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Is the incidence of primary adenocarcinoma of the lung increasing?

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Abstract Primary carcinoma of the bronchus is a major cause of death in males and females. Several studies report an increase in the incidence of adenocarcinoma and have suggested that this reflects changes in smoking habits or, alternatively, that it is a spurious rise due to changes in diagnostic criteria. To examine the latter suggestion we reviewed three cohorts of bronchial carcinoma from 1970, 1980 and 1990, using immunocytochemical techniques to refine diagnosis. We found that squamous cell carcinoma had been consistently overdiagnosed and adenocarcinoma and adenosquamous carcinoma consistently underdiagnosed in all groups. Also, many tumours showed evidence of divergent differentiation with both squamous and glandular components present. There was a small, but real temporal increase in the proportion of adenocarcinoma over the 10 years between 1970 and 1980, but this was not sustained between 1980 and 1990.

Key words Lung · Carcinoma · Incidence · Immunocytochemistry

Introduction

Carcinoma of the lung is the commonest malignancy in males and the second commonest in females in England and Wales [9]. Several studies in the United States have suggested that the prevalence of one particular subtype, adenocarcinoma, appears to be rising particularly rapidly. Cox and Yesner [5] recorded a modest increase in adenocarcinoma from 25.5% in 1958–1967 to 32.2% in 1968–1977. Valaitis et al. [24] noted an increase from 33% to 44% over a 10-year period, Khiyami et al. [13] recorded an increase from 4.3% in 1950–1958 to 22.4% in 1983–1986, and El-Torky et al. [7] showed a rise from 13% in 1964 to 31% in 1985.

Adenocarcinoma is considered to have a less close association with tobacco smoking than other primary lung tumours [15]. It is possible that the rising incidence of lung tumours in females who have a propensity to develop adenocarcinoma [7] is responsible, but alternatively, might reflect changes in the type of cigarette smoked [2, 17, 28]. Another possibility has been raised by Vincent et al. [25] and by Campabasso et al. [3], who have suggested that at least part of the rise is spurious and merely reflects temporal changes in the interpretation of histopathological data. All of these studies have relied on simple morphological methods, and evaluation of the more poorly differentiated tumours was necessarily subjective; in support of this explanation of the change, Keehn et al. [12] have demonstrated significant inter-observer variability in a recent study of primary bronchial tumours in which eight pathologists showed only a 56% consensus in diagnosis for adenocarcinoma and 48% for squamous cell carcinoma.

We examined the prevalence of different histological subtypes of lung carcinoma cases in the archives of the Royal London Hospital over a 30-year period. In the period 1970–1974, 12.9% of a total of 671 primary lung tumours were classified as adenocarcinomas. By 1980–1984, this had risen to 17.3% of a total of 476 cases and by 1990–1994, adenocarcinoma represented 15.0% of a total of 456 cases. The decrease in the total number of primary bronchial tumours available for study probably reflects changes in surgical practice. We suggest that at least some of the increase in the proportion of adenocarcinoma may result from a refinement of histological criteria; in particular, during the earlier period, 1970–1974, some tumours were given designations such as 'oval-celled' carcinoma, which do not fit into any of the currently used classifications.

We have reviewed all cases of primary carcinoma of the lung in 1970, 1980, and 1990, and using immunocytochemical techniques for identification of carcinoem-

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bryonic antigen (CEA) and involucrin, have reallocated them to the current WHO classification [26] to see whether the apparent increase in adenocarcinoma is maintained. CEA is variably present in all types of bronchial carcinoma and therefore is not specific, but it is strongly and consistently positive in adenocarcinoma and it can aid in the histological subtyping of poorly differentiated tumours [15, 21]. Involucrin is a precursor of the cornified cell envelope in human stratum corneum [18], and it has therefore been used as a marker of squamous differentiation in lung and other tumours [20, 23], although Mayall et al. [14] have disputed its reliability.

Materials and methods

All primary bronchial tumours submitted to the Royal London Hospital in 1970, 1980 and 1990 were reviewed using WHO criteria. In all, 162 cases from 1970, 110 cases from 1980 and 104 cases from 1990 were retrieved (see Table 1). Details of patient age and sex, and the nature of the material (biopsy or resection) are given in Table 2. It was not possible to obtain details of each patient's smoking or occupational history. Those tumours that were considered to be poorly differentiated squamous cell carcinomas or adenocarcinomas, or large cell (undifferentiated) carcinomas on light microscopy were then subjected to immunocytochemical study to aid in classification. This involved 72 of the 1970 cases, 61 of the 1980 cases and 53 of the 1990 cases. Immunocytochemistry was carried out using antibodies to involucrin (NovaCastra, dilution 1:50) and carcinoembryonic antigen (DAKO, dilution 1:300). A streptavidin–biotin detection system was used and developed with diaminobenzidine. Tumours which expressed involucrin, but little or no CEA, were designated squamous cell carcinomas; this included cases where the CEA was expressed only in the periphery of cells or in the same distribution as involucrin, as it may be present in up to 50% of squamous cell carcinomas [4]. Tumours that strongly expressed cytoplasmic CEA, but not involucrin, were designated adenocarcinomas, and those expressing both antigens were designated adenosquamous. Those expressing neither were placed in the large cell category. On the basis of these results, the cases were reallocated to the appropriate categories.

Table 1 Histological subtypes in original reports (*SCC* squamous cell carcinoma)

Histology	No.	Percentage
1970		
SCC	103	63.6
Adenocarcinoma	25	15.4
Small cell carcinoma	15	9.3
Large cell/undifferentiated[a]	14	8.6
Others[b]	5	3.1
Total	162	
1980		
SCC	71	64.6
Adenocarcinoma	10	9.1
Small cell carcinoma	15	13.6
Large cell /undifferentiated[a]	12	10.9
Others[b]	2	1.8
Total	110	
1990		
SCC	54	51.9
Adenocarcinoma	16	15.4
Small cell carcinoma	23	22.1
Large cell carcinoma	11	10.6
Total	104	

[a] Includes tumours given designations such as undifferentiated carcinomas, oval-celled carcinoma, spheroidal celled carcinoma
[b] Includes soft tissue tumours and carcinoids

Table 2 Patient details

	1970	1980	1990
No.	162	110	104
Male (%)	83.2	77.4	65
Female (%)	16.8	22.6	35
Resections (%)	63.6	34.3	32
Biopsy (%)	36.4	65.7	68
Age range (years)	10–76	44–86	42–82

Results

1970 Cohort

Of the 72 cases that merited immunocytochemical study, 39 were subsequently reallocated to different histological categories. Most commonly squamous cell carcinoma was reclassified as adenocarcinoma or adenosquamous carcinoma (Table 3).

1980 Cohort

Of the 61 cases that merited immunocytochemical study, 47 were subsequently reallocated to different histological categories. Most commonly squamous cell carcinoma was reclassified as adenocarcinoma or adenosquamous carcinoma (Table 3).

1990 Cohort

Of the 53 cases that merited immunocytochemical study, 30 were subsequently reallocated to different histological categories. Most commonly squamous cell carcinoma was reclassified as adenocarcinoma or as adenosquamous carcinoma (Table 3).

Table 4 summarises this reallocation and shows that in all groups, histological review with the aid of immunocytochemistry results in a decrease in the number of squamous cell carcinomas with a concomitant increase in the number of adenocarcinomas and adenosquamous carcinomas, suggesting they are consistently underdiagnosed. Table 5 shows the temporal changes in the different histological subtypes following review and demonstrates a small, but definite increase in the relative proportions of adenocarcinoma, from 21.0% in 1970 to 30.0% in 1980. This increase does not reach statistical significance (P=0.114), however, and was not sustained from 1980 to 1990, 1990 levels being similar to those in 1970.

Table 3 Reallocation of cases following immunocytochemistry

Review diagnosis	Original diagnosis			
	SCC	Adeno-carcinoma	Large cell	Total
1970 (n=72)				
SCC	16	–	–	16
Adenocarcinoma	10	11	2	23
Large cell	7	–	6	13
Adenosquamous	14	3	3	20
1980 (n=61)				
SCC	9	–	1	10
Adenocarcinoma	23	2	2	27
Large cell	4	–	3	7
Adenosquamous	13	2	2	17
1990 (n=53)				
SCC	16	–	–	16
Adenocarcinoma	7	4	4	15
Large cell	2	2	3	7
Adenosquamous	11	3	1	15

Table 4 Changes in proportions of subtypes following review

	Pre-review		Post-review		Change
	No.	%	No.	%	%
1970 cohort (162 reviewed, ICC on 72)					
SCC	103	63.6	72	44.4	−19.2
Adenocarcinoma	25	15.4	34	20.9	+5.5
Small cell carcinoma	15	9.3	15	9.3	No change
Large cell carcinoma	14	8.6	16	9.9	+1.3
Adenosquamous	–	–	20	12.4	+12.4
Others	5	3.1	5	3.1	No change
1980 cohort (110 reviewed, ICC on 61)					
SCC	71	64.6	32	29.1	−35.5
Adenocarcinoma	10	9.1	33	30.0	+20.9
Small cell carcinoma	15	13.6	15	13.6	No change
Large cell carcinoma	12	10.9	11	10.0	−0.9
Adenosquamous	–	–	17	15.5	+15.5
Others	2	1.8	2	1.8	No change
1990 cohort (104 reviewed, ICC on 53)					
SCC	54	51.9	34	32.7	−19.2
Adenocarcinoma	16	15.4	22	21.2	+5.8
Small cell carcinoma	23	22.1	23	22.1	No change
Large cell carcinoma	11	10.6	10	9.6	−1.0
Adenosquamous	–	–	15	14.4	+14.4

Table 5 Temporal change in proportion of histological subtypes from 1970 to 1990 (after review)

	1970		1980		Change (1970–1980)	1990		Change (1970–1990)
	No.	%	No.	%	(%)	No.	%	(%)
SCC	72	44.4	32	29.1	−15.3	34	32.7	−11.7
Adenocarcinoma	34	20.9	33	30.0	+9.1	22	21.2	+0.3
Small cell carcinoma	15	9.3	15	13.6	+4.3	23	22.1	+12.8
Large cell carcinoma	16	9.9	11	10.0	+0.1	10	9.6	−0.3
Adenosquamous	20	12.4	17	15.5	+3.1	15	14.4	+2.0
Others	5	3.1	2	1.8	−1.3	–	–	–

Discussion

We have reviewed all primary bronchial carcinomas from three years, 1970, 1980 and 1990 and, with the aid of immunocytochemistry for the undifferentiated and poorly differentiated tumours, have reallocated them to the histological subtypes laid down by the WHO. We have noted certain trends: first, within all groups, histological and immunocytochemical review has resulted in consistent changes in diagnosis, with a reduction in the numbers of squamous cell carcinomas, an increase in the relative proportions of adenocarcinoma and the addition of the new category of adenosquamous carcinomas. It seems therefore that squamous cell carcinoma has been consistently overdiagnosed and adenocarcinoma and adenosquamous carcinoma consistently underdiagnosed. However, from our data it seems unlikely that changes in diagnostic criteria could account for an apparent increase in adenocarcinoma: our figures show that it was actually underdiagnosed more frequently in 1980 than in 1970 (Table 4).

Secondly, there have been small, but definite temporal changes in the proportions of different tumours. Over the 10-year period from 1970 to 1980 there was a reduction of 15.3% in the incidence of squamous cell carcinoma (from 44.4% in 1970 to 29.1% in 1980), with a concomitant increase of 9.1% in the incidence of adenocarcinoma (from 20.9% in 1970 to 30% in 1980) and smaller rises in adenosquamous carcinoma and small cell carcinoma. Sridhar et al. also made broadly similar observations [22]. However, this rise in adenocarcinoma was only a temporary trend in our material; it did not reach statistical significance and was not sustained during 1980–1990; the 1990 levels resemble those of 1970. Over the period 1970–1990, the decline in squamous cell carcinoma (44.4% to 32.7%) was almost exactly matched by an increase in small cell carcinoma (9.3% to 22.1%). Thus, once consistent and more exact diagnostic criteria are applied, any increase in adenocarcinoma is shown to be only temporary.

The category of 'adenosquamous carcinoma' requires further qualification, as there is considerable debate regarding the morphological criteria for diagnosis of this entity. According to Fitzgibbons et al. [8], the glandular and squamous components may be present in any proportions, and we have followed this principle in our study. Ishida et al. [11] and Naunheim et al. [16] consider that it is a diagnosis that should be made on the basis of light microscopy alone, and using this criterion it is comparatively rare, with an incidence of 0.6–2.3% of all primary bronchial tumours. However, Roggli et al. [19] have demonstrated that 45% of primary bronchial tumours show major heterogeneity on light microscopy, an observation that is supported by Auerbach et al. [2] in an ultrastructural study. We have diagnosed 'adenosquamous carcinoma' in any cases showing evidence of dual differentiation by light microscopy or immunocytochemistry, and have found that the proportion is 12.4–15.5% (somewhere between these two extremes). The reason for the observed different incidences in dual differentiation of lung tumours in different studies is not entirely clear, but is probably due to a combination of examination methods (light or electron microscopy or immunocytochemistry) and to the different amounts of tissue available for study (biopsy or resection). These observations, together with previous studies such as those of Ishida et al. [10] and Ando et al. [1], suggest therefore that primary bronchial tumours represent a continuum of differentiation. Dunnill et al. [6] and Ishida et al. [10] have suggested that non-small cell primary tumours arise from primitive multipotential stem cells, which are capable of divergent differentiation along glandular and squamous pathways. If this is indeed the case, then it seems that the rigid segregation of non-small cell lung tumours into histological subtypes is neither appropriate or accurate. Additionally, given the evident inaccuracy of delineation of the different subtypes by histological criteria alone, the view that adenocarcinomas represent a better prognostic group or have a different aetiology requires reappraisal.

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