Meeting Report

Adenocarcinoma of the Lung

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A workshop on adenocarcinoma of the lung was held at the Pooks Hill Marriott Hotel, Bethesda, Maryland, on May 10–11, 1993. The goals of the workshop were to address: (a) time trends and pathological classification; (b) environmental determinants; (c) animal models; (d) genetic susceptibility; (e) molecular markers; and (f) prospects for prevention.

Time Trends in Lung Cancer Incidence
Susan Devesa (National Cancer Institute) presented lung cancer incidence data for the period 1969–1986 for five geographic areas (Atlanta, GA; Connecticut; Detroit, MI; Iowa; San Francisco, CA; and Oakland, CA) covering 7% of the United States population. Overall, the rate of lung cancer increased 3%/year from 38.6 to 58.4/100,000 person-years, exceeding that of melanoma. Women at highest risk for squamous cell carcinoma accounted for 31.5% of all lung carcinomas for squamous cell carcinoma. Cohorts at highest risk included those with adenocarcinoma and small cell carcinoma. Among women, however, adenocarcinoma was the most frequent cell type, followed by adenocarcinoma and small cell carcinoma. Among women, however, adenocarcinoma was the most frequent cell type. On the basis of SEER data for the period 1983–1987, for both sexes and all races combined, adenocarcinoma accounted for 31.5% of all lung carcinomas with a rate of 16.7/100,000 person-years, exceeding that of 15.3 for squamous cell carcinoma. Cohorts at highest risk for adenocarcinoma were born somewhat later than those at highest risk for squamous cell carcinoma. Women at highest risk were born later than men at highest risk for both cell types. Adenocarcinoma was the most frequent type of lung carcinoma among black men under age 50, white men under age 60, black women under age 65, and white women of all ages. The ratio of adenocarcinoma to squamous cell carcinoma has been steadily increasing; in white males, this ratio was 1.23 from 1969 to 1971 but 1.4 from 1984 to 1986. These data suggest that exposure and mechanisms may vary by histological type.

Lung Cancer Pathology and Scar Cancers
William Travis (National Cancer Institute) described the histological appearance of various lung cancer types. He pointed out that the WHO changed its classification of large cell carcinoma and adenocarcinoma from 1967 to 1981; this change is important to keep in mind with regard to the potential increase in incidence of adenocarcinoma. Over the years there have been attempts to identify precursor lesions for adenocarcinoma, and the concept of “scar” carcinoma was one of those attempts. To explain the presence of focal fibrosis within adenocarcinoma of the lung, it was hypothesized that the fibrosis in most cases was due to either old granulomatous disease from tuberculosis or histoplasmosis, infarcts, or old exposure to foreign bodies such as shrapnel injury. Carcinomas were recognized to occur in the setting of diffuse interstitial fibrosis, in patients with idiopathic pulmonary fibrosis, collagen vascular disease, particularly scleroderma and rheumatoid lung disease, asbestosis and silicosis. Most scar carcinomas occur in the upper lobes. In 1979, Auerbach et al. (1) suggested that scar carcinomas had increased dramatically over a 21-year period from less than 2% of all lung cancers in 1955–1959 to 16% in the 1970s. He claimed that the etiology of these tumors was related to a preexisting scar. Shimosato et al. (2) argued that the scar is caused by tumor; central fibrosis (scar) is seen in metastatic tumors from scar primary tumors. Further fibrosis is confined to the tumor itself, while the rest of the lung tissue is normal. Thus, there is disagreement regarding the role of scars in predisposing to carcinogenesis versus being formed secondary to tumor.

Frank Speizer (Channing Laboratory, Boston, MA) discussed several definitions of scar carcinoma that have been offered over the last 50 years. These definitions have been based on location in the lung, proximity to nonneoplastic lesions, histological features, and cellular or biochemical composition. A less encompassing definition was based on the view that preexisting, clinically recognizable conditions predispose to the development of these peripherally located cancers, often adenocarcinomas. In 1965, a strong association of lung cancer with apical tuberculosis scars was reported (3). The peripheral nature of the lesion was described. The relationship between apical scarring from tuberculosis and the occurrence of lung cancer as documented by studies from the 1930s and 1940s could be explained simply by the onset of lung cancer in a high prevalence background of tuberculosis.

Several studies have assessed the association of fibrosis and lung cancer. Lombard et al. (4) reviewed the studies published between 1965 and 1987 and found that of a total of 63 reported cases of fibrosis and cancer only 2 were in nonsmokers, suggesting that fibrosis was not the only inciting mechanism for lung cancer. Wu et al. (5) conducted a population-based case-control study of adenocarcinomas of the lung to assess the association with other lung diseases. After adjustment for smoking, the only disease for which there was a significant association was tuberculosis, and that association was based on 7 cases and 1 control. In general, the ability to assess lung diseases unrelated to smoking in terms of subtype and etiology is severely hampered by the overwhelming effect of smoking. Follow-up of large cohorts in which exposure to cigarette smoke...
has been well characterized and diagnoses of competing diseases of the chest have been confirmed may offer an opportunity to assess the risks for adenocarcinoma.

Tobacco Smoking

Michael Guerin (Oak Ridge National Laboratory, Oak Ridge, TN) discussed the chemistry of mainstream versus environmental tobacco smoke and highlighted differences in particle size, phase, and composition. Given levels of dilution of sidestream smoke from mainstream smoke of 10,000–100,000 and assuming 1 m³/h is inhaled, the concentration of carcinogenic N-nitrosamines inhaled from mainstream and sidestream smoke are estimated as shown in Table 1.

David Burns (University of California, San Diego, CA) presented a discussion of smoking and histological types of lung cancer. The relative risk for adenocarcinoma of the lung in smokers is lower than that for small cell and squamous cell carcinomas. The relative risk of adenocarcinoma in nonsmokers versus smokers has not been clearly established. The pattern of smoking (depth of inhalation, frequency, etc.) in response to changes in the nicotine yield of the cigarette has never been investigated in terms of its potential to influence the types of carcinoma that occur in the lung. The time from exposure to occurrence of carcinomas may not be the same for all histological types. Lung cancer may be due to the cumulative exposure to various carcinogens, including environmental tobacco smoke.

Dietrich Hoffmann (American Health Foundation, Valhalla, NY) described how the ratio of squamous cell carcinoma to adenocarcinoma, which was 16:1 over 20 years ago, has changed significantly in the last 10 years in favor of adenocarcinoma. This may be due to changes in the composition of cigarette fillers and increasing production of filter cigarettes. Significant reduction in tar yield of cigarettes over the past 4 decades has caused smokers to inhale more deeply and with greater puff volume, which has resulted in smoke particles being deposited in peripheral lung bronchi where adenocarcinomas are usually found. To make the cigarette more combustible, cigarette manufacturers use tobacco leaf stems in the blended cigarette, which increases the nitrate content of the cigarette, and thereby increases nitrosamine content. During tobacco processing as well as during smoking, several different nitrosamines are formed which are proven animal carcinogens. One of these, NNK,

Environmental Tobacco Smoke and Radon

Elizabeth Fontham (Louisiana State University, New Orleans, LA) described that environmental tobacco smoke and radon are probably the most ubiquitous indoor air polluants in this country, albeit at low levels. Studies that have looked at cotinine levels as an indicator of tobacco smoke exposure in reported nonsmokers have found detectable levels in 50–75% of individuals studied. A recent Environmental Protection Agency report concluded that approximately 3000 lung cancer deaths/year were attributable to environmental tobacco smoke. A total of 30 epidemiological studies were evaluated for this report; 20 of 26 case-control studies reported an increased risk of lung cancer in female nonsmokers who were exposed to spousal smoking, although the risk estimates were not statistically significant in many of these studies due to small sample size. In 13 studies of lung cancer in nonsmokers that had data on histological type, the proportion of adenocarcinomas ranged from 43 to 100%.

Among studies discussed, Wu et al. (9) investigated the role of smoking and other factors in the etiology of lung cancer by histological type in white women residing in Los Angeles County. Among nonsmokers, the risk for adenocarcinoma was 1.2 for passive smoke exposure from a spouse, quite similar to the summary estimate for the United States of 1.19 and not statistically significant. The same study reported a 3-fold increase in risk of adenocarcinoma associated with coal burning in the home during childhood. Garfinkel et al. (10), who conducted a hospital-based case-control study, reported that of 134 cases of lung cancer among nonsmoking women, 87 (65%) cases were adenocarcinoma. An elevated risk of lung cancer ranging from 13 to 31% in women exposed to sidestream smoke was observed. Women who were married to smokers of 40 or more cigarettes/day or who were exposed to the smoke of at least 20 cigarettes/day at home had double the risk compared to nonexposed women. Brownson et al. (11) also observed an elevated risk of lung cancer among lifetime nonsmoking women for the highest quartile of passive smoke exposure.

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<tr>
<th>Table 1</th>
<th>Concentration of carcinogenic N-nitrosamines inhaled from mainstream and sidestream smoke</th>
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<tr>
<td></td>
<td>Mainstream</td>
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<tr>
<td>NDMA*</td>
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<td>NNK</td>
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<td>NNN</td>
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* NDMA, N-nitrosodimethylamine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNN, N-nitrosornicotine.

metabolic activation in order to be biologically active. Smokers are exposed to a dose of NNK that is somewhat comparable with the dose needed to induce the tumors in laboratory animals. The increase in NNK content of cigarette smoke has been accompanied by decreased levels of PAH such as benzo(a)pyrene. The latter induces squamous cell carcinoma of the lung in rats. Thus, the shift in cell type may reflect changes in the chemical composition of mainstream and sidestream smoke.

Ernst Wynder (American Health Foundation, New York, NY) stated that while cigarette smoking is the major cause of lung cancer in women, other factors may act as cocarcinogens. There is some evidence in the literature suggesting that hormonal and reproductive factors may play a role in lung cancer development. Adami et al. (6) reported an association between lung cancer and the use of estrogen replacement therapy in women. Estrogen and progesterone receptors have been characterized in some lung cancer tissue specimens. Short menstrual cycles in Chinese women have been linked to an increased risk of adenocarcinoma (7). Smoking of charcoal filter cigarettes at a later age, consumption of green tea, and a low fat diet may be responsible for the much lower risk of lung cancer in the Japanese compared to Caucasians.
in adulthood. At an exposure level of more than 40 pack-years, lifetime nonsmokers showed a 30% increase in risk whether the source of exposure was all household members or spouse only. In this study population, 62% of cases had adenocarcinoma. Similar findings were reported by Stockwell et al. (12). Preliminary findings from a multicenter population-based case-control study also show a 30% increased risk of lung cancer associated with exposure to environmental tobacco smoke from a spouse and a 50% increase specifically in adenocarcinoma of the lung (13). A statistically significant positive trend in risk with increasing exposure was observed; a relative risk of 1.7 for pulmonary adenocarcinoma was found with exposure of 80 or more pack-years. No association was seen between risk of any type of lung cancer and childhood exposures.

Radon and its decay products are present in indoor environments. Most homes in the United States have concentrations of <1 pCi/liter; however, some geographic regions have homes with much higher levels. Epidemiological studies of underground miners suggest that radon causes lung cancer in smokers and nonsmokers. The Environmental Protection Agency estimates that about 14,000 lung cancer deaths/year in the United States, primarily in smokers, are attributable to residential radon exposures. Data from uranium miners in New Mexico indicate multiplicative interaction between cigarette smoking and exposure to radon decay products. There is an unusually high frequency of small cell carcinoma in both smokers and nonsmokers among radon-exposed underground miners, although other histological types of lung cancer have also been found to occur in excess.

**Occupation**

Shelia Zahm (National Cancer Institute) summarized occupational hazards. Published occupational epidemiological studies have reported very few histology-specific results. There are real barriers to looking at histology in cohort studies because outcome is based primarily on death certificates that lack information on histological type, and most studies have no smoking data. Misclassification of histological type is another barrier to research in occupational epidemiology studies. A critical issue in occupational studies is diagnostic bias, caused when an exposed group undergoes more intensive screening and diagnostic work-up than the unexposed group. Epidemiological studies of workers in shipbuilding and cement industries have reported an association of asbestos exposure with adenocarcinoma of the lung. There is a positive dose response, and adenocarcinoma is the only cell type that shows an interaction with smoking for this exposure. Chinese women exposed to vapors from cooking oils have one of the highest rates of lung adenocarcinoma. Rapeseed oil used in deep frying and stir frying has been implicated, and PAHs produced may be responsible for the observed association.

**Dietary Factors**

Laurence Kolonel (University of Hawaii, Honolulu, HI) commented that dietary factors have been associated both positively and inversely with lung cancer. Positive associations have been seen in association with lipid consumption, fat, and cholesterol. In a Hawaiian study, the increase in risk associated with dietary cholesterol was twice as high for cases of squamous cell carcinoma compared to pulmonary adenocarcinomas (14). This is in contrast to the findings of a Canadian case-control study (15), where the significant increase in risk associated with dietary cholesterol was restricted to adenocarcinoma. Inverse associations have been seen with various carotenoids, vitamin C, retinol, and with fruits and vegetables as a group. The inverse association with vegetable intake may be strongest in smokers, but Koo (16) found the strongest protective association of vegetable consumption to be with adenocarcinomas and large cell carcinomas of the lung among female nonsmokers. In general, the outstanding issue is whether the dietary associations are specific and whether they apply equally to adenocarcinomas and squamous carcinomas.

**Rat Silica Model**

Umberto Saffiotti (National Cancer Institute) described an animal model of fibrosis-associated lung adenocarcinoma, closely comparable to the human counterpart, that has been obtained in rats by a single i.t. instillation of crystalline silica dust (quartz). Silica is the second most common mineral on earth; there is a common background exposure level of silica, and all humans have some silica in their lung tissue. With silica exposure, female rats showed an earlier onset and a higher number of carcinomas than did male rats. In both sexes, adenocarcinoma represented 75% of the observed tumors. There were also epidermoid carcinomas (7%), large cell undifferentiated carcinomas (2%), and mixed carcinomas with an adenocarcinoma component (7%). All tumors developed in the peripheral lung parenchyma adjacent to the silicotic granulomas with fibrosis. Over 30% of the adenocarcinomas showed a fibrous core interspersed with acini of malignant epithelial cells, surrounded by adenocarcinomatous growth extending into the parenchyma. These fibrosis-associated adenocarcinomas represent a unique model of human scar cancer (17–19).

**Strain A Mouse Lung Tumor Model**

Gary Stoner (Ohio State University, Columbus, OH) commented that the strain A mouse lung model was developed
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The tumorigenic potential of these compounds is correlated with the levels of PAH-DNA adducts, and these PAHs induce mutations in the K-ras gene which correlate with the profile of adducts that they produce in DNA. The tumors produced in strain A mice are not highly malignant and do not have a tendency to metastasize. Most of the tumors are in the alveolar region of the lung, the peripheral lung, and the lung tumors under the peripheral pleura. They grow mainly by expansion rather than by invasion. The multistage development of these lung tumors in mice begins with hyperplasia, followed by adenoma, carcinoma within adenoma, and then frank carcinoma that may involve quite a large portion of the lung. Metastasis of these particular tumors is a fairly rare phenomenon.

Genetic Susceptibility

Thomas Sellers (University of Minnesota, Minneapolis, MN) reviewed evidence that genetic susceptibility contributes to the development of adenocarcinoma of the lung. He reminded the participants that familial aggregation occurs for both genetic and nongenetic reasons. Since environmental factors contribute to lung cancer pathogenesis, any studies designed to address the role of host factors in the disease process must take into consideration measured environmental factors. Published studies have suggested that relatives of lung cancer patients are at approximately twice the risk of developing the disease as relatives of cancer-free controls. A number of studies have examined familial aggregation of lung and other cancers by histological subtypes. In general, they tend to find the same magnitude of excess risk for patients with adenocarcinoma as for patients with other cell types. Only one report has appeared in the literature suggesting that the familial clustering of lung cancer may be influenced by inheritance of a major gene. Unfortunately, this study did not examine inheritance patterns separately for adenocarcinoma. Several important questions remain to be answered in this area. Is the familial aggregation of adenocarcinoma of the lung explained by shared culture and environment or genetic makeup? Or both? What is the concordance of histological types in family members with lung cancer? And finally, is there evidence for Mendelian inheritance of susceptibility to adenocarcinoma of the lung?

Molecular Markers

Sharon Murphy (American Health Foundation, Valhalla, NY) stated that most carcinogens require metabolic activation to exert their carcinogenic potential. Typically, a carcinogen is oxygenated to produce metabolites which are either excreted directly or further metabolized to polar conjugates. A small portion of the oxygenated carcinogen is metabolized to the ultimate carcinogen which reacts with DNA, RNA, or proteins to form adducts. Some of these adducts are responsible for the carcinogenic activity of the chemical. If tissue is obtainable, DNA adducts may be assessed as markers of carcinogen exposure and activation. When this is not practical, hemoglobin adducts may serve as surrogates for DNA adducts. Carcinogen metabolites which are excreted in the urine may also be used as biochemical markers of exposure and potentially as markers of activation.

NNK is a tobacco-specific nitrosamine believed to contribute to lung cancer in smokers. In animals, it induces lung tumors independent of the route of administration. Two metabolites of NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its O-glucuronide have been identified and quantified in human urine, and together they account for over 40% of the NNK dose. These metabolites permit assessment of NNK uptake in smokers, tobacco chewers, and people exposed to environmental tobacco smoke. NNK also undergoes metabolic activation by α-hydroxylation to form hemoglobin and DNA adducts. These adducts release 4-hydroxy-1-(3-pyridyl)-1-butanone on hydrolysis which can be quantified. A subset of smokers and most tobacco chewers have hemoglobin adduct levels which are higher than detected in nonsmokers. 4-Hydroxy-1-(3-pyridyl)-1-butanone-releasing DNA adducts are also higher in lung tissue from smokers than from nonsmokers.

Marshall Anderson (National Institute of Environmental Health Sciences, Research Triangle Park, NC) commented that the development of lung cancer is a multistep process that results from the accumulation of genetic damage in the form of activated proto-oncogenes and inactivated tumor suppressor genes. For example, both the activation of proto-oncogenes, such as K-ras, and the inactivation of several tumor suppressor genes, including p53, have been observed in the development of human lung tumors. Activation of the K-ras proto-oncogene has also been observed in numerous rodent lung tumors. The activation of K-ras can be an early event, perhaps an initiating agent, in mouse lung tumorigenesis. It may also be an early event in the development of human adenocarcinoma. In human tumorigenesis, the activation of ras is probably caused by carcinogens in tobacco smoke since oncogenic ras is frequently detected in adenocarcinomas from nonsmokers (5% in nonsmokers versus 33% in smokers). K-ras oncogenes are also infrequently detected in some rodent lung tumors.

Mutations in the p53 gene are detected in over 50% of squamous cell carcinomas of the lung and, to a lesser extent, in adenocarcinomas. Mutation profiles in the p53 gene may provide clues to cancer etiology. For example, a very specific p53 mutation on codon 247 appears to be induced in miners by radon. Analysis of p53 overexpression by immunohistochemical staining in squamous metaplasia and dysplasia suggests that alterations in p53 may be an early event in human lung tumorigenesis. In contrast, mutations in the p53 gene are not commonly involved in the development of rodent tumors. However, a tumor suppressor gene located on mouse chromosome 4 has been implicated in the development of some mouse lung tumors. This region of chromosome 4 is syntenic with the portion of human 9p containing a tumor suppressor gene implicated in human non-small cell lung tumors.

Inbred mice having varying susceptibility to spontaneously occurring and chemically induced lung tumors, ranging from the most susceptible AJ mice to the most resistant strains, such as AKR/J and C57BL/6. Chen et al. (20) have suggested that the K-ras allele of the AJ mouse is one of the mouse lung tumor susceptibility loci. Differences in nuclear
protein binding in the polymorphic repetitive region in the second intron of K-ras may regulate differences in K-ras expression between various alleles from susceptible and resistant mice strains.

Steven Belinsky (Inhalation Toxicology Research Institute, Albuquerque, NM) examined the frequency of alterations in the K-ras and p53 genes in lung tumors induced in the F344/N rat by tetranitromethane, plutonium, X-ray, NNK, diesel exhaust, and beryllium. Activation of K-ras gene was detected in 100 and 46% of tumors induced by tetranitromethane and plutonium, respectively. In contrast, the frequency of mutation of this gene in tumors induced by NNK, diesel exhaust, X-ray, and beryllium was less than 15%. These results demonstrate that activation of this gene is exposure specific. Overexpression of the p53 protein in squamous cell carcinomas also varied (5–60%) as a function of exposure, while the altered protein was not detected in any adenocarcinomas.

William Bennett (National Cancer Institute) commented that the presence of p53 mutations in about one-half of all common cancers allows meaningful comparison of mutational spectra among different cancer types, as well as different populations with the same type of cancer. In vitro studies show that chemicals and radiation can produce distinctive mutational spectra, suggesting “fingerprints” of genetic damage. For example, a mutational “hotspot” in the third base of codon 249 in human hepatocellular carcinoma is common in people exposed to high levels of dietary aflatoxin. Pyrimidine dimers have been shown to result from UV light damage, and p53 mutations characteristic of this type of damage have been found in human skin cancers.

Neil Caporaso (National Cancer Institute) noted that there is an increasing awareness that the genetic profile of an individual plays an important role in cancer susceptibility. Individual differences in metabolism of certain substances have been reported to be associated with genetic susceptibility to cancer. A number of Phase I (e.g., cytochrome P-450) and Phase II enzymes have been proposed as susceptibility factors for lung cancer due to their differential ability to activate or detoxify carcinogens present in tobacco. On the basis of their own work, as well as published data, Caporaso et al. found that for three putative genetic risk factors, CYP2D6, CYP1A1, and GST-μ-deficient phenotype, there was consistently a decreased risk for adenocarcinoma histological subtype compared to nonadenocarcinoma histological type.

Prevention

Stephen Hecht (American Health Foundation, Valhalla, NY) commented that no data have demonstrated that anything other than smoking is a strong determinant of adenocarcinoma. Chemoprevention is a viable approach for decreasing the risk of lung cancers in smokers who cannot give up the tobacco habit. Former smokers, who are also at a higher risk for lung cancer, may also benefit from chemopreventive approaches. There are two types of chemopreventive agents: (a) blocking agents that prevent carcinogens from reaching critical sites (by scavenging or by interfering with the metabolic activation of a carcinogen); and (b) suppressing agents that prevent the evolution of the neoplastic process in cells that would otherwise become malignant. In general, with respect to lung cancer, animal data on suppressing agents are not as strong as data on blocking agents. Nonnutritive blocking agents include, for example, terpenes, organosulfides, inodoles, phenols, flavones, tannins, and ellagic acid. Suppressing agents include retinoids, β-carotene, vitamin A, protease inhibitors, arachidonic acid cascade inhibitors, and aromatic isothiocyanates, among others.

In order to develop effective chemopreventive agents, Hecht et al. have focused their efforts on inhibiting the effects of lung carcinogens, especially NNK, present in tobacco smoke. Smokers are chronically exposed to NNK, which on activation may be responsible for multiple alterations in oncogenes and tumor suppressor genes associated with the carcinogenic process. Agents that inhibit the activation of NNK and PAHs in tobacco smoke would be good candidates for chemoprevention. Hecht et al. have found that isothiocyanates, both naturally occurring and synthetic, inhibit the metabolic activation of NNK. Phenylethyl isothiocyanate and 6-phenylhexyl isothiocyanate have been found to significantly reduce the incidence of adenocarcinoma of the lung in laboratory animals and would be suitable candidates for Phase I and II chemoprevention trials.

Future Directions

Following the formal presentations, there was a session of general discussions among the workshop participants to identify areas of future research: (a) a standardized slide review within all SEER areas covering all age-sex-race group to determine if there has been a temporal shift from 1973 to 1993 in SEER; (b) a combined analysis of existing data sets for lung adenocarcinoma; (c) epidemiological studies of adenocarcinoma in smokers, with better collection of tobacco use data and correlation with lung cancer by cell type; (d) studies of occupational exposures and lung adenocarcinoma risk and development of biomarkers specific for chemicals that induce lung adenocarcinoma; (e) studies of chemoprevention of adenocarcinoma and the role of diet and hormones; (f) studies of the molecular mechanisms of lung adenocarcinoma formation in laboratory animals and humans and searches for novel oncogenes or tumor suppressor genes in adenocarcinoma; and (g) epidemiological and multidisciplinary studies of host susceptibility for lung adenocarcinoma in humans, including sex and race.

References

8. Office of Health and Environment Assessment, Office of Research and Development. Respiratory Health Effects of Passive Smoking: Lung Cancer...


