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1. Introduction

1.1. This report describes the evolution of scientific knowledge about smoking and health during the half-century before 1964, the year of issuance of the Report of the Advisory Committee to the U.S. Surgeon General (U.S. Public Health Service 1964).

1.2. Although the Surgeon General's Report gained widespread public attention, substantive evidence on the harmful effects of smoking had accumulated in the scientific literature for at least four decades before the 1964 report.

1.3. Although tobacco use has been linked to a number of illnesses (U.S. Public Health Service 1964, 1971, 1979, 1980), the report considers mostly the relation between smoking and cancer, especially cigarette smoking and lung cancer.

1.4. This analysis of the state of the art relies substantially upon articles published in scientific and professional journals.

1.5. By "state of the art," I mean the body of knowledge, evidence and opinion that was reasonably ascertainable by a scientific expert at a particular point in time. "State of the art" does not necessarily mean the perceptions of general medical practitioners, the product standards of the cigarette manufacturers, or the beliefs of the public at large.

1.6. By 1964, the experimental and clinical literature on tobacco and health already exceeded 7,000 titles (Larson, Haag and Silvette 1961; U.S. Public Health Service 1964, at 14). Rather than producing an exhaustive, year-by-year scorecard of articles pro and con, my report points out the salient features of this massive literature.

1.7. As part of my report on the state of the art, I shall address three questions:

1.8. First, when (if at any time) should a reasonably prudent manufacturer of cigarettes have conducted or sponsored careful scientific research into the potentially cancer-causing effects (or other harmful effects) of its products?

1.9. Second, what methods of scientific research (if any) were available for a reasonably prudent manufacturer of cigarettes to evaluate the potentially cancer-causing effects (or other harmful effects) of its products?

1.10. Third, when (if at any time) should a reasonably prudent manufacturer of cigarettes have warned its customers of the potentially cancer-causing effects (or other harmful effects) of its products?

1.11. A reasonably prudent manufacturer of cigarettes, in determining when to initiate its own scientific research, or what types of research to perform, or when to issue warnings to customers, need not have waited for definitive proof that cigarette smoking causes cancer or any other specific disease in humans.

## 2. Tobacco Use among Men and Women

2.1. Up to the 19th century, tobacco was consumed by men mostly in pipes, cigars, snuff, and chewable forms. Hand-rolled cigarettes, composed mainly of imported tobaccos, appeared in the United States in 1854. Although cigarette manufacture grew after the Civil War, it remained a relatively small fraction of American tobacco trade up to 1885.

2.2. After the invention of a practical cigarette-rolling machine and a shift to domestic tobaccos, cigarette smoking in the United States became more widespread. Especially after 1900, cigarette use accelerated markedly as a consequence of further innovations in cigarette production and marketing. In the United States, Camel cigarettes appeared in 1913, Lucky Strike in 1916, Chesterfield in 1919. During the period 1900-1920, U.S. cigarette consumption per capita increased by more than tenfold. (U.S. Public Health Service 1980, at 15-42; Bailey and Petre 1937)

2.3. The rise of cigarette smoking after the turn of the century was composed of two main trends: the adoption of cigarettes by men who had previously used pipes, cigars and smokeless tobacco; and the recruitment of a new generation of younger male cigarette smokers during World

War I. Thus, by 1923, fifty two percent of adult males in the Milwaukee area smoked cigarettes, most of whom also smoked pipes and cigars; in total, 87 percent of adult men used some type of tobacco.

2.4. Cigarettes increasingly dominated other forms of tobacco among male smokers throughout the 1920s and 1930s. Thus, by 1935, 63 percent of adult males in the Milwaukee area smoked cigarettes, while the percentages of pipe and cigar users had declined substantially.

2.5. Although men took up cigarette smoking during the early part of the 20th century, the growth of cigarette use among women occurred much later. In 1924, only about 6 percent of adult women smoked cigarettes. By 1935, the proportion was about 18 percent. By the end of World War II, the proportion of adult women smokers exceeded 25 percent.

2.6. Thus, in the early decades of the 20th century, men began to switch from pipes and cigars to cigarettes. In the 1920s and 1930s, women began to take up cigarette smoking. These general patterns were observed in Europe as well as in the United States (e.g., Kennaway and Kennaway 1947, at 293-294).

### 3. Tobacco and Oral Cancer, 1915-1945

3.1. The early dominance of pipes, cigars, and smokeless tobacco over cigarettes had an important bearing on scientific inquiry about tobacco and health. The scientific literature during the earlier part of this century emphasized the harmful consequences of non-cigarette forms of tobacco use-- especially the connection between pipe or cigar smoking and oral cancer. The link between pipe or cigar smoking and cancer-- established during the earlier part of the 20th century-- served as a logical foundation for subsequent study of the health consequences of cigarette smoking.

3.2. Reports of oral cancer among tobacco users appeared sporadically in the scientific literature during the period from 1795 to the first decade of the 20th century (Lickint 1930; Ebenius 1943). Thereafter, the role of tobacco in oral cancer was increasingly acknowledged by surgeons, pathologists, cancer specialists, and other researchers.

3.3. Table 1 highlights the scientific literature on tobacco and oral cancer-- including cancer of the lips, tongue, inner cheek, and other oral tissues-- during the period 1915-45. This literature, based upon the clinical study of human patients, had several notable characteristics.

3.4. First, many different physicians with substantial clinical experience reported that tobacco use, especially heavy tobacco use, was very frequent in patients with oral cancer. This finding was confirmed many times at different geographic sites and among different patient populations (Table 1).

3.5. Second, the disproportionate incidence of oral cancer in men was found to be consistent with the fact that tobacco was used predominantly by males. As smoking among women became more prominent, evidence of cancerous and precancerous oral lesions among women increased (e.g., Jacobs 1941).

3.6. Third, physicians were able to document the carcinogenic role of tobacco use in individual cancer patients (e.g., Fordyce and MacKee 1926; Mowat 1929). Of note is the repeated finding of that cancers occurred at the site where the patient's tobacco was typically applied (e.g., Abbe 1915; Mowat 1929; Padgett 1936).

3.7. Fourth, physicians linked tobacco use to specific precancerous lesions of the oral cavity (e.g., Fordyce and MacKee 1926; Mowat 1929; Wile and Hand 1936; Jacobs 1941; Lamb and Eastland 1941; Grace 1944). Cessation or moderation of tobacco use, some reported, might arrest progression of a precancerous lesion into the malignant stage.



3.8. Fifth, the scientific literature recognized that tobacco need not be the sole causative agent in oral cancer. Consideration of other possible factors (e.g., mechanical irritation, occupation, oral syphilis) did not automatically exclude tobacco as a cancer-causing agent (e.g., Judd and New 1923; Mowat 1929; Lickint 1930; Hoffman 1931; Martin and Pfleuger 1935; Ebenius 1943).

3.9. Seventh, studies of patient populations confirmed the clinical finding that tobacco use was more common in certain oral cancer patients than in comparison subjects (e.g., Lombard and Doering 1928; Hoffman 1931; Bigelow and Lombard 1933; Ebenius 1941). Such studies ascertained relationships between the site of cancer and the type of tobacco used (e.g., Broders 1920; Ahlbom 1937). A dose-response relation between the extent of tobacco use and the incidence of oral cancer could be established (e.g., Lombard and Doering 1928; Potter and Tully 1945).

3.10. Sixth, clinicians recognized that chemical and thermal irritation related to tobacco use might have a role in the production of cancer (e.g., Judd and New 1923; Lickint 1930; Martin and Pfleuger 1935; Padgett 1936; Ebenius 1943; Grace 1944).

4. Experimental and Chemical Studies, 1900-1947

4.1. Scientific articles concerning the potentially cancer-causing effects of tobacco products on laboratory animals date back to 1900. (See references in Schurch and Winterstein 1935, 1937; Muller 1939; Campbell 1939; Sugiura 1940; Flory 1941; Ebenius 1943; Wynder, Graham and Croninger 1953; Graham, Croninger and Wynder 1957; Wynder 1955; Wynder and Hoffman 1967.)

4.2. Such experimental attempts to induce cancers in laboratory species with tobacco products were motivated, in great part, by the clinical literature linking tobacco and cancer (e.g., Roffo 1930b, 1937b; Cooper et al. 1932).

4.3. During the 1920s and 1930s, experimental scientists increasingly recognized that specific chemicals or mixtures of chemicals could cause cancer. Moreover, the scientific community increasingly acknowledged the complementary roles played by experimental studies in animals and clinical observations in humans. For example, epidemiological studies of bladder cancer among aniline dye workers ultimately lead to the experimental induction of bladder cancers by the chemical beta-naphthylamine in 1938.

4.4. Similarly, Passey's (1922) experimental finding of the carcinogenicity of soot extracts confirmed the frequent clinical observation of cancer in soot-exposed

workers. Likewise, clinical observations of skin cancers in coal tar and pitch workers stimulated a detailed study of high-boiling fractions of coal tar distillates (.e.g, Kennaway 1925). By the early 1930s, such studies had lead to the identification of at least two specific chemical carcinogens, dibenzanthracene and benzo(a)pyrene. (See references cited in Berenblum and Schoental 1947; U.S. Public Health Service 1964.)

4.5. In the 1920s and early 1930s, experimental scientists had found that carcinogenic tars could be formed from the pyrogenous products of a variety of organic materials (Kennaway 1925; Kennaway and Sampson 1928; Watson 1933). Given the clinical evidence on tobacco and cancer, it was logical that a carcinogenic tar could likewise be formed during tobacco smoking (e.g., Cooper et al. 1932; Bogen and Loomis 1932; McNally 1932).

4.6. Following such logic, Roffo published an extensive series of papers on tobacco carcinogenesis in Spanish, German and French language scientific journals during the 1930s (Roffo 1930ab, 1931ab, 1932, 1936, 1937abcd, 1938, 1939abcde, 1943). Roffo's findings were cited repeatedly in the world scientific literature, including English language journals (McNally 1932; Campbell 1939; Ochsner and DeBakey 1941; Flory 1941; Editorial 1941; Menne and Anderson 1941; Grace 1943, 1944; Ochsner 1945).

4.7. Among Roffo's experimental findings were: production of oral leukoplakia after exposing rabbits to tobacco smoke (1930a); production of an infiltrative, metaplastic epithelial tumor after 8 months of painting rabbit ears with the water-soluble components of tobacco smoke (1930b; 1931a, 1937d); failure to produce such a cancerous lesion by application of nicotine alone (1930b, 1931a, 1937d); production of a metastatic carcinoma in a rabbit exposed for 3 years to a jet of whole tobacco smoke (1931b, 1932); production of squamous cell carcinomas in multiple experiments by 8 to 14 months' of application high-temperature, destructive distillates of various types of tobacco (1936, 1937acd, 1938, 1939ac); induction of neoplasms in rats with implanted pellets of tobacco tar (1936); spectroscopic identification of benzo(a)pyrene in the tobacco distillates (1937b, 1939bd); production of squamous cell cancers in rabbits after 12 months' application of tars prepared from condensed tobacco smoke (1939e); and production of lung cancer in rabbits after direct injection of tobacco distillate into the lung (1943).

4.8. Many of Roffo's findings were confirmed by other investigators. Cooper et al. (1932) produced a carcinoma in mice after 18 months' application of a condensate of pipe tobacco smoke. Campbell produced a skin cancer in mice with tar from a cigarette smoke condensate (1939) and lung tumors

in mice exposed to whole smoke (1936). Flory (1941) produced cancer-like skin tumors in rabbits with a distilled tobacco tar. Taki produced skin cancers in mice with tar from pipe smoke (see Kinoshita 1937). The fact that tobacco tars were carcinogenic in more than one species of animal increased the significance of the experimental findings.

4.9. In some of the animal carcinogenesis experiments, scientists prepared tars by distilling rather than by smoking tobacco (Bogen and Loomis 1932; Roffo 1936, 1937ac, 1938, 1939ac; Flory 1941). Although such high-temperature distillates of tobacco might contain substances different than those encountered in human smoking, other experiments showed that tars prepared from tobacco smoke also caused cancer in laboratory animals (Campbell 1936; Roffo 1930b, 1931a, 1937, 1939e).

4.10. In such animal experiments, tobacco tars were consistently weaker carcinogens than coal tars (Campbell 1939; Sugiura 1940). The finding that tobacco tar was a relatively weak, slowly acting carcinogen in animals was consistent with clinical evidence on the incidence and time course of cancer in human smokers (Editorial 1941).

4.11. An incomplete experiment, in progress in 1942, in which mice were exposed to whole cigarette smoke for only 1 to 7 months, demonstrated that inhaled tars passed the upper respiratory tract and were directly deposited in the animals' lungs (Lorenz et al. 1943).

4.12. Cancer biology was advancing. By the late 1930s, there was evidence that cancer-causing tars might contain mixtures of several carcinogenic compounds. By the 1940s, previously established methods of solvent extraction and chromatography had been employed to show that coal tar contained several distinct carcinogenic fractions (Berenblum and Schoental 1947). Controlled, standardized biological testing of individual carcinogenic chemicals became practical. (See citations in Bryan and Shimkin 1943; Hartwell 1951.) Quantitative methods for estimation of safety margins had been developed (Foster 1939). Chronic toxicity studies were being performed on various chemicals in the environment and food supply (e.g., Fitzhugh and Nelson 1947). By the early 1940s, a wide variety of laboratory methods were available to study cancer, including tissue culture, tumor transplantation, metabolic studies of tumors, analyses of differences in cancer susceptibility among strains of animals, studies of dose and time relationships in chemical carcinogenesis, and experimental skin cancer models with polyaromatic hydrocarbons and other carcinogens (e.g., American Association for Cancer Research 1943).

4.13. For centuries, tobacco had been recognized as a source of the chemical nicotine-- a poison that was used mostly as an insecticide (Balandrin et al. 1985).

Accordingly, numerous analyses of the nicotine content of tobacco and tobacco smoke were performed (e.g., Jensen and Haley 1935).

4.14. By the late 1920s and early 1930s, however, nicotine was not the only suspected deleterious agent in tobacco (e.g., Armstrong and Evans 1922; Baumberger 1923; see also the citations in Bradford, Harlan and Hanmer 1936; Gross and Nelson 1934; Bradford, Harlow, Harlan and Hanmer 1937; Kosak 1955; Wynder and Hoffman 1967). Investigators recognized the distinction between mainstream and sidestream smoke (e.g., Bogen 1929; Bradford, Harlan and Hanmer 1936), as well as the distinction between volatile and particulate components of smoke (e.g., Bradford, Harlan and Hanmer 1936). At the same time, researchers also understood that the yield of nicotine and other noxious agents depended on the rate of puffing, and that the butt end of the cigarette contained most of the tar and other products of incomplete combustion (e.g., Bogen 1929; McNally 1932).

4.15. By the mid 1930s, the list of recognized, potentially deleterious chemicals in tobacco smoke included: nicotine; carbon monoxide; ammonia; cyanide; pyridine bases and pyridine derivatives; pyrrole derivatives; phenols; various aldehydes including acetaldehyde, formaldehyde and acrolein; furfural; hydrogen sulfide; arsenic; heterocyclic nitrogenous bases and other complex chemicals within the

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intermittent-suction smoking machines to collect cigarette smoke for chemical analysis and for experiments in laboratory animals; spectroscopic, chromatographic and other means of chemical analysis of cigarette smoke constituents; preparation and fractionation of cigarette smoke condensates; and short-term and long-term experimental studies (for carcinogenicity and other toxic endpoints) on exposure of various laboratory animals to whole cigarette or other tobacco smoke, to cigarette or other tobacco smoke condensates, to components or fractions of cigarette and other tobacco tar, and to individual chemical constituents of smoke.

5. Cigarette Smoking and Lung Cancer, 1927-1948

5.1. During the period prior to World War I, pathologists, clinicians and vital statisticians began to note an increase in lung cancer-- a disease that was relatively obscure prior to 1900. By the late 1920s and 1930s, a dramatic increase in primary lung cancer, predominantly among males, was recognized throughout the United States and Europe. Lung cancer began to overtake cancer of the stomach in clinical and autopsy series and in vital statistics analyses (see Perret 1927; Hoffman 1929, 1931; Arkin and Wagner 1936; Muller 1939; Ochsner and DeBakey 1939, 1941; Menne and Anderson 1941).

5.2. At the start, there was controversy concerning the genuineness of the increase in lung cancer incidence. Alternative explanations emphasized improved methods of diagnosis, increased autopsy rates, population aging, changes in disease classification and generally enhanced cancer awareness among physicians. However, such explanations did not accord with other facts, including the increase in the age-specific incidence of lung cancer, the disproportionate rise in lung cancer among males, the rise in lung cancer relative to cancers of other internal organs, and the increased proportion of lung cancers seen at autopsy. Beginning in the late 1920s, a growing number of

pathologists, surgeons, vital statisticians, and other scientists realized that, at least since 1920, the rise in lung cancer was genuine, both relatively and absolutely (see Perret 1927; Hoffman 1929, 1931; Mertens 1930; Arkin and Wagner 1936; Muller 1939; Ochsner and DeBaakey 1939, 1941; Menne and Anderson 1941; Kennaway and Kennaway 1936, 1947; see also Graham 1951).

5.3. Beginning in the 1920s, a variety of factors were hypothesized as contributing to the striking rise in lung cancer. These included: the influenza pandemic of 1918; old tuberculous lesions in lung cancer patients; pre-existing bronchitis and emphysema in lung cancer victims; gasoline fumes containing lead; diesel and gasoline-powered automobile emissions; irritant gases used in World War I warfare; soots, tars and other air pollutants from roads, fuel combustion, and various industrial processes; as well as the rise in cigarette smoking. A concentration of lung cancer cases in the mining district of Schneeberg in Saxony stimulated interest in radioactive substances and certain heavy metals as possible contributors. (See Perret 1929; Hoffman 1929, 1931; Ochsner and DeBaakey 1941; Kennaway and Kennaway 1936, 1941).

5.4. Beginning in the late 1920s, many surgeons, cancer specialists and other physicians, reporting their clinical experiences with this relatively new cancer, noted

that lung cancer patients were almost always heavy cigarette smokers (Table 2).

5.5. During the 1930s and early 1940s, the proposition that cigarette smoking caused lung cancer received increasing scientific support (Table 2). Among the several lines of supporting evidence were the following.

5.6. The concept of cigarette smoking as a cause of lung cancer was consistent with the previously recognized link between pipe or cigar smoking and oral cancer (e.g., Hoffman 1931; Editorial 1941).

5.7. Further, while pipe and cigar smoking were linked with oral cancer, the widespread inhalation of cigarette smoke, it was reasoned, should be linked mostly to cancer of the lower respiratory tract (e.g., Hoffman 1931; Thys 1935; Ochsner and DeBaakey 1939). Such an hypothesis was supported by observations in cancer patients relating the site of cancer to the type of tobacco used (e.g., Lombard and Doering 1928; Fleckseder 1936; Ahlbom 1937).

5.8. Moreover, the rise in lung cancer in men paralleled the growth in male cigarette use. The relatively low incidence of lung cancer in women accorded with the delayed emergence of widespread cigarette smoking among females (e.g., Mertens 1930; Lickint 1930; Hoffman 1931; Thys 1932; Arkin and Wagner 1936; Muller 1939; Menne and Anderson 1941; Ochsner and DeBaakey 1939, 1941).

5.9. In addition, the notion that cigarette smoking caused lung cancer was consistent with the evidence that various tarry products of combustion might be carcinogenic in humans and laboratory animals. Some scientists had produced cancerous lesions in laboratory animals with tobacco smoke and tobacco tars (see Section 4 supra; also Lickint 1930; Muller 1939; Ochsner and DeBakey 1941).

5.10. The fact that not all smokers developed lung cancer was consistent with the recognized notion that susceptibility to carcinogens varied among both human populations and experimental strains of animals (e.g., Roffo, as quoted by Grace 1944; American Association for Cancer Research 1943).

5.11. What is more, the evidence in support of alternative explanations was much less impressive. Bronchitis, influenza, and tuberculosis were soon rejected. The growth in lung cancer appeared to precede tarring of the roads. Lung cancer incidence had risen in locations where there had been no increase in coal dust, road tarring or automobile traffic. The predominance of lung cancer among men went against the role of generalized air pollution. Comparisons of lung cancer incidence across occupational categories were inconclusive.

5.12. Finally, although coal dust, radioactive isotopes, chromates, nickel and arsenic compounds and silica

remained suspect, exposures to such agents did not appear sufficient to account for the large, dramatic increase in lung cancer. As in the earlier experience with oral cancer, researchers recognized that tobacco need not be the only causative factor. (See citations in Ochsner and DeBakey 1941; Menne and Anderson 1941; also Kennaway and Kennaway 1947).

5.13. By the late 1930s, cigarette smoking histories were being intentionally taken among lung cancer patients at major cancer hospitals and centers (see Levin, Goldstein and Gerhardt 1950; Sadowsky, Gilliam and Cornfield 1953).

5.14. By 1939, a carefully age-matched comparison of lung cancer patients with non-cancer patients confirmed a significant excess of heavy smokers in the cancer group and a marked excess of nonsmokers in the control group (Muller 1939).

5.15. During the 1940s, three additional clinical studies comparing lung cancer patients and control subjects (Schairer and Schoniger 1943; Potter and Tully 1945; Wassink 1948) confirmed the previously reported excess of heavy smokers among lung cancer cases (Table 2).

5.16. Thus, by late 1930s and early 1940s, a substantial number of researchers had already pointed to cigarette smoking as the main cause of lung cancer (Table 2). Although definitive, unimpeachable evidence was not yet

available, the cigarette smoking-lung cancer connection was a sufficiently real possibility to merit serious concern. The notion that cigarette smoking caused lung cancer was well reasoned, clearly articulated, and repeatedly asserted.

6. Cigarette Smoking and Lung Cancer, 1949-1964

6.1. In 1950, researchers in the United States and Great Britain published the results of five independent, carefully designed, clinical studies on the extent of cigarette smoking among lung cancer patients and matched comparison subjects (Table 3).

6.2. The 1950 studies confirmed that "Excessive and prolonged use of tobacco, especially cigarets, seems to be an important factor in the induction of bronchiogenic carcinoma." (Wynder and Graham 1950, at 336)

6.3. During 1952-1954, there appeared ten additional papers on the extent of cigarette smoking among subjects with and without lung cancer. The papers confirmed and elaborated the cancer-smoking relationship (Table 3).

6.4. Many of the 1950-1954 clinical studies were conceived, initiated and, in some cases, completed in the 1940s (see Doll and Hill 1950; Hill 1953; Breslow et al. 1954; Sadowsky, Gilliam and Cornfield 1953; Levin, Goldstein and Gerhardt 1950). One paper's results were presented to the scientific community in 1949 (Wynder and Graham 1950).

6.5. The 1950-1954 studies showed that the risk of developing lung cancer increased steadily as the amount or duration of smoking increased. The marked excess of lung cancer in men over women, the studies confirmed, could be



attributed to the relatively small numbers of inveterate women cigarette smokers in the older age groups. The studies confirmed that cigarette smoking was more closely connected to lung cancer than was pipe or cigar smoking.

6.6. The 1950-1954 studies showed a link between cigarette smoking and lung cancer even when industrial exposures were taken into account (Wynder and Graham 1951; Breslow et al. 1954). The link between cigarette smoking and lung cancer obtained even when the subjects were restricted to a homogeneous group, such as physicians (Wynder and Cornfield 1953).

6.7. The 1950-1954 studies ascertained cancer cases, controls and smoking habits by different methods. Cigarette smoking was found to be responsible for at least 80 percent of lung cancer (Doll 1953).

6.8. The positive results of such "retrospective" studies, as they came to be called, stimulated researchers to plan and execute much larger, longer term "prospective" analyses. In such prospective studies, smoking and nonsmoking subjects were enrolled and followed for years (Hill 1953).

6.9. The preliminary results of such prospective studies, published in 1954 (Table 3), showed that lung cancer constituted only a fraction of the total excess mortality attributable to cigarette smoking. In males, the

risk of lung cancer among cigarette smokers was 20 to 40 times that of nonsmokers. Ex-smokers had lower lung cancer risks than continuing smokers.

6.10. By 1955, new analyses of vital statistics reinforced the results of the clinical and epidemiological studies. Lung cancer, it was found, had increased sharply throughout those countries where the rise in cigarette smoking had been most marked. A paper on the incidence of lung cancer in Iceland, where tobacco consumption was low, reinforced such a conclusion (Dungal 1950). The slight increase in lung cancer among women was found compatible with an increase in female smoking two decades previously. The age distribution of lung cancer was found consistent with the introduction of a carcinogen into the environment about thirty to thirty-five years previously (Wynder 1955).

6.11. During the period 1956-63, positive results were reported in 11 additional retrospective studies and in six prospective studies (Table 3). The studies confirmed the relationship between cigarette smoking and lung cancer in women as well as men (Wynder, Bross et al. 1956; Haenszel, Shimkin and Mantel 1958; Hammond and Garfinkel 1961; Haenszel and Taeuber 1963). The studies showed that the link between cigarette smoking and lung was independent of geographic residence (Haenszel and Shimkin 1956; Haenszel, Loveland, Sirken 1962; Haenszel and Taeuber 1963).

6.12. By 1951, pathological studies had suggested that lung cancer, like several other human cancers, exhibited a detectable precancerous stage (Papanicolaou and Koprowska 1951). By 1956, Auerbach and colleagues had demonstrated the presence of such precancerous changes in the lining cells of the lungs of cigarette smokers. The extent of such precancerous changes was related to the number of cigarettes smoked (see Auerbach et al. 1958; U.S. Public Health Service 1964, at 167-173).

6.13. Other clinical studies confirmed and elaborated the relations between type of tobacco smoking and site of cancer. The relations between smoking and cancers of the upper respiratory tract and other organs were confirmed and elaborated (Mills and Porter 1950; Sanghvi, Rao and Khanolkar 1955; Schwartz, Denoix and Anguera 1957; Pernu 1960; Schwartz et al. 1961)

6.14. A carefully designed experimental study, abstracted in the scientific literature in 1952 and published in full during 1953, confirmed that the tars in cigarette smoke cause cancer in laboratory animals (Graham, Wynder and Croninger 1952; Wynder, Graham and Croninger 1953). Thereafter, numerous experimental and chemical studies elaborated and refined the cigarette smoking-cancer connection (Table 4).

6.15. Prior to 1954, a few criticisms of the evidence were offered (e.g., Passey 1953; Rigdon and Kirchoff 1953). Beginning in 1954-1955, however, a critical counterattack was launched (e.g., Berkson 1955, 1958, 1959; Hueper 1954, 1955; Neyman 1955; Haag and Hanmer 1957; Fisher 1959; Little 1957, 1958; Rigdon 1957; MacDonald 1958).

6.16. The critics generally did not dispute the repeated finding that the risk of lung cancer in cigarette smokers was 20 to 40-fold greater than in nonsmokers. Their main point was that such evidence did not constitute proof of a cause-effect relationship. Each of the numerous clinical and epidemiological studies, it was claimed, had one or another bias. The experimental and chemical evidence, to the extent that it was addressed at all, was disputed or dismissed as irrelevant.

6.17. Many review articles (e.g., Cornfield et al. 1959; Davies 1960) showed how the existing evidence already rebutted the critics' arguments.

6.18. For example, proponents of the "constitutional hypothesis" argued that cigarette smoking and lung cancer both have a common cause, usually specified as a special constitutional or genetic characteristic, that predisposes certain persons to lung cancer and also makes them cigarette smokers. Such an hypothesis was found inconsistent with: the cohort-specific changes in lung cancer mortality over

the past half-century; the carcinogenicity of tobacco tars for experimental animals; the large effect of pipe and cigar tobacco on oral and laryngeal cancer but not on lung cancer; and the reduced lung cancer mortality among those who quit smoking.

6.19. Beginning in about 1952, numerous professional societies, scientific advisory committees and learned journals concluded that cigarette smoking caused cancer (Table 5). The U.S. Surgeon General concurred in 1957 (Table 5).

6.20. In 1964, the Advisory Committee to the U.S. Surgeon General similarly concluded that cigarette smoking caused lung cancer (Table 5). The latter Report reiterated a conclusion that had already been widely acknowledged in the scientific community.

7. Cigarette Smoking and Diseases Other than Lung Cancer

7.1. In the decades before the 1964 Surgeon General's Report, substantive evidence had accumulated on potentially harmful effects of cigarette smoking other than lung cancer (U.S. Public Health Service 1964, 1971, 1979, 1980).

7.2. The following were among the potential hazards of cigarette smoking for which substantive evidence had accumulated by the late 1930s and early 1940s.

7.3. Cigarette smoking might result in an overall decline in longevity (Pearl 1938; see also Hammond and Horn 1954, 1958; Doll and Hill 1954, 1956; Dorn 1959).

7.4. Cigarette smoking might increase the risk of fatal and nonfatal events of coronary heart disease. Nicotine might have an adverse effect on the coronary circulation (English, Willius and Berkson 1940; Bellet et al. 1941; see also Hammond and Horn 1954; Doll and Hill 1956; Study Group on Smoking and Health 1957).

7.5. Cigarette smoking might cause other cancers, including cancer of the larynx and esophagus (Lickint 1930; Ahlbom 1937; Mustakallio 1944).

7.6. Cigarette smoking might cause chronic bronchitis and other non-cancerous lung disease (McNally 1932; Short, Johnson and Ley 1939).

7.7. Cigarette smoking during pregnancy might harm the fetus (Sontag and Wallace 1935; see also Simpson 1957; U.S. Public Health Service 1980). Cigarette smoking during lactation might adversely affect the nursing baby (Perlman et al. 1942).

7.8. Cigarette smoking might be habit-forming or addictive, the main psycho-active component in smoke being nicotine (Head 1939; Johnston 1942, 1944, 1952; Kuschinsky and Hotovy 1943; Finnegan, Larson and Haag 1945).

7.9. During the first four decades of the 20th century, a wide variety of health effects were attributed to cigarette smoking and other forms of tobacco use (e.g., Carlson and Lewis 1914; Appleton and Lehner 1928; Dill, Edwards and Forbes 1934). However, claims of possibly salubrious effects of smoking did not detract from the substantial and growing evidence on the potentially harmful consequences of smoking. Although at one time tobacco was ascribed a role in the causation of tuberculosis, such an hypothesis was not seriously entertained by the late 1930s (Bogen 1937).

8. Research on Smoking and Health Performed or Sponsored  
Cigarette Manufacturers

8.1. The published scientific literature of the 1930s and 1940s shows that American cigarette manufacturers performed or supported certain narrowly focused research inquiries on smoking and health (Table 6). In addition, manufacturers issued or supported scientific articles that did not bear directly upon questions of smoking and health (e.g., Cone and Davis 1937).

8.2. Among those investigations supported by cigarette manufacturers, one paper (Mulinos and Cockrill 1938) addressed the relation between nicotine delivery and butt length. Another paper (Mulinos and Shulman 1940) purported that the blood-vessel constriction commonly observed during cigarette smoking might result not from nicotine but from the act of deep inspiration (see also Lieb, Mulinos and Taylor 1936; Shulman, Mulinos and Lieb 1938; Mulinos and Shulman 1939).

8.3. For the most part, however, manufacturer-supported research was concerned with the locally irritative effects of cigarette smoke on the throat and upper respiratory tract (Mulinos and Osborne 1934, 1935; Flinn 1935, 1937; Greenwald 1935, 1936; Wallace, Reinhard and Osborne 1936; Proetz 1939a; Fabricant 1943; see also Proetz 1939b; Fabricant 1946ab).



8.4. Manufacturer-supported research on smoking and cancer was not readily apparent in the scientific literature of the 1930s and 1940s. Before the 1950s, there were few if any published, manufacturer-sponsored attempts to corroborate or contradict the smoking-cancer hypothesis-- either by clinical case study, by analysis of cancer patient populations, by experimental animal work on cigarette tars, or by chemical analysis of aromatic hydrocarbons, heterocyclic compounds and other potentially carcinogenic components of cigarette smoke.

8.5. In 1936-1937, researchers at the American Tobacco Company in Richmond, Virginia published two articles on the development of a standardized cigarette smoking machine (Bradford, Harlan and Hanmer 1936; Bradford, Harlow, Harlan and Hanmer 1937).

8.6. Thereafter, the published scientific literature during the period 1938-1952 reveals little if any research explicitly issued or supported by the American Tobacco Company.

8.7. Published research explicitly issued or supported by the American Tobacco Company appeared in the 1950s (e.g., Rayburn, Harlan and Hanmer 1953; Bennett, Tedeschi and Larson 1954; Harlow 1956; Haag and Hanmer 1957; Silvette, Larson and Haag 1957, 1958; Wartman, Cogbill and Harlow 1959). Harlow's (1956) paper appears to be the first to mention cancer or carcinogenesis explicitly.

8.8. In a number of papers published during the 1930s and 1940s, researchers at the Department of Pharmacology, Medical College of Virginia in Richmond, Virginia employed an automatic smoking machine of the type described by Bradford and colleagues (e.g., Forbes and Haag 1938; Haag 1940; Finnegan, Fordham, Larson and Haag 1947). Researchers at the Medical College of Virginia acknowledged communications with persons connected to the American Tobacco Company and to Philip Morris & Co., Ltd. (Haag and Ambrose 1937; Forbes and Haag 1938).

8.9. From at least 1936 through 1953, Philip Morris & Co., Ltd., Inc. ran cigarette advertisements in the journals of various state medical societies (e.g., Philip Morris 1936ab, 1938ab, 1939abc, 1940, 1941, 1942ab, 1944abc, 1946, 1950, 1951, 1953). Such advertisements asserted that Philip Morris cigarettes produced less local irritation to the throat and upper respiratory tract than other brands of cigarettes.

8.10. The main rationale for the claimed reduction in local irritation was Philip Morris's use of diethylene glycol instead of glycerine as a moistening or "hygroscopic" agent (Philip Morris 1936ab; Greenwald 1935, 1936; Cone, Hatcher and Greenwald 1936). Philip Morris's use of diethylene glycol in cigarettes began in 1933 (Bailey and Petre 1937).

8.11. Philip Morris substituted diethylene glycol for glycerine because glycerine was thought to be a precursor of the highly irritating chemical acrolein (Greenwald 1935, 1936; Bogen 1936; Cone, Hatcher and Greenwald 1936).

8.12. From at least 1936 through 1951, the Philip Morris advertisements contained one or more citations from a set of five journal articles published during 1934-1937 (Mulinos and Osborne 1934, 1935; Wallace, Reinhard and Osborne 1936; Flinn 1935, 1937). Such articles involved a proposed animal model of cigarette-induced irritation (Mulinos and Osborne 1934, 1935; Wallace, Reinhard and Osborne 1936), self-reports of hoarseness, cough and dry throat among smokers (Flinn 1935), and clinical case reports by physicians on coughing, sore throats and the like (Flinn, 1937).

8.13. The findings and conclusions of the experimental and clinical articles cited in the Philip Morris advertisements could not be independently confirmed by other investigators (Sharlit 1935; Haag 1937; Holck and Carlson 1937; Ballenger and Johnson 1937; Ballenger 1939; McNally, Bergman and Foster 1945; Holinger, Rigby, Andrews et al. 1946; Finnegan et al. 1947; Andrews, Lenth, Staunton and Holinger 1947; see also Lesser 1937; Fishbein 1937).

8.14. During the 1930s and 1940s, scientists at the U.S. Food and Drug Administration and at other institutions

reported diethylene glycol to be a toxic chemical (Laug, Calvery, Morris and Woodard 1939; Morris, Nelson and Calvery 1942; see also Holck 1937) and a potential cause of bladder cancer (Fitzhugh and Nelson 1946). Diethylene glycol was identified in the smoke of cigarette brands that contained the chemical as a moistening agent (Forbes and Haag 1938).

8.15. Diethylene glycol was the main solvent in Elixir of Sulfanilamide, the proprietary remedy that caused mass poisoning in the fall of 1937 (Schoeffel et al. 1937; Geiling and Cannon 1938; Calvery and Klumpp 1939; see also Editorial 1937).

8.16. In state medical journals during 1951-1953, Philip Morris & Co. ran cigarette advertisements that described a "nose test" to discriminate local chemical irritation (Philip Morris 1951, 1953). Except for a remark in a paper by Sharlit (1935), there appears to have been little published scientific support for the validity of the "nose test" (see also Myerson 1950; Editorial 1952a).

8.17. In a paper supported by P. Lorillard Company, Fishel and Haskins (1949) found acetylene and other unsaturated hydrocarbons in the gaseous phase of cigarette smoke. Carbon monoxide, hydrogen sulfide, and hydrogen cyanide were also measured. The relation of the findings to questions of smoking and health was not addressed. Fishbein (1955), at "the request of the manufacturer of the Micronite filter tip" (p. 479), reported on throat irritation.

8.18. In state medical journals from at least 1941 through 1950, R.J. Reynolds Tobacco Company ran advertisements for Camel cigarettes (R.J. Reynolds 1941ab; 1942ab; 1944; 1950).

8.19. In some Camel cigarette advertisements (e.g., R.J. Reynolds 1944), a paper by Fabricant (1943) concerning local throat irritation was cited.

8.20. Especially during 1941-1942, the advertisements suggested that Camel cigarettes, by reason of their slower burning characteristics, delivered less nicotine. The latter advertisements cited, in particular, a paper by Crampton (1941). The Crampton paper (1941, at 7 and note 37) in turn cited an unpublished report that an unnamed brand of cigarettes contained less nicotine than four others.

8.21. From 1934 through 1953, cigarette manufacturers' advertisements in medical journals implied the existence of large-scale literature surveys (Philip Morris 1938b, 1939b), research grant programs (Philip Morris 1939a), internally conducted research and testing (e.g., R.J. Reynolds 1942b, 1950), or scientifically based quality controls (Liggett & Myers 1934ab). Beyond the above-cited papers, such activities are not readily apparent in the published scientific literature.

8.22. In 1954, the American cigarette manufacturers and other tobacco representatives established the Tobacco Industry Research Committee ("TIRC"). The TIRC sponsored literature reviews and other research into questions of tobacco use and health (U.S. Public Health Service 1964, at 6; Silvette, Larson and Haag 1957, 1958; Larson, Haag and Silvette 1961). Through a Scientific Director and Scientific Advisory Board, TIRC issued a number of reports (Tobacco Information Committee 1958, 1959, 1960).

9. Further Conclusions

9.1. During the early 1930s-- and unquestionably by no later than the late 1930s-- a reasonably prudent manufacturer of cigarettes should have been conducting or sponsoring careful, sustained scientific research into the potentially cancer-causing effects of its products.

9.2. Among the methods of scientific research available by the late 1930s, a reasonably prudent manufacturer of cigarettes could have employed the following: controlled, detailed clinical or epidemiological studies of smoking habits among cancer patients and comparison subjects; detailed chemical analyses of potentially carcinogenic compounds in cigarette smoke and smoke components; and controlled, long-term experimental carcinogenicity studies in various laboratory animals exposed to whole cigarette smoke or smoke components.

9.3. During the 1920s and 1930s, cancer research was supported mainly by private charitable foundations. Not until after World War II was there substantial government funding for cancer research grants (Triolo and Shimkin 1969; Shimkin 1977). The relative lack of research funds through the late 1930s enhanced the obligation of American cigarette manufacturers to conduct or support their own careful scientific inquiries into smoking and cancer.

9.4. During the late 1930s-- and unquestionably by no later than 1942-- the scientific evidence that cigarette smoking caused cancer, though not definitive, was sufficient that a reasonably prudent manufacturer of cigarettes should have been warning customers of the potentially harmful effects of its products.

9.5. During the late 1930s-- and unquestionably by no later than 1942-- the scientific evidence on other potentially harmful effects of cigarette smoking, though not definitive, reinforced the obligation of a reasonably prudent manufacturer to warn.

9.6. The published scientific literature offers little if any evidence that American cigarette manufacturers conducted or sponsored research into the potential cancer-causing effects of their products prior to 1953.

9.7. The highly restricted scope of manufacturer-sponsored research on smoking and health during the 1930s and 1940s-- especially the concentration on questions of local throat irritation-- is consistent with a concerted strategy neither to test, to corroborate nor otherwise to broach the possibility that cigarette smoking caused cancer.



TABLE 1.  
SCIENTIFIC ARTICLES ON TOBACCO AND ORAL CANCER  
1915-1945.

Authors	Year	Case Material and Clinical Observations
Abbe	1915	"It has been doubly impressed on me, of late years, that most cancers, not only of the tongue, but anywhere in the mouth, are seen in men who smoke heavily." (p. 1) Among 80 males with cancer of the tongue, inner cheek, gums and throat, 89 were heavy smokers, mostly of cigars. In tongue cancer cases, "Many used a pipe, which often caused cancer to begin where the pipe end allowed the hot smoke to come upon the tongue." (p. 1) Among women with oral cancer, cigarette smoking was found. One woman who had repeatedly rubbed snuff on her tongue developed cancer on the site of application.
Broders	1920	537 cases of cancer of the lip (average age 57.3 years), compared to 500 men without cancer (average age 36.07 years). Among cancer cases, 78.48% smoked pipe; 1.16% smoked cigarettes. Among comparison group, 38.03% smoked pipe; 59.04% smoked cigarettes.
Judd & New	1923	"In about nine of ten instances cancer of the tongue occurs in men. Personal habits, particularly the use of tobacco, undoubtedly are factors. The irritation from a pipe, and the heat and irritation from cigar or cigarette should affect the lip more often than the tongue; however, the excessive use of tobacco in any form, particularly the irritation from snuff, might affect the tissues of the mouth." (p. 164)

TABLE 1 (Continued).  
 SCIENTIFIC ARTICLES ON TOBACCO AND ORAL CANCER  
 1915-1945.

Authors	Year	Case Material and Clinical Observations
Fordyce & MacKee	1926	Extensive review of diseases of the mouth, based upon accumulated literature and authors' clinical experience. "The influence of smoking cigars in the development of cancer of the mouth is emphasized in the much larger percentage of cases in men." (p. 640) Certain oral lesions called "keratosis" and "leukoplakia," which were often seen in cigar and pipe smokers, could turn into cancers. With respect to such a precancerous lesion in one patient, "The keratosis in this man resulted in a rapidly progressive carcinoma of the mucous membrane of the cheek at the site of a leukoplakia which had become verrucous. It is not unusual to see minor grades of this condition in smokers extending backward from the commissures in the form of patches or radiating lines. It often remains stationary if moderate smoking is continued. It is, however, the duty of the medical adviser under these conditions to discourage this habit and to protect the vulnerable mucosa from irritation and possible danger of malignant change." (p. 635)
Lombard & Doering	1928	Survey of 217 cancer cases and 217 non-cancer controls. Among cancer cases, 47.3% were heavy smokers; among controls, 20% were heavy smokers. The use of tobacco has long been considered a factor in the incidence of cancer of the buccal cavity." (p. 485) "The difference between our control group and the cancer group in respect to heavy smoking is twenty-seven percent. This is highly significant which suggests that heavy smoking has some relation to cancer in general." (p. 486) "In our sample heavy smoking was largely pipe smoking and was particularly more common in those individuals with cancer of the buccal cavity." (p. 487)

TABLE 1 (Continued).  
 SCIENTIFIC ARTICLES ON TOBACCO AND ORAL CANCER  
 1915-1945.

Authors	Year	Case Material and Clinical Observations
Mowat	1929	<p>Analysis of 244 cases of cancer of the lips, tongue, gums, tonsils, floor of the mouth, and other oral sites. Among these, 238 were pipe smokers and one was a cigarette smoker. For lip cancer, "Seventy-three out of the 74 cases were heavy smokers, averaging 3 to 6 ounces of tobacco weekly; one only was a cigarette smoker." (p. 145) In 70 such cases, the tumors began at "the point where the pipe was habitually held." (p. 145) All 93 cases of tongue cancer were pipe smokers; such cancers were preceded by "smoker's tongue." (p. 149) All 30 cases of gum cancer, all 9 cases of cancer of the floor of the mouth, and 32 of 33 cases of cancer of the pillars and tonsils, were pipe smokers. Findings could not be attributed to other potential causative factors, such as dentures, prior oral injury, or syphilis. "The evidence in favour of pipe smoking being the principal predisposing factor in the production of epithelioma of the tongue is very strong. The rarity of the disease among the female sex, the factor of prolonged smoking being present in every case, the recognition of a pre-malignant condition of a chronic thickening of the mucous membrane with hyperkeratosis, furring, furrows, and, in extreme cases, fissures, typical of the chronic smoker's tongue, lead one strongly to the belief that pipe smoking is at the present time the principal factor in malignancy." (p. 152) "The persistence of a 'smoker's throat' over a long period before malignancy began, the history of intermittent sensation of irritation in the throat, the morning 'hawk' and cough, and the way in which the individual patient himself realizes that he has been persistently irritating his throat for the past few decades, all tend to the reluctant conclusion that in modern times excessive pipe smoking is the principal factor in epithelioma of the fauces." (p. 155)</p>

TABLE 1 (Continued).  
 SCIENTIFIC ARTICLES ON TOBACCO AND ORAL CANCER  
 1915-1945.

Authors	Year	Case Material and Clinical Observations
Lickint	1930	Review and analysis of literature on tobacco as a causative factor in cancer. In humans, tobacco can produce cancerous growths on the lips, tongue, oral mucous membrane, gums, and other parts of the digestive tract (p. 363)
Hoffman	1931	Analysis of 1413 living male cancer patients for whom smoking habits were ascertainable (San Francisco Cancer Survey). For cancer of the buccal cavity, 83.8% were smokers, compared to 79.2% of those with cancer of the stomach and 86.3% of those with cancer of the intestines. Patients with cancer of the buccal cavity had a higher proportion of heavy pipe and cigar smokers. "Smoking habits may possibly constitute but one of a number of factors which must enter into the development of malignant tumors, the absence of any one of which might preclude such a development. Unfortunately the subject has not been studied as thoroughly as its importance would justify. But the observed excess in cancer of the buccal cavity in men, as well as in cancer of the oesophagus and the lungs, is highly suggestive of the influence of smoking habits, however difficult it may be to establish this conclusion statistically." (p. 53)
Fraser	1932	"In our series (105 cases) we have to record that in eighty-eight male cases sixty-five were heavy pipe smokers, and of the remaining thirteen there was no individual who was a rigid non-smoker." (p. 496)
Bigelow & Lombard	1933	Among several hundred clinic and hospital patients with oral cancer, 14.2% were non-users of tobacco and 36.4% were excessive tobacco users. Among a comparable number of comparison patients without cancer, 26.5% were non-users and 24.0% were excessive users (Table 111). "This means that buccal cavity cancer is more prevalent among excessive users of tobacco." (p. 118)

TABLE 1 (Continued).  
 SCIENTIFIC ARTICLES ON TOBACCO AND ORAL CANCER  
 1915-1945.

Authors	Year	Case Material and Clinical Observations
Martin & Pfleuger	1935	Ninety-nine cases of cancer of the cheek encountered during 1925-29. Tobacco "acts both by the production of heat and by chemical irritation." (p. 732)
Padgett	1936	"Tobacco also has some definite influence in the development of lip and oral cancer. It stimulates the epithelium, produces a chronic hyperemia, local erosions, edema, and lymphocytic infiltrates. In smoking, heat effects may be added. This is especially true in pipe smokers. Tobacco chewers are somewhat more prone to develop cancer where the quid is held against the cheek." (p. 286)
Wile & Hand	1936	Review of 425 cases of cancer of the lip. "In a number of cases the cancer definitely appeared on the site of the smoker's patch or leukoplakia where the pipe had rested for years." (p. 375) "Smoking is apparently of some importance in the background of cancer of the lip." (p. 380)

TABLE 1 (Continued).  
 SCIENTIFIC ARTICLES ON TOBACCO AND ORAL CANCER  
 1915-1945.

Authors	Year	Case Material and Clinical Observations
Ahlbom	1937	Analysis of cancer patients observed during 1931-36 by site of cancer. Among males, 86% of 312 cases of cancer of the lip and 98% of 233 cases of cancer of the oral cavity, pharynx, larynx and esophagus were tobacco users (Table 1, p. 168). Among lip cancer cases (p. 168) and oral cancer cases (p. 171) patients had generally used tobacco for 30-40 years. In at least 70% of cases, the oral cancers developed at the site where the tobacco had been situated (p. 171). Among male cancer patients who consumed tobacco, the proportion of cigar and cigarette smokers was 6% for lip cancer, 7% for outer mouth cancer, 39% for inner mouth cancer, and 64% for pharyngeal, laryngeal and esophageal cancer (Table 5, p. 177). As a rule, men with cancer of the pharynx, larynx and esophagus were fairly intensive smokers, many reporting smoking 20 cigarettes or more daily (p. 176). Among females, 12 of 23 cases of lip cancer were avid pipe smokers (p. 169); smaller percentages of other cancer cases were tobacco users (Figure 3, p. 181).
Jacobs	1941	Review of malignancies of the oral cavity. "That tobacco smoking in any form, or tobacco chewing, is influential in forming leucoplakia as well as definite malignancy can no longer be questioned. It is evidenced by the number of women presenting leucoplakic lesions since smoking by women has increased markedly" (p. 253).
Lamb & Eastland	1941	"The use of tobacco predisposes to leukoplakia, which leads to leukokeratosis and finally to carcinoma." (p. 602)

TABLE 1 (Continued).  
SCIENTIFIC ARTICLES ON TOBACCO AND ORAL CANCER  
1915-1945.

Authors	Year	Case Material and Clinical Observations
Ebenius	1943	Among 439 male cases of lip cancer, 79.7% were tobacco users, mostly of pipes. Among male non-cancer patients, 68.7% were tobacco users, with a much smaller percentage of pipe smokers. Among 33 female cases of lip cancer, 57.6% used tobacco, exclusively by pipe smoking. Author estimated only 1 to 2% of females non-cancer patients smoked pipes. (Table 6) "This thus provides further support for the assumption that pipe smoking in one way or another predisposes to lip cancer." (p. 94) Connection between pipe smoking and lip cancer was observed even when occupation was considered (Tables 10 and 11).
Grace	1944	"During my unusual opportunities over a period of years I have noted that cancer of the lip and tongue was almost invariably associated with a smoking habit dating back many years." (p. 322) "The seriousness of cell damage in the oral cavity which may follow simple leukoplakia may ultimately result in a high grade undifferentiated cancer from constant irritation from tobacco tar and its carcinogenic compound, benzpyrene." (p. 322)
Potter & Tully	1945	Use of tobacco among 2,927 male clinic patients aged over 40 years. Incidence rate of buccal (cheek) cancer per 100 was 3.7 in 655 nonsmokers, 8.1 in 357 light users of tobacco, 11.5 in 1155 moderate users of tobacco, and 17.9 in excessive users of tobacco. "There was a definite association between cancer of the buccal cavity and the use of tobacco." (p. 488)

TABLE 2.  
 SCIENTIFIC ARTICLES ON CIGARETTE SMOKING AND LUNG CANCER  
 1927-1948.

Authors	Year	Case Material and Clinical Observations
Perret	1927	Review of 6 cases of cancer within chest cavity. All 4 of the lung cancer cases for which smoking histories were available reported "excess" use of tobacco ("Table of Personal History Data," p. 217). "Although fully realizing that our series of cases is too small to draw any general conclusions, we have been struck by the excessive smoking of many of the patients, and that all the cases occurred in males." (p. 225)
Tylecote	1927	"I have no statistics with regard to tobacco, but I think that in almost every case I have seen and known of the patient has been a regular smoker, generally of cigarettes."
Lickint	1930	Review of laboratory and clinical evidence on tobacco and cancer. Rise in cigarette use linked to rise in lung cancer.
Mertens	1930	Increased incidence of lung cancer linked to tobacco. Shift in cancer from oral sites to lower respiratory tract linked to shift from pipes and cigars to inhaled cigarettes.



TABLE 2 (Continued).  
 SCIENTIFIC ARTICLES ON CIGARETTE SMOKING AND LUNG CANCER  
 1927-1948.

Authors	Year	Case Material and Clinical Observations
Hoffman	1931	<p>Analysis of San Francisco Cancer Survey. Review of nation-wide vital statistics. "I am strongly inclined to think that the increase [in lung cancer] is directly connected with the much wider spread of cigarette smoking habits, including the inhaling of smoke which must enter the lungs to a considerable extent in many cases." (p. 56) "The observed increase in cancer of the lungs during recent years is highly suggestive of its correlation to the immense spread of cigarette-smoking habits." (p. 62) "Yet smoking habits have proportionately increased faster among women during recent years than among men. But the fact must not be lost sight of that the injurious effects of tobacco smoking in their relation to cancer probably require quite a long period of time to become noticeable." (p. 62) "The increase of cancer of the lung observed in this and many other countries is in all probability to a certain extent directly traceable to the common practice of cigarette smoking and inhalation of cigarette smoke. The latter practice unquestionably increases the danger of cancer development." (p. 67)</p>
McNally	1932	<p>Review of chemical constituents of cigarette smoke and their biological effects. "Comparing the enormous consumption of cigarettes in 1925-1931 with the increase in pulmonary cancer, one is certainly led to believe that cigarette smoking is an important factor in the increase of cancer of the lungs." (pp. 1511-1512) "The tar of cigarette smoke contains nicotine, phenolic bodies, pyridine bases, and ammonia, irritants which could account for 'cigarette cough,' the chronic bronchitis of the cigarette smoker, the leukoplakia in heavy smokers, and the recorded increase of cancer of the lung." (p. 1513)</p>

TABLE 2 (Continued).  
 SCIENTIFIC ARTICLES ON CIGARETTE SMOKING AND LUNG CANCER  
 1927-1948.

Authors	Year	Case Material and Clinical Observations
Thys	1935	Review of etiology of lung cancer. Observed shift in cancer incidence from oral cavity to lung explained by the change from noninhaled pipes and cigars to inhaled cigarettes. "En conclusion, il nous semble legitime de faire un rapprochement entre le cancer bronchique, cancer des fumeurs d'apres-guerre, et al vogue de la cigarette. Cette notion complete simplement celle des classiques qui imputent a la pipe le cancer labial et lingual, vieille forme du cancer des fumeurs." (p. 643)
Arkin & Wagner	1936	135 cases of lung cancer diagnosed over 4-year period. "Ninety percent of all our patients were chronic smokers, and we believe that the inhalation of tobacco smoke may be an important factor in producing chronic irritation with epithelial metaplasia in the bronchi or bronchioles." (p. 586)
Fleckseder	1936	Among 54 male cases of bronchial carcinoma, 94.4% smoked and 68.5% were heavy cigarette (as opposed to pipe and cigar) smokers. "So erklart sich wohl der Umstand, dass unter unseren Bronchialkrebskranken die starken Zigaretten raucher in der Ueberzahl waren, sie bringen eben durch das sogenannte Inhalieren den Tabakrauch in ausreichender Konzentration in die grosse Luftwege, wahrend Zigarren- und Pfeifenraucher den Tabakrauch zumeist nicht so tief einziehen." (p. 1588)
Ahlbom	1937	Analysis of cancer patients observed during 1931-36 by site of cancer. Site of cancer linked to form of tobacco use (pipes and cigars versus cigarettes). See Table 1.
Ochsner & DeBakey	1939	Clinical review of primary lung cancer. "In our opinion the increase in smoking with the universal custom of inhaling is probably a responsible factor, as the inhaled smoke, constantly repeated over a long period of time, undoubtedly is a source of chronic irritation to the bronchial mucosa." (p. 435)

TABLE 2 (Continued).  
 SCIENTIFIC ARTICLES ON CIGARETTE SMOKING AND LUNG CANCER  
 1927-1948.

Authors	Year	Case Material and Clinical Observations
Muller	1939	Comparison of 86 male lung cancer decedents with 86 healthy men of the same age. 65.1% heavy smokers and 3.5% nonsmokers among the lung cancer cases. 36.0% heavy smokers and 16.3% nonsmokers among the control cases.
Ochsner & DeBakey	1941	Clinical review of lung cancer. "It is our definite conviction that the increase in the incidence of pulmonary carcinoma is due largely to the increase in smoking, particularly cigaret smoking, which is universally associated with inhalation. Every one of our patients, with the exception of 2 women, was an excessive smoker." (p. 221)
Grace	1943	"After having had an opportunity to observe, over a period of ten years, an unusually large series of patients with cancer of the lung, in two of the large municipal hospitals in New York City, two very distinct elements were noted in these patients: First, they were always men; second, they were heavy cigarette smokers and almost always inhalers." (p. 361) "It is obvious, therefore, that this product of combustion deeply inhaled into the lungs of cigarette smokers-- for cigarette smokers usually inhale-- is deposited in the lung along the entire bronchial system, and most of the biologic principles are present, I believe, to produce bronchogenic carcinoma in accordance with well known animal experiments." (p. 361)
Wallace & Jackson	1943	"We believe that tobacco smoking plays a definite role in the causation of primary lung carcinoma." (p. 607) "In connection with tobacco smoke we should like to point out the increase in incidence of bronchogenic carcinoma in women in the past several decades and the relationship of this to the increased incidence of smoking in women during this period." (p. 607)

TABLE 2 (Continued).  
 SCIENTIFIC ARTICLES ON CIGARETTE SMOKING AND LUNG CANCER  
 1927-1948.

Authors	Year	Case Material and Clinical Observations
Schairer & Schoeniger	1943	Comparison of 93 male lung cancer decedents autopsied (average 53.9 years) with 270 men aged 53 and 54. 31.2% heavy smokers and 3.2% nonsmokers among lung cancer cases. 9.3% heavy smokers and 15.9% nonsmokers among controls.
Grace	1944	"Using the numerous investigations [by Roffo and others] reported in the preceding pages as a springboard from which to make further conjectures on the relationship between tobacco poisoning and certain clinical entities which are generally associated with a heavy smoking habit, we may differentiate two such groups: 1. cancer of the lip and oral cavity, and 2. cancer of the lung. The former is most frequently encountered in pipe and cigar smokers who rarely inhale, but in whom the irritating substance of tobacco is deposited on the lips and tongue. In cancer of the lung, often occurring in cigarette smokers, this toxic irritant is deposited in the bronchi during the process of inhaling smoke. There appears to be no doubt whatsoever that, in the heavy smoker, tar, with its chemical by-products, enters the etiological picture in the development of neoplasms." (p. 328)
Potter & Tully	1945	43 male lung cancer clinic patients, aged over 40 years, compared to 1,847 male clinic patients with diagnoses other than cancer. 30.2% heavy smokers and 7.0% nonsmokers among lung cancer cases. 23.0% heavy smokers and 26.0% nonsmokers among controls.

TABLE 2 (Continued).  
 SCIENTIFIC ARTICLES ON CIGARETTE SMOKING AND LUNG CANCER  
 1927-1948.

Authors	Year	Case Material and Clinical Observations
Ochsner	1945	"On the other hand, there is a distinct parallelism between the incidence of cancer of the lung and the sale of cigarettes, and it is our belief that the increased incidence of lung cancer is due to the chronic irritation that it produces. It is well known that the smoker has a chronic cough, the so-called smoker's cough, which because of its irritation might alone be responsible for the development of lung cancer. However, in addition to this it has been shown by Professor Roffo, Director of the Institute for Malignant Diseases in Buenos Aires, tobacco contains a tar which has a carcinogenic effect and that the application of this tar to the skin and the mucous membrane of the respiratory tract in animals will produce cancer." (p. 105)
Kennaway & Kennaway	1947	"No evidence has been found that tarring of roads has affected the incidence of cancer of the lung." (p. 297) "Soot is probably a decreasing contaminant of the air owing to the substitution of other sources of heat for the domestic fire, which is the chief source of soot-containing smoke. Hence coal smoke does not account well for any recent increase in cancer of the lung. Among various possible factors which have been suggested to account for the increase is tobacco smoke; the consumption of tobacco has risen, and so has the percentage of it smoked in the form of cigarettes, of which the smoke is often inhaled; such an effect of tobacco would accord well with the absence of a social gradient." (p. 297)
Wassink	1948	134 male clinic patients with lung cancer compared to 100 normal men of same age groups as cases. 54.8% heavy smokers and 4.8% nonsmokers in lung cancer group. 19.2% heavy smokers and 19.2% nonsmokers in the control group.

TABLE 3.  
 EPIDEMIOLOGIC STUDIES ON  
 CIGARETTE SMOKING AND LUNG CANCER,  
 1950-1963.

Authors	R/P*	Year	Country
Schrek et al.	R	1950	U.S.
Mills, Porter	R	1950	U.S.
Levin, Goldstein, Gerhardt	R	1950	U.S.
Doll, Hill	R*	1950	Great Britain
Wynder, Graham	R	1950	U.S.
McConnell, Gordon, Jones	R	1952	England
Doll, Hill	R	1952	Great Britain
Sadowsky, Gilliam, Cornfield	R	1953	U.S.
Wynder, Cornfield	R	1953	U.S.
Koulumies	R	1953	Finland
Lickint	R	1953	Germany
Breslow, Hoaglin et al.	R	1954	U.S.
Watson, Conte	R	1954	U.S.
Gsell	R	1954	Finland
Randig	R	1954	Germany
Doll, Hill	P**	1954	Great Britain
Hammond, Horn	P**	1954	U.S.
Stocks, Campbell	R**	1955	England
Wynder, Bross et al.	R	1956	U.S.
Doll, Hill	P	1956	Great Britain
Segi, Fukushima et al.	R	1957	Japan
Mills, Porter	R	1957	U.S.
Stocks	R	1957	England
Schwartz, Denoix	R	1957	France
Haenszel, Shimkin, Mantel	R	1958	U.S.
Hammond, Horn	P	1958	U.S.
Lombard, Snegireff	R	1959	U.S.
Dorn	P	1959	U.S.
Pernu	R	1960	Finland
Dunn, Linden, Breslow	P	1960	U.S.
Best, Josie, Walker	P	1961	U.S.
Hammond, Garfinkel	P**	1961	U.S.
Haenszel, Loveland, Sirkin	R	1962	U.S.
Lancaster	R	1962	Australia
Haenszel, Taeuber	R	1963	U.S.

\*R = retrospective study; P = prospective study.  
 \*\*preliminary report.

TABLE 4.  
 EXPERIMENTAL AND CHEMICAL STUDIES ON  
 CIGARETTE SMOKING AND LUNG CANCER, 1952-1958.

Year and Authors	Findings
<u>1952</u>	
Essenberg	Induction of adenomas and papillary adenocarcinomas of the lung in mice exposed to whole cigarette smoke.
<u>1953</u>	
Wynder, Graham & Croninger	Induction of skin cancers in mice with whole cigarette smoke condensate.
<u>1955</u>	
Cooper & Lindsey	Benzo(a)pyrene and other polycyclic hydrocarbons in cigarette smoke.
Muhlbock	Induction of alveolar carcinomas in mice exposed to whole cigarette smoke.
<u>1956</u>	
Commins & Lindsey	Phenols, cresols, naphthols in cigarette smoke.
Cardon et al.	Benzo(a)pyrene in cigarette paper, tobacco and cigarettes.
Hilding	Cigarette tars deposited at areas of injured respiratory epithelium. Cigarette smoke inhibits cilia in respiratory tract.
Mellors, Hlinka & Stoholski	Cells of buccal mucosa absorbed cigarette tars.

TABLE 4 (Continued).  
 EXPERIMENTAL AND CHEMICAL STUDIES ON  
 CIGARETTE SMOKING AND LUNG CANCER, 1952-1958.

Year and Authors	Findings
<u>1957</u>	
Blacklock	Induction of oat cell carcinoma of lung in rat injected with cigarette smoke condensate.
Graham, Croninger & Wynder	Induction of cancer in rabbit ear with cigarette tar.
Guerin & Cuzin	Confirmation of carcinogenicity of various cigarette smoke condensates for mouse skin.
Lyons & Johnston	Dibenzpyrene reported in cigarette smoke.
Wynder & Wright	Carcinogenic activity of cigarette smoke condensate not due solely to benzo(a)pyrene content.
<u>1958</u>	
Kennaway & Lindsey	Ten carcinogenic compounds identified in cigarette smoke.
Van Duuren	Additional carcinogenic polyaromatic hydrocarbons identified in cigarette smoke.
Rockey et al.	Produced squamous metaplasia upon application of tobacco tar directly to bronchial mucosa of dogs.
Leuchtenberger et al.	Produced atypical hyperplasia and squamous metaplasia in mice exposed to cigarette smoke.
Gellhorn	Tobacco tar increased rate of conversion of benzpyrene-induced papillomas to carcinomas; consistent with co-carcinogenic effect of tar.



TABLE 5.  
 CIGARETTE SMOKING AS A CAUSE OF LUNG CANCER:  
 STATEMENTS BY PROFESSIONAL SOCIETIES,  
 SCIENTIFIC ADVISORY COMMITTEES AND LEARNED JOURNALS  
 1952-1964.

Source	Year	
British Medical Journal	1952	"Where do we go from here? Statistics, it is said, cannot prove causation, but neither could Koch's postulates, although the lives of millions are affected and controlled on the assumption that they have established beyond question the causative agents of certain infective diseases. All that these things can do is to show that the probability of a causative connexion between an agent and a disease is so great that we are bound to take what preventive action we can, accepting the theory as though the proof were absolute until further research leads to some modification. It would seem that such a position has now been reached with lung carcinoma, in that tobacco has been incriminated as the vehicle conveying an agent responsible for a large proportion of the cases." (p. 1300)
New England Journal of Medicine	1953	"The latest study of Doll and Hill, based on 1465 patients with cancer of the lung and 1465 matched controls, was carefully conducted and yielded evidence of an association between cigarette smoking and lung cancer so strong as to be considered proof within the everyday meaning of the word." (p. 465) "If similar data had incriminated a food contaminant that was not habit forming and was not supported by the advertising of a financial empire, there is little doubt that effective countermeasures would have followed quickly." (p. 466)
British Standing Advisory Committee on Cancer and Radiotherapy	1954	"...it must be regarded as established that there is a relationship between smoking and cancer of the lung." (p. 254)

TABLE 5 (Continued).  
 CIGARETTE SMOKING AS A CAUSE OF LUNG CANCER:  
 STATEMENTS BY PROFESSIONAL SOCIETIES,  
 SCIENTIFIC ADVISORY COMMITTEES AND LEARNED JOURNALS  
 1952-1964.

Source	Year	
British Medical Research Council	1957	"1. A very great increase has occurred during the past 25 years in the death rate from lung cancer in Great Britain and other countries. 2. A relatively small number of the total cases can be attributed to specific industrial hazards. 3. A proportion of cases, the exact extent of which cannot yet be defined, may be due to atmospheric pollution. 4. Evidence from many investigations in different countries indicates that a major part of the increase is associated with tobacco smoking, particularly in the form of cigarettes. In the opinion of the Council, the most reasonable interpretation of this evidence is that the relationship is one of direct cause and effect." (p. 1524).
Study Group on Smoking & Health (American Cancer Society, American Heart Association, National Cancer Institute, National Heart Institute)	1957	"At least 16 independent studies carried on in five countries during the past 18 years have shown that there is a statistical association between smoking and the occurrence of lung cancer..." "The epidemiologic evidence is supported by laboratory studies on animals." "Studies on the pathogenesis of human lung cancer are also compatible with the causal relationship." "Thus, every morphologic stage of carcinogenesis, as it is understood at present, has been observed and related to the smoking habit." "The sum total of scientific evidence establishes beyond reasonable doubt that cigarette smoking is a causative factor in the rapidly increasing incidence of human epidermoid carcinoma of the lung." (p. 1129)
Burney (U.S. Surgeon General)	1957	"In light of these studies, it is clear that there is an increasing and consistent body of evidence that excessive cigarette smoking is one of the causative factors in lung cancer." (p. 44)

TABLE 5 (Continued).  
 CIGARETTE SMOKING AS A CAUSE OF LUNG CANCER:  
 STATEMENTS BY PROFESSIONAL SOCIETIES,  
 SCIENTIFIC ADVISORY COMMITTEES AND LEARNED JOURNALS  
 1952-1964.

Source	Year	
Burney (U.S. Surgeon General)	1959	"1. The weight of evidence at present implicates smoking as the principal etiologic factor in the increased incidence of lung cancer. 2. Cigarette smoking is particularly associated with an increased chance of developing lung cancer." (pp. 141-142.)
Royal College of Physicians of London	1962	"Cigarette smoking is a cause of lung cancer and bronchitis, and probably contributes to the development of coronary heart disease and various other less common diseases. It delays healing of gastric and duodenal ulcers."
Advisory Committee to the U.S. Surgeon General	1964	"Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, though less extensive, point in the same direction." (p. 37)

TABLE 6.  
 PUBLISHED SCIENTIFIC ARTICLES ON SMOKING AND HEALTH  
 ACKNOWLEDGING COMMUNICATION, AFFILIATION, OR  
 RESEARCH SUPPORT FROM CIGARETTE MANUFACTURERS,  
 1934-1949.

Authors	Year	Nature of Communication, Affiliation or Support
Mulinos & Osborne	1934	Grant by Phillip Morris & Co., Ltd.
Flinn	1935	Grant by Phillip Morris & Co., Ltd.
Greenwald	1935	Director, research department, Phillip Morris & Co., Ltd.
Greenwald	1936	Research Director, Phillip Morris & Co., Ltd.
Cone, Hatcher & Greenwald	1936	Phillip Morris & Co., Ltd.
Bradford, Harlan & Hanmer	1936	American Tobacco Company
Bradford, Harlow, Harlan & Hanmer	1937	American Tobacco Company
Wallace, Reinhard & Osborne	1936	Experimental cigarettes supplied by Phillip Morris & Co., Ltd.
Haag & Ambrose	1937	Hanmer: personal communication
Bailey & Petre	1937	Industrial Fellows of the Phillip Morris & Company, Ltd., Inc. Industrial Fellowship at Mellon Institute for Industrial Research
Mulinos & Cockrill	1938	Grant by Phillip Morris & Company
Forbes & Haag	1938	Bailey, C.F.: unpublished data.

TABLE 6 (Continued).  
 PUBLISHED SCIENTIFIC ARTICLES ON SMOKING AND HEALTH  
 ACKNOWLEDGING COMMUNICATION, AFFILIATION, OR  
 RESEARCH SUPPORT FROM CIGARETTE MANUFACTURERS,  
 1934-1949.

Authors	Year	Nature of Communication, Affiliation or Support
Proetz	1939a	Grant to Department of Otolaryngology, Washington University School of Medicine, by Philip Morris Company
Mulinos & Shulman	1940	Expenses defrayed by Philip Morris Fund
Fabricant	1943	Grant from Medical Relations Division, Camel Cigarettes
Larson, Haag & Finnegan	1946	Experimental nicotine by-product prepared by C.H. Rayburn and H.N. Wingfield, Research Laboratory, American Tobacco Company
Fishel & Haskins	1949	Cooperative research contribution of P. Lorillard Company and Ohio State University Research Foundation

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