The Changing Cigarette and Disease Risk: Current Status of the Evidence

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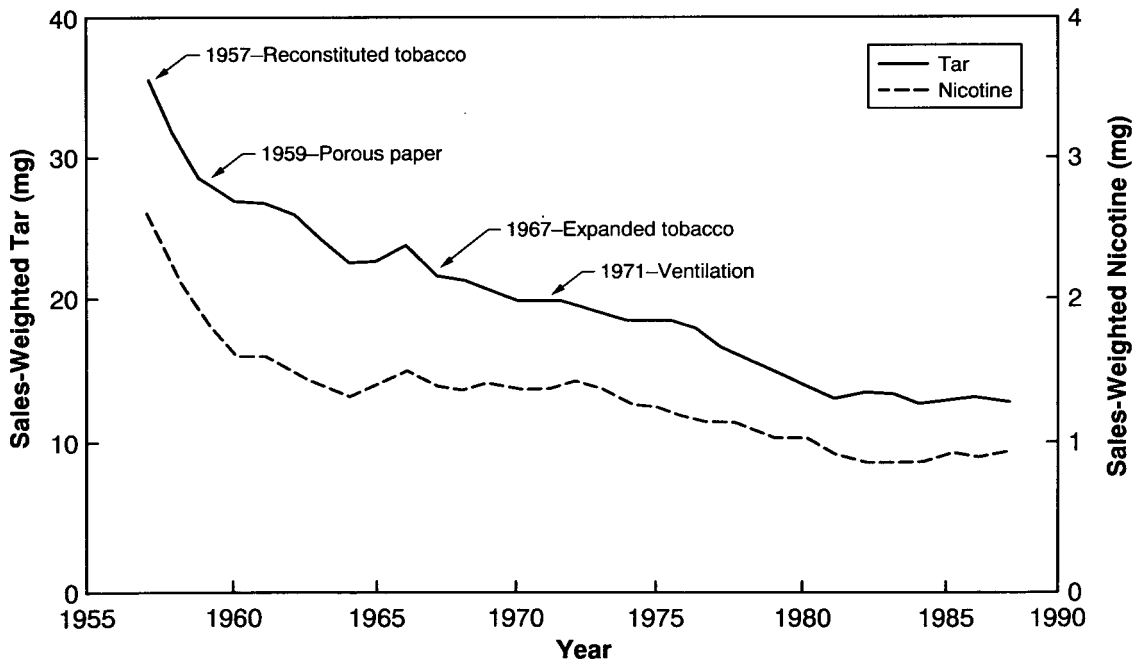
INTRODUCTION Since the early 1950's when filter tip cigarettes were first widely introduced, the cigarette has evolved continually through modifications intended to reduce yields of tar and nicotine (U.S. Department of Health and Human Services, 1991). Following the introduction of the filter tip cigarette, sales-weighted averages of tar and nicotine deliveries show a temporal trend of declining yield, which continues to the present (Figure 1). In the face of continued modifications of the cigarette and the seemingly associated changes in exposure of smokers to cigarette smoke components, questions have been raised concerning the implications of the changing cigarette for disease risks in smokers.

Only epidemiologic studies can provide information on modification of the risks of smoking as the cigarette has evolved, and only epidemiologic data

Figure 1
Tar and nicotine content of U.S. cigarettes, sales-weighted average basis, 1957-1987



Source: U.S. Department of Health and Human Services, 1989.

can measure the risks of cigarettes under the "natural" circumstances of use. However, the dynamic nature of the exposure (Figure 1) challenges the epidemiologic researcher to classify accurately the pattern of cigarette use when changes are made that may not be indexed by tar and nicotine yields measured with a smoking machine.

In considering the health implications of the changing cigarette, the concepts of exposure and dose are fundamental. Exposure has been defined by the National Research Council (1991) as the amount of material potentially available for interaction with a human, that is, material in contact with a person at a boundary, whether that boundary be the skin, lung, or the alimentary tract. On the other hand, dose is the amount of material that enters the organism. Dose may be further classified as the internal dose (i.e., the amount of material deposited) or as the biologically effective dose (i.e., the amount of material delivered to some biologically relevant site). Changes in the cigarette can be interpreted as potentially leading to changes in exposure; the health consequences of changing exposure vary with any resultant changes in dose of components of cigarette smoke that cause disease.

The physiological functioning of the lung is also relevant to understanding the linkages in changes in the cigarette to changes in exposure and dose. The lung is a complex organ with several different "compartments," including the upper airway that extends from the nose and mouth to the larynx; the airways of the lung itself, which include the trachea, bronchi, and bronchioles; and the parenchyma of the lung, which includes the interstitium and the airspaces, or alveoli. The lung behaves as a filter that absorbs and deposits gaseous and particulate components of smoke throughout its surfaces during the act of smoking. The sites and extent of deposition of inhaled mainstream components vary, depending on solubility and other characteristics of gas phase components and the sizes of the particles. Cigarette smoke is a dynamic mixture in the respiratory tract, changing with humidification of the mixture, growth of particles, and changing composition as components are selectively removed by the filtration process (U.S. Department of Health and Human Services, 1984). These physiological considerations imply that there is no simple relationship, linear or nonlinear, between reported tar and nicotine yields—a measure of exposure—and biologically effective doses of toxic smoke components delivered to the sites of injury in the respiratory tract.

The measures of cigarette smoking used in epidemiologic research on smoking and health can be classified as estimating either exposure or dose. The most widely used measures, for example, information on cigarette smoking (duration of smoking, number of cigarettes smoked per day, and type or brand of cigarettes smoked), are exposure measures. Biomarkers that can be interpreted as indicators of dose include levels of carboxyhemoglobin, nicotine, and cotinine (U.S. Department of Health and Human Services, 1990). Thus, for epidemiological purposes, researchers use exposure measures, typically obtained by questionnaire, and dose measures, based on biomarkers. For example, cigarettes smoked per day is an exposure measure, whereas

pack-years (packs smoked per day multiplied by the number of years smoked) is a cumulative exposure measure. An estimate of kilograms of tar deposited in the lung is an absorbed dose measure; nanograms of benzo(*a*)pyrene, for example, reaching basal cells might be considered a biologically effective dose for carcinogenesis. New markers take dose measures to the molecular level (Vineis and Caporaso, 1995).

To assess the consequences of changes in the cigarette, it is necessary to have information on how changes in tar and nicotine yield, as assessed by the Federal Trade Commission (FTC) method, affect dose measures, extending to the molecular level. Any new approach to testing cigarette yields should be designed to be informative both as an exposure measure and as an indicator of biologically relevant doses of cigarette smoke components.

EPIDEMIOLOGIC EVIDENCE ON THE CHANGING CIGARETTE AND DISEASE RISKS

Overview

Epidemiologic evidence is available on the effect of the changing cigarette on all-cause mortality and on three major categories of disease caused by cigarette smoking: lung and other cancers, nonmalignant respiratory diseases, and cardiovascular disease (CVD). *The Health Consequences of Smoking: The Changing Cigarette. A Report of the Surgeon General* (U.S. Department of Health and Human Services, 1981) addressed the changing cigarette, covering the relevant toxicologic and epidemiologic evidence. This chapter considers key epidemiologic publications since that report but does not provide a systematic overview of the many studies on the changing cigarette.

The principal study designs that have been used to address the health consequences of the changing cigarette are the ecological study, a descriptive approach conducted at the group level, and cohort and case-control studies, analytic approaches conducted at the individual level. Cross-sectional studies have proven informative in investigating nonmalignant respiratory diseases. The ecological approach is exemplified by a comparison of temporal changes in rates of smoking-related diseases with patterns of consumption of various types of cigarettes. The American Cancer Society (ACS) studies of large groups of volunteer participants are cohort studies; the participants were enrolled, information about smoking was obtained on enrollment and periodically thereafter, the population was followed over time, and mortality was ascertained. Some of the earliest evidence on smoking and lung cancer was obtained in the classic case-control studies conducted by Doll and Hill (1950) and Wynder and Graham (1950). In these studies, the smoking habits of patients hospitalized with lung cancer were compared with the smoking habits of control patients having another disease.

Evidence from epidemiologic studies has well-known strengths and limitations (Rothman, 1986). Epidemiologic research has had a central role in characterizing the consequences of the changing cigarette because it supplies direct information on the consequences of varying tar and nicotine yield products. Thus, the findings inherently consider compensatory changes in inhalation patterns or in numbers of cigarettes smoked and provide the evidence needed to answer the question of immediate public

health relevance: whether disease risk varies with cigarette tar and nicotine yield as determined by the FTC method.

Exposure misclassification is a potential threat to the validity of studies of the changing cigarette. Typically, the exposure of smokers to cigarettes of varying tar and nicotine yields is estimated based on information on brands and types of cigarettes smoked. However, smokers may not be able to provide a fully accurate history of brands used throughout their lifetimes; therefore, estimates of tar and nicotine yield are potentially subject to error (U.S. Department of Health and Human Services, 1990). The consequences of misclassification include biased estimates of the effect of tar and nicotine yields and reduction of statistical power. Additional methodological concerns include the possibility of selection bias if smokers affected by symptoms or disease tend to switch to lower yield products; another concern is confounding by other aspects of lifestyle if smokers of lower yield cigarettes differ substantially in lifestyle characteristics from those smoking higher yield products. However, the research challenge of studying the consequences of the changing cigarette is no different from the challenge posed by other complex mixtures of inhaled agents, and epidemiologic research has the advantage of integrating the effects of the mixture, even though individual components may be interacting in ways that are difficult to characterize.

Lung Cancer The ACS's Cancer Prevention Study I (CPS-I) provided early evidence on the risks of lower tar and nicotine cigarettes (Hammond et al., 1976). CPS-I included about 1 million volunteers who were followed from 1960 to 1972. Mortality was examined by three categories of tar intake—high, medium, and low. For all causes of mortality and for lung cancer mortality, the standardized mortality ratios declined as estimated tar or nicotine intake declined (Table 1). The findings were similar for males (Table 1) and for females (data not shown). However, comparison with mortality in never-smokers shows that smokers of even the lowest tar and nicotine products nonetheless had substantially higher mortality rates.

Other studies have had similar findings for lung cancer. Wynder and colleagues at the American Health Foundation have conducted an ongoing case-control study of smoking and lung cancer that provides information on cigarette type and lung cancer risk over decades since the 1950's. Reports from this study have consistently shown that smokers of lower tar products, indexed in a variety of ways, have reduced lung cancer risk (Wynder et al., 1970; Wynder and Kabat, 1988). For example, in a recent report based on cases from the late 1970's and early 1980's, risks were examined separately for persons with squamous cell and small cell carcinomas of the lung (Kreyberg I) and adenocarcinoma of the lung (Kreyberg II) (Wynder and Kabat, 1988). Smoking was classified as 100 percent filter, 100 percent nonfilter, or intermediate, by number of switchers from nonfilter to filter. For smokers of filter cigarettes only, risks were approximately 10 to 30 percent less than those of smokers of nonfilters only (Table 2).

Table 1
Standardized mortality ratios for men in Cancer Prevention Study I for total mortality, lung cancer, and coronary heart disease (CHD) by tar and nicotine intake

Deaths	Tar and Nicotine Intake		
	High[a]	Medium[b]	Low[c]
Total Deaths			
1960-1966	1.00	0.90	0.88
1967-1972	1.00	0.98	0.81
Lung Cancer			
1960-1966	1.00	0.96	0.83
1967-1972	1.00	0.94	0.79
CHD			
1960-1966	1.00	0.91	0.93
1967-1972	1.00	1.03	0.82

[a] *High = 2.0 to 2.7 mg nicotine and 25.8 to 35.7 mg tar.*
[b] *Medium = intermediate.*
[c] *Low = <1.2 mg nicotine and tar generally <17.6 mg.*

Source: Hammond et al., 1976.

Table 2
Adjusted odds ratios and 95-percent confidence intervals for males in the American Health Foundation case-control study, by level of filter smoking

Pattern of Smoking	Tumor Type			
	Kreyberg I		Kreyberg II	
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Nonfilter Only	1.00	–	1.00	–
Switchers (1-9 years)	0.83	0.59 - 1.17	0.96	0.61 - 1.51
Switchers (10+ years)	0.66	0.49 - 0.90	0.79	0.53 - 1.18
Filter Only	0.69	0.37 - 1.27	0.87	0.43 - 1.54

Source: Wynder and Kabat, 1988.

A multicenter case-control study conducted in Europe during the late 1970's also provided information on cigarette type and lung cancer risk (Lubin et al., 1984). In this study, risk for lung cancer increased progressively in both males and females as the proportion of filter use declined from 100 percent. Findings were similar in a case-control study that was conducted in New Mexico from 1980 through 1983, although a linear

dose-response relationship between lung cancer risk and the extent of filter cigarette smoking was not observed (Pathak et al., 1986). Other recent case-control studies have provided comparable results (Wilcox et al., 1988; Kaufman et al., 1989).

Temporal patterns of lung cancer rates also have been interpreted as indicating lower lung cancer risks among smokers of lower tar and nicotine cigarettes. It has been suggested that the recent decline in lung cancer mortality rates among younger males may reflect changes in the cigarette (World Health Organization, 1986). This downturn has been observed in the United States and other countries (Gilliland and Samet, 1994).

Nonmalignant Respiratory Diseases

Cigarette smoking has diverse effects on the structure and function of the lung and is a cause of chronic bronchitis and chronic obstructive pulmonary disease (COPD) (U.S. Department of Health and Human Services, 1984). The persistent obstruction to airflow in the lung that is the hallmark of COPD reflects underlying changes in the small airways of the lung and emphysema, which is the permanent destruction of the air spaces of the lung. Chronic bronchitis, a condition of chronic sputum production, reflects hyperplasia of the lining of the airways of the lung and mucous gland proliferation. Compared with nonsmokers, smokers have a greater frequency of cough and production of phlegm, manifestations of the inflammation of the lung and increased mucus production secondary to smoking, and wheezing; smokers also have lower lung function.

A significant number of adults in the United States have COPD, which now causes more than 60,000 deaths annually (U.S. Department of Health and Human Services, 1984). The natural history of this disorder has been described through longitudinal investigations that have monitored lung function over time in smokers and nonsmokers (U.S. Department of Health and Human Services, 1984; Sherman et al., 1993). In nonsmokers, lung function increases through late adolescence and early adulthood, maintains a plateau across the third and fourth decades, and then begins to decline. In smokers, the decline begins at a younger age and tends to be steeper. The rate of decline increases with the number of cigarettes smoked per day but varies widely among smokers. With continued smoking, those with more rapid rates of decline eventually deteriorate to a level of lung function associated with impairment, and COPD is diagnosed. Although cessation earlier in the evolution of the disease is followed by return of the rate of decline to that of nonsmokers (U.S. Department of Health and Human Services, 1990), smoking cessation at this point in the natural history of the disease is not followed by improvement in lung function.

Findings have been reported that provide insights concerning tar and nicotine yields and respiratory symptoms and lung function level. Auerbach and colleagues (1979) quantitated smoking-related changes in the lungs of men having autopsies at a Veterans Administration hospital in New Jersey. In a rigorously investigated series of autopsied lungs, these investigators showed that smokers from a period during which cigarettes had comparatively high yields of tar and nicotine (1955 to 1960) had more changes in the airways at

various smoking levels compared with smokers from a later period (1970 to 1977). They interpreted this temporal pattern as indicating that cigarettes with lower tar and nicotine yields had less effect on lungs than did higher yield cigarettes.

A number of studies have shown that smokers of lower yield cigarettes have comparatively lower rates of respiratory symptoms. Respiratory questionnaire data collected in the late 1970's from approximately 6,000 Pennsylvania women are illustrative (Schenker et al., 1982). The brand of cigarettes currently smoked was determined and used with FTC tar yield information to classify the smokers by tar exposure. Tar yield was positively associated with cough and phlegm but not with wheezing or shortness of breath. For cough and phlegm, there were consistent exposure-response relationships with an approximate doubling of symptom frequency from the lowest to the highest exposure category (Table 3). The findings of other studies are similar. For example, a large study of civil servants in the United Kingdom, the Whitehall study, showed that the percentage of smokers reporting phlegm increased with tar yield within each stratum of cigarettes smoked per day, even the lowest (Higenbottam et al., 1980).

Table 3
Absolute and relative risks of chronic cough and chronic phlegm in Pennsylvania women by smoking status, cigarettes smoked per day (CPD), and tar yield of current brand

Smoker Classification	Chronic Cough		Chronic Phlegm	
	Risk	Relative Risk	Risk	Relative Risk
Never-Smokers	0.038	1.00	0.033	1.00
Ex-Smokers	0.056	1.46	0.052	1.58
Current Smokers				
1-14 CPD				
7 mg tar	0.073	1.92	0.067	2.04
15 mg tar	0.103	2.71	0.085	2.56
22 mg tar	0.137	3.61	0.103	3.12
15-24 CPD				
7 mg tar	0.136	3.58	0.155	4.67
15 mg tar	0.185	4.87	0.190	5.74
22 mg tar	0.240	6.32	0.226	6.82
25+ CPD				
7 mg tar	0.273	7.18	0.234	7.05
15 mg tar	0.353	9.29	0.281	8.48
22 mg tar	0.430	11.32	0.327	9.87

Source: Schenker et al., 1982.

Respiratory morbidity also has been investigated. Followup of outpatient visits by enrollees in a Kaiser-Permanente group over 1 year showed that there was a reduced risk for pneumonia and influenza but not other respiratory conditions, associated with use of low-tar and -nicotine products (Petitti and Friedman, 1985a). However, in comparison with nonsmokers, smokers using low-tar and -nicotine cigarettes had an increased risk for pneumonia, influenza, and COPD.

Not all studies show less disease associated with lower yield cigarettes. One recent study from Finland found that symptom levels in young smokers who were just initiating smoking did not depend greatly on tar yield (Rimpela and Teperi, 1989). In this 6-year followup study, the youths were surveyed on several occasions, and the relationship between tar yield and symptom onset was determined. There was little evidence of less symptom occurrence in the new smokers using low-tar cigarettes in comparison with those smoking higher tar cigarettes. Moreover, symptoms were far more frequent in the smokers of low-tar cigarettes in comparison with nonsmokers. In a randomized trial in the United Kingdom, lower tar cigarettes were not associated with either lower symptom frequency or higher level of ventilatory function, as assessed by measuring the peak expiratory flow rate (Withey et al., 1992a and 1992b). The investigators monitored urinary nicotine metabolites and concluded that compensation led to comparable levels across the trial period.

The evidence does not suggest a relationship between tar yield and lung function level. For example, in the Whitehall study (Higenbottam et al., 1980), there was no cross-sectional relationship between tar yield and level of the forced expiratory volume in 1 second. In the Normative Aging Study (Sparrow et al., 1983), a longitudinal study of U.S. veterans, tar yield of the usual brand of cigarettes smoked was not associated with decline of forced expiratory volume in 1 second.

Cardiovascular Disease

Harris (this volume) discusses mechanisms by which cigarette smoking causes CVD. Through some of these mechanisms, cigarette smoking is anticipated to increase the incidence of new cases (i.e., to cause more disease), whereas other mechanisms are anticipated to exacerbate the status of those who already had disease (U.S. Department of Health and Human Services, 1990). Thus, factors promoting atherogenesis would increase incidence, whereas factors such as sympathomimetic stimulation by nicotine or impairment of oxygen delivery by carbon monoxide might be expected to have more immediate effects and contribute to morbidity and mortality among those with coronary artery disease.

Strong evidence does not exist for either lower incidence or less morbidity from coronary heart disease (CHD) among smokers of lower yield cigarettes. In the American Cancer Society's CPS-I study (Hammond et al., 1976), smokers of lower tar products did have lower mortality from heart disease (Table 1). On the other hand, two case-control studies carried out during

the 1980's, one involving men (Kaufman et al., 1989) and the other involving women (Palmer et al., 1989), did not show evidence of reduced risk for smokers smoking lower nicotine products. Both studies included persons with a first and nonfatal myocardial infarction. In the 1980-1981 study of men younger than 54, neither nicotine nor carbon monoxide yields of current brand were associated with risk of myocardial infarction (Table 4). From 1985 to 1988, a similar case-control study of women as old as 65 with nonfatal myocardial infarction also showed no relationship between nicotine or carbon monoxide yields of current brand of cigarettes and risk of myocardial infarction (Table 5).

The study of Kaiser-Permanente enrollees also supplied relevant information (Petitti and Friedman, 1985b). Hospitalization for a variety of cardiovascular outcomes was assessed in relation to type of cigarettes smoked, after adjusting for other predictors. Using a multivariate regression model, the investigators found relatively small increases in risk for hospitalization as tar yield increased.

Table 4
Relative adjusted risk of myocardial infarction in men by nicotine and carbon monoxide yield of cigarettes smoked

Smoker Status	Relative Risk	95% Confidence Interval
Never-Smoker	1.0	2.5 - 6.7
Current Smoker		
Nicotine yield (mg)		
< 0.8	3.8	2.3 - 6.5
0.8-0.9	4.1	2.5 - 6.7
1.0-1.1	3.4	2.2 - 5.3
1.2-1.4	2.4	1.5 - 3.8
≥ 1.5	3.2	1.9 - 5.6
Carbon monoxide yield (mg)		
< 10	3.5	1.9 - 6.6
10-14	4.4	2.6 - 7.5
15-17	3.2	2.1 - 5.0
18	2.9	1.8 - 4.5
≥ 19	3.3	1.8 - 6.0

Source: Kaufman et al., 1983.

Table 5
Relative adjusted risk of myocardial infarction in women by nicotine and carbon monoxide yield of cigarettes smoked

Smoker Status	Relative Risk	95% Confidence Interval
Never-Smoker	1.0	–
Current Smoker		
Nicotine yield (mg)		
< 0.40	4.7	2.8 - 8.0
0.40-0.63	3.3	2.3 - 4.8
0.64-0.75	3.2	2.2 - 4.5
0.75-1.00	4.7	3.4 - 6.5
1.01-1.06	3.6	2.6 - 5.0
1.07-1.29	5.1	3.4 - 7.5
≥1.30	4.2	2.4 - 7.2
Carbon monoxide yield (mg)		
< 4.8	4.9	2.9 - 8.2
4.8-9.1	4.4	2.4 - 4.9
9.2-11.1	3.8	2.7 - 5.4
11.2-14.4	3.8	2.7 - 5.2
14.5-15.0	4.1	2.9 - 5.7
15.1-18.0	4.2	2.9 - 6.2
> 18.0	4.8	2.8 - 8.1

Source: Palmer et al., 1989.

CONCLUSIONS *The Health Consequences of Smoking: The Changing Cigarette: A Report of the Surgeon General* (U.S. Department of Health and Human Services, 1981) offered conclusions on these three major classes of disease. Do these conclusions remain tenable in light of more recent evidence?

With regard to cancer, the report concluded that:

> Today's filter-tipped, lower 'tar' and nicotine cigarettes produce lower rates of lung cancer than do their higher 'tar' and nicotine predecessors. Nonetheless, smokers of lower 'tar' and nicotine cigarettes have much higher lung cancer incidence and mortality than do nonsmokers (U.S. Department of Health and Human Services, 1981, p. 18).

The more recent case-control evidence remains consistent with the first component of this conclusion.

With regard to COPD, the report concluded that it was unknown whether risk was lower for smokers of low-tar and -nicotine cigarettes

compared with risk for smokers of higher tar and nicotine cigarettes. There is no consistent evidence that risk for this disease is associated with the tar and nicotine yield of the cigarettes smoked.

> For CVD, the 1981 conclusion remains appropriate: . . . the overall changes in the composition of cigarettes that have occurred during the last 10 to 15 years have not produced a clearly demonstrated effect on cardiovascular disease, and some studies suggest that a decreased risk of CHD may not have occurred (U.S. Department of Health and Human Services, 1981, p. 125).

Our research needs have changed little from the agenda set out in that report 15 years ago. The report called for further surveillance of the characteristics of smoke in relation to the type of cigarettes, further characterization of compensatory changes in smoking, better understanding of doses of tobacco smoke components delivered to the lung, and additional epidemiologic research. Ongoing characterization of the health consequences of the changing cigarette should be implemented and maintained through cohort studies such as CPS-I or case-control methods. New biomarkers of exposure and dose should be applied to better understand the relationships of FTC tar and nicotine yields with biologically effective doses of smoke components.

QUESTION-AND-ANSWER SESSION

DR. PETITTI: It actually does amaze me that the conclusions of this report are the same as they were in 1981. It also amazes me how little information has developed in this field over the past 14 years.

I wanted you to comment on an issue that was, I think, not particularly well addressed in the 1981 report and has troubled me about the epidemiological data. It has to do with the tendency to examine the risk of lung cancer in strata defined by number of cigarettes smoked per day. When you define smoking by number of cigarettes smoked per day, you do take into account compensation by inhalation and amount smoked, but you don't take into account any kind of compensation that might occur because of a tendency to smoke an increased number of cigarettes per day and smoking a lower yield brand. That would suggest that in order to take that into account in the epidemiology, you would have to move people to a different category of number of cigarettes smoked per day.

Do you think that epidemiology can address this issue, and how do you think that places limitations on the first conclusion related to lung cancer, particularly?

DR. SAMET: It is a good question and I think much of the discussion about smokers' behavior that will follow will get at just how complex the physiology is and how difficult it is to make these determinations in the laboratory.

Then, if you think about trying to develop approaches that might be used in epidemiological studies, based around questionnaires to try to develop tools that would provide a better measure of dose, which I think is what you are calling for, it becomes very difficult.

You know, using some of our nested approaches, one might begin to use biomarkers within studies, within cohort studies, probably particularly, to sort this out. But I think you are pointing to a significant limitation of approaching this question in large population studies.

DR. BENOWITZ: The biggest effect was clearly in the lung cancer data, and the lung cancers occurred as a result of cigarettes smoked a long time ago. Is there any evidence that there is any difference in risk if you looked at modern or filtered cigarettes?

DR. SAMET: Let me see if I can rephrase the question. Are you asking, has there been an attempt to assess whether some estimate of tar dose, or tar received, is a better predictor of lung cancer risk than simply proportion of filter use?

DR. BENOWITZ: Yes. What I am wondering is, is there any relevance to the data when people were mostly smoking nonfiltered cigarettes to today's cigarette market, where they are filtered? Can the whole thing be done just by adding a filter?

DR. SAMET: Probably the right answer to the question is: I do not know. But if we think we could begin to use the information from studies of smokers of old nonfiltered products, through smokers of newer products, to try and define some kind of an exposure-response relationship, then I suppose it could be done. But I think that, if we were to do that, it would be subject to a great deal of uncertainty.

DR. HARRIS: I noticed that one of the studies omitted from your review was the second American Cancer Study, CPS-II, which followed people from 1982 to 1986. I am wondering if anyone knows whether that study will be analyzed in terms of the yield or type of cigarette and health outcomes.

DR. SAMET: There has already been a paper describing the demographics of tobacco use in that study and predictors of tar yield by various demographic predictors. I would anticipate seeing such an analysis eventually.

DR. WOOSLEY: We have already heard this morning how the marketing and the promotion of the low-tar and -nicotine cigarettes have been toward the more highly educated portion of the population. We have already seen how they responded to that by switching. We have already heard how they have expressed greater concern for their overall health.

I have a serious concern. Do you feel the data have adequately addressed the possibility that you are looking at a subset of the population who have done something else to modify their health risks and, therefore, have looked at a selected population with decreased negative outcomes because of these

other factors, and that we really have not seen any influence of the cigarettes themselves?

DR. SAMET: I referred to that set of concerns under the rubric of selection bias. That is, people may select themselves to products based on either their response to what they were smoking or other characteristics that are relevant—an argument in epidemiology called confounding.

I think you are right; these are concerns. I think, on the other hand, in many of the studies there have been attempts to "adjust," to the extent one can, for such differences in the characteristics of those using different types of products. As you look across the consistency of the evidence in different populations with different approaches to controlling for such factors, and different study designs, a consistency emerges, I think at least for lung cancer, that would suggest some modest reduction of risk for those using the lower delivery products.

Could there be some element of residual bias in there? I certainly could not exclude it. But when we weigh the evidence in an attempt to understand those other factors, the socioeconomic indices and other measures in different studies would support that conclusion.

DR. BENOWITZ: I think that is the most important issue that we have to address here today. If labeling something low-tar and -nicotine implies improved health compared with higher tar and nicotine, I think those confounders have the most impact on that decision.

DR. HOFFMANN: With regard to Dr. Benowitz' question to me, it is rather interesting to see that multiple studies have shown that the increase in adenocarcinoma today is much higher than previously, because the nature has changed. So, to me, this has something to do with the cigarette. You get more adenocarcinoma in the peripheral lung than in former times; it is a ratio of 20 to 1 squamous cells, and today you have 1 to 1. So, I think at least the type of lung cancer that appears today has something to do with the change in cigarettes.

DR. SAMET: But certainly the histologic distribution of lung cancers has changed and I agree; we would like to know why.

DR. DEBETHIZY: Your data about the relationship between nicotine and cardiovascular disease are curious to me, because most of the data in the literature show that people who smoke low-yielding cigarettes actually absorb less nicotine. Could you comment on the fact that you do not see any dose-response relationship there?

DR. SAMET: I am not sure how you would like me to comment. I am describing the findings of a case-control study that describes how risks of nonfatal myocardial infarction varied with the level of nicotine or carbon monoxide intake, as estimated by what brand was being smoked at the time of the infarct.

These are not biomarker data, so there is no inference in these particular subjects as to what the level of nicotine or carbon monoxide may have been. The question is, again, looking at the yield or brand as an estimate of exposure, there was simply no relationship observed in these observational studies.

DR. HUGHES: In most of these studies, the control group is labeled nonsmokers. Is that usually never-smokers?

DR. SAMET: In most of the studies that are labeled nonsmokers, that is a never-smoker group. You basically will see two contrasts: vs. never-smokers or, in some of the studies, the contrast has been made between sort of the lower exposure group vs. the higher exposure group.

DR. HUGHES: The reason I asked that is, it seems to me that using controls of ex-smokers would be important for two reasons. One, it would be a control for the confounds that Dr. Woosley mentioned earlier. Second, all your studies have to do with switching cigarettes. None of them has to do with the alternative of either quitting or switching to a low-nicotine cigarette. Are there data to inform the consumer of the question, how much do I want to improve my health by quitting, vs. how much do I improve my health by switching to a low-tar cigarette?

DR. SAMET: Certainly, there are abundant data on how risks of diseases vary following cessation. I do not want to complicate this, and it was the subject of the 1990 Surgeon General's report. These risks vary in complex ways for different diseases, depending on the age at which the smoker stopped smoking and the duration of successful abstinence from smoking.

So, it is somewhat difficult to capture a single number that describes the risk in ex-smokers. It has to be done in a far more complex way. But, on the other hand, there are data sets, like the American Cancer Society data sets, that would allow one to describe how risks change following smoking cessation, for example. And it would be possible to derive some quantitative contrast between what might happen to smokers of different ages, different prior smoking histories, with switching products vs. cessation.

DR. RICKERT: On your emphysema slide, the one that dealt with the changes in lung function, there was a label that said, "never smoked and not susceptible to the effects of tobacco smoke." Do you have any idea what proportion of the population of smokers fell into the category "not susceptible"?

DR. SAMET: Such numbers are not readily available. I think most people who work in this field would guess that with regard to COPD, perhaps 20 to 25 percent of continued smokers seemed to fall into this group of rapid lung function decline.

DR. RICKERT: Are there any postulated mechanisms why smokers should be in that group?

DR. SAMET: There are many postulated mechanisms, some of which Dr. Harris already surveyed. They are essentially mechanisms having to do with the balance between factors in the lung that injure it and those that protect it, and how that balance may be shifted in individual smokers, either by virtue of genetics or aspects of smoking, toward destruction rather than susceptibility. It is the subject of a great deal of research.

DR. HEADEN: The next Surgeon General's report will be on smoking and tobacco use among ethnic minorities. I want to remind the group that some smoking patterns among ethnic minorities, particularly African-Americans, differ substantially from smoking patterns of whites. For example, African-Americans have extremely low daily rates of smoking, but they smoke very high tar and nicotine cigarettes. Thus, it suggests that perhaps we need some new data, oversampling for African-Americans and perhaps other ethnic groups, particularly males, to find out what the relationships would be for these subgroups.

DR. SAMET: I would certainly agree.

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