Potential bias in epidemiological studies of lung cancer and type of cigarette due to failure to control for cigarette consumption

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I have recently reviewed the epidemiological evidence relating lung cancer risk to type of cigarette smoked (filter/plain, high tar/low tar, handrolled/manufactured, menthol/nonmenthol, black/blond) both in a paper submitted to the British Medical Journal and in a more extensive unpublished review paper. My general conclusions with regard to the switch to low tar/filter cigarettes is that this is associated with a moderate reduction in risk which is likely to be an underestimate of the true difference in risk between that of lifetime high tar/plain cigarette smokers and that of lifetime low tar/filter cigarette smokers. Thus, the relative risk of lung cancer in filter and plain cigarette smokers (or with most and least filter use) was estimated as 0.64 (95% confidence interval 0.56-0.73) based on 43 sex-specific estimates, while that comparing risk in higher and lower tar cigarette smokers was 0.77 (95% confidence interval 0.69-0.87), equivalent to about a 2 to 3% risk reduction per mg tar per cigarette. I considered compensation in terms of switchers to low tar/filter increasing their numbers of cigarettes smoked to be a minor issue in the interpretation of the evidence.

In a recent presentation at a meeting organised by the US Institute of Medicine, David Burns has, I am told, put forward the view that the trend towards low tar cigarettes has been of no benefit whatsoever, the epidemiological evidence being flawed due to failure to take account of compensation in terms of numbers smoked.

It is worth considering the merits of the alternative views in a little more detail. One has to be aware that there are two distinct questions one might wish to answer when comparing the relative risks of smoking lower and higher tar cigarettes. Firstly, one might answer the question:

Q1. Is the risk associated with smoking a given number of lower tar cigarettes less than that associated with smoking the same number of higher tar cigarettes?

This question relates to the specific carcinogenicity of the different types of cigarette.

Secondly, one might answer the question:

Q2. Will a typical higher tar cigarette smoker reduce their risk of lung cancer by switching to lower tar cigarettes?

This is the relevant public health question. It is scarcely much use if lower tar cigarettes are less carcinogenic to the lung than are higher tar cigarettes, if in fact the advantage is cancelled out in practice by the increased consumption following switching.

It is important to realise that there are actually two quite separate and quite plausible possibilities to be taken into account when considering how to take into account potential biases due to differences in numbers smoked by lower and higher tar cigarette smokers.

First, those who choose to switch may well be a nonrepresentative sample of those originally smoking the higher tar cigarettes. It is plausible that those who choose to switch are less "addicted" and more health-conscious and may smoke less cigarettes than average.

Second, as we have already noted, those who switch may increase their consumption following switching.

Suppose that we consider a population consisting of two groups:

A. Higher tar cigarette smokers who choose not to switch to lower tar cigarettes.

B. Higher tar cigarette smokers who choose to switch.

Let:

μ be the mean cigarette consumption of group A,

μ/F be the mean cigarette consumption of group B before the switch, and

$\mu G/F$ be the mean cigarette consumption of group B after the switch.

We assume both F and G are ≥ 1.

Suppose that risk of lung cancer is proportional to the product of the number of cigarettes smoked after the switch and the relative carcinogenicity of the two types of cigarette (per cigarette). Suppose that this relative carcinogenicity is 1 unit for higher tar cigarettes and is 1/H units for lower tar cigarettes.

We assume H is ≥ 1.

To answer the public health question and demonstrate an advantage to lower tar cigarettes, we have to demonstrate that the risk of switchers following the switch, which is proportional to $\mu G/(FH)$, is less than the risk of switchers before the switch, which is proportional to μ/F. In other words, we have to demonstrate that $G/H < 1$ or that $G < H$, i.e. that the proportional reduction in relative carcinogenicity is greater than the proportional increase in cigarette consumption resulting from the switch.

Epidemiological studies can, in principle, carry out four types of comparison of lower and higher tar cigarettes:

1) Risk can be compared unadjusted for cigarette consumption. The relative risk, so calculated, R_1, should be an estimate of G/FH. This underestimates the ratio of interest, G/H, by a factor F.

2) Risk can be compared adjusted for cigarette consumption following the switch. The relative risk, so calculated, R_2, should be an estimate of 1/H. This underestimates the ratio of interest by a factor G.

3) Risk can be compared adjusted for cigarette consumption before the switch. This should correctly estimate the ratio of interest.

4) Risk can be compared adjusted for average lifetime cigarette consumption. This should underestimate the ratio of interest, but by a smaller factor than G.

The same conclusions regarding the ability of the three types of comparison to estimate the ratio of interest correctly can also be reached if, instead of assuming that risk is dependent on current consumption and tar level, one assumes it is dependent both on current consumption and tar level and on previous consumption and tar level.

The problem, of course, is that in practice researchers typically do not report results for comparison 3. They report results sometimes for comparison 1, sometimes for comparison 2, sometimes for comparison 4, and sometimes for more than one of these comparisons. All are biased downwards.

Alright, reported epidemiological analyses are likely to be biased downwards for these reasons, but is this bias likely to be material?

The most convenient way to look at this is to restrict attention to the epidemiological studies which have adjusted for number of cigarettes smoked, look at the overall estimate of reduction in risk from these studies, and then compare this estimate with external evidence on changes in consumption within-smoker on switching to lower tar cigarettes.

In Table 1 of my paper submitted to the BMJ, I give 43 filter/plain relative risk estimates which can be used in a meta-analysis. For all the estimates combined the random-effects meta-analysis estimate was 0.64 (0.56-0.73). Restricting attention to the 26 which had adjusted for amount smoked (or pack years) the random-effects meta-analysis was 0.65 (0.56-0.77).

In Table 3 of my paper, I give 22 usable estimates of the lower tar/higher tar relative risk, which combined give a figure of 0.77 (0.68-0.88). Restricting attention to the 20 which adjust

for amount smoked, the combined estimate is 0.75 (0.66-0.85). This is equivalent to about a 2 to 3% increase in risk of lung cancer per mg tar/cigarette. For a 50% decrease in tar, from say 20 to 10 mg/cigarette, the reduction in risk of lung cancer estimated by the epidemiology would be to $(0.97)^{10}$ to $(0.98)^{10}$ of its original level, i.e. to 0.74 to 0.82 or an 18-26% decrease.

The two best sets of data I am aware of regarding change in consumption following change in tar/nicotine delivery are both quite old.

One comes from an excellent and concise review by Stepney[1] of the published experimental data on the issue. His analysis came up with the following predictions:

Reduction in nicotine delivery	10%	30%	50%	70%	90%
Increase in consumption	1%	5%	9%	13%	18%

In other words, his conclusion was that reducing tar and nicotine caused an increase in consumption, but to only a proportionately quite small degree.

It is clear that his analysis is reporting an increase in consumption following switching that is too small to explain the more substantial reduction in risk observed epidemiologically.

The other is the analysis by Garfinkel[2] of data from the ACS CPS-I study relating changes in tar/nicotine level of cigarettes smoked between 1959 and 1972 in relation to changes in cigarette consumption. The main data are summarised below:

Change in T/N Level of Cigarette 1959-72	Changes in number of cigarettes smoked 1959-72 Total No.	%	Increased (Row %)	Same (Row %)	Decreased (Row %)
Increased	3380	11.8	29.1	32.2	38.7
Same	8190	28.7	31.7	33.8	34.7
Decreased	16991	59.5	31.5	34.1	34.4
TOTAL	28561	100.0	31.2	33.8	35.0

The table shows that the proportion of smokers reporting increases, decreases or no change in the number of cigarettes smoked between 1959 and 1972 was virtually identical in the 3 groups of smokers compared - those reporting increases, decreases or no change between 1959 and 1971 in the tar/nicotine level of the cigarette smoked.

These data suggest essentially no change in consumption following tar reduction.

Obviously one would like more data, but until I see more details of Burns' claim I see no reason to change my view that the switch to low tar/filter cigarettes has led to a substantial reduction in risk of lung cancer.

REFERENCES

Stepney R. Consumption of cigarettes of reduced tar and nicotine delivery. *Br J Addict* 1980;**75**:81-8.

Garfinkel L. Changes in the cigarette consumption of smokers in relation to changes in tar/nicotine content of cigarettes smoked. *Am J Public Health* 1979;**69**:1274-6.