Trends in lung cancer in nonsmokers

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It has been suggested by a number of authors that factors other than smoking are playing an increasing role in the aetiology of lung cancer. In theory, one of the most direct methods of obtaining evidence on this would be to study trends over time in the risk of lung cancer among lifelong nonsmokers. In practice, there are a number of reasons why it is quite difficult to obtain such evidence.

Firstly, it should be realized that national mortality statistics, which give voluminous data on risk of disease by cause, age, sex, country and year, do not give data broken down by smoking habits. This is because they are based on death certificates, where smoking habits are not recorded. Estimates of risk of lung cancer in nonsmokers can only be obtained from prospective epidemiological studies (case-control studies can only determine relative, not absolute, risk). Such studies have to be very large indeed to get reliable results, given the rarity of lung cancer in nonsmokers. For example, 20 years' observations on 34,440 male British doctors (Doll and Peto, 1976) only yielded 10 lung cancer deaths in nonsmokers, far too few to determine any time trend reliably. There are only a very limited number of studies which have the potential to produce useful data.

Based on the two American Cancer Society (ACS) Cancer Prevention Studies (CPS), each of over a million men and women, the first starting in 1959 with follow-up for 12 years, the second starting in 1982 with follow-up for four years, Garfinkel and Silverberg (1990) compared age-standardized lung cancer death rates in four four-year periods. As shown in Table 1, there was no real evidence of a time trend, with, in each sex, rates quite comparable in the four periods. A similar conclusion can be reached from results of an earlier analysis (data also shown in the table) based on partly incomplete follow-up (US Surgeon-General, 1989).

There are some difficulties in interpreting directly from these data that no increase has occurred:

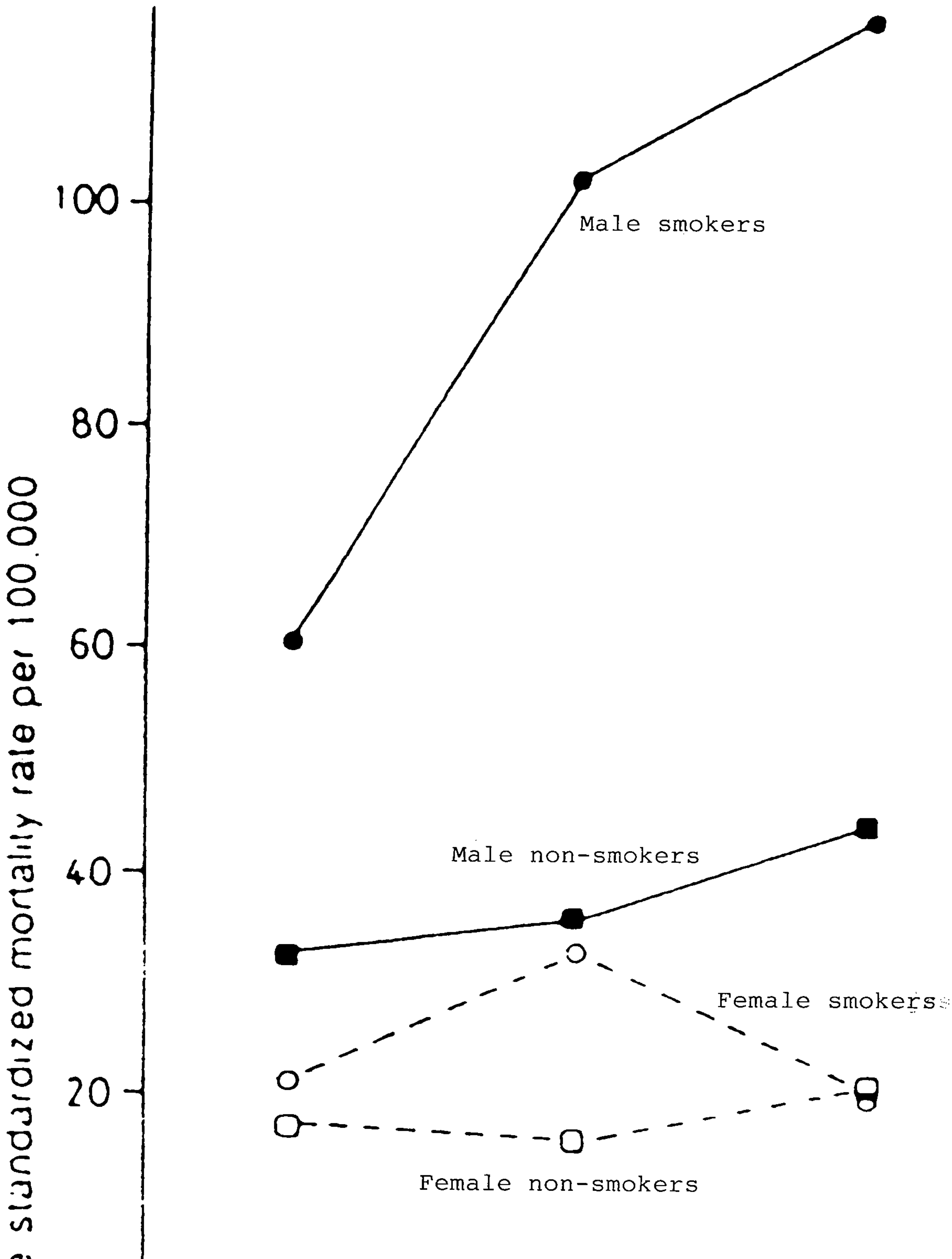
(a) Sampling variation does not exclude the possibility of a modest true increase having occurred.

(b) The populations studied are known to be unrepresentative of the US population at large, being virtually wholly white, much more educated and affluent than average, and much less likely to work in occupations that incur a high risk of lung cancer.

(c) The diagnoses are based on death certificates which are known to be unreliable. In the absence of autopsy, which infrequently occurs, clinical diagnosis of lung cancer has been shown to be inaccurate, with evidence (Feinstein and Wells, 1974) of a particular problem in nonsmokers. It is not clear, however, what effect such inaccuracy should have on trends.

Another US study which has been studied for trends in nonsmokers' lung cancer death rates is the US Veterans' Study, in which over a quarter of a million US veterans were interviewed in 1954 or 1957 and followed-up for up to 16 years. Doll and Peto (1981) presented results of an analysis (see Table 2) which again showed no evidence of any significant trends over time. Considering these data, and also those from CPS-I, Doll and Peto remained "unconvinced that any material trends in true lung cancer death rates among American non-smokers have occurred in recent decades", though they noted that "some such increases should be expected if the effects of passive smoking reported by Hirayama (1981) and Trichopoulos et al (1981) are confirmed".

A third large prospective study which has provided some data on trends in lung cancer is the Japanese study of Hirayama in which over a quarter of a million Japanese men and women, interviewed in 1965, were followed up for 17 years. In his book, Hirayama (1990) presented a graph (reproduced below) showing trends in age-standardized lung cancer rates over three periods, 1966-72, 1973-77, and 1978-82. In both sexes a slight increase is seen in nonsmokers' lung cancer rates over the period, but Hirayama makes no statement as to statistical significance. Given further data presented in the same book (see Table 3) showing inconsistent time trends in nonsmokers in different age groups, it appears the increases are probably not significant. One must have considerable reservations about the validity of these analyses, since they do not show the expected rise in risk with age, and because of a number of other study weaknesses discussed elsewhere (Lee, 1992).


Age standardized mortality rate per 100,000
100
80
60
40
20
0
Male smokers
Male non-smokers
Female smokers
Female non-smokers
1966-72
1973-77
1978-82

There have been a number of other attempts to try to gain information on trends in lung cancer among nonsmokers.

Enstrom (1979) presented a paper claiming that lung cancer mortality among persons who never smoked cigarettes rose substantially between 1914 and 1968. Though he concluded that most of the relative increase that occurred before 1935 was probably due to changes in diagnostic criteria, he considered that real increases had occurred since 1935, and that factors other than cigarette smoking had had a significant effect on the mortality rate from this disease. In order to obtain data on trends in this period he used four sources of information:

1914: Data for 24 states on overall lung cancer rates, it being assumed that the data were representative of the US and that they would have been unaffected by smoking at that time, i.e. they could be assumed to be nonsmokers' rates.

1935: National data on overall lung cancer rates, it being assumed that for those aged 65 or over, nonsmokers had the same rates as the total population;

1958: Data from the 1958-59 National Mortality Survey, which combined information from a nationally representative 10% sample of all deaths in the US, for whom data on smoking were obtained by a questionnaire sent to the family informant, and a representative sample of the living population, who were asked questions *inter alia* on smoking.

1966-68: Similarly to the 1958 data.

The main results from Enstrom's analysis are summarized in Table 4. Although they shown a markedly increasing trend, there are two major problems in inferring any true increase in lung cancer rates. The first, noted by Enstrom, is that substantial improvements in diagnosis had occurred. Certainly it is well known that in 1914 the ability to detect lung cancer in-life was very limited. The second major problem is that the smoking data collected in 1958 and 1966-68 came from proxies. Given a proportion of respondents would never have known the full life history of the decedent, it is likely, as pointed out by Doll and Peto (1981), that some of the so-called lifelong nonsmokers were in fact ex-smokers. As the risk of lung cancer in ex-smokers was increasing with time, correlated with the increasing likelihood of having smoked for longer periods of time, this inclusion of ex-smokers might have caused an apparent increase in risk among men and women reported to be smokers when no true increase in fact existed. In support of this argument, Doll and Peto pointed out that age-adjusted lung cancer death rates in nonsmokers in the 1966-68 National Mortality Survey were actually 80% higher than seen in CPS-I (1960-72). However, it must be pointed out that it is not clear whether the whole of this excess is due to more true ex-smokers being included since, as noted above, the CPS-I population is unrepresentative in many ways.

Enstrom (1979) also included a comparison (reproduced in Table 5) of lung cancer rates in men who had never smoked in the US Veterans Study and in the ACS CPS-I study, referable to the period 1954-63, and in active Mormons in California, referable to the period 1968-75. Although death rates in the Mormons were about twice as high as those in the other groups, Doll and Peto (1981) point out that this is not actually evidence that nonsmoker death rates increased at all between 1960 and the early 1970's, the reason being that about one-third of active Mormons in California are actually ex-smokers and not all lifelong never smokers, as would be necessary for a valid comparison. It is also far from clear that the populations of the three studies are comparable in respect of many variables other than smoking.

Mori and Sakai (1984) carried out a study involving all 15,367 cases autopsied over the period 1936 to 1978 in the Department of Pathology at the University of Tokyo. From the clinical history abstracts attached to the autopsy protocol 6610 cases, 4269 men and 2341 women, were selected who were aged 20 or over and who had cigarette smoking history available. As shown in Table 6, there was a striking tendency for age adjusted incidence of lung cancer to rise among nonsmokers, with risk rising significantly ($p<0.05$) in both sexes. In interpreting this finding, a number of points have to be considered:

(i) Since these were all autopsy cases, improvements in diagnosis can effectively be excluded as an explanation for the increase.

(ii) There was a striking increase in average age of the cases over the study period, but age adjustment should have accounted for this.

(iii) It is unclear how representative the autopsied population is of all deaths. The autopsy rate is known to be very low in Japan.

(iv) Smoking data taken from clinical notes may be seriously inaccurate. The probability of cigarette smoking history being available for a lung cancer case might have increased dramatically. At the beginning of the study lung cancer was not known to be associated with smoking, but at the end it would be difficult to imagine a suspect lung cancer case not being asked about his smoking habits.

(v) Lung cancer rates have risen very steeply in Japan since the war, much more so than in Western countries. Hirayama (1981) presented a graph showing a 10-fold increase between 1947 and 1978, whereas Hirayama (1984) reported smoker/nonsmoker relative risks much lower than this. This suggests a major effect of factors other than smoking in Japan.

(vi) Mori and Sakai themselves felt their results indicated that factors such as atmospheric pollution, heavy metals, asbestos, diesel exhaust, and urbanization were possibly as important or more important than cigarette smoking.

Stevens and Moolgavkar (1984) carried out a statistical analysis relating age-specific data on trends in male lung cancer deaths in England and Wales over the period 1941-45 to 1971-75 to UK data on the annual percentage of smokers and an estimated cumulative constant tar cigarette consumption by age and birth cohort. They fitted a model in which risk was estimated as a product of terms representing effects of age, cigarette consumption and period of death. Their model explained more than 99% of the observed variation in death rates. One conclusion of their model was that lung cancer rates among nonsmokers had been declining continuously since 1951-55 (see Table 7), a decline they attribute to reductions in smoke and SO_2 pollution. Although Lee, Fry and Forey (1990) also concluded, by means of a rather different approach, that there had been some decline in lung cancer rates in young men and women that cannot be attributed to cigarette smoking, Stevens and

Moolgavkar's paper is weak in that the function they fit to account for effects of cigarette smoking is totally implausible, implying inter alia that a smoker aged 75 who smoked two packs a day would have 7000 times the risk of lung cancer of a smoker aged 75 who did not smoke. Clearly the form of the function used to fit cigarette smoking effects may have a dramatic effect on conclusions regarding nonsmokers.

Another indirect attempt to estimate trends in nonsmokers' death rates is the truly dismal paper by Axelson et al (1990). They correctly pointed out that, given the lung cancer rate for the total population (L), the proportion of the population who have ever smoked (S), and the relative risk of lung cancer for ever smokers compared to never smokers (R), one can easily estimate the lung cancer rate for never smokers. Using estimates of L, S and R for Japan, Italy and the US at various time points they then concluded that there has been a positive time trend in each country in rates for never smokers. An obvious major flaw in their analysis is that they assumed R does not vary over time when there is good evidence that it has increased substantially. (Compare, for example, the estimates of R=2.69 for 1959-65 and R=11.94 for 1982-86 given in the 1989 Surgeon-General's Report based on the two American Cancer Society Cancer Prevention Studies). This on its own is sufficient to totally invalidate their analysis, but there are a number of other weaknesses too, including failure to study age-specific rates, failure to consider possible effects of smoking habit misclassification on the estimates of R, and assuming that lung cancer rates can be accurately estimated simply on the basis of the percentage of smokers 20 years earlier. At one point in their paper they did consider the possibility that increased duration of smoking might have biased their analysis but they dismissed this on the basis of results of Garfinkel and Stellman (1988) which they interpreted as showing only a weak effect of duration. However, their interpretation is totally erroneous, based on a false comparison of two standardized mortality rates with different bases. The whole paper, which is extremely superficial, can be considered worthless.

A better indirect attempt to estimate trends in nonsmokers' death rates was made by Forastière et al (1993). Based on smoking habit surveys conducted in Italy in 1957, 1965, 1980 and 1986-87 and national estimates of lung cancer mortality rates for 1956-58, 1965-67, 1980-82 and 1987-89, the authors estimated lung cancer death rates in nonsmokers based on four different models:

Model 1 - Relative risks for smokers and ex-smokers constant over the period (10 and 4 for males; 4 and 1.6 for females)

Model 2 - Relative risks for smokers and ex-smokers depend on the average number of cigarettes smoked per day, but not on duration of smoking

Model 3 - Relative risks for smokers and ex-smokers depend on a function given by Whittemore (1988) in which excess risk is a product of duration of smoking and packs per day

Model 4 - Relative risks for smokers and ex-smokers depend on a "multistage" function fitted by Whittemore (1988) to data for British doctors.

As shown in Table 8, all models in both sexes showed a consistent rise over the period studied. The authors reported that the rises were evident in analysis by separate age group and claimed that in sensitivity analysis (using Model 4) the conclusions were similar even after taking account of possible underestimation of smoking, different assumed values of age of starting to smoke (data for 1957 and 1965 were not available and had to be estimated), and different assumed values of the parameters in Whittemore's "multistage" function.

Though suggestive that, as the authors conclude, "factors other than smoking play an important role in causing lung cancer in Italy", one must have reservations for a number of reasons. Firstly, the results involving Model 1 and Model 2 are likely to be irrelevant since they do not take duration of smoking into account at all. Secondly, the functions used in Model 3 and Model 4, and the assumed data for age of starting to smoke in 1956-58 and 1965-67, may not have taken duration of smoking properly into account. Observed trends over time in smokers' relative risk reported elsewhere (see comments on the Axelson et al paper) have been much greater than those fitted here from Model 4 (rising from 7.2 to 13.1 in males and from 2.6 to 4.0 in females between 1956-58 and 1987-89), which may be indicative of poor fit of the model or use of inappropriate data. Also it should be noted that Whittemore's Model 4 for the risk at age t in smokers starting at age t_0 and stopping at age t_1 is not actually multistage at all. (Ignoring the lag period of five years) she uses a function of the form

$$R = At^k + B(t_1-t_0)^k + C(t_1{}^k-t_0{}^k) + D(t_1-t_0)^k$$

where the proper function under the assumptions she makes (first and penultimate stages of the cancer process affected) should be of the form

$$R = At^k + B((t-t_1)^k-(t-t_0)^k) + C(t_1{}^k-t_0{}^k) + D(t_1-t_0)^k$$

The functions are the same for current smokers (t_1=t) but not for ex-smokers.

Further work using these data seems necessary (and is planned) to check the validity of the authors' conclusions.

Summary

Direct observations of trends in nonsmokers' lung cancer rates do not suggest any obvious increase in risk has occurred since the second World War, though the possibility of a modest increase is not ruled out, especially in Japan. Indirect estimates of trends which purport to indicate much larger variations in risk tend to have obvious technical weaknesses and be difficult to interpret, though the analysis by Forastière et al demands further attention. It must be concluded that at this point in time there is no very good evidence that lung cancer death rates in nonsmokers have actually increased in recent years.

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TABLE 1: Trends in lung cancer rates (per 100,000 per year) in US nonsmokers (ACS data)

		Male	Female
From Garfinkel and Silverberg (1990)[1]			
1960-64	CPS-I	14.6	11.7
1965-68		16.6	12.4
1969-72		16.7	12.2
1982-86	CPS-II	15.4	12.1
From US Surgeon-General (1989)[2]			
1959-65	CPS-I	15.5(12.5-19.3)	10.3(8.9-11.9)
1982-86	CPS-II	13.6(10.8-17.0)	11.4(9.8-13.3)

[1]Rates standardized to the age distribution of the US population in 1970.

[2]Rates standardized to the age distribution of the US population in 1965; death rates for CPS-II corrected for delayed ascertainment of cause of death, all death certificates not having been received at the time the analysis was conducted; numbers in parentheses are 95% confidence intervals.

TABLE 2: Trends in lung cancer rates in male US nonsmokers (US veterans' data)

Years since entry to study[1]	Lung cancers Observed	Expected[2]	Ratio
1	6	6.5	0.9
2,3,4	24	23.6	1.0
5,6,7	31	30.9	1.0
8,9,10	40	39.2	1.0
11,12,13	41	43.9	0.9
14,15,16	35	33.0	1.0
Total	177	177.0	1.0

[1] There were two samples of veterans, one interviewed in early 1954, one in early 1957.

[2] Expected assuming there is no trend over time in lung cancer rate.

TABLE 3: Trends in lung cancer rates (per 100,000 per year) in male Japanese nonsmokers (Hirayama data)

Period	Age group 55-59	60-64	65-69	70-74
1966-72	7	15	28	51
1973-77	43	24	49	72
1978-82	0	37	13	48

TABLE 4: Trends in US lung cancer rates (per 100,000 per year) in nonsmokers (Enstrom data)

Sex	Year	Smoking[1]	Age group 55-64	65-74	75-84	35-84[2]
Male	1914	NSC	3.0	2.6	1.2	1.6(148)
	1935	NSC	-	26.7	23.3	-
	1958	NS	12.7	25.0	55.0	10.8(80)
	1958	NSC	14.8	33.7	69.7	13.3(80)
	1966-68	NSC	32.2	65.6	89.9	22.8(108)
Female	1914	NS	2.2	2.2	1.5	1.3(124)
	1935	NS	9.8	14.5	14.5	-
	1958-9	NS	10.4	21.0	34.0	8.3(456)
	1966-68	NS	11.4	19.6	38.8	8.3(123)

[1] NS = never smoked, NSC = never smoked cigarettes

[2] Age adjusted to the 1960 US population, numbers of deaths in parentheses

TABLE 5: Comparison of lung cancer rates (per 100,000 per year) in three groups of white males (Enstrom data)

Study population	Year	Age group 55-64	65-74	75-84	35-84[1]
US Veterans					
Never smoked or occasionally only	1954-62	10	32	50	9.4(78)
Never smoked cigarettes	1954-62	12	38	60	12.7(156)
ACS CPS-I					
Never smoked regularly	1960-63	15	15	44	10.4(49)
Never smoked cigarettes	1960-63	18	29	56	13.4(104)
US Veterans + ACS CPS-I combined					
Never smoked	1954-63	12	26	45	10.8(127)
Never smoked cigarettes	1954-63	14	35	57	13.1(260)
Active Mormons					
All	1968-75	28	54	145	24.5(63)

[1] Age adjusted to the 1960 US population, numbers of deaths in parentheses.

TABLE 6: Trends in lung cancer incidence[1] among autopsied men and women in Tokyo (Mori and Sakai, 1984)

Period	Men	Women	Total
1936-45	0.2%	1.2%	0.8%
1946-55	1.8%	1.6%	2.0%
1959-68	3.2%	3.9%	4.0%
1969-78	6.0%	4.2%	4.7%
Trend p	<0.05	<0.05	<0.02

[1]Age adjusted.

TABLE 7: Trends in estimated lung cancer death rate (per 100,000 per year) among British male nonsmokers aged 35-84 (from Moolgavkar and Stevens)

Year	Lung cancer rate
1941-45	14.9
1946-50	17.8
1951-55	19.3
1956-60	18.8
1961-65	14.0
1966-70	12.0
1971-75	8.6

TABLE 8: Estimated trends in lung cancer rates (per 100,000 per year) in Italy (Forastière data)

Model (see text)	Sex	Years 1956-58	1965-67	1980-82	1987-89
1. (constant RRs)	Male	3.2	6.0	12.4	15.8
	Female	4.6	6.1	7.2	8.2
2. (dose)	Male	4.1	7.8	12.9	16.6
	Female	4.5	6.1	5.6	6.3
3. (dose and duration, packs-function)	Male	3.3	6.0	9.3	10.6
	Female	5.1	6.8	7.1	7.5
4. (dose and duration, multistage)	Male	4.4	7.9	11.8	12.3
	Female	5.1	6.9	7.4	8.1