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CIGARETTE YIELD AND CANCER RISK: EVIDENCE FROM CASE-CONTROL AND PROSPECTIVE STUDIES

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INTRODUCTION

The belief that cancer risk can be reduced by lowering the tar yield of cigarettes has been developed from three basic observations: (1) many cancers exhibit a dose-response with respect to the number of cigarettes smoked per day, as shown in Figure 1 (Wynder & Stellman, 1977); (2) cancer risk decreases with number of years of smoking cessation (Fig. 2); (3) tumours can be produced quantitatively in animals using cigarette combustion products (Wynder & Hoffmann, 1967).

Although quantitative relationships between cigarette smoking and cancer risk had been developed in both case-control and prospective studies in the 1950s and even earlier, epidemiological confirmation of a specific relationship with cigarette tar yield was not achieved consistently until the late 1960s. Since that time, differences in relative risk have been observed for at least four cancer sites: lung, larynx, oral cavity, and bladder.

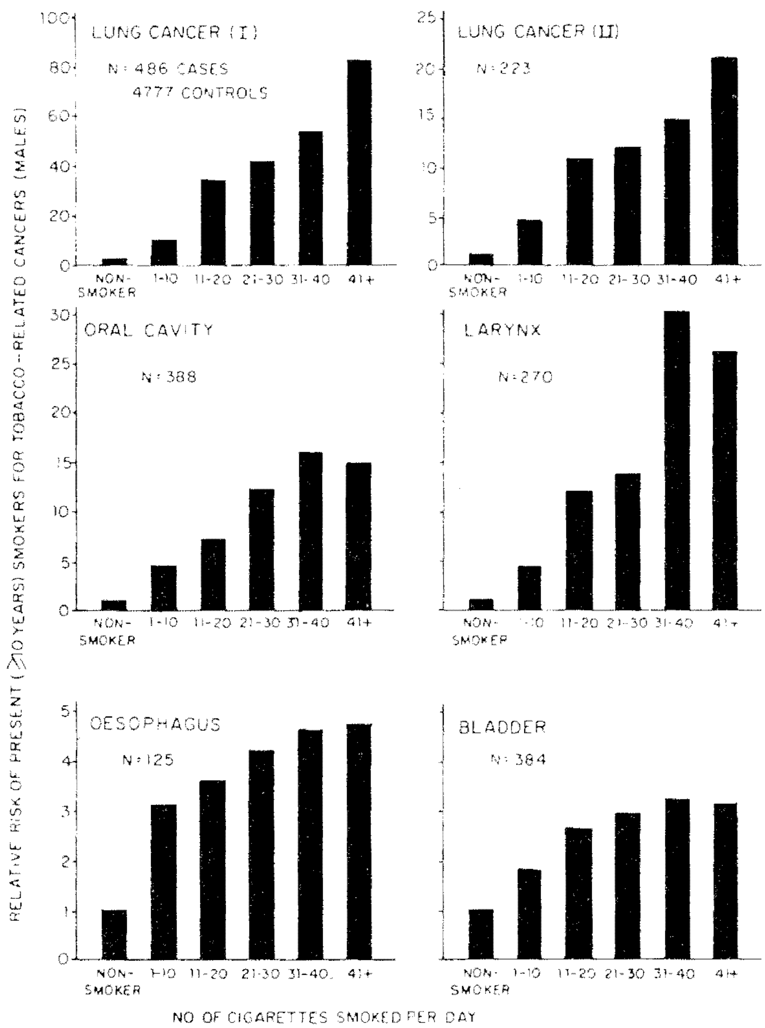
In this paper we review the data which have led to these conclusions, and discuss some of the similarities and differences in the studies.

LUNG CANCER

Case-control studies

Three series of case-control studies have estimated the relative risk for developing lung cancer in relation to cigarette yield: Bross and Gibson (1968), the series begun by Wynder in the 1960s and continuing into the present (Wynder *et al.*, 1970; Wynder *et al.*, 1976; Wynder & Goldsmith, 1977; Wynder & Stellman, 1977; Mushinski & Stellman, 1978; Wynder & Stellman, 1979; Wynder *et al.*, 1984), and a cooperative European study begun in 1976 under the auspices of the US National Cancer Institute, covering five countries: Italy, France, Scotland, the Federal Republic of Germany and Austria. In the latter series, the results have been presented as a whole (Lubin *et al.*, 1984a,b) and the Austrian

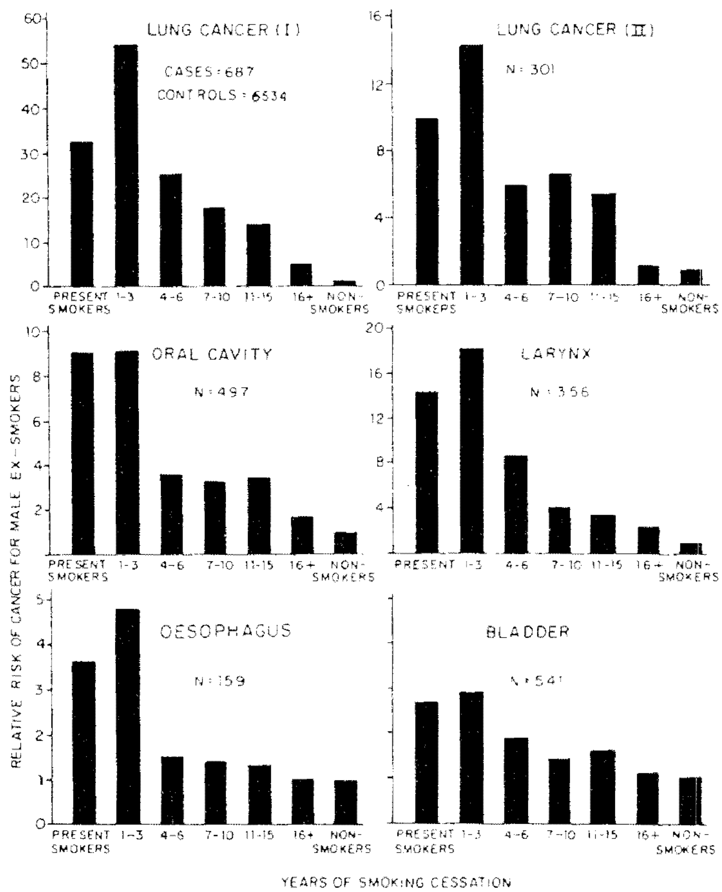
Fig. 1. Relative risk for cancers of the lung (Kreyberg types I and II), oral cavity, larynx, oesophagus, and bladder for male current smokers, according to number of cigarettes smoked per day. N, number of cases in case-control study (from Wynder & Stellman, 1977)



component has also been published separately (Kunze & Vutuc, 1980; Vutuc & Kunze, 1982a,b, 1983).

Results of these case-control studies are summarized in Table 1, in which comparisons are made between smokers of filter *versus* nonfilter cigarettes. The relative risk of lung cancer in nonfilter as compared to filter cigarette smokers as a referent ranges from 1.3 to 2.3. This must be understood in the context of an individual's lifetime exposure to cigarette tar. The average age of lung cancer diagnosis in the USA is now about 58 years. Most

Fig. 2. Relative risk for cancers of the lung (Kreyberg types I and II), oral cavity, larynx, oesophagus, and bladder for male former cigarette smokers, according to number of years since cessation of smoking. N, number of cases in case-control study (from Wynder & Stellman, 1977)



smokers in this cohort began smoking at a time when there were very few filter cigarettes on the market, and the tar yield of nonfilter cigarettes was over 30 mg. Data from the new American Cancer Society study (Stellman & Garfinkel, 1986) suggest that a wave of switching from nonfilter to filter cigarettes occurred in the mid-1960s immediately after the appearance of the Surgeon General's report in 1964, which received widespread publicity. Figure 3 shows the proportion of a smoker's lifetime which would have been spent with filter cigarettes, assuming smokers switched from nonfilter cigarettes at about that time, and assuming average ages of beginning to smoke characteristic of this population. It is obvious that recent lung cancer cases received a great deal of their tar exposure in their early smoking years from nonfilter, or from the early high-tar filter cigarettes, irrespective of the types of cigarette they smoke today.

Table 1. Relative risks for lung cancer reported from case-control studies, in relation to filter usage[a]

Study	Sex	Comparison	Relative risk
Bross & Gibson (1968)	Males	F to NSR	3.8
		NF to NSR	6.5
		NF to F	1.7
Wynder *et al.* (1970)[b]	Males	F to NSR	23.6
		NF to NSR	38.3
		NF to F	1.6
Wynder & Stellman (1979)	Males	NF to LTF	1.3
	Females	NF to LTF	1.4
Lubin *et al.* (1984 a, b)	Males	Mixed F and NF to F	2.1
		NF to F	2.1
	Females	Mixed F and NF to F	2.3
		NF to F	2.3

[a] Abbreviations: F, filter cigarette smokers; NSR, nonsmokers; NF, nonfilter cigarette smokers; LTF, long-term filter cigarette smokers

[b] Cases were Kreyberg type I only

In three of these case-control series, results have also been presented in terms of specific tar yields. These findings, shown in Table 2, demonstrate that, even allowing for substantial differences in schemes for estimating smokers' tar dosage, dose-response relationships are easily discernible.

Follow-up studies

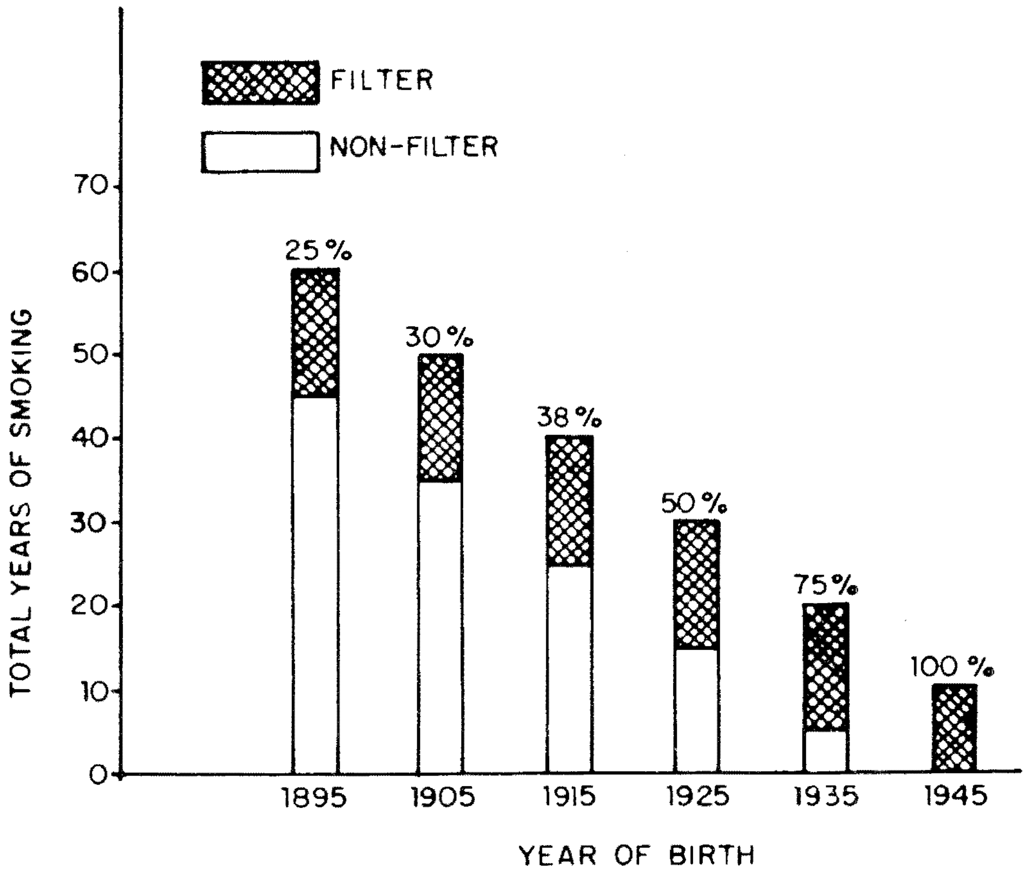
There have been three important follow-up studies of lung cancer in relation to cigarette smoking in which cigarette yield has been studied in detail.

The American Cancer Society enrolled over one million men and women aged 40 years and over, in 25 states, in a prospective study in 1959. Follow-ups were conducted annually through 1966, and again in 1971 and 1972. Analyses of lung cancer death rates in relation to smoking habits were originally published by Hammond (1966).

Hammond *et al.* (1976, 1977) later presented evidence from this study showing that the lung cancer mortality rates for smokers of 'low tar-nicotine' cigarettes, compared to rates in smokers of 'high tar-nicotine' cigarettes, were reduced by about 20% in men and by about 40% in women. These estimates were made using a matched group analysis which permitted adjustment for many variables at once, including age, race, number of cigarettes smoked per day, age smoking began, urban/rural residence, education, job exposure to chemicals, X-rays, or other toxicants, history of prior illness, and calendar period (Hammond, 1985). Hammond's results are shown in Table 3.

For the present review we have re-calculated the standard mortality ratios (SMR) according to quantity smoked daily by current smokers, and by tar yield of cigarette at baseline, for lung cancer in men during 1960–1966, the six years when annual follow-up was done. Calculations were also restricted to this period to minimize effects of changes in

Fig. 3. Filter cigarette usage as a percentage of total smoking experience, by birth cohort (from Wynder & Stellman, 1979)



smoking habits. In addition, during the first six years of the study, additional confirmation was sought whenever cancer was mentioned on the death certificate, so that the cause of death was based upon 'best evidence'.

Results of this new calculation are shown in Figure 4. There were 967 deaths from lung cancer during this period. For statistical convenience, the reference population is the largest subgroup, namely, smokers of 'medium tar-nicotine' cigarettes, who smoked 20 cigarettes per day. For all other tar-nicotine and quantity categories of smokers, as well as for exsmokers and nonsmokers, expected numbers of deaths were computed by multiplying age-calendar-year-specific lung cancer death rates in the reference population by the person-years of exposure to risk of dying in the target group, and summing over age-calendar-year strata. The SMR is the number of observed divided by expected deaths. Data were renormalized to give lifetime nonsmokers an SMR of 1.0.

Table 2. Relative risk for lung cancer according to tar exposure indices proposed by various authors[a]

Reference	Sex	Relative risk								
Mushinski & Stellman (1978)		Current tar level (mg/day)								
		0	1–199	200–399	400–599	600–799	800–999	1000–1199	1200–1399	1400+
		Kreyberg I								
	Males	1.0	5.1	7.4	12.2	20.1	24.8	34.2	30.6	29.9
	Females	1.0	7.9	9.6	18.9	28.5	14.8			
Kunze & Vutuc (1980); Vutuc & Kunze (1982b)		Lifetime tar score								
		Below 500	501–1000	1001–2000	2001–3000	3001+				
		Kreyberg I								
	Males	2.0	2.6	5.3	7.2	8.3				
	Females	1.5	4.2	4.8	4.9	6.8				
		Kreyberg II								
	Males	–	1.8	1.8	3.5	3.9				
	Females	–	1.1	3.1	–	2.3				
Lubin *et al.* (1984a)		Mean cigarette tar content (mg)[b]								
		(15.6)	(18.5)	(20.6)	(23.6)	(25.2)	(28.8)			
		Lung cancer								
	Males	1.0	1.2	1.7	1.3	1.3	1.4			
	Females	1.0	1.9	1.3	1.1	1.5	–			

[a] Nonsmokers and referent; see Table 5 for definitions of tar exposure indices

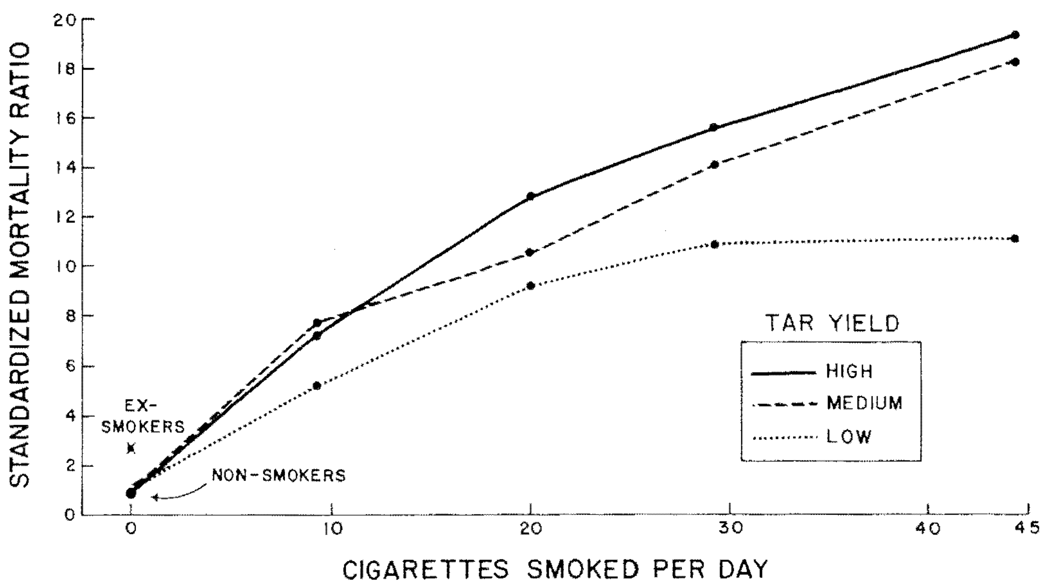
[b] Categories were combined from within-country 10, 25, 50, 75, and 90th percentiles. Mean tar values (given in brackets) are within each such category

Table 3. Standardized mortality ratio for lung cancer among one million men and women followed up for twelve years, relative to lifetime nonsmokers, according to tar-nicotine yield of usual cigarettes, adjusted for age, calendar year, and many other variables (see text)[a]

	Standardized mortality ratio		
	'Low T/N'	'Medium T/N'	'High T/N'
Males	0.81	0.95	1.00
Females	0.60	0.79	1.00
'Adjusted' deaths:	235.2	285.5	318.4

[a] From Hammond *et al.* (1976)

Fig. 4. Standardized mortality ratios for lung cancer in males, among nonsmokers, exsmokers, and current smokers of low-, medium-, and high-tar/nicotine (T/N) cigarettes (defined by Hammond *et al.*, 1976). The group was enrolled in 1959, and followed up through 1966.



At each tar-nicotine level, the SMR increased with quantity smoked, in an approximately linear dose-response relationship. For current smokers of at least 20 cigarettes per day, at each value of daily quantity smoked, the SMR for the 'high tar-nicotine' cigarette smokers exceeded that for the 'medium' group, which in turn exceeded that for the 'low' group. Lifetime non-smokers had lung cancer death rates well below any of the current smokers, irrespective of cigarette yield for the latter.

Two other studies are worthy of mention. Rimington (1981) observed 104 lung cancer cases in a follow-up study of 10 414 male volunteers for a mass radiography screening in England. Subjects were enrolled in 1970–1971, and followed for 69 to 81 months. The relative risk for nonfilter *versus* filter cigarette smokers was reported as 1.54. The incidence was computed by dividing the numbers of cases by numbers enrolled, without considering person-years at risk. Adjustment was made for age and for quantity smoked.

In the Whitehall study (Higenbottam *et al.*, 1982), smoking data were available for 17 475 of 18 403 male civil servants aged 40–64 years who were enrolled during 1967–1969 and followed for at least ten years. Ten-year death rates, adjusted for age and employment grade, were computed for current smokers within categories of inhalation, quantity and tar-yield.

There were 108 deaths due to lung cancer among inhalers, and 35 among noninhalers, with tar- and quantity-specific rates for both groups shown in Table 4. Among inhalers, the data show a distinct dose-response at the two lowest consumption levels (1–9 and 10–19 cigarettes per day), although not at the highest, and among noninhalers there is a possible dose-response at the two highest levels (10–19 and 20 or more cigarettes per day).

Table 4. Ten-year lung cancer mortality rates (and number of deaths) among 17 475 male British civil servants in the Whitehall study, according to quantity smoked, tar yield, and inhalation [a]

No. cigarettes smoked per day	Tar yield (mg)		
	18–23	24–32	33+
Inhalers			
1–9	0.39 (2)	0.53 (1)	1.62 (7)
10–19	1.46 (19)	1.55 (8)	2.61 (20)
20+	2.23 (35)	2.00 (13)	1.79 (3)
Noninhalers			
1–9	1.08 (4)	0.00 (0)	0.93 (1)
10–19	1.25 (5)	1.28 (2)	4.18 (5)
20+	1.71 (7)	5.81 (9)	5.85 (2)

[a] From Higenbottam *et al.* (1982)

CANCERS OTHER THAN LUNG

Studies of cigarette yield and cancer have focused mainly on lung cancer, for the obvious reason that, having the greatest incidence and mortality rate of tobacco-related cancers, the numbers of cases available for study are greater than for other sites. Several studies, however, have examined the possible influence of cigarette yield on other cancers. In the American Health Foundation case-control studies, interviewers were instructed to see patients with cancers of the lung, mouth, oesophagus, larynx and bladder. Wynder and Stellman (1979) published relative risks for cancer of the larynx based on 286 male and 64 female cases. After adjusting for age, duration of smoking, number of cigarettes per day, and alcohol consumption, the risk of larynx cancer in nonfilter *versus* long-term filter cigarette smokers (at least ten years on filters) was 1.49 for men and 3.97 for women (both significant). The relative risk was greater for nonfilter than for filter cigarette smokers at every quantity level.

Lee and Garfinkel (1981) reported new analyses of data from the American Cancer Society follow-up study of 1959–1972, in which the relative mortality for smokers of low tar/nicotine cigarettes (as defined by Hammond *et al.*, 1976) was consistently lower in both men and women than for high tar/nicotine cigarettes for cancer of the buccal cavity and pharynx, oesophagus, larynx, bladder and pancreas. The adjustment procedure, based upon simultaneous matching for nine separate variables, rendered the numbers of effective ('adjusted') cases very small. The mortality ratios were statistically significant only for cancers of the oesophagus and bladder in women, and for none of the sites in men.

Wynder *et al.* (1976) gave relative risks for cancer of the oral cavity in a case-control study of 593 men and 280 women and matched controls: for nonfilter cigarette smokers *versus* nonsmokers, 7.8; for long-term filter cigarette smokers *versus* nonsmokers, 5.7; and for nonfilter *versus* long-term filter cigarette smokers, 1.4. Adjustment was made for age, but not for alcohol consumption. Significance levels were not given.

In a Canadian, population-based, case-control study of 480 male and 152 female case-control pairs, Howe *et al.* (1980) reported a reduced risk associated with the use of filter cigarettes compared to nonfilter cigarettes. A recent Italian study of 512 male bladder cancer cases and 596 controls gave a relative risk of 3.0 for nonfilter *versus* filter cigarette smokers (Vineis *et al.,* 1984). On the other hand, there was no difference for men between long-term filter and nonfilter cigarette smokers in the relative risk for bladder cancer in a case-control study by Wynder and Goldsmith (1977), which involved 574 cases and an equal number of matched controls.

DISCUSSION

There are many methodological issues which must be dealt with in the assessment of the relationship between cigarette yield and cancer outcomes. These fall roughly into four categories: questions of dosage, outcome, other etiological factors and confounding. The strengths and weaknesses of the studies described may be examined largely through attention to these four items.

Dosage

In any study of cigarette type and disease, dosage is the most important – and in some ways the most difficult – variable to estimate. There are many reasons for this.

In the first place, the average tar content of cigarettes has fallen considerably during the past 30 years, even within the same brand. Secondly, some smokers switch brands frequently, particularly in response to promotion of the new brands or in response to 'health' publicity. Thirdly, most smokers try to quit at some time in their lives; some are successful, others quit and begin again repeatedly. The actual lifetime dosage of persons in the latter category is quite difficult to determine. Finally, even in well-conducted interviews, subjects sometimes recall their smoking history imperfectly, especially regarding duration of smoking specific brands.

Many different ways of expressing cigarette dosage have been used, ranging from simple classification as filter *versus* nonfilter, to elaborate algorithms designed to account for 'complete' year-by-year smoking histories. Cumulative dosage measures have the advantage of taking into account the subject's entire history, including early smoking, which may have contributed disproportionately to lifetime tar exposure, since the cigarettes first smoked by persons now in the cancer age group had tar contents two to three times those of current cigarettes. It has the disadvantage of making cumulative scores 'pile up' at the beginning of a smoker's life, during the years when all cigarettes had high tar levels. Such scores may be insensitive to differences in tar levels between recent brands. Furthermore, cumulative dosage scores, particularly when expressed as 'pack-years', have the disadvantage of making two packs per day for 10 years equivalent to one pack per day for 20 years, necessitating further adjustment for duration or other parameters.

The wide range of tar exposure indices which have been used by various authors is shown in Table 5. These range from categorization of smokers as either filter or nonfilter cigarette smokers (Bross & Gibson, 1968; Wynder & Stellman, 1979), use of the tar rating of the

Table 5. Tar exposure indices used by various authors

Reference	Indices
Bross & Gibson (1968)	1. Quantity-duration combinations (low, medium, high) 2. Filter *versus* nonfilter
Hammond *et al.* (1976, 1977)	High, 25.8–35.7 mg; medium, 17.6–25.7 mg; low, below 17.6 mg
Mushinski & Stellman (1978)	Tar rating of current cigarette
Kunze & Vutuc (1980)	Σ(quantity × duration × k) where $k = 1$, below 15 mg; $k = 2$, 15–24 mg; $k = 3$, above 24 mg
Lubin *et al.* (1984a)	1. Lifetime filter *versus* mixed filter and nonfilter *versus* lifetime nonfilter 2. Within-country quintiles of: Σ(tar × quantity) / Σ(quantity) combined across five countries

current cigarette (Hammond *et al.*, 1976; Mushinski & Stellman, 1978), to fairly elaborate scoring systems presented by Lubin *et al.* (1984a), and Kunze and Vutuc (1980).

Finally, it has been repeatedly demonstrated and emphasized that people do not smoke identically to machines, and that the tar yields upon which machine analyses are based do not represent the true quantities of particulates or concentrations of vapour phase toxicants to which people were actually exposed (Kozlowski *et al.*, 1980; Benowitz *et al.*, 1983). At best, machine-determined yields give relative representations of degree of exposure to cigarette combustion products, such as tar.

Since, as has been seen in the preceding sections, the results of studies using different dosage measures are remarkably consistent, we may reasonably conclude that the basic principle that relative risk for lung cancer is in rough proportion to tar yield has been confirmed, despite these many difficulties and the disparities between studies, and that age-specific lung cancer rates may be expected eventually to reflect the falling average tar levels in many Western countries.

Outcome

In both case-control and follow-up studies, specification of the outcome under investigation is not trivial and may strongly influence interpretation of results. In the series of studies by Wynder and colleagues, and in those by Kunze and Vutuc, lung cancers were classified as Kreyberg Types I or II, the former invariably exhibiting a stronger dose-response to quantity of cigarettes smoked per day. If these observations are correct, it follows that any ameliorative effect of lower tar yield will be of lesser importance for adenocarcinoma of the lung than for squamous-cell carcinoma.

Other etiological factors

Smoking is the major cause of lung cancer in the populations studied, but it is not the only cause. Few of the studies mentioned have made adjustment for exposure to other factors related to occupation, environment, or nutrition. We have recently shown (Stellman, 1985) that smokers consume foods rich in vitamins A and C much less frequently than nonsmokers. Since vitamin A and similar compounds have been suggested as possible inhibitors of epidermoid cancers, it may in the future be desirable to examine dietary intake along with smoking history. None of the studies reviewed here have done so.

Other confounding factors

Most of the studies have adjusted for age and sex, but few have examined other potential biases in selection of subjects, differences in social class between cases and controls, etc. These are factors which, especially in hospitalized populations, can strongly affect smoking habits (Wynder *et al.*, 1984). Considering the consistency of results, despite the variety of study designs and populations summarized above, it is not likely that these confounding fachors have played a major role in the studies summarized here. However, it is important to keep them in mind when designing future studies.

CONCLUSIONS

In three series of case-control studies and three prospective studies conducted in the USA and Europe, the relative risk for lung cancer was found to be consistently lower in both male and female smokers of lower-yield cigarettes. This basic finding continued to hold irrespective of the many different ways in which dosage was expressed, whether qualitatively (filter *versus* nonfilter) or quantitatively (with explicit tar yields or ranges). Risks for other types of cancer, notably mouth, larynx and bladder, were also found to be lower in smokers of filter cigarettes in a number of North American and European studies.

This is all the more remarkable since the designs of studies differed considerably, and the designation of cigarette tar yields for specific cigarettes reflected only crudely true lifetime exposures for individuals. Smokers reaching lung cancer age during the past few years have almost invariably begun smoking nonfilter cigarettes, and many switched to filters during the 1960s, when health warnings gained prominence. It is very likely that as successive cohorts of smokers are exposed to cigarettes of much lower yield for much greater proportions of their lives, the associated risks will decline even further. However, it is to be emphasized that in all studies, risks of smokers of all types of cigarettes, no matter the yields, were significantly higher than those of lifetime nonsmokers.

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