Analysis of 974 white male lung cancer patients and a case-for-case matched control series of patients without neoplastic diagnoses indicates that some reduction in the risk of lung cancer can be achieved by switching to filter cigarettes. The findings here suggest the feasibility of monitoring progress toward safer cigarettes by a retrospective surveillance system patterned after the present study.

RISKS OF LUNG CANCER IN SMOKERS WHO SWITCH TO FILTER CIGARETTES

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THE difficulties that our technological societies have in dealing effectively with the adverse side-effects of the products of technology are well exemplified by our efforts to control the health hazards of cigarettes. For more than 12 years the evidence has been incontrovertible that cigarette smoking is one of the major public health problems of our era. A number of different technological means are available for the control of cigarette hazards. One technological mean is the use of filter tips to reduce the amount of tar and nicotine in the smoke. But progress along this and other lines has been held up by continuing controversies over whether the dangers to human beings are actually reduced by any of these methods. The recent criticism of Columbia University for sponsoring a new filter[1] is one example of these controversies. Ironically enough, the one point on which spokesmen for health agencies and the tobacco industry agreed was that there was a dearth of factual evidence on the effectiveness of filters in controlling human health hazards.

Surveillance System

Evolution of a safer product will necessarily be slow and difficult when there is no way to tell whether a given change has reduced the hazard to human beings or has made it worse. To make progress, an effective surveillance system is needed to monitor the products. From a scientific standpoint, it is not particularly difficult to set up a surveillance system—the main problems lie in the area of funding and administration. One approach, a "prospective" approach, is to take a large sample of healthy persons and reinterview them each year to determine their smoking habits and health status. This approach has some marked technical advantages but a sample of several million would be needed in order to obtain an evaluation within a period of three to five years. A much less costly approach, a "retrospective" approach, is to interview persons who are admitted to hospitals with lung cancer or other smoking-related diseases. A control series of persons hospitalized for other diseases would also be inter-

viewed. The number of persons interviewed could then be of the order of 50,000 instead of several million. At a cost of $100 to $200 per completed case, the surveillance system would be expensive but not prohibitively so. Unfortunately, a retrospective system is open to a number of technical objections and the feasibility of such a system has often been questioned. The original purpose of the present study was to assess the feasibility of a retrospective surveillance system for monitoring tobacco products.

The manifest difficulties in obtaining reliable lifetime smoking histories from a patient interview had made us so skeptical of the feasibility of a retrospective system that we had some hesitation about going ahead with the study. However, the special facilities of the Departments of Epidemiology and Biostatistics at Roswell Park Memorial Institute (RPMI) made it comparatively quick and easy to obtain a preliminary assessment. Hence it was worthwhile to go ahead on the off-chance that something interesting would turn up. Due to the foresight of Dr. Abraham Lilienfeld and the efforts of Dr. Saxon Graham and Dr. Morton Levin, all patients who had been admitted to RPMI in the past decade had been interviewed prior to their diagnostic processing. In December, 1959, the interview schedule was modified to include a set of questions on brands of cigarettes smoked during the patient's lifetime. This information was then coded, key-punched, and stored on magnetic tape to facilitate computer operations. During the period 1960-1966, 990 white male patients were diagnosed as having lung cancer. During the same period, 1,709 white males were seen at RPMI and had a diagnosis which did not involve a neoplastic disease. These patients were used to obtain a control series which was case-for-case matched to the lung cancer patients. Ages were matched to within five years and admission dates to within four years. An acceptable control was found for 974 of the lung cancer patients by using a computerized matching procedure. The initial tabulations were obtained within two weeks, with the help of Dr. Roger Priore, George Dillon, Jack Tidings, and Daniel Jarnot.

Our approach was to use the epidemiological data as if it were a pilot study of a potential surveillance system. We were not expecting any clear-cut substantive findings from this work, and we had intended to base the feasibility assessment on differentials between smokers and ex-smokers. However, it quickly became apparent that the distributions for nonfilter and filter cigarettes were distinctly different. More specifically, the "case-control ratio" for filter smokers (subscript for filter=f), $CA_f/CO_f=R_f$, was smaller than the corresponding ratio for the regular cigarette smokers, $CA_r/CO_r=R_r$ (subscript for regular=r). Both ratios, R_f and R_r, were much larger than the ratio for nonsmokers, R_0 (subscript for nonsmokers=0). This result had to be viewed with some caution since there was the distinct possibility that differences in lifetime exposure to cigarettes smoked (quite apart from the filtration) might account for the data. That is, it seemed possible that the persons who switched from regular cigarettes to filters might have smoked for fewer years or might have smoked fewer cigarettes per day than persons who did not switch.

To investigate this possibility, the various types of cigarettes (on the basis of most recent brand smoked) were cross-tabulated by the current amount smoked and by the total number of years that the person had been smoking any type of cigarette. The original cross-tabulation distinguished three categories of daily amount smoked by number of packs (less than one-half, one-half to one, over one) and four categories of duration in years (under 30, 30-39, 40-49, over 50). The counts for the persons

smoking less than half a pack a day were small and erratic and, in all but one instance, the amount was consolidated into the category "one pack or less." Even with almost a thousand case-control pairs, the above cross-tabulation led to small numbers in some of the cells. To avoid such small numbers, a scale for the degree of exposure to cigarette smoke was constructed. This was done by calculating the "risks of lung cancer" relative to nonsmokers for each of the time-amount categories. We then combined over those categories with similar relative risks.

By definition, the "relative risk" in a given cross category is the ratio of case-control ratios. Let the subscript "i" denote a given exposure category for the regular cigarette smoker and let "o" denote nonsmokers. Let CA be the number in the case series and CO be the number in the controls. Then the relative risk in any exposure category is the case-control ratio in the category divided by the case-control ratio of the nonsmokers in the study*:

$$\text{Relative Risk in i-th category} = \frac{\frac{CA_i}{CO_i}}{\frac{CA_o}{CO_o}}$$

The results are shown in Table 1. The people who have smoked less than 30 years have lower risks than the others—a risk of about 3. They are taken as the "low" exposure group although it should be remembered that even in this group the risks are three times the risk for nonsmokers. In the people who have smoked more than 30 years the risks that stand out are the high values for those who smoke more than a pack a day. The risk is also elevated in the pack-a-day smokers who have smoked for 50 years or more. These people form the "high" exposure group. The rest of the figures fluctuate around a risk of about 6. These cross-categories have been combined to form the "medium" exposure group. *The specific cross-categories included in each degree of exposure category are shown in the third column of Table 1.* In going from low to medium exposure, the risks are about doubled. This also occurs in going from medium to high exposure.

The degree-of-exposure scale was constructed using the fairly large series of patients who were currently smoking specific brands of regular cigarettes. This same grouping was used in describing the degree of exposure to other types of cigarettes. All comparisons between types of cigarettes are based on the last reported brand or type smoked. The relative risks for smokers of regular cigarettes with different degrees of exposure are shown graphically in Figure 1. The respective risks for the low, medium, and high exposure categories are 3.0, 5.6, and 12.0. Also shown in Figure 1 are the risks for another fairly large series of patients who smoked regular cigarettes but who fall in the "no specific brand" category. These people said that they did not smoke any one brand, constantly switched from brand to brand, or smoked odd brands. Apart from the low exposure category (where the numbers become small), the relative risks for the no specific brand smokers are similar to those in the base-line series. This indicates that the retrospective procedure gives fairly reproducible estimates when there are more than 20 patients in the minimum cell. About 60 per cent of all smokers in the cases (and 52

* A terminology note: the index used here is commonly called an "odds ratio" by theorists and a "relative risk" by research workers. The "odds ratio" is related to the theoretical "relative risk" by the formula:

$$\text{Odds ratio} = \text{relative risk} \times \left[\frac{1-\text{probability of nonsmokers having lung cancer}}{1-\text{probability of smokers having lung cancer}}\right],$$

where the bracketed quantity is negligible relative to sampling error in the vast majority of actual study situations (including the present one).

Table 1—Risks of lung cancer (relative to nonsmokers) for persons currently smoking regular and filtered cigarettes by total years smoked cigarettes and daily amount smoked

Exposure			Regular			Filter		
			No.		Relative	No.		Relative
Years smoked	Daily quantity	Degree	Case	Control	risk	Case	Control	risk
Under 30	1 pack or less	Low	15	20	3.35	3	11	1.22
	More than 1 pack	Low	6	12	2.24	2	5	1.79
30–39	1 pack or less	Medium	30	21	6.39	11	16	3.07
	More than 1 pack	High	28	10	12.52	9	11	3.66
40–49	1 pack or less	Medium	46	43	4.78	15	15	4.47
	More than 1 pack	High	24	9	11.93	12	9	5.96
50 and over	Under ½ pack	Medium	13	8	7.27	2	2	4.47
	½–1 pack	High	26	13	8.94	9	6	6.71
	More than 1 pack	High	12	2	26.83	2	1	8.94
Total			200	138	6.48	65	76	3.83

per cent in the controls) smoked regular cigarettes (either no specific brand or specific brands).

The relative risks have been plotted on a logarithmic scale in Figure 1. One reason for this choice is that the error is more nearly symmetric on this scale and can be readily estimated by standard methods.[2] A more important reason is that the relationship between degree of exposure and relative risk is roughly linear on the logarithmic scale. This fa-

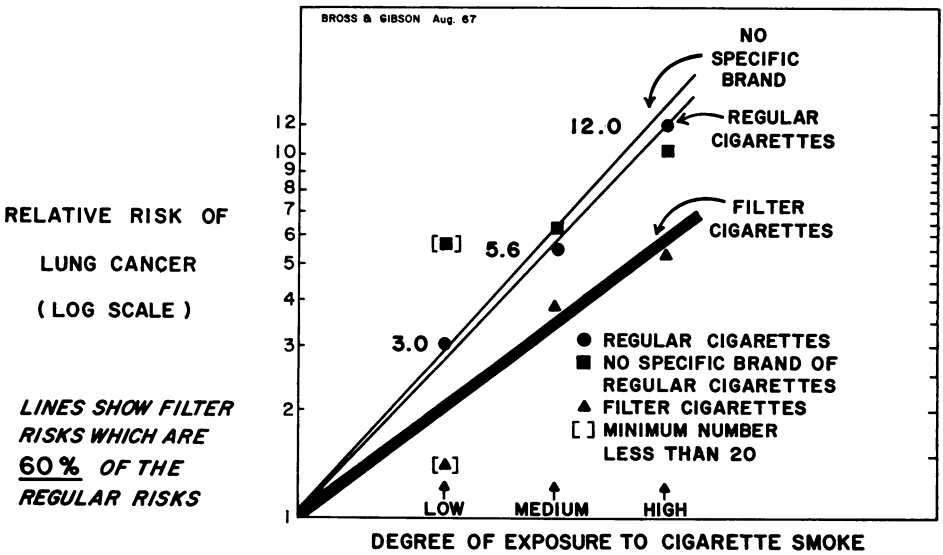

Figure 1—Relative risk of lung cancer by type of cigarette and degree of exposure: risks relative to nonsmokers

cilitates comparisons between types of cigarettes. When the points for the different degrees of exposure lie on a line, the relationship between two types of cigarettes can be characterized by the ratio of the slopes of the two lines. This gives a single measure which is applicable for all degrees of exposure. In Figure 1 the lines have been drawn by connecting the over-all values for each type (average degree of exposure, over-all relative risk) with the origin (no exposure, unit relative risk). Except at the low degree of exposure where the numbers become small, the individual points tend to lie near the lines.

Taking the degree of exposure into account by the procedures used in constructing Figure 1 brings out very clearly the differential in risks between persons who switched to filter cigarettes and those who did not. From the ratio of the slopes it can be seen that the risk for filter smokers is about 60 per cent of the corresponding risk for the regular smoker. The confidence limits on this estimate are fairly wide—from 38 per cent to 91 per cent—but there clearly is some reduction in risk. A formal procedure for assessing the differences between the two types of cigarettes without any assumption of linearity is a weighted chi-square test commonly called "Cochran's Test."[3] Comparing either the regular smokers or the no specific brand smokers with the filter smokers leads to a Cochran Test which is statistically significant at the 1 per cent level ($P=0.004$). In sum, Figure 1 provides fairly clear-cut and convincing evidence that switching to filter cigarettes has reduced the risk of lung cancer in these smokers.

Although the risk of lung cancer has been reduced, it is clear from Figure 1 that this is only a step in the right direction. Thus the filter cigarette smokers with high exposure have a risk of lung cancer which is still five times as great as the risk for nonsmokers. This risk is slightly less than the risk for non-filter smokers with medium exposure. The filter cigarettes in this study cannot be called "safe." Switching to these cigarettes is not as good as stopping completely. The filters have reduced the risk but a much greater reduction is needed. From a public health standpoint, the main point is that these filters were a step in the right direction. Existing filter technology would enable further steps in this direction to be taken immediately.

Findings and Implications

Figure 1 gives, in a simplified form, the gist of our findings. It presents strong evidence that a retrospective surveillance system patterned after the RPMI procedures is feasible. With only a thousand pairs of patients it was possible to obtain a clear and coherent picture of differentials between generic types of cigarettes. There are more than 50,000 cases of lung cancer in the United States each year and most of these cases are hospitalized at some stage. With a nationwide reporting network (or even a network covering one or two large states) 5,000 lung cancer patients (and a corresponding control series) could be interviewed each year. If desired, a series of patients with coronary artery disease or other smoking-related diseases could also be obtained. With 50,000 interviews per year a substantial improvement in a generic type of cigarette (or even in an individual brand that had a large share of the market) could be detected within three to five years.

These results have broad practical implications and a thoughtful reader will probably have in mind a number of questions related to these implications. We would therefore like to depart from the customary "discussion" and to formulate and briefly answer some of the specific questions which might be raised.

Q: The data in Table 1 include less than half of the patients in the series. What has happened to the other patients? What are their relative risks?

Table 2—Present smoking behavior of lung cancer cases and matched controls

Present smoking behavior	1 Case no.	2 Control no.	3 Relative risk
Present smokers			
Regular	200	138	6.48
King	73	60	5.44
Menthol	29	17	7.63
Filter—present	65	76	3.83
past	13	11	5.29
No specific brand	137	85	7.21
Unknown brand, time, quantity	48	40	—
Total cigarette smokers	565	427	5.92
Pipe/cigar only	71	172	1.85
Ex-smokers			
5 years or less	169	67	11.29
6 years or more	43	79	2.44
Switched to pipe/cigar	54	39	6.20
Nonsmokers	38	170	1.00
Not interviewed	34	20	—
Total	974	974	

A: A complete accounting of patients is given in Table 2. We have already shown that the no specific brand smokers do not differ from the regular cigarette smokers. We could have combined these two groups for the comparison with filter smokers but the results would have been very similar. However combining the groups might be criticized and by keeping them separate the reader can see the similarities. The three groups shown in Figure 1 account for 72 per cent of the cigarette smokers in the cases and 70 per cent of those in the controls.

Q: Why is the proportion of persons who switched to filter cigarettes much less than what would be expected from the figures on cigarette sales?

A: The average age in this series of patients is 60.2 years—these are older men. Nearly all of them had smoked regular cigarettes for many years before filter cigarettes came on the market. These men seem to have a strong brand loyalty and do not do much switching.

Q: What actual evidence do you have of this "brand loyalty"?

A: The strength of this loyalty can be seen in Table 3. At least half of the

Table 3—Total number of brands regularly used during lifetime by type of cigarette currently being smoked

Type of cigarette currently smoked	Number of brands: One No.	One %	Two No.	Two %	Three or more No.	Three or more %	Unknown No.	Unknown %	Total
Regular									
Case	103	50.0	69	33.5	29	14.1	5	2.4	206
Control	86	61.9	36	25.9	17	12.2	0	0.0	139
Filter									
Case	3	4.4	42	61.8	16	23.5	7	10.3	68
Control	5	6.5	53	68.8	14	18.2	5	6.5	77
No specific brand*									
Case	16	11.0	30	20.7	19	13.1	80	55.2	145
Control	5	5.7	21	24.1	3	3.4	58	66.7	87

* This is a loosely defined group and includes smokers who alternated between brands, and who rolled their own or smoked foreign brands. The latter group accounts for the 16 cases and five controls who used only one "brand" during their lifetime.

persons who say they smoke a specific regular brand of cigarette have smoked a single brand predominantly or exclusively for their lifetime. More than four out of five have smoked no more than two brands. Even those who have switched to a filter cigarette have usually smoked only one other brand. This striking brand loyalty is one of the main reasons why many of the anticipated difficulties in obtaining retrospective lifetime smoking histories were less important than we thought they would be.

Q: In dealing with generic types of cigarettes you have lumped together brands of cigarettes which may have had very different tar yields.[4] How can you justify this?

A: The brands were looked at individually prior to combining. For the regular cigarettes the series were fairly large and no marked differences in relative risks were found. This agrees with the results of tar-testing studies since they show a rather narrow range for tar yields for regular cigarettes.[4] Larger differences might have been expected for filter cigarettes and, indeed, the relative risks did fluctuate more widely. However this fluctuation might also have been due to the small number of persons smoking some of the brands. As can be seen from Table 4, the number of patients in the cross-categories is not large enough to permit a further cross-tabulation by brand. There are fewer objections to lumping all filters together than to excluding brands on such fragmentary evidence. The statistical effect of pooling the brands is to reduce the differentials between filter and nonfilter cigarettes.

Q: The non-neoplastic control series includes some patients with smoking-related diseases, doesn't it? Why didn't you eliminate these patients?

A: This is a case of "damned if you do, damned if you don't." If we eliminated patients with certain diagnoses, there would be the objection that we were picking and choosing the controls. Moreover each cause for elimination might be contested. The inclusion of smoking-related diseases in the controls leads to some underestimation of the relative risks and differentials in risks. This is the conservative course.

Q: Going back to Table 2, there are some oddities in your results for ex-smokers. Why is the proportion of ex-smokers so high?

A: All of the people in this study have come to a cancer hospital for a medical examination. Even when no malignancy was found, these people had some health problem which brought them in. The experience of the RPMI Smoking Withdrawal Clinic shows that white males with certain health problems are much more successful in quitting than males without these problems.[5] In examining these tables it should be kept in mind that this group is selected in a particular way so it does not represent the proportion of ex-smokers in the general population. It does, however, represent the situation for the group of smokers who are the focus of the current public health problem.

Q: But Table 2 shows that the risk of ex-smokers who have quit for less than six years is *higher* than the risk for persons who continued to smoke. How can this be?

Table 4—Number of present smokers by exposure and type of cigarette currently used

	Regular		No specific brand		Filter	
Exposure	CA	CO	CA	CO	CA	CO
Low	21	32	18	14	5	16
Medium	89	72	64	47	28	33
High	90	34	55	24	32	27
Total	200	138	137	85	65	76

A: The root of the difficulty is that many of the persons who have stopped smoking have done so because of physical symptoms that were pre-symptomatic of the lung cancer or other health problems that led to their RPMI admission. Similar elevations in the risks of ex-smokers for a few years after quitting have been noted by E. Cuyler Hammond[6] and others in prospective studies. This effect comes in more strongly in retrospective hospital studies than in prospective studies.

Q: In hindsight, what factors were responsible for changing your initially pessimistic evaluation of the feasibility of a retrospective surveillance system into an optimistic one?

A: For one thing we underestimated the importance of brand loyalty. We had anticipated very complicated smoking histories and consequent problems both in collecting the data and in analyzing it. A second important factor is that the switchover to filters appears to occur at about the time when there is a rapidly increasing risk among persons who continue to smoke the regular cigarettes. After 30 years of smoking regular cigarettes (and in this age group most people had been smoking this long before filter cigarettes became popular) the risk doubles for pack-a-day smokers and redoubles for those who smoke more than a pack a day. Switching to filters seems to put the smoker in an "effective degree of exposure" category one step lower on the scale than he would otherwise be. This large difference is detectable in the system.

We originally thought the risk might be proportional to the total lifetime exposure to tar. The differences in total tar exposure are less than 10 per cent and would be difficult to detect in the present system. For example, if a person had smoked regular cigarettes for 30 years and filter cigarettes for ten years or less, the reduction in total tar intake (assuming that filtration reduces this from 33 mg to 22 mg per cigarette) would only amount to about one-twelfth of the total tar exposure. Without facts as a buttress, it would have seemed unduly optimistic that a smoker could sharply reduce his risk by switching to a lower-tar cigarette at this late stage in his lifetime smoking history.

Q: What brands of cigarettes are mainly involved in the nonfilter cigarettes? In the filter cigarettes?

A: The regular brands are Camels, Lucky Strikes, Chesterfields, Old Golds, Philip Morris, and Raleighs. The filter brands are Winston, Marlboro, Kent, L & M, Parliament, Viceroy, Tareyton, and Lark.

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