Lung Cancer: Is the Increasing Incidence Due to Radioactive Polonium in Cigarettes?*

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ABSTRACT: This paper presents clinical, experimental, and epidemiologic evidence to help explain the rapidly increasing incidence of primary lung cancer, with recently observed reversal in leading cell type from squamous cell to adenocarcinoma. It postulates that this may be due to changes in modern cigarettes, with or without filters, which allow inhalation of increased amounts of radioactive lead and polonium and decreased amounts of benzopyrene. This hypothesis is based upon measurements of increased concentrations of radioactive polonium in the lungs of cigarette smokers, in modern tobaccos grown since 1950, and in high-phosphate fertilizers used for tobacco farming in industrialized countries. Critical support for this thesis is based upon experimental animal studies in which lung cancers that resemble adenocarcinomas are induced with as little as 15 rads of radioactive polonium, equal to one fifth the dosage inhaled by cigarette smokers who average two packs a day during a 25-year period.

PARADOXICALLY, the incidence of lung cancer has greatly increased in the past two decades even though 15% of the population (30 million Americans) have quit smoking. In addition, 90% of American cigarettes now have filters that reduce concentrations of tars and nicotine in the smoke.[1,2] Nevertheless, age-adjusted death rates show that twice as many American men died of lung cancer in 1980 than in 1960, and three times as many women.[3]

Because at least 85% of lung cancers are reported to occur in cigarette smokers, the major carcinogens must be within the cigarettes themselves.[4] Furthermore, incidences of lung cancer are directly proportional to daily cigarette consumption.[5]

CRITERIA FOR MAJOR TOBACCO CARCINOGENS

Whatever the major tobacco carcinogens, they should prove to be inadequately filtered by cigarette filters and small doses should cause lung cancers in experimental animals. Greater concentrations of these chemicals should be found in the lungs of cigarette smokers than in nonsmokers, and there should be some reason for an increased concentration of these carcinogens in tobacco smoke.

INDUCTION OF LUNG CANCERS IN ANIMALS

Of more than 100 carcinogens found in cigarette smoke, three types of substances have been shown to cause lung cancers by inhalation or tracheal instillation into experimental animals.[1] Since 1957, polyaromatic hydrocarbons such as benzopyrene have been shown to cause lung cancers in experimental animals.[6] Benzopyrene caused squamous cell cancers of the lung when it was instilled into the respiratory tracts of hamsters and mice. However, benzopyrene's concentration in tobacco smoke has been greatly reduced in the last 20 years by changes in tobacco processing and use of filters.[1] Therefore, benzopyrene seems unlikely to be responsible for the continued increase in lung cancer, especially adenocarcinoma. Several nitrosamines found in trace amounts of tobacco smoke can also induce respiratory cancers in experimental animals, but with greater difficulty. Furthermore, since 80% of nitrosamines are eliminated by cigarette filters, these chemicals should be of decreased importance.[1]

RADIOACTIVE POLONIUM

The only other carcinogen in tobacco smoke shown to cause lung cancers in experimental animals is radioactive polonium, which emits the most powerfully carcinogenic form of radiation known, alpha radiation.[7,8] Of the three tobacco carcinogens, radioactive polonium is the least reduced by cigarette filters and is the only one shown to cause lung cancers in animals by actual inhalation (Table 1).[9,10]

Radioactive polonium is completely volatized

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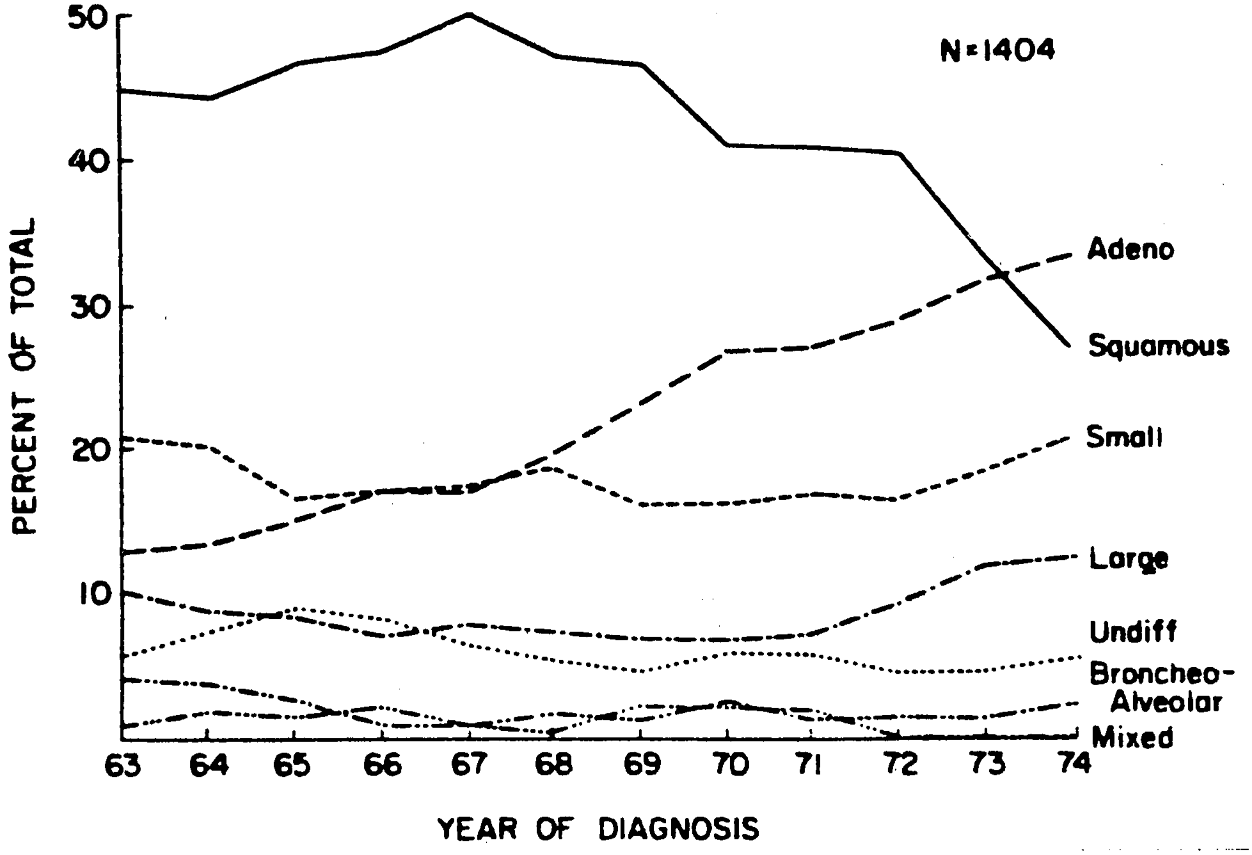


Increasing incidence of adenocarcinoma of lung. (From Valaitis et al.[24])

at the combustion temperature of cigarettes, and half is transferred directly into the mainstream smoke. Radioactive polonium produced lung cancers that had features of both adenocarcinoma and squamous cell carcinoma on instillation into the trachea of Syrian hamsters, but they more closely resembled adenocarcinoma. Furthermore, when transplanted into a host animal, these tumors became pure adenocarcinomas. Lung cancers could be induced in 97% of Syrian hamsters with radioactive polonium in doses so small that no inflammation occurred (Table 2).[11] Doses as low as 15 rads could induce lung cancer in 13% of the hamsters. This is equivalent to less than one fifth the amount of radioactive polonium inhaled by an individual smoking two packs of cigarettes per day over a 25-year period.[12] Lung cancer could be induced in 13% of rats inhaling 583 rads of this chemical. Unlike alpha radiation, thousands to tens of thousands of rads from beta- or gamma-emitting radioactive chemicals were required to induce lung cancers in experimental animals. Giving both radioactive polonium and benzopyrene at the same time produced twice the number of lung cancers that would have been expected from the additive effects of either carcinogen alone.[13]

RADIOACTIVE POLONIUM IN LUNGS OF SMOKERS

Radioactive polonium from cigarette smoke is concentrated in lungs of human smokers. Measurements of radioactive polonium made on lung specimens obtained at autopsy and at surgery revealed that the average concentration of radioactive polonium in peripheral lung tissue was more than four times as great in cigarette smokers as

TABLE 1. Polonium Content in American Cigarettes and Smoke

^{210}Po Content							
Whole Cigarette	*Ash*	*Butt*	*Total Smoke*	*Total in Ash, Butt, and Smoke*	*Recovery**	*^{210}Po in Mainstream Smoke*	*Ratio of Mainstream to Total Smoke (%)*
Brand A, nonfilter							
0.43 (4)	0.031 (2)	0.13 (2)	0.19 (2)	0.35	81	0.10 (3)	52
Brand B, nonfilter							
0.48 (5)	0.053 (2)	0.12 (2)	0.26 (2)	0.43	90	0.12 (2)	46
Brand C, filter							
0.39 (4)	0.035 (2)	0.094 (2)	0.19 (2)	0.32	82	0.088 (2)	47
Brand D, filter							
0.40 (4)	0.033 (2)	0.15 (2)	0.17 (2)	0.35	88	0.070 (3)	41

*Ratio of total in ash, butt, and smoke to total in whole cigarette.
From Radford and Hunt.[9]

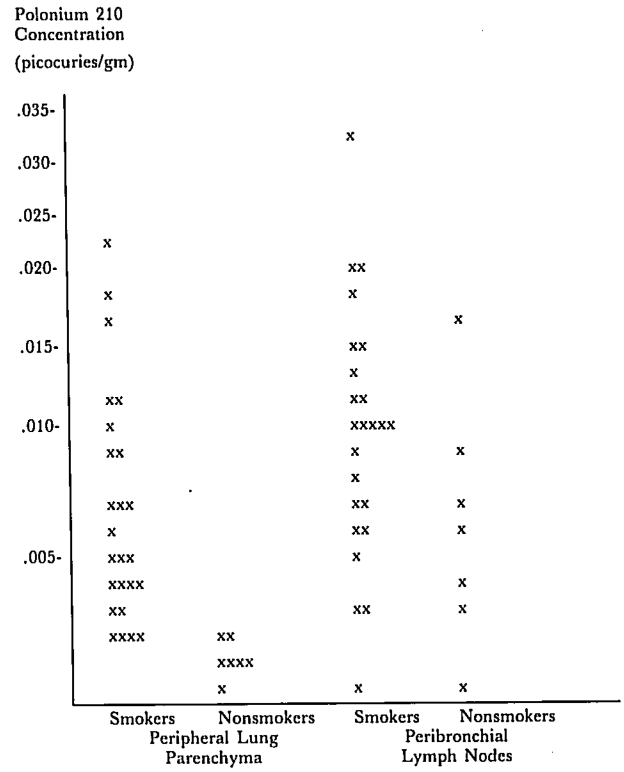
TABLE 2. Tumor Incidence in Hamsters Given Multiple Intratracheal Instillations of Polonium or Benzopyrene

Treatment Group	*Carcinogen*	*Dose/ Instillation*	*No. of Animals Autopsied*	*No. Respiratory Tumors*	*Tumor Incidence (%)*
1	Control; no instillations		60	0	0
2	Control; hematite only		34	0	0
3	Polonium	0.2 μCi	35	35	97
4	Polonium	0.2 μCi	37	25	68
5	Polonium	0.01 μCi	32	17	53
6	Benzopyrene	3.0 mg	39	24	62
7	Benzopyrene	0.3 mg	37	3	8

From Little and O'Toole.[11]

in nonsmokers. Radioactive concentrations were highest in those with greatest daily cigarette consumptions. Furthermore, the average concentration of radioactive polonium was more than 100 times as great in the basilar bronchial epithelium as in the rest of the lung (Table 3).[14] Other studies have also shown four times the concentration of radioactive polonium in peripheral lung tissue, as well as twice the concentration in the blood, urine, bones, and some soft tissues in cigarette smokers.[15]

TABLE 3. Polonium 210 Concentrations in Peripheral Lung Parenchyma and Peribronchial Lymph Nodes in 25 Current Cigarette Smokers and Eight Nonsmokers



From Little et al.[14]

ALPHA RADIATION FROM MINING

Alpha radiation from polonium and related sources such as radon gas has been implicated in very high lung cancer rates, accounting for 40% to 80% of all deaths among central European miners in Joachimsthal and Schneeberg. More recently, α-radiation-induced lung cancers have been found among Newfoundland fluospar miners, West Cumberland hematite miners, and Colorado plateau uranium miners. The lung cancer rate for nonsmoking uranium miners was seven times higher than that for nonminers who did not smoke. For those uranium miners who did smoke cigarettes, the incidence was six times higher still.[16]

BIOLOGIC NATURE OF ALPHA RADIATION

Why should the relatively low levels of radiation found in tobacco smoke, measured in picocuries, be able to cause lung cancer? Because radioactive polonium emits alpha radiation, which picocurie for picocurie has at least ten to 20 times the cancer-causing disruption for living cells as other forms of radiation. Some scientists estimate that it may be as high as 100 times, because its higher density of radiation damage produces an increased relative biologic effect on the DNA, causing fractures and translocations of the chromosomes. Alpha radiation is also known to cause cancer more readily with low doses frequently given than with a few large doses.[17] While radioactive polonium has a half-life of only about a third of a year, its precursor, radioactive lead, which accompanies it, has a half-life of 22 years. Furthermore, the average cigarette smoker continues to repeatedly bathe his lungs in radioactive polonium day after day, year after year.

INSOLUBLE RADIOACTIVE PARTICLES

One reason for early skepticism about radioactive polonium's role in causing lung cancer was that it was soluble in water, and thus rapidly cleared. Therefore, the mechanism for prolonged retention in the lung was questioned. In 1974, however, Martell[17,18] demonstrated insoluble microscopic particles of radioactive lead in cigarette smoke, which decomposes into radioactive polonium. These insoluble crystals are formed by combustion of tobacco containing calcium phosphate and radioactive lead and polonium, especially from tobacco grown with high-phosphate fertilizer. Furthermore, these insoluble radioactive particles are not uniformly distributed throughout the lungs, but are localized in small areas of the lung tissue. As a result, the small volume of lung tissue around each cluster of insoluble radioactive particles receives from 100 to 10,000 times the natural level of alpha radiation exposure.[18,19]

TABLE 4. Polonium 210 Content of Various Cigarette Tobaccos

Origin of Sample	No. of Samples	^{210}Po Activity (pc/kg) Max.	Min.	Mean
United States	8	650	390	510
Central and South America	6	1,350	290	370
Rhodesia	3	700	600	650
Australia	2	669	610	640
India and Pakistan	2	570	250	410
Indonesia	1	—	—	230
Turkey and Greece	3	280	210	240

From Hill.[22]

RADIOACTIVE POLONIUM AND LEAD IN TOBACCO PLANTS

How does radioactive polonium and its immediate precursor, radioactive lead, get into tobacco leaves, and why is it increasing? Studies have shown that most of these radioactive chemicals enter the tobacco plant from the soil during growth, with lesser amounts of radioactive polonium and lead entering the tobacco leaves directly from the atmosphere. The major reason for the increased amounts of radioactive polonium and lead in tobacco in recent decades is the increased use of artificial high-phosphate fertilizers in moderately industrialized countries. Made from apatite rock, which contains radium, polonium, and radioactive lead, they are ground up and dissolved in sulfuric acid. Their widespread use did not occur in this country until after the opening of the Tennessee Valley Authority in 1940, which developed the fertilizer manufacturing plants.[20,21]

Tobacco is a unique farm product in that its quality of flavor depends upon reduction of tobacco nitrogen. Therefore, large amounts of high-phosphate fertilizers are repeatedly applied to restricted amounts of land to use up the soil's nitrogen while stimulating greater tobacco growth. The concentration of these radioactive chemicals found in the soil and in the tobacco leaves increases with the amounts of high-phosphate fertilizer used.[21]

Since the highest lung cancer rates occur among smokers in the more highly industrialized countries, their use of high-phosphate fertilizers may be a major factor. Lesser developed countries use natural fertilizers and apply it to lands less densely cultivated. Tobacco samples from lesser developed countries such as India, Indonesia, and Turkey have been found to have about one third the radioactivity of tobacco from more developed countries (Table 4).[22]

Measured radioactivity in tobacco has been found to be increased in this country. Studies showed radioactivity in tobacco samples from 1938 to be only one third to one sixth the amounts found in samples obtained in the 1950s and 1960s (Table 5).[21]

AIR POLLUTION

Although only relatively slight differences in lung cancer incidence have been shown between

TABLE 5. Natural Radioactivity in Tobaccos

Tobacco Type	Year Produced	Activity (pg) (A) Measured ^{226}Ra (May 1964)	(B) Calc. ^{210}Pb From ^{226}Ra (May 1964)	(C) Calc. ^{210}Pb From ^{210}Po (At Harvest)	(C/A) Pb/Ra	(D) Measured ^{210}Po (May 1964)
Air-cured						
Maryland	1938	0.059 ± 0.038*	0.03	0.27	4.6	0.15 ± 0.01*
Pennsylvania cigar	1938	0.059 ± 0.006	0.03	0.32	5.4	0.17 ± 0.01
Flue-cured						
Georgia	1950	0.31 ± 0.002	0.11	0.46	1.5	0.41 ± 0.01
(Tifton	1950	0.37 ± 0.26	0.13	0.54	1.5	0.48 ± 0.01
only)	1963	0.15 ± 0.011	0.004	0.41	2.7	0.40 ± 0.02
Georgia	1959	0.39 ± 0.002	0.06	0.27	0.7	0.30 ± 0.01
(mixed)	1960	0.30 ± 0.016	0.03	0.25	0.8	0.25 ± 0.01
	1961	0.30 ± 0.008	0.02	0.42	1.4	0.40 ± 0.01
	1962	0.21 ± 0.018	0.01	0.36	1.7	0.35 ± 0.03
	1963	0.30 ± 0.018	0.008	0.42	1.4	0.42 ± 0.06
East North	1955	0.15 ± 0.002	0.04	0.28	1.9	0.25 ± 0.03
Carolina	1956	0.14 ± 0.000	0.03	0.38	2.7	0.33 ± 0.02
	1959	0.19 ± 0.001	0.03	0.37	1.9	0.35 ± 0.14
	1960	0.25 ± 0.007	0.03	0.41	1.6	0.39 ± 0.03
	1961	0.16 ± 0.007	0.01	0.51	3.2	0.48 ± 0.01
	1962	0.14 ± 0.013	0.008	0.45	3.2	0.43 ± 0.03
	1963	0.16 ± 0.011	0.004	0.31	1.9	0.30 ± 0.01

*Error terms are one standard deviation calculated from two measurements of each radium sample and at least three measurements of each ^{210}Po sample.
From Tso et al.[21]

city and rural nonsmokers, significantly more lung cancer does occur in cigarette smokers who live in cities. These differences, however, are still relatively small when compared to the overwhelming influence of cigarette smoking itself.[23] City cigarette smokers are more likely to spend more time indoors in smoke-filled, crowded rooms. Martell[18] has shown that radioactive polonium and lead particles adhere to other smoke particles and remain suspended in room air, to be breathed over and over by smoker and nonsmoker alike. He found the greater the smoke concentration, the longer and the denser the suspension in room air.

CHANGING TYPE OF PREDOMINANT LUNG CANCER

Contrary to what most textbooks have reported in the past, the most common type of primary lung cancer reported in a number of recent surveys is primary adenocarcinoma rather than squamous cell carcinoma.[24]

A 1977 article from the Roswell Park Memorial Institute based on 1,600 cases indicated that their primary lung adenocarcinoma rate surpassed squamous cell cancer for the first time in 1974.[25] To determine whether changes in the interpretation of pathology slides could be a factor, they reevaluated their slides and found that this trend was not factitious. The Roswell Park group found that 95% of all their patients with lung cancer had smoked tobacco, as did 89% of those with adenocarcinoma, thereby refuting previous impressions that primary lung adenocarcinomas were frequently found in nonsmokers. They concluded that some type of alteration in tobacco carcinogens may be responsible (Figure).[25] Similarly, Melamed et al,[26] working at the Memorial Sloan-Kettering Cancer Center, were surprised to find that among 288 male smokers primary adenocarcinoma was the most frequent type of lung cancer detected by screening between 1974 and 1982. Conversely, Auerbach et al[27] found dramatic reductions in squamous metaplasia in smokers between the 1950s and 1970s.

Although small (oat) cell lung cancer was the most frequent type noted in earlier studies of uranium miners, a decrease in this type has been observed in recent years from 59% in 1960 to 22% in 1980, with a proportionate increase in adenocarcinoma.[28]

Among survivors of an atomic bomb blast, women had a preponderance of pulmonary adenocarcinoma; men had a preponderance of squamous carcinoma. Both showed an increased incidence of small cell cancer.[29]

CONCLUSIONS

In hamsters, benzopyrene induced mainly squamous cell carcinomas in proximal bronchi, and radioactive polonium produced mainly peripheral lung cancers that more closely resembled adenocarcinomas. This finding suggests a cause-and-effect relationship between benzopyrene and squamous cell carcinoma and between radioactive polonium and adenocarcinoma. Accordingly, the decreased proportion of human squamous cell lung cancer has occurred during a period of decreasing concentration of benzopyrene in modern filtered cigarette smoke. During the same period, an increased proportion of human lung adenocarcinomas has been observed in association with greatly increased concentrations of radioactive polonium and lead in tobacco.

Therefore, the continued escalation of lung cancer rates, especially of adenocarcinoma, among Americans may be related to the increased amounts of radioactive polonium and lead inhaled from modern cigarettes. These substances may also contribute to the increase in oat cell types, and are likely to interact and potentiate any amounts of other tobacco carcinogens, such as benzopyrene or nitrosamines. At the same time the decreased percentage of pulmonary squamous carcinomas may be due to decreased amounts of benzopyrene and other polyaromatic hydrocarbons in modern filtered cigarette smoke.

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