do the other groups for which statistics are available: Native American, Asian American and Pacific Islander, and Hispanic. Death rates for lung cancer in African American men are 87.5 per 100,000 population, more than twice that of the lowest group, the Hispanic population, at 32.5 per 100,000 population. This figure has been linked with higher levels of smoking among African Americans.[3] For women, non-Hispanic Caucasian whites have a slightly higher rate of both incidence and mortality of lung cancer than the other groups, with African American women the next highest.

African Americans have poorer survival once diagnosed.[3] Minority populations are often diagnosed at a later stage of disease than Caucasian whites,[34] and in addition, the 5-year survival for African Americans is lower for every stage of diagnosis.[3] Education levels, socioeconomic status, medical insurance, access to health care, and receipt of good-quality health care all play roles in these inequalities. However, ethnicity was shown in a United States study to be a predictor of more advanced disease at diagnosis after controlling for insurance status, suggesting that other factors are present.[34]

Place of birth and cultural influences may also affect the risk of lung cancer within racial groups. Asians have a lower overall rate of lung cancers and have a relatively higher proportion of well-differentiated or minimally invasive adenocarcinoma, which carries a better prognosis. However, Asian men and women who are born in other countries have a 35% higher incidence of NSCLC than United States–born Asian Americans. High smoking rates among foreign-born Asian men may contribute to this difference.[35]

Behavioral Factors

Tobacco and smoking

Tobacco cigarette smoking is the predominant risk factor for lung cancer. There is a direct dose-response relationship between the number of cigarettes smoked and the risk of lung cancer.[5,36,37] Although the association had been proposed by clinicians and others in the first half of the twentieth century, it was not widely given credit. The 1950 publication of two landmark studies, in Britain[36] and the United States,[37] promoted recognition and acceptance of cigarette smoking as the cause of rising rates of lung cancer.

In retrospect, the correlation between consumption of cigarettes and rates of lung cancer is much more apparent than it likely was prospectively. Following its introduction to Europe from the New World in the sixteenth century, tobacco was used mainly in the forms of pipe-smoking, cigars, and snuff up until the late nineteenth century.[6] It was suspected by some observers that cancers

of the mouth and lips were related to these practices.[6] Cigarettes were hand rolled and were smoked by relatively few people.

Several developments beginning in the 1880s dramatically changed the consumption of tobacco. A cigarette-rolling machine was patented, leading to mass production, a drop in prices, and wide availability.[38] A new method of curing tobacco, flue-curing, made the smoke smoother and more palatable.[6] Lastly, safety matches were invented, leading to increased convenience.[39] In 1880, the number of manufactured cigarettes consumed was almost zero.[6] By 1928, the consumption of so-called light cigarettes was 108 billion.[5] At present, more than 5.7 trillion cigarettes are produced annually.[40]

Composition of tobacco smoke Tobacco smoke contains some 4000 chemical substances, of which approximately 60 are known carcinogens. The most important molecules implicated in the development of lung cancer are PAHs, of which the most significant is benzo[*a*]pyrene (B[a]P); nitrates; and tobacco-specific *N*-nitrosamines (TSNAs), particularly 4-(methylnitrosamino)-1-(13-pyridyl-1-butanone) (NNK).[10,41] Polonium-210, an α-particle–emitting radon daughter element, is also present. Tobacco smoke has both a vapor phase, made up of molecules smaller than 0.1 μm that can pass through the cigarette filter, and a particulate phase. The concentration of free-radical production in these 2 phases is 10^{15} free radicals per gram and 10^{17} free radicals per gram, respectively.[42]

Cigarettes manufactured in the United States use a blend of different types of tobacco, including bright (flue-cured) and burley (air-cured) tobacco, with small fractions of Turkish (sun-cured) and Maryland (air-cured) tobacco. Over the last several decades there have been changes in the proportions of these constituents, as well as increased use of tobacco parts that were previously considered discard but which now make up about 30% of a cigarette.[9] These constituents include reconstituted tobacco, a homogenized tobacco sheet made from the pulp of mashed tobacco stems and sprayed with additives; expanded tobacco, made by freeze-drying saturated tobacco leaves to expand them; and the ribs and stems from tobacco plants. The filling weight of tobacco used in a cigarette has decreased from 1.2 g in the 1950s to approximately 0.7 to 0.8 mg today.[9]

These changes have significantly affected the composition of cigarette smoke. The introduction of filters has also changed the content of inhaled smoke. The amount of tar emissions from cigarette smoke has decreased from 38 mg to 12 mg. B[a]P concentration in smoke, which is linked with squamous cell lung cancer and coronary artery disease, has decreased by 62% since 1959.[9] Several other toxic elements in smoke have also lessened by about 60%.[9] However, nitrates and TSNAs have actually increased. NNK concentration in cigarettes is now 73% higher than it was in 1978.[9] Higher levels of TSNAs in cigarette smoke are associated with an increased risk of lung cancer, and NNK is implicated specifically with adenocarcinoma development in laboratory animals.[41,43] The mechanisms of tobacco carcinogenesis include free-radical damage and the formation of DNA adducts by tobacco carcinogens and their metabolites.[44]

Nicotine Nicotine levels in cigarettes blended in the United States have decreased, concomitant with other changes in the composition of cigarettes. In the 1950s, the average cigarette contained 2.7 mg of nicotine. At present, the nicotine yield is approximately 0.8 to 0.9 mg per cigarette.[9] It has been speculated that this decrease has led to changes in smoking behavior, including an increased number of cigarettes smoked, deeper inhalations, and smoking cigarettes to a shorter stump, to satisfy the smoker's programmed level of nicotine dependence.[10]

Nicotine binds to nicotinic acetylcholine receptors (NAChR) at the cell membrane, activating calcium and other ion channels. Nicotine addiction is caused by increased nicotinic receptor expression induced by long-term exposure.[42] The 15q25-26 susceptibility gene for lung cancer is positively linked to nicotine dependence.[24]

There is no evidence that nicotine itself induces tumorigenesis, but it is associated with progression of existing tumors, primarily lung, colon, and gastric cancers. Increasing data suggests a proangiogenic effect of nicotine, possibly through the activation of α7-NAChR but also by induction of proangiogenic signaling molecules including basic fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor.[42]

Cannabis sativa Limited evidence is available on a potential association between marijuana (*Cannabis sativa*) smoking and risk of lung cancer. Studies are difficult to undertake in many parts of the world because of legal restrictions on marijuana use. Confounding variables are also present, because tobacco use is concurrent with marijuana smoking in some users, and there is a practice of cutting hashish with tobacco in some parts of the world.[45–47] Nevertheless, several studies point to an increased risk of lung cancer among the heaviest one-third of marijuana smokers, after adjusting for confounders.[45] These patients tend to be in a younger age cohort. Several factors that may affect risk include the PAH concentration in

marijuana cigarettes (twice that of tobacco), lack of a filter, and smoking habits that include deep inhalation.[45]

Socioeconomic status Studies of incidence of lung cancer relative to socioeconomic status have shown that there is an overall increased risk of lung cancer in persons of lower educational levels, lower income, and low occupational positions.[48] There is a striking correlation in the United States population between levels of educational achievement and lung cancer death rates. In men with more than 16 years of formal schooling, age-adjusted death rates for lung cancer are 10.35 per 100,000 population, whereas in men with less than a high school education, there are 51.63 deaths per 100,000 population, or 5 times the rate of the most educated group. Women with less education are 4 times more likely to die of lung cancer than the best educated.[3]

In some studies, the increased risk of lung cancer in lower socioeconomic groups has been linked with the greater prevalence of cigarette smoking in this population.[3,49] A recent British study of hardcore smokers, as defined by defensive and defiant attitudes regarding smoking, found that this group was overwhelmingly white, single, male, poor, poorly educated, and living in rented accommodation.[50] However, other studies that have focused on nonsmokers or have adjusted for smoking habits show a correlation between lower socioeconomic status and incidence of lung cancer apart from smoking.[48] Multiple factors, including occupational exposure to carcinogens, environmental tobacco smoke, suboptimal housing conditions, poor diet, and, in many parts of the world, unequal access to health care resources, likely play a part.[48,49]

Diet

The human diet contains both mutagenic and antimutagenic natural substances. The typical diet of the developed Western world, with processed foods containing high levels of fat and sodium, is promoting poor health in general and is estimated to be responsible for up to one-third of cancer deaths in Western countries.[51]

Macronutrients Some specific carcinogens associated with diet include heterocyclic amines (HCAs), which are produced by cooking meat and fish. Charring of protein causes particularly high levels of HCAs in the resulting crust. HCAs are broken down by the cytochrome P450s enzymes, chiefly CYP1A2. The derivatives of this process can form DNA adducts, leading to transcription changes in the genome. In rodent experiments, HCAs have produced mutations of H-Ras, K-Ras, and p53, among other cancer-linked genes. HCAs have been listed as a possible risk factor for carcinogenesis in humans by the International Agency for Research on Cancer.[52]

Excess calorie intake is also a risk factor for cancer. Elevated levels of dietary fat have been linked with breast and colon cancer in particular. Sodium chloride is associated with gastric cancer.[52,53] Saturated fatty acids from animal fat and polyunsaturated fatty acids found in some plant-derived oils (corn, safflower) have been shown to enhance cancer development in animal models. Conversely, homounsaturated fatty acids such as oleic acid in olive oil have no effect on cancer development.[52]

Micronutrients There have been contradictory data regarding vitamins as chemopreventive agents in lung cancer. The B vitamins are essential for DNA replication and repair of DNA damage. Several studies have found that folate (vitamin B_9) is associated with increased risk for lung cancer, both as a dietary supplement and in high dietary concentrations.[54,55] A more recent study, however, found no association between vitamin B supplementation and lung cancer, other than a possible weak connection of riboflavin (Vitamin B_2) with decreased risk in current smokers.[56]

Based on some early studies of vitamin A and its precursor β-carotene, which showed low levels of serum β-carotene in smokers and an increased risk for lung cancer at low serum levels, 2 large-scale studies looked at supplementation of this micronutrient.[57,58] Both showed higher than expected mortality from lung cancer in the β-carotene group, and those arms of the studies were terminated. A third study found neither harm nor benefit from β-carotene supplementation, although the dose was lower than in the other 2 trials.[59]

Preexisting lung disease Inflammatory processes are thought to play a role in lung carcinogenesis through increased genetic mutation, antiapoptotic signaling, and increased angiogenesis. Several preexisting lung conditions have been implicated to increase the risk for lung cancer. Emphysema and chronic obstructive pulmonary disease carry an elevated risk but have the confounding effect of being related to tobacco smoking. However, asthma and chronic bronchitis are associated with risk of lung cancer in nonsmokers.[60]

The presence of fibrosis in the lung parenchyma has been associated with an increased risk for lung cancer. Fibrosis includes idiopathic pulmonary fibrosis (IPF) as well as fibrosis related to systemic autoimmune diseases and to asbestos exposure. Focal scarring in the lung is also linked

with the development of lung cancer at that site.[18] Several pulmonary and systemic infections are known to increase the risk for lung cancer.

Pneumonia and mycobacterial disease A history of pneumonia or of *Mycobacterium tuberculosis* infection is associated with odds ratios of developing lung cancer of 1.43 and 1.76, respectively. This ratio holds true independently of smoking status, with never-smokers having a similar increased risk.[61] It is not known whether the inflammatory processes related to infection increase the risk of tumorigenesis or whether there is a specific pathophysiology related to the disease. The increase in cancer risk is maintained over considerable latency periods following the diagnosis of infection, up to 20 years in some cases of tuberculosis.[61]

Human papillomavirus More than 50% of the world's population is infected during their lifetime with human papillomavirus (HPV). More than 100 serotypes of the virus are known; several of these (types 16, 18, 31, 33, and 35) are oncogenic, and have known causal relationships with anogenital malignancies in both sexes and with head and neck squamous cell carcinomas. Recent work has suggested a possible association of HPV with lung carcinoma, with traces of HPV DNA being found in 24.5% of lung cancers.[62] The overall association is not dependent on lung cancer cell type, although lung squamous cell cancer is reported to be more associated with the lower-risk HPV serotypes 6 and 11,[62] whereas HPV types 16 and 18 are seen in 56% of adenocarcinomas.[63] Geographic variations are present, with reported frequencies of HPV in tissue samples of lung cancer being lower in Europe (17%) and America (15%) than in Asia (35.7%–54.6%).[11,12,62,63]

The method of HPV transmission to the lungs is debated, because the historically validated mode of communication of this virus is direct mucosal contact. It is posited that HPV may pass to the oral cavity through sexual contact and from there directly into the upper aerodigestive tract and the lung. Alternatively, HPV DNA and mRNA has been found in the peripheral blood cells, plasma, and serum of patients with both cervical cancers and head and neck cancers, raising the possibility of hematogenous dissemination.[11]

The proposed mechanisms of carcinogenesis of HPV in studies thus far show a role for the E6 and E7 oncoproteins produced by the virus. E6 binds to tumor suppressor gene p53 and inactivates it, inhibiting cell apoptosis. E7 degrades the RB tumor suppressor and activates cell proliferation. The presence of HPV DNA in normal lung tissue as well as in tumor tissue raises questions about causality.[11] If a causal link between HPV and lung cancer can be proved, HPV infection will constitute the second most important risk factor for lung cancer, following tobacco smoking.[62]

Human immunodeficiency virus Lung cancer is the leading cause of death among the non–AIDS-defining malignancies (NADC) in the population infected by human immunodeficiency virus (HIV).[64,65] The incidence in this population has risen in the era of highly active antiretroviral therapy (HAART), as AIDS-defining cancers have decreased. Some studies suggest that the increased incidence is due to improved survival and the aging of the HIV-positive population.[64] A prospective study of HIV-infected women and at-risk but noninfected women found no difference in rates of lung cancer between these groups, and also no difference between the pre-HAART and post-HAART time periods.[66]

However, other work suggests that immunosuppression plays a role in the development of malignancy. HIV patients and organ-transplant patients have a similarly increased rate of cancer occurrence, 2 to 4 times that of the general population.[67] CD4 cell counts do not have a linear relationship with development of lung cancer, but may have an indirect association with cancer risk, as patients with CD4 levels higher than 500 cells/mL have incidence rates approaching those of the overall population. Declining CD4 counts increase the rate of lung cancer[68] and low CD4 counts are associated with advanced stage at diagnosis.[65,68] Viral loads have not been shown to have a correlation.[64]

The HIV-infected population has a higher prevalence of smoking than does the general population; however, this alone does not explain the increased risk. Lung cancer affects younger patients in the HIV population; in one study, the median age was 52 years.[64] The latency from diagnosis of HIV to lung cancer is shorter for women than for men.[64] A mechanism of oncogenesis has not been established for the HIV virus itself, although proteins involved in viral replication could affect the expression of genes that control the cell cycle in the host.[65]

Environmental Factors

Second-hand tobacco smoke

Environmental exposure to second-hand tobacco smoke, also known as passive or involuntary smoking, has been recognized as a major contributor to worldwide morbidity and mortality.[40,69,70] Much of the epidemiologic data regarding the risk of lung cancer from environmental tobacco smoke (ETS) has focused on nonsmokers,

especially women, who have smoking spouses, because exposure in workplaces and social settings is more difficult to quantify.[18,71] Multiple studies have shown that nonsmoking spouses of smokers have an approximately 20% to 30% increased risk of lung cancer, with remarkable agreement between almost all studies.[71,72] A dose-response relationship between lung cancer and ETS has been confirmed; there is no safe level of second-hand tobacco exposure.[70]

Side-stream smoke from the burning end of a cigarette is unfiltered and can contain increased concentrations of proven carcinogens, including PAHs, nitrosamines, and aromatic amines. B[a]P levels are up to 4 times higher in side-stream smoke than in the mainstream smoke inhaled by the active smoker.[71] Both nicotine and its metabolite cotinine, which are specific to tobacco smoking, can be detected in the body fluids of exposed nonsmokers.[71,73] Overall, lung function is affected adversely in workers exposed to tobacco smoke in the workplace.[73] DNA adducts from tobacco carcinogens have also been found in the urine of nonsmokers with second-hand exposure to ETS.[71]

There is evidence that exposure to second-hand cigarette smoke varies according to ethnicity, gender, and socioeconomic status.[70] Certain workplaces are also disproportionately affected, particularly in the entertainment and hospitality industries.[70]

Other environmental pollutants

It was suggested as early as 1927 that pollution in the ambient environment could be linked to lung cancer.[74] Acceptable levels of air pollutants began to be legislated in the 1950s, following thousands of deaths during the London "great smog" of 1952.[18] Studies showing unexpected adverse health effects at low levels of air-particulate concentrations motivated the US Environmental Protection Agency in 1997 to revise its air quality standards, imposing regulatory limits on fine particles less than 2.5 μm in diameter ($PM_{2.5}$).[75] Studies have shown a robust association between risk of lung cancer and levels of fine-particulate pollution regardless of smoking status, though strongest in nonsmokers. Each 10-$\mu g/m^3$ increase in the average long-term $PM_{2.5}$ concentration is associated with an 8% increased risk of death by lung cancer. Risk is not differentiated based on age or sex, but a higher risk is strongly linked with a lower level of education.[75] Of the gaseous pollutants from fossil-fuel combustion, sulfur dioxide is associated with increased risk of mortality from lung cancer. Other gases and coarse-particulate fractions in the atmosphere are not consistently linked with mortality.[75] Diesel engine exhaust, however, contains known and suspected carcinogens, and occupational exposures in the trucking industry are associated with a 30% to 50% increase in the relative risk of lung cancer.[18]

Indoor air pollution from cooking-oil fumes and the burning of solid fuels such as coal are also implicated in the development of lung cancer in some parts of the world, including Asia.[12,13] Air pollution as a risk factor for lung cancer is potentiated in combination with other risk factors.

Radon

Radon (^{222}Rn) is recognized as the second leading cause of lung cancer, with approximately 10% of all deaths from lung cancer attributed to radon exposure in homes.[60] Designated a carcinogen in 1988 by the International Agency for Research on Cancer, radon is omnipresent in the earth's crust, including rocks, soil, and water.[76] An inert gas formed by the decay of uranium (^{238}Ur), radon produces radioactive polonium daughters. Both radon and its daughter elements are α-particle emitters. Most of the data involving the cancer risk of radon have been acquired through epidemiologic studies of miners, who experience significantly higher levels of radon underground compared with the average residential exposure.[60,77] In the United States, levels of occupational radon exposure in underground workplaces are governed by legislation.[18]

The amount of radon in homes is variable, influenced by factors such as the local bedrock, the type of building foundation, and ventilation of the living areas within the home. Radon leakage into buildings tends to accumulate in basements and lower levels.[78] The average environmental radon concentration is 0.2 pCi/L.[18] A 1991 survey found that the mean indoor radon level in United States homes was 1.25 pCi/L, ranging from 0.2 pCi/L to 100 pCi/L.[18]

The mechanism whereby radon initiates tumor genesis is not completely known. The α particles in radon generate free radicals and oxidative stress, which can directly damage DNA in exposed cell nuclei. There is also evidence that adjacent cells may sustain damage via a "bystander effect," even if not directly radiated.[60] The risk of lung cancer from radon is increased in combination with cigarette use.[79]

Asbestos

Asbestos is a naturally occurring silicate mineral that has been used since the late nineteenth century in construction and insulation. It is therefore ubiquitous in the environment of industrialized countries. However, prolonged and heavy

exposure to asbestos, such as in occupational settings, is required to trigger nonmalignant lung and pleural disease as well as increased risk for thoracic malignancies. There is some debate about whether asbestosis is a prerequisite for the development of lung carcinoma, or whether asbestos fibers themselves act as carcinogens in the absence of fibrosis. Asbestos fibers are of 2 types: the amphibole (amosite, crocidolite, trenolite, and others) and the serpentine (chrysotile). Chrysotile fibers are most closely linked with thoracic malignancies. Exposure to both asbestos and tobacco smoking has a synergistic effect; together, they confer a 15- to 50-fold increased risk of developing carcinoma of the lung over individuals without exposure to either.[18]

Other occupational exposures

Industries and occupations that are either known or suspected to be associated with lung cancer have been listed since 1982. List A contains those occupations known to increase the risk of pulmonary tumors and includes mining and quarrying; metal production industries, including smelting and refining; asbestos production; shipbuilding; and construction. List B enumerates occupations and industries suspected to be associated with risk of lung cancer, such as meat-production industries, leather working, wood working, rubber and glass manufacture, motor vehicle production, and the transport industry.[1] A recent study in France demonstrated that men who had ever worked in a List A occupation had an odds ratio for lung cancer twice that of men who had never been employed in a list A or B occupation. Former employment in a list B occupation also conferred increased risk.[1]

The greatest risk for developing lung cancer is cigarette smoking, by a large margin. Age, radon exposure, environmental pollution, occupational exposures, gender, race, and lung disease also are important contributors. However, not all people with these risk factors develop lung cancer, and some without any known risk factors do, which indicates the importance of genetic factors in contributing to the development of lung cancer. Future developments in understanding and treating lung cancer will be based on genetic analysis.

PREVENTION

In 2011, the National Lung Cancer Screening Trial reported that low-dose computed tomography scanning of the lungs is effective in reducing lung cancer mortality, proving that screening can affect outcomes in high-risk patients.[80] Ongoing research efforts for ways to identify early markers of disease, such as volatile organic compounds (VOCs) that are found in the breath, blood, and urine, are undergoing intensive study.[81]

Although screening for cancer to identify it in its potentially curable stages is important, total prevention should be the preferred goal. There are several ways through which the incidence of lung cancer might be reduced.

Tobacco Cessation

As tobacco use is the premier cause of lung cancers, reduction in the number of smokers is the most important step. Epidemiologic data from the twentieth and twenty-first centuries has shown a decline in male deaths from lung cancer since 1990, directly related to the decreasing proportion of male smokers.[3] However, smoking prevalence has diminished while the absolute numbers of smokers and former smokers at risk for disease has remained static in the growing population. There are an estimated 54.9 million active smokers and 50 million former smokers in the United States, similar to 1960.[32]

Smoking cessation results in reduced risk of all histologic types of cancer, but particularly in SCLC and squamous cell types. The reduction in risk is most pronounced in heavier smokers, especially women.[82] Risk of lung cancer in former smokers is decreased by 50% within the first 15 years after quitting.[83]

The Affordable Health Care Act of March 2010 contains provisions for coverage of evidence-based tobacco-cessation programs, including pharmacologic therapy and counseling, for previously uninsured persons, and also for expanding Medicare coverage for these programs; in the past coverage has been limited to those with diagnosed tobacco-related illnesses.[84]

Tobacco-Control Legislation

The World Health Organization has made the Tobacco-Free Initiative a priority. Data have shown that tobacco-control legislation such as bans on smoking in workplaces has resulted in reductions in nonmalignant diseases related to tobacco use, such as cardiovascular disease, in as little as 1 year. Bans on tobacco smoking in the workplace and social settings reduce exposure for nonsmokers and also result in less smoking by active smokers.[40,72] Despite this, only 11% of the world's population resides in areas with some form of protection from ETS.[40] This number is higher in the United States, with

approximately 23 states in addition to the District of Columbia and 2 United States territories having complete protection from second-hand smoke in workplaces, restaurants, and bars. In the rest of the country, however, local laws govern the extent of the ban.[84] In fact, the seventh largest metropolitan area in the United States, with a population of more than 1.3 million people, only recently enacted a smoking ban in restaurants and bars on August 19, 2011, which remained controversial.

Vaccination

At this time there is a proposed association between HPV and lung cancer, rather than a proven causal link. Nevertheless, HPV is implicated as a causative agent in other types of cancer, and a vaccine has been developed. Since 2006, the Centers for Disease Control and Prevention (CDC) has recommended that all preteen girls of 11 to 12 years of age be routinely vaccinated and that young women from age 13 through 26 also receive vaccination for HPV to prevent genital cancers. The CDC now recommends routine vaccination of all boys 11 to 12 years of age, plus vaccination of young men 13 through 21 years if not previously completed, and vaccination of high-risk men through age 26, based on the accumulating data that HPV and HPV-related disease is widespread.[85] If future research reveals a stronger and contributory relationship between HPV and lung cancer, the vaccination program may be very helpful, and similar strategies could be used in other nations with high HPV prevalence.

Radon Control

Radon testing kits are easily available, and the US Environmental Protection Agency has advised that houses with radon levels of 4 pCi/L or above should undergo interventions to reduce the radon level in living areas. There are well-established ventilation techniques, and foundation and other home repairs may also be beneficial.

Diet

A diet of moderation rich in fruits and vegetables is recommended as the healthiest alternative. The possibility of chemoprevention of cancer by dietary strategies has been informed by the study of molecules in common food sources that have antiangiogenic properties.[51] Angiogenesis is a critical process in the transformation of indolent precursor lesions into invasive and metastatic malignancies. Antiangiogenic pharmaceutical therapy is a validated treatment of already developed tumors.

Dietary sources with antiangiogenic properties include green tea and its catechols; the isoflavonoid genistein in soybeans; resveratrol, a polyphenol found in grapes, red and rosé wine, and peanuts; lycopene in tomatoes and papayas; ω-3 fatty acids from cold-water fish; and isothiocyanates and related compounds in cruciferous vegetables. Other compounds are quercetin in leafy greens and red onions, and anthocyanins and proanthocyanidins in berries, cocoa, and cinnamon. Apples and pears contain procyanidins as well as quercetin and catechols. Menaquinone, the fat-soluble vitamin K_2, is found in fermented dairy products such as yogurt and cheese. Curcumin is a flavonoid found in turmeric spice. Mechanisms of action of these molecules differ. Many of them have been shown in epidemiologic studies and clinical trials to significantly reduce the risk of lung cancer, among other malignancies.[51]

Proper diet, therefore, constitutes an important contribution to the prevention of lung cancer and offers a widely available way, through education, to reduce the risk of cancer in the general population.

SUMMARY

As the leading cause of cancer death in the world, lung cancer is a high priority for the health care community. Many of the most significant risk factors for lung cancer are preventable. Efforts in the twenty-first century should focus not just on early detection, but on eradication.

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