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Epidemiologic Patterns in Lung Cancer by Histologic Type

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Abstract—*Three thousand and ninety-seven lung cancer patients interviewed in different U.S. hospitals in 1977–1984 were classified into Kreyberg I and Kreyberg II categories. In both sexes, Kreyberg II patients were found to be younger and more frequently Jewish; among the male patients only, Kreyberg II cases were higher in educational and occupational level. These differences remained when the effect of cigarette smoking was controlled. Study data showed an increase in the frequency of Kreyberg II cases over time, and significantly, a decrease with younger age of the Kreyberg I : Kreyberg II ratio in both sexes. It is concluded that the observed secular increase in Kreyberg II is real and not merely due to changes in diagnostic methodology. On the basis of demographic differences noted, possible etiologic factors that may have contributed to the recent changes in lung cancer distribution by cell type are suggested.*

INTRODUCTION

ADENOCARCINOMA of the lung is relatively more common in women than in men, in nonsmokers than in cigarette smokers, and compared to tumors of the squamous and epidermoid type, is relatively lower in incidence [1]. The histologic predominance of squamous cell tumors in men may be seen to reflect the influence of cigarette smoking, and to a lesser extent, of selected occupational exposures, both of which are more prevalent in men. The predominance of adenocarcinomas in women, however, holds even in the absence of smoking. This, and the greater frequency of adenocarcinoma among nonsmokers diagnosed with lung cancer, have led to speculation regarding the causal role of a non-cigarette-linked factor that is more common in women.

Since 1977, increases in the rate of adenocarcinoma of the lung, particularly in men, without a similar increase for squamous cell lung cancers have been reported [2–7]. In data obtained in 1962–1975 from 1682 cases at the Roswell Park Memorial Institute, Vincent *et al.* [2] found that, by 1974, adenocarcinoma had overtaken squamous cell lung cancer as the predominant form among their male cases while continuing to be the major histologic type among the women. Similarly, Valaitis *et al.* [3], studying 219 lung cancer patients admitted to a private hospital in Illinois, found a shift in later years (1963–1967 compared to 1974–1976) to an excess of adenocarcinoma over squamous cell cancer among the men while among the women, the incidence of adenocarcinoma was higher in both periods. In a study of 235 male patients seen in 1974–1978 at the Strang Clinic in New York City, Melamed *et al.* also found a higher frequency of adenocarcinoma over epidermoid cancers (48% vs. 31%) [4]. Studying autopsy specimens from 1017 male patients seen by the Veterans Administration Group in 1958–1977, Cox and Yesner [5] saw the proportion of adenocarcinomas rise from 25.6% in 1958–1967 to 32.2% in the succeeding decade, whereas the proportion of squamous cell cancers dropped from 34.5% to 30.8% in the same periods.

The rising incidence of adenocarcinoma indicated by these hospital-based case studies finds agreement in results of studies which used population-based data. Dodds *et al.* using 1974–1981 SEER data from the Washington State area [6]; Wu *et al.*, using 1972–1981 data from the University of South California, Los Angeles County Cancer Surveillance Program [7], and Percy *et al.* reporting on lung cancer data obtained in 1973–1981 from the seven original SEER areas [8], all found increasing rates of adenocarcinoma in men, while the rates of squamous cell cancers did not change markedly. These studies also found increasing rates of adeno-

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carcinoma in women, but Dodds *et al.* [6] and Wu *et al.* [7] also found the rates of squamous cell cancers to be on the rise. We are impressed with the consistency of these findings with regard to the rise in adenocarcinoma starting at about the mid-1970s. While these changes may simply reflect improvements in diagnostic methodology, we are inclined to believe they provide important clues regarding etiologic factors not hitherto considered. These may be factors newly occurring in the environment, or factors that, although existing previously, are newly dominant in their effect relative to other agents, e.g. smoking, whose influence has declined.

In this study, we compared selected demographic characteristics of two main lung cancer cell types. Following Kreyberg's classification [9], these consisted of: Group I—squamous, large cell, small cell and oat cell carcinomas—and Group II—consisting mainly of adenocarcinomas. We observed differences that led us to speculate regarding possible directions for investigating other contributors to the incidence of lung cancer. We also compared the histologic groups with regard to their smoking history, to determine whether previous knowledge about the high prevalence of cigarette smoking in all lung cancer cell types and its greater dominance in male than female patients are reflected in our data. Finally, we examined our data to determine whether they reflect the trend towards increasing rates of Kreyberg I lung cancer that was noted in other studies.

We did not compare lung cancer patients against controls because the design of the parent study [10] involved matching on variables considered in this study (i.e. sex, age and social class).

METHODS

The subjects for this study were patients between 20 and 80 years old who had been diagnosed with lung cancer within 12 months prior to the interview. All cases included in the study were histologically confirmed by the Pathology Departments of the participating hospitals. For the purposes of this research, pathological diagnoses were coded either as Kreyberg I (epidermoid, squamous, large cell, small cell, oat cell, spindle cell, clear cell, large cell undifferentiated) or Kreyberg II (adenocarcinoma, terminal bronchiolar, bronchiolar, alveolar cell, bronchial 'adenoma', acinar, papillary, bronchiolar–alveolar cells). We had a third category of lung cancers consisting of anaplastic, undifferentiated and mixed epidermoid-adenocarcinomas. The numbers in this group are small (men = 118; women = 49) and were not included in this analysis. The subjects were interviewed between 1977 and 1984 as part of an ongoing study of tobacco-related diseases. They had been seen in various hospitals located in various cities. The distribution of patients by city is as follows: for Kreyberg I males: New York City, 52% (45.6% were seen in Memorial Hospital); Atlanta, 11.8%; Philadelphia, 13.6%; Pittsburgh, 5.6%; Chicago, 14.7%; San Francisco, 3.3%. For Kreyberg I females: New York City, 52.8% (46.4% were seen in Memorial Hospital); Atlanta, 7.0%; Philadelphia, 19.5%; Pittsburgh, 8.4%; Chicago, 9.0%; San Francisco, 3.3%. For Kreyberg II males: New York City, 70.8% (62.2% were seen in Memorial Hospital); Atlanta, 5.7%; Philadelphia, 9.9%; Pittsburgh, 2.4%; Chicago, 7.6%; San Francisco, 3.7%. For Kreyberg II females: New York City, 74.7%; (68.9% were seen in Memorial Hospital); Atlanta, 3.4%; Philadelphia, 11%; Pittsburgh, 2.6%; Chicago, 5.6%; San Francisco, 2.6%.

One thousand, two hundred seventy-eight male and 513 female cases with Kreyberg I lung cancer, and 807 male and 499 female cases with Kreyberg II lung cancer were seen.

Cigarette smoking and demographic information were obtained using a structured standardized form. Although this form had undergone changes over the course of the study, the sections on cigarette smoking and demographic information used for the present report had remained the same. Interviewers were carefully trained and monitored throughout the study. Other details of the study methods used have been described in a previous publication [10].

Our main objective was to compare Kreyberg I and Kreyberg II lung cancer patients on major demographic characteristics that would reflect lifestyle differences. The significance of observed differences was evaluated by chi-square analysis. Since such demographic variables tend to be highly intercorrelated among themselves and with cigarette smoking, we performed multiple logistic regression analysis to control for possible confounding.

RESULTS

Unadjusted comparisons of demographic and smoking characteristics between histologic patient groups are shown in Table 1. In both sexes, the proportion of Kreyberg II cases under 55 years was greater than the proportion of Kreyberg I cases ($P < 0.01$), and the proportion of Jewish patients was greater in the Kreyberg II than Kreyberg I group ($P < 0.01$). The proportion who had more than 12 years of formal education was also greater among the Kreyberg II cases, the differences being significant in the males ($P < 0.01$) only. The distribution of the two histological types of cancer by occupational categories reflected the patterns shown by educational attainment with which occupation is, of course, highly correlated.

Never smokers were rare among Kreyberg I patients of both sexes, and male patients with

Table 1. *Demographic data for lung cancer patients by histologic type*

	Males		Females	
	Kreyberg I	Kreyberg II	Kreyberg I	Kreyberg II
n	1278	807	513	499
	(%)	(%)	(%)	(%)
Age				
< 45	6	10	8	14
45–54	19	24	22	25
55–64	43	38	42	33
65–74	29	25	24	24
75+	3	4	4	4
	$P < 0.01$		$P < 0.01$	
Religion				
Protestant	35	26	34	26
Catholic	48	50	47	41
Jewish	9	18	14	27
Other	8	6	6	5
	$P < 0.01$		$P < 0.01$	
Years of education				
1–8	24	15	14	10
9–12	46	42	56	55
13–15	13	15	18	20
16	10	13	7	10
17+	7	14	5	6
	$P < 0.01$		N.S.	
Occupation				
Professional management	28	37	16	16
Skilled	38	36	36	37
Semi-skilled	19	15	7	7
Unskilled	15	11	8	6
Housewife/other	—	—	34	34
	$P < 0.01$		N.S.	

Kreyberg II. However, never smokers comprised 18.9% of female patients, a figure significantly higher ($P < 0.03$) than the corresponding proportion among the female Kreyberg II patients.

To control for confounding effects, since intercorrelation among the variables of interest may account for some of the differences observed, we performed logistic regression analyses separately by sex with cigarette smoking, age, religion (Jewish vs. non-Jewish), years of education and occupational level, as the regressors, and histologic type (Kreyberg I vs. Kreyberg II) as the response variable. The results seen earlier in bivariate analyses were confirmed. For males, the significant effect of age, religion, and years of education remained ($P > 0.0001$). Occupational level was significant when years of education were not included in the model. For females, significant effects were indicated for age and religion ($P < 0.0001$), but not for education or occupational status.

We also examined our data to determine whether they reflected the rising rates in lung adenocarcinoma. Since we had collected information from several hospitals in different geographic areas and our cases were reviewed by different pathologists, we recognize that our histology data are subject to problems of observer variability. Hence, interpretations of results must be made with caution. With this consideration, we note that our data are in agreement with other studies in showing an increase of Kreyberg II type cancers over time, particularly in males. Among the latter, the Kreyberg I : Kreyberg II ratio dropped from 2.2 in 1970–1976 to 1.58 in 1977–1984 (Table 3). For females, the ratio changed very slightly from 1.09 to 1.03. As we stated in the Methods section, our Kreyberg I classification included small cell cancers. The separ-

Table 3. *Number of lung cancer patients in* 1970–1976* *and* 1977–1984 *by histologic type*

Sex/time period of lung cancer diagnosis	Kreyberg I *n*	Kreyberg II *n*	KI : KII ratio
Males			
(a) 1970–1976	728	324	2.24
(b) 1977–1984	1278	807	1.58
Females			
(c) 1970–1976	161	148	1.09
(d) 1977–1984	513	499	1.03

*Reported in Wynder and Stellman [9].

Table 2. Lung cancer cases by histologic type and smoking habits

	Males		Females	
	Kreyberg I	Kreyberg II	Kreyberg I	Kreyberg II
n	1278	807	513	499
	(%)	(%)	(%)	(%)
Never smoked	1.7	5.2	6.0	18.9
Cigarette smokers				
Current	64.0	62.0	74.7	60.6
Ex-smoker	31.7	30.9	19.3	20.5
Cigar and pipe only				
Current	1.9	0.9	—	—
Ex-smoker	0.8	1.1	—	—

Table 4. Number of cases of Kreyberg I and Kreyberg II and KI : KII ratio by age and sex

	Males			Females		
Age group	KI	KII	Ratio	KI	KII	Ratio
< 45	73	78	0.93	40	71	0.56
45–54	241	191	1.26	113	123	0.92
55–64	547	306	1.79	218	167	1.31
65+	417	232	1.80	142	138	1.03

ation of this cell type, reported to be increasing in incidence as well [7, 11] from our Kreyberg I group, is likely to amplify the observed trend in males of a decreasing rate of Kreyberg I when compared to Kreyberg II lung cancers.

We then compared the ratio of Kreyberg I to Kreyberg II for the period 1977–1984 by age group in order to detect a real change over time (since it is unlikely that the patient's age would affect the pathologist's diagnostic criteria). As shown in Table 4, an increasing predominance of Kreyberg II with younger age is quite apparent in males, and also among the females, although with less regularity.

DISCUSSION

We found evidence consistent with recent observations of an increasing incidence of Kreyberg II lung cancers. Although improvements in diagnostic methodology may account for a part of the secular changes, we are inclined to believe that a substantial portion of the change is real. In this regard, of particular note is our finding (Table 4) of a decreasing Kreyberg I : Kreyberg II ratio with younger age in both men and women during the interviewing period 1977–1984. The cohort differences indicated by these data could be due to alterations in the relative influence of etiologic factors rather than to changes in methods of ascertainment since pathologists' determinations are not likely to be influenced by the age of the patient. Furthermore, the rate of increase in adenocarcinoma was greater in men. If technological advances are the sole cause of the observed increase, the rate of change should have been uniform in both sexes.

The data indicated a female predisposition to adenocarcinoma of the lung in the absence of cigarette smoking, suggesting nonsmoking risk factors that are more predominant in women. Such factors could include indirect exposure to cigarette smoke (passive smoking), or an estrogen-related factor. Numerous studies have investigated the effect of passive smoking, and although debate continues, an accumulation of evidence points towards a possible effect of this factor [12]. Concerning an estrogen-related cause, recent findings have been reported that are consistent with this explanation. In Shanghai, a case-control study found that a history of short menstrual cycles (< 26 days) and late menopause, were significant risk factors for lung cancer among nonsmoking women and that this relationship was stronger for adenocarcinoma than other lung cancer cell types (Zheng, personal communication). Also in line with an estrogen hypothesis are the findings that adenocarcinomas of the lung frequently contain estrogen receptors [13] and are frequently found in women who had been treated for endometrial cancer 10 or more years ago [14].

Our data also showed relative differences in demographic characteristics between Kreyberg I and Kreyberg II patients that remained even when the effect of cigarette smoking was controlled. In both sexes, Kreyberg II patients were younger and more frequently Jewish. Among the men only, Kreyberg II patients also differed from the Kreyberg I group in reporting higher educational and occupational level. Younger age and higher frequency of Jewish patients among the Kreyberg II group may be indicative of the action of other nonhormonal carcinogens and tumor promoters similar to those that affect other glandular cancers. Just as glandular tissues of the breast, prostate and pancreas respond to endogenous agents, perhaps lung tissue, certainly in contact with elements in the blood, responds likewise. Recent findings of

increased lung cancer risk with higher dietary cholesterol intake as reported by Shekelle *et al.* [15] and Winds *et al.* [16] are in line with this explanation.

We also found Kreyberg II male patients to be significantly higher in social class than same-sex Kreyberg I patients. Perhaps this finding points to clues in the changing cigarette smoking habits of men who, with the introduction of filter cigarettes in the early 1950s, increasingly shifted to filter cigarettes delivering lower levels of nicotine and 'tar'. Notably, this trend has been seen to be more pronounced among younger and better educated men [17].

It is significant that the studies cited here [2–6, 8] squamous to adenocarcinoma were consistent in their observation that this change began at about the mid-1970s. If it takes roughly 20 years for changes in exposure to cigarette smoke to take effect, perhaps the change in ratio of Kreyberg I to Kreyberg II beginning in the 1970s, particularly in men, is in part an effect of changes in tar exposure due to shifts from nonfilter to filter cigarettes which began in the early to mid-1950s. On the other hand the absence of a major shift in the Kreyberg I to Kreyberg II ratio in women found in our data and by other studies may relate to the fact that a substantial percentage of women are lifetime filter smokers.

Perhaps, as smokers shift to the lower yield cigaretes, and in compensation take large puffs [18] or hold in the smoke longer [19], secondary and tertiary bronchi receive more smoke. It is possible that cancers from smaller bronchi are more commonly glandular cancers than those arising from the major bronchi, largely because of differences of thickness in the epithelium.

We call these findings to the attention of the metabolic epidemiologist and experimentalist. We also suggest that in the search for possible etiological factors for lung cancer, particularly of the adenocarcinoma cell type, we should, in addition to substances that are inhaled, be concerned about the role of endogenous factors. To the epidemiologist, we note that the dominance of cigarette smoking as a risk factor has led to a focus on this variable to the relative neglect of other factors. Research advances achieved so far point towards consideration of a range of factors in addition to active smoking, especially as each relates to different cell types of lung cancer. These factors could include dietary intake (vitamin A, beta carotene, fats and cholesterol), hormonal status and passive smoking.

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