Familial Aggregation of Lung Cancer Among Hospital Patients

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NUMEROUS clinical, statistical, or epidemiologic studies of lung cancer in man reported in recent decades have dealt almost exclusively with the exogenous, or environmental, factors associated with this disease. A number of investigators, however, have speculated that endogenous, or genetic, factors may be of etiological importance (*1–8*). These speculations can be summarized by four statements of somewhat different perspective and specificity: (*a*) lung cancer is more likely to develop in those who are genetically prone or susceptible to the disease; (*b*) development of lung cancer may be influenced by the sex-linked genetic mechanism or constitutional sex differences, particularly with respect to hormonal balance; (*c*) incidence of lung cancer may be related to the differential constitutional makeup of a population, as caused by the temporal, general improvement in longevity, with respect to disease resistance and susceptibility; and (*d*) both lung cancer and smoking habits may be determined by a common genotype.

It is generally assumed that individuals of susceptible genotype are widely distributed in the population, and those susceptibles who are actually exposed to the carcinogenic agent are more likely to develop the disease than those who are not so exposed. Despite such theoretical interests, few empirical studies of human populations have been reported which indicate the possible importance of the genetic factor in lung cancer. Data indicating the presence of familial aggregation of lung cancer would provide the first-step clue for the existence of such a factor.

We have attempted to demonstrate the presence of familial aggregation of lung cancer in two different, but related, studies; one conducted in Buffalo, N.Y., and the other in Baltimore, Md. (*9*). The major findings of the two studies were similar; however, some differences were noted in certain specific details. Since the method of selection and the characteristics of control subjects were different, and the smoking factor was considered only in the Baltimore study, the results of the two studies should be analyzed separately and compared. The findings of the Buffalo study are presented here.

Method

Subjects for the study were selected among white patients admitted during a period from 1957 to 1960 to the Roswell Park Memorial Institute, Buffalo, N.Y., a State-operated hospital and research institute for the diagnosis of patients suspected of having cancer and for treatment of cancer patients. All patients admitted to the institute are interviewed by questionnaire with respect to various characteristics

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of epidemiologic interest. Consequently, over a number of years certain familial data, such as name, age, sex, and address of all living parents and siblings, and name, sex, age at death, and year and place of death of all dead parents and siblings, have been collected routinely. The hospital records necessary for this study were made available by the department of epidemiology.

Of 493 white patients with lung cancer admitted during 1957–60, 132 were eliminated from the study because their questionnaires lacked essential information regarding living or dead relatives or the deaths of most relatives were recorded in non-English-speaking countries. For the remaining 361 subjects, 722 noncancerous patients were selected as controls. The control subjects were matched for race, sex, age (allowing plus or minus 5 years), admission year, and residence as delineated according to size of community. The distribution of case and control subjects by age group and sex is shown in table 1.

As expected, selection at the institute of noncancerous patients as controls with several matching criteria was difficult. The distribution of control patients by diagnosis and sex is shown in table 2. Of the male controls, 28.2 percent had diseases of the digestive system; 15.2 percent, diseases of the skin and cellular tissue; 11.9 percent, diseases of the genitourinary system; 10.8 percent, benign neoplasms; and 9.6 percent, unknown diagnoses. In comparison, 39.7 percent of the female controls had diseases of the genitourinary system; 17.2 percent, benign neoplasms; 13.8 percent, diseases of the digestive system; and 8.6 percent, unknown diagnoses.

Since the data obtained on admission were not complete for many patients, for the purpose of this study it was necessary to obtain additional information or to confirm that already given, particularly regarding dead family members. Form letters with simple questionnaires requesting specific information, such as proper spelling of names, age, and place and year of death, were mailed to the subjects or their immediate living relatives, or both, so that death certificates could be located and causes of death ascertained. Approximately 90 percent of these questionnaires were returned with the desired information, including those returned after a series of followup contacts.

Certificates were located for 2,649 (92 percent) of 2,876 dead relatives, including spouses, reported by the subjects. Often the cause of death reported by family members was useful as reference information in the search for the correct death certificate. Of the 227 deaths for which certificates were not located, 26 had occurred before local registration was required, and for 201 necessary information was not available.

Regarding geographic distribution of deaths for which certificates were located, 78 percent were registered in New York State, including

Table 1. Distribution of case and control patients, by age group and sex

Age group	Number				Percent			
	Males		Females		Males		Females	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Under 40	12	23	3	5	3. 6	3. 5	10. 3	8. 6
40–44	7	35	2	5	2. 1	5. 3	6. 9	8. 6
45–49	28	69	4	10	8. 4	10. 4	13. 8	17. 2
50–54	40	85	6	9	12. 0	12. 8	20. 7	15. 5
55–59	69	111	4	9	20. 8	16. 7	13. 8	15. 5
60–64	60	92	2	6	18. 1	13. 9	6. 9	10. 3
65–69	58	97	3	5	17. 5	14. 6	10. 3	8. 6
70–74	38	92	3	5	11. 4	13. 9	10. 3	8. 6
75–79	16	42	1	3	4. 8	6. 3	3. 4	5. 2
80 and over	4	18	1	1	1. 2	2. 7	3. 4	1. 7
All ages	332	664	29	58	99. 9	100. 1	99. 8	99. 8

the State's vital statistics office, municipal offices of several large cities, and offices of county clerks. Approximately 85 percent of the certificates were located for 61 deaths which occurred in Canada and 16 deaths in other English-speaking countries in Europe.

Results

The distribution of parents and siblings by year of birth was quite similar for the case and the control groups (table 3). However, a more precise analysis of the data was made by comparing the observed mortality measures of the case relatives with the expected mortality measures of the same relatives as computed on the basis of age-specific mortality measures of the control relatives. This was done for each of the four categories of relatives: mothers, fathers, sisters, and brothers; thus the effects of sex, age, and generation were taken into account simultaneously.

The specific formulas used for computing the average number of individuals exposed to risk

Table 2. Distribution of control subjects, by diagnosis and sex

Diagnostic category [1]	Males		Females		Both sexes	
	Number	Percent	Number	Percent	Number	Percent
Infective and parasitic diseases (000–138)	11	1. 7	2	3. 4	13	1. 8
Benign neoplasm (210–229)	72	10. 8	10	17. 2	82	11. 4
Neoplasm of unspecified nature (230–239)	2	. 3	0	0	2	. 3
Allergic, endocrine system, metabolic, and nutritional diseases (240–289)	18	2. 7	3	5. 2	21	2. 9
Diseases of the blood and blood-forming organs (290–299)	9	1. 4	0	0	9	1. 2
Mental, psychoneurotic, and personality disorders (300–326)	4	. 6	0	0	4	. 5
Diseases of nervous system and sense organs (330–398)	7	1. 1	0	0	7	1. 1
Diseases of the circulatory system (400–468)	26	3. 9	1	1. 7	27	3. 7
Diseases of the respiratory system (470–527)	36	5. 4	0	0	36	5. 0
Diseases of the digestive system (530–587)	187	28. 2	8	13. 8	195	27. 0
Diseases of the genitourinary system (590–637)	79	11. 9	23	39. 7	102	14. 1
Diseases of the skin and cellular tissue (690–716)	101	15. 2	5	8. 6	106	14. 7
Diseases of the bones and organs of movement (720–749)	17	2. 6	0	0	17	2. 4
Congenital malformations (750–759)	10	1. 5	0	0	10	1. 4
Symptoms, senility, and ill-defined conditions (780–795)	18	2. 7	1	1. 7	19	2. 6
Accidents, poisonings, and violence (796+)	3	. 5	0	0	3	. 4
Unknown	64	9. 6	5	8. 6	69	9. 6
Total	664	100. 1	58	99. 9	722	100. 0

[1] Figures in parentheses refer to International List numbers.

Table 3. Distribution of parents and siblings of lung cancer and control subjects, by year of birth

Year of birth	Mothers		Fathers		Sisters		Brothers	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Before 1850	13	41	33	87	4	21	5	17
1850–59	57	117	74	151	36	85	41	101
1860–69	90	177	96	178	88	235	118	220
1870–79	111	191	90	161	163	339	159	299
1880–89	64	126	49	95	149	298	158	313
1890–99	18	50	11	37	105	192	111	202
1900 and after	3	14	3	6	38	94	41	124
Unknown	5	6	5	7	15	22	12	26
Total	361	722	361	722	599	1, 286	645	1, 302

in each age group, and the number of deaths expected to occur among the case relatives are shown below. As an illustration, the specific computations for sisters are presented in table 4. In analyzing the data, the observed and the expected figures were compared first with respect to overall mortality, then cancer mortality, and then lung cancer mortality. No individuals under 30 years of age or of unknown age were included. In addition, spouses of the case and control subjects were compared with respect to lung cancer deaths.

Ni (average number of relatives in a given category exposed to risk in ith age group) $=$

$$Oxi - \frac{1}{2}Qxi$$

Oxi = Number of all relatives in a given category who have reached the youngest age in ith group.

Qxi = Number of relatives, both living and dead, in ith age group.

Expected number of deaths among case relatives $= \sum_{i}^{n} \frac{Dci}{Nci} Npi$

Dci = Number of deaths in ith age group of control relatives.

Nci = Average number of control relatives exposed to risk in ith age group.

Npi = Average number of case relatives exposed to risk in ith age group.

n = Number of age groups.

i = A given age group (for example, 30–34; 35–39).

All-cause mortality among relatives. Deaths from all causes had claimed 622 (86 percent) of 722 case parents, compared with 1,190 (82 percent) of 1,444 control parents, and 290 (23 percent) of 1,244 case siblings compared with 638 (25 percent) of 2,588 control siblings. As indicated in table 5, there was no significant difference between the observed and expected mortality experience among the case relatives after adjusting for the effect of age, sex, and generation factors. This was true for all categories of relatives under consideration. This can be interpreted that the case and control relatives had a similar mortality experience.

Cancer (all sites) mortality among relatives. Of 912 deaths identified in the case group, 141, or 7 percent, were attributed to cancer. Similarly, 283, or 7 percent, of the total of 1,828 deaths in the control group were caused by cancer. Data pertaining to the adjustment of the effects of sex, age, and generation on cancer deaths are given in table 6. There was no significant difference between the observed and expected overall cancer mortality for parents or

Table 4. Calculation of expected number of deaths from all causes among sisters of lung cancer subjects, by application of experience of sisters of controls

Age at report	Controls				Cases				
	Number of sisters [1]	Average number exposed to risk [2]	Observed number of deaths	Proportion of deaths	Number of sisters [3]	Average number exposed to risk [4]	Observed number of deaths	Expected number of deaths	Average person-years
30–39	118	1,180	32	0.0271	41	555	11	15.04	5,550
40–49	219	1,012	34	.0334	126	471	21	15.73	4,710
50–59	335	735	59	.0803	165	326	28	26.18	3,260
60–69	317	409	65	.1589	152	167	25	26.54	1,670
70–79	182	159	42	.2642	60	61	11	16.12	610
80+	68	34	18	.5294	31	16	7	8.47	160
Total	1,239		250		575		103	108.08	15,960

[1] Number of living sisters plus the number who died in a given age group (Qxi in formula above). [2] Number of all sisters who have ever entered a given age group (Oxi in formula) minus one-half those in the same age group (Qxi in formula) for controls. [3] Number of living sisters plus the number who died in a given age group for cases. [4] Number of all sisters who have ever entered a given age group minus one-half those in the same age group for cases.

NOTE: Persons of unknown age or under 30 years old were excluded.

siblings of the lung cancer patients. However, it was noted that the observed mortality was consistently greater than expected when female relatives were considered separately.

Lung cancer mortality among relatives. The analysis of lung cancer mortality included both categories, cancer of the lung and bronchus specified as primary and that not specified as primary or secondary. However, those specified as secondary or metastatic were excluded. Sixteen lung cancer deaths were found among the case relatives including four mothers, six sisters, one father, and five brothers. These 16 lung cancer deaths represented 0.81 percent of all parents and siblings reported in this group. Among the control relatives, there were 14 lung cancer deaths including 2 mothers, 1 sister, 3 fathers, and 8 brothers. These 14 lung cancer deaths represented 0.34 percent of all parents and siblings reported in this group. Compared in crude terms, there was an approximate 2.5-fold excess mortality from this disease among the case relatives.

The data pertaining to the adjustment of the effects of sex, age, and generation on lung cancer mortality are summarized in table 7. The overall difference in the mortality between the case and control groups was statistically sig-

Table 5. Observed and expected numbers of deaths from all causes and death rate per 1,000 person-years by specific category of case relatives

Case relatives	Number of relatives	Average person-years	All-cause deaths				Death rate per 1,000 person-years	
			Number		Percent			
			Observed	Expected	Observed	Expected	Observed	Expected
Females	931	29,980	396	389.1	42.5	41.8	13.2	13.0
Mothers	356	14,020	293	281.0	82.3	79.2	20.9	20.0
Sisters	575	15,960	103	108.1	17.9	18.8	6.5	6.7
Males	953	29,760	460	464.5	48.3	48.9	15.5	15.6
Fathers	352	13,900	316	308.4	89.8	87.5	22.7	22.2
Brothers	601	15,860	144	156.1	24.0	26.0	9.1	9.8
Total	1,884	59,740	856	853.6	45.4	45.3	14.3	14.3

NOTE: Persons of unknown age or under 30 years old were excluded. The differences between the observed and expected values were not statistically significant at the 5 percent level when comparison was made for mothers, sisters, fathers, brothers, males, females, or both sexes.

Table 6. Observed and expected numbers of cancer deaths and cancer death rate per 1,000 person-years by specific category of case relatives

Case relatives	Number of relatives	Average person-years	Cancer deaths				Death rate per 1,000 person-years	
			Number		Percent			
			Observed	Expected	Observed	Expected	Observed	Expected
Females	931	29,980	86	78.7	9.2	8.5	2.9	2.6
Mothers	356	14,020	51	46.9	14.3	13.2	3.6	3.4
Sisters	575	15,960	35	31.8	6.1	5.6	2.2	2.0
Males	953	29,760	55	57.0	5.8	6.0	1.8	1.9
Fathers	352	13,900	32	30.6	9.1	8.8	2.3	2.2
Brothers	601	15,860	23	26.4	3.8	4.3	1.5	1.6
Total	1,884	59,740	141	135.7	7.5	7.2	2.4	2.3

NOTE: Persons of unknown age or under 30 years old were excluded. The differences between the observed and expected values were not statistically significant at the 5 percent level when comparison was made for mothers, sisters, fathers, brothers, males, females, or both sexes.

nificant, indicating that parents and siblings of lung cancer patients had a substantially higher risk of dying from the same disease. However, the difference was actually accounted for by the female relatives, particularly sisters, of the cases.

In order to check the possible existence of an environmental factor common to members of married pairs, spouses of the case subjects were compared with those of the control subjects with respect to lung cancer mortality. Of 396 spouses of the case subjects, one was identified as having died of lung cancer. Similarly, one lung cancer death was reported among 774 spouses of the control subjects. This difference was not statistically significant.

Discussion

Analyses of the data in the Buffalo study present suggestive evidence that the genetic factor may play a role in the pathogenesis of lung cancer. A significant aggregation of lung cancer deaths occurred among blood relatives of lung cancer patients. The aggregation was not explained by the effects of sex, age, and generation factors of the relatives. No significant difference in lung cancer mortality was seen between spouses of case subjects and those of controls. And the majority of dead relatives of both groups had lived in the same general geographic areas, northern communities of New York State. Since the excess lung cancer mortality was found in the female relatives, it is not likely that the observed aggregation was due to an environmental factor such as occupation.

The effect of cigarette smoking, an environmental factor which has been implicated as etiologically important in lung cancer, was not considered in this study. However, in the Baltimore study (*9*) in which the smoking factor was considered, familial aggregation of lung cancer was shown to exist with or without the influence of the effect of smoking, although cigarette smoking was found to contribute to an increased risk of developing lung cancer.

Since the results of the Baltimore study were reported separately, some of the differences in methodology and the findings of the two studies are presented below.

1. In the Baltimore study, control index subjects were selected among apparently healthy community residents, whereas controls for the Buffalo study were patients admitted to the same hospital as the lung cancer patients. Some investigators have claimed that an unknown nature and degree of selectivity is attached to hospital patients. For example, patients admitted to the same hospital may manifest certain similarities in socioeconomic characteristics, ethnic background, and smoking and other habits. If such selectivity existed, the true difference in mortality, including lung can-

Table 7. Observed and expected numbers of lung cancer deaths and lung cancer death rate per 1,000 person-years, by specific category of case relatives

Case relatives	Number of relatives	Average person-years	Lung cancer deaths				Death rate per 1,000 person-years	
			Number		Percent			
			Observed	Expected	Observed	Expected	Observed	Expected
Females	931	29, 980	10	1. 4	1. 1	0. 2	0. 3	0. 0
Mothers	356	14, 020	4	0. 9	1. 1	. 3	. 3	. 1
Sisters	575	15, 960	6	. 5	1. 0	. 1	. 4	. 0
Males	953	29, 760	6	5. 4	. 6	. 5	. 2	. 2
Fathers	352	13, 900	1	1. 5	. 3	. 4	. 1	. 1
Brothers	601	15, 860	5	3. 9	. 8	. 7	. 3	. 3
Total	1, 884	59, 740	16	6. 8	. 8	. 4	. 3	. 1

NOTE: Persons of unknown age or under 30 years old were excluded. The differences between the observed and expected values were significant for sisters (P=0.05), females (P=0.003), and both sexes (P=0.04).

cer mortality, between the case and control relatives probably would have been greater than observed in the Buffalo study.

The difference in frequency of smokers between case and control index subjects in the Buffalo study was considerably smaller than in the Baltimore study. Since smoking habits tend to aggregate in families, this suggests that the difference in smoking habits between relatives of the two groups of index subjects in the Buffalo study may also have been smaller than that in the Baltimore study. Further, the Baltimore study found the effect of smoking on lung cancer relatively insignificant in women, whereas in men it was greater than that of the familial factor. Therefore, the difference in frequency of lung cancer deaths between the case and control male relatives may be determined to a large extent by a difference in effect of smoking. These differences may explain, at least partially, the following contrasting results: (*a*) a significant excess of lung cancer mortality occurred among male relatives of the cases in the Baltimore study (a like tendency also was indicated among female relatives); and (*b*) this excess mortality occurred only among female relatives of the cases in the Buffalo study.

2. Of the control index subjects selected at the Roswell Park Memorial Institute, 11.4 percent had benign neoplasms and 9.6 percent unknown diagnoses. We do not know how many of these patients subsequently developed or actually had malignant neoplasms. The answer to this would be important if nonspecific genetic-constitutional factors were contributing to general susceptibility to neoplastic diseases as a whole. In this situation, the degree of familial aggregation of lung cancer as observed in this study would have been under-represented.

3. The Baltimore study also found that relatives of case subjects had a higher mortality from all causes and from cancer of all sites than relatives of controls. No such differences were found in the Buffalo study. These observations also may be partly attributed to differences between the two studies in method of selection and characteristics of controls.

Summary and Conclusion

Results of an epidemiologic study among lung cancer patients and noncancerous patients admitted to the same hospital and their relatives are consistent with a genetic-constitutional hypothesis in lung cancer.

A significant excess in lung cancer mortality was found among case relatives, particularly females, which was not accounted for by sex, age, and generation factors associated with the relatives. No such relationship was found among spouses of the cases and controls. Although the effect of cigarette smoking was not considered in this study, the major finding was consistent with that of another study conducted in Baltimore, Md.

A further epidemiologic study is indicated in which different sets of controls, particularly a large random sample of a community population, would be used. Emphasis would be placed on detailed analyses of the interaction between the host and environmental factors.

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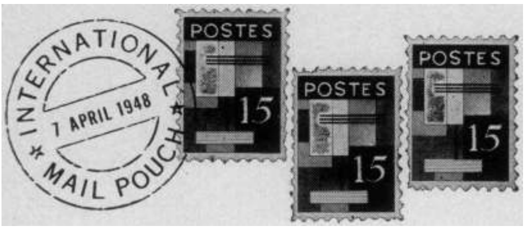

Pacific Teamwork

International teamwork among scientists, described in the October 1962 issue of the *South Pacific Bulletin,* has scored against eosinophilic meningitis, a disease which has attracted attention in the South Pacific only in the last 10 years.

A Chinese parasitologist first found, in a rat in Canton, the worm suspected to be the agent. Physicians in Nouméa first described the disease. Investigators in Tahiti worked up the epidemiology. Australians in Brisbane discovered the role of a garden slug. Americans in Hawaii linked the separate investigations. And scientists in Nouméa confirmed the hypothesis with experiments on laboratory monkeys.

Battlefront

Viet-Cong threats, attacks, abductions, and murders of government village health workers testify to the significance of health efforts in the ideological battle in Vietnam. For prompt results, it was decided to start services, both preventive and curative, at the village level rather than first building a strong central structure and extending it. More than 70 percent of the population live in hamlets or small towns, earning a living from the soil, animal husbandry, or fishing.

The rural areas lack private physicians and medical facilities. However, nearly all babies are born in maternity units and are delivered by trained midwives. (Two-thirds of all the nurses in Vietnam are men, as are almost all rural and village health workers.)

The villagers' desire for health services is reflected by the fact that in prosperous hamlets, the inhabitants paid for maternity buildings; some provinces pay the salaries of village health workers; in others, they are paid smaller salaries by the villages, but many receive no pay.

In a drive to provide manpower and facilities in rural areas, the Vietnam Ministry of Health, with support from the U.S. Operations Mission, chalked up these accomplishments by December 31, 1961: trained the staff and stocked the drugs and supplies for 120 district health teams; set up 3,270 village or hamlet health centers; and constructed 44 district health centers, 3 training centers, a tuberculosis control center, a surgical wing of a provincial hospital, and 11 water supplies. In addition, the public health training centers have prepared 157 sanitarians, 564 district health workers, and 170 health technicians and supervisory nurses and given special courses to 85 students and refresher courses to 394.

In addition to the programs of the Ministry of Health, seven other health programs are supported by agencies of the Vietnam Government and two additional ones by military support agencies.

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Hospital Alcoholism Units

Treatment for alcoholism and alcoholic psychosis should, as far as possible, be given in specialized units in psychiatric hospitals or in psychiatric sections of general hospitals, the Ministry of Health of England and Wales has recommended in a memorandum to hospital authorities.

Hospital boards which have not established such units should do so, the memorandum suggested. The initial aim is to have one such unit per region.

The recommendations are the outcome of a recent review of hospital provision for treatment of alcoholism by the Standing Medical and Standing Mental Health Advisory Committees. Their recommendations were endorsed by the Central Health Services Council.

The hospital units will normally be headed by psychiatrists or operated in association with them. It is suggested that the units have 8 to 16 beds, a number convenient for group therapy, which the advisory committees regard as a valuable form of treatment. It will be necessary, the memorandum states, for the special units to conduct outpatient clinics and to cooperate in aftercare with Alcoholics Anonymous and, where appropriate, with the local health authority and other interested agencies.

—*Excerpted from "Public Health Notes," The Journal of the Royal Institute of Public Health and Hygiene, August 1962, p. 180.*