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Relationship between cigarette smoking and histological type of lung cancer in women

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In recent years there has been an increase in the incidence of lung cancer in women so much so that the rate of increase exceeds the rate of increase in men. This change in incidence has been associated with cigarette smoking and as it is considered that smoking is connected mainly with the squamous and undifferentiated forms of tumour it might be expected that a recent change in the proportions of the different histological groups would be demonstrable.

All histological sections of proven cases of lung cancer in women seen between 1955 and 1971 at the Sheffield Royal Infirmary have been reviewed. A rise in the proportion of female cases attending hospital was noted but this rise has been associated with an increase in the proportion of cigarette smokers only in recent years. However, there is no good evidence of a change in the histological pattern of the disease and no statistically significant evidence of a connection between cigarette smoking and any particular cell type in the cases studied. Comparison with other studies confirms that cigarette smoking has only a small influence on the cell type of lung cancers in British women, but in American women there is a strong association between smoking and tumours of Kreyberg's group I. This appears to be a real and unexplained difference between the behaviour of lung cancers in British and American women.

Lung cancer in women is on the increase and the rate of increase is now greater than the rate of increase in men (*Lancet*, 1971; Royal College of Physicians, 1971). In their report the Royal College of Physicians associate this rise with an increase in cigarette consumption by women. It might then be expected that a change in the histological type of lung cancer might be demonstrable for it is the squamous, oat-cell, and large-cell undifferentiated tumours which in males have been particularly associated with cigarette smoking whereas adenocarcinomas do not show such a strong association (Doll, Hill, and Kreyberg, 1957; Kreyberg, 1962; Wynder, Mabuchi, and Beattie, 1970; Kreyberg, 1971). In order to see whether such changes have taken place all the histologically proven cases of lung cancer in women seen at the Sheffield Royal Infirmary during the last 17 years have been reviewed from the point of view of the type of tumour involved and the smoking history. The results of this retrospective survey indicate that cigarette smoking has little influence on the histological appearance of lung cancer in British women.

MATERIALS AND METHODS

All female cases of lung cancer found in the surgical pathology and necropsy files for the years 1955 to 1971 were included if satisfactory paraffin blocks were available for study. Paraffin sections were stained with haematoxylin and eosin and by the modified Masson technique of Kreyberg, Liebow, and Uehlinger (1967) which stains both mucin and keratin. Additional stains for mucin and elastic tissue were used when appropriate. The tumours were classified, using the same principles as Whitwell (1961), into squamous-cell, oat-cell, large-cell undifferentiated, and adenocarcinoma. Because of the relatively small numbers in some groups of tumours, the large-cell undifferentiated tumours were grouped with the oat-cell carcinomas for statistical purposes. For comparison with the results of other authors the Kreyberg system of grouping was used—squamous, oat-cell, and large-cell undifferentiated carcinomas forming group I and the adenocarcinomas forming group II. Combined squamous and adenocarcinomas, the tumours of bronchial gland origin, sarcomas, and other non-epithelial tumours were not included.

The clinical records were studied only after the tumours had been classified. Particular attention was

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paid to the care with which the history of smoking was recorded. All patients in whom a regular daily cigarette consumption was recorded, varying from 2 to over 40 per day, were regarded as smokers. Many patients had been described as non-smokers and in some no smoking history was available.

In order to assess the change over the 17 years studied the years were divided into three four-year periods and one five-year period (1955–59). The significance of the results was tested using the chi-squared method.

RESULTS

The findings are based on 168 cases which occurred in the periods of time shown in Table I: this shows an increase in each four-year period from 5 to 15 cases per annum. Not only has the absolute number of cases increased but there has also been an increase relative to the number of males as shown in Table II which includes only the cases diagnosed at thoracotomy or by bronchial biopsy. In this group there has been a fall in the male: female ratio from 14·9:1 to 6·0:1; this change in the proportions is very significant ($\chi^2=11{\cdot}69$ $P<0{\cdot}01$) but as the changes in the numbers of both men and women are not smooth it is probable that there has been some variability in the pattern of referral to hospital.

TABLE I

DISTRIBUTION OF 168 CASES OF LUNG CANCER IN WOMEN BY YEAR OF DIAGNOSIS

1955–59	1960–63	1964–67	1968–71	Total
23	38	49	58	168

TABLE II

NUMBER OF MALE AND FEMALE CASES[1] OF LUNG CANCER DIAGNOSED BY BRONCHIAL BIOPSY AND THORACOTOMY DURING THE PERIOD STUDIED

	1955–59	1960–63	1964–67	1968–71	Totals
Males	254	225	268	318	1,065
Females	17	33	43	53	146
M/F ratio	14·9	6·8	6·2	6·0	7·3

[1]Cases diagnosed only at necropsy are not included.

The smoking history was available in only 112 cases; the number of cases was so small in the earlier years that the period 1955–63 has had to be treated as one unit (Table III). The proportion of the patients who were cigarette smokers rose from 61% in the first nine years, fell to 56%, and then rose to 88% during the last four years, an increase which is significant ($P<0{\cdot}02$).

Table IV shows the proportions of the different cell types seen during the period under study. The figures show that there has been a small rise in the proportion of squamous-cell carcinomas but also there have been irregular fluctuations in the proportions of oat-cell and adenocarcinomas. There is perhaps a fall in the number of large-cell undifferentiated tumours. For the purposes of statistical analysis the large-cell undifferentiated tumours, being few in number, were combined with the oat-cell cancers and they were all treated as undifferentiated tumours. No statistically significant change is revealed over the 17-year period studied.

If the figures are combined, as in the Kreyberg system of grouping, the changes are again not statistically significant and, contrary to what might be expected, the proportion of group I tumours shows an irregular slight decline from over 90% to the region of 70% in the period 1968–71.

TABLE III

SMOKING HISTORY IN 112 FEMALE CASES OF LUNG CANCER

	1955–63	1964–67	1968–71	Totals
Cigarette smokers	19 (61%)	18 (56%)	43 (88%)	80
Non-smokers	12	14	6	32
Totals	31	32	49	112

The proportion of smokers rose from 61% in the years 1955–63 to 88% during the last 4 years ($\chi^2=10{\cdot}895$, df=2, $P<0{\cdot}02$).

TABLE IV

DISTRIBUTION OF DIFFERENT CELL TYPES BY YEAR OF DIAGNOSIS

Cell Type	1955–59	1960–63	1964–67	1968–71	Totals
Squamous-cell ..	4 (17%)	7 (18%)	16 (33%)	16 (28%)	43
Oat-cell	13 (57%)	16 (42%)	20 (41%)	26 (45%)	75
Large-cell undifferentiated	4 (17%)	4 (11%)	4 (8%)	2 (3%)	14
Adenocarcinoma	2 (9%)	11 (29%)	9 (18%)	14 (24%)	36
Totals	23 (100%)	38 (100%)	49 (100%)	58 (100%)	168

There is no consistent alteration in the proportion of any one type of tumour apart from a small rise in the proportion of squamous tumours which is not statistically significant. This table includes 48 cases in which the smoking history is unknown.

TABLE V

RELATIONSHIP BETWEEN TYPE OF TUMOUR PRESENT AND SMOKING HISTORY IN 112 FEMALE CASES OF LUNG CANCER

	Squamous-cell Carcinoma	Undifferentiated Carcinoma	Adeno-carcinoma	Total
Smokers	23	42	15	80
Non-smokers	7	15	10	32

There is a slight excess of adenocarcinomas among the non-smokers but this is not statistically significant ($\chi^2=2{\cdot}509$, df=2, $0{\cdot}20<P<0{\cdot}30$).

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The relationship of the cell type of the tumours to the smoking history is shown in Tables V and VI. The large-cell undifferentiated tumours have been grouped with the oat-cell carcinomas as mentioned above. There are fewer adenocarcinomas among the smokers as compared with the non-smokers but the trend is not statistically significant whichever way the tumours are grouped.

TABLE VI

RELATIONSHIP BETWEEN KREYBERG GROUP OF TUMOURS AND CIGARETTE SMOKING

	Kreyberg Group I	Kreyberg Group II	Totals
Smokers ..	65	15	80
Non-smokers ..	22	10	32
Totals	87	25	112

As in Table V, the slight excess of adenocarcinomas among the non-smokers is not statistically significant ($\chi^2 = 2{\cdot}283$, df = 1, $0{\cdot}1 < P < 0{\cdot}2$).

DISCUSSION

These results confirm that the national increase in lung cancer observed in women has also been reflected in the pattern of cases attending Sheffield Royal Infirmary, although the trend may have been magnified by local factors governing the referral of cases as the enormous change in the incidence in women is much greater than the national change (*Lancet*, 1971). There has been an increase in the absolute number of cases in women and in the numbers relative to the number of male cases, and as there is no suggestion that the number of male cases is falling this must be regarded as confirmatory evidence that a rise of incidence in women has taken place.

The increase in the proportion of cigarette smokers among the patients is not consistent and involves only the period 1968–71; without a control group to show the change in smoking habits in women without lung cancer no firm conclusions can be drawn as to whether this change could be causal. As the association of smoking with lung cancer is already well established this point was not pursued. The change is so uneven over the periods considered that it is probable that the sharp rise in the number of smokers in the last four years is partially due to some bias in the collection of the data. What is of interest is that while there may be some recent increase in the proportion of smokers there does not appear to have been any change in the proportions of the different types of tumour and that there is only weak evidence of any connection between smoking and the histological type of tumour found. This is in contrast to the findings in men in whom the squamous and oat-cell varieties have been found to be particularly associated with cigarette smoking (Doll *et al.*, 1957; Kreyberg, 1962; Wynder *et al.*, 1970).

These findings could be explained in several ways. The failure to find any change in the proportion of the different types over the time studied could be due to some bias in the proportions of biopsy, surgical, and necropsy material at different times. In this connection the material is not homogeneous in that in recent years the proportion diagnosed by biopsy has increased enormously but this would, if Whitwell's (1961) conclusions are correct, tend to accentuate any increase in the proportion of squamous and oat-cell carcinomas, a change which has not occurred to any significant extent (Table IV). Also this would not explain the lack of a relationship between smoking and cell types (Tables V and VI).

The conclusions are partially dependent upon the reliability of the recorded information about smoking habits, and the retrospective collection of such information may conceal errors due to casual interviews or recordings. The smoking habits were not known at the time of collecting and reviewing the histological material and while it might be expected that any errors would therefore affect all groups equally this may not be so as some patients might describe themselves as non-smokers after they had given up smoking several weeks previously at the onset of symptoms. Such a bias would be more likely to affect the central tumours, i.e., squamous and oat-cell tumours, rather than the more silent peripheral adenocarcinomas.

Some authors have taken the view that hospital records of smoking habits are reasonably reliable (Berry, Newhouse, and Turok, 1972) but some of the conclusions would be invalidated if a substantial number of the 'non-smokers' were really recent 'ex-smokers'. With this in mind the histories of the 32 non-smokers were reviewed. Of these, five were stated never to have smoked, eight were recorded as non-smokers by two or more doctors on different occasions, and six had either a sudden onset of symptoms or were discovered as a result of routine chest radiography; it might be expected that this last group would be unlikely to have had a recent change in smoking habits. Of the remainder, misleading errors would arise only if patients with tumours of group I were classified as non-smokers. One of the remainder had a tumour of group II and if she was really a cigarette smoker or ex-smoker the resultant error would if anything reduce the significance of the conclusions. Therefore it can be concluded that in at least 62% of the patients recorded as non-

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smokers the history is reliable, or else, if wrong, would not alter the conclusions.

The proportion of women whose smoking habits were either unrecorded or could not be traced varied from 50% in the earliest years to 20% in the more recent cases but while this might cast doubt on the significance of Table III it could hardly account for the conclusions drawn from Tables V and VI. In order to allow for different cigarette consumptions the recorded number of cigarettes smoked per day was correlated with the cell type but no constant relationship was found. The four cell types were found in groups of women with similar consumptions; this applied whether or not the non-smokers were taken into consideration. The woman recorded as having the greatest daily consumption actually had an adenocarcinoma.

The position of the large-cell undifferentiated tumours is of some doubt. Although these have been placed in group I it is possible that some of them may actually be very poorly differentiated adenocarcinomas. The smoking history is known in nine of this small group of 14 and it can be calculated that even if all of these are included among the adenocarcinomas the conclusions are not influenced.

A study of the recent literature shows that these results are in keeping with the findings of other authors who have used material derived from the British Isles (see Tables VII and VIII). Doll and his colleagues (1957) concluded that on a basis of 61 females they had an insufficient number to demonstrate a connection between cell type and smoking in women. Hanbury (1964) concluded that there were more squamous and oat-cell carcinomas than adenocarcinomas among the smokers in a series of 100 female cases but the differences shown in his Table II are not large and are not statistically significant ($\chi^2=5{\cdot}299$, df=3, $0{\cdot}1>P>0{\cdot}2$). Ashley and Davies (1969) in Wales concluded that there was no particular cell type which was associated with smoking but they give both smoking and histological data on only 39 cases. Thus, including the present series, four separate investigations of lung cancer in British women show only weak evidence of a connection between smoking and cell type. It is doubtful whether the results of Doll *et al.* (1957), Hanbury (1964), and the present series are sufficiently homogeous to be combined, but if this is done, the large sample of 312 women still fails to provide concrete evidence of a relationship between smoking and cell type in British women; although there is a weak relationship between smoking and tumours of group I it is not statistically significant. If there is no firm evidence of a relationship in a sample of over 300 cases it must be concluded that smoking has only a small influence on the histology of lung cancer in British women. It is perhaps relevant that in le Roux's (1968) large series of 4,000 cases collected in Scotland one-third of the non-smokers had squamous tumours.

The evidence available in the more recent American literature leads to a different conclusion. Vincent, Satterfield, and Ackerman (1965) found a considerable excess of adenocarcinomas relative to other types among female non-smokers and a corresponding excess of group I tumours among female smokers. This evidence, based on 134 cases, is convincing by itself ($\chi^2=32{\cdot}998$, df=3, $P<0{\cdot}001$). Deaner and Trummer's (1970) series contains too few non-smokers to be useful in this respect but their six non-smokers all had adenocarcinomas. The recent large series of Wynder *et al.* (1970) also shows an association between tumours of group I and smoking in women as well as in men. Again this association is a significant one. The results of Vincent *et al.* (1965) and Wynder *et al.* (1970) vary in their proportions of smokers; they are not homogeneous and so cannot be combined but there seems no doubt that in at least two American series there is a strong association between smoking and tumours of group I in women.

TABLE VII

DISTRIBUTION OF CELL TYPES OF LUNG CANCER IN WOMEN, GROUPED ACCORDING TO KREYBERG SYSTEM, IN BRITISH AND AMERICAN CIGARETTE SMOKERS

	Group I	Group II	No. of Cases
British women			
Doll *et al.* (1957) ..	32 (80%)	8 (20%)	40
Hanbury (1964)	36 (95%)	2 (5%)	38
Ashley and Davies (1969)	19 (76%)	6 (24%)	25
Present series	65 (81%)	15 (19%)	80
American women			
Vincent *et al.* (1965) ..	32 (70%)	14 (30%)	46
Deaner and Trummer (1970)	49 (82%)	11 (18%)	60
Wynder *et al.* (1970) .. (smokers and ex-smokers)	24 (53%)	21 (47%)	45

TABLE VIII

DISTRIBUTION OF CELL TYPES OF LUNG CANCER GROUPED ACCORDING TO KREYBERG SYSTEM IN BRITISH AND AMERICAN WOMEN NON-SMOKERS

	Group I	Group II	Total
British women			
Doll *et al.* (1957) ..	16 (76%)	5 (24%)	21
Hanbury (1964)	47 (76%)	15 (24%)	62
Ashley and Davies (1969)	8 (57%)	6 (43%)	14
Present series	22 (69%)	10 (31%)	32
American women			
Vincent *et al.* (1965) ..	24 (26%)	64 (74%)	88
Deaner and Trummer (1970)	0 (0%)	6 (100%)	6
Wynder *et al.* (1970) .. (smokers and ex-smokers)	5 (25%)	15 (75%)	20

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The comparative data are summarized in Tables VII and VIII which show that there is little difference between American and British female smokers as regards the cytology of their lung tumours (Table VII) but that the corresponding groups of non-smokers have a completely different pathological pattern (Table VIII). It needs no mathematical calculation to see that the make-up of the tumours in these two groups of non-smokers is totally different. The difference which was first noted by Haenszel, Shimkin, and Mantel (1958) may have arisen due to differences in interpretation of sections between British and American pathologists, but such a possibility seems remote in view of the large discrepancy and almost inverse distribution of the cell types shown in the upper and lower sections of Table VIII.

It appears therefore that Kreyberg's hypothesis concerning the connection between tumours of group I and environmental carcinogens is valid for British males (Doll *et al.*, 1957; Kreyberg, 1962), Norwegian males (Kreyberg, 1962), and American men and women (Haenszel *et al.*, 1958; Wynder *et al.*, 1970) but not for British women. A more reasonable explanation of the facts would be that British women are being subjected to some unidentified environmental hazard which is responsible, at least in part, for tumours of group I so that the incidence of cigarette smoking has little influence on the type of tumour found. It seems that the whole question of cell type and smoking might repay further investigation in women and possibly in men, especially if comparative studies could be arranged between different countries, as suggested by Haenszel *et al.* (1958). It also raises the disturbing possibility that the current increase in the incidence of lung cancer in women may be due not to smoking but to some as yet unrecognized cause.

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