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Cancer aggregation and complex segregation analysis of families with female non-smoking lung cancer probands in Taiwan

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Abstract

Previous studies have found that having a first-degree blood relative with lung cancer was a possible predictor of lung cancer risk, but some studies have indicated that the association is non-significant or only significant for a subset of the studied population. To determine the familial aggregation and whether there is any evidence for a gene controlling the susceptibility to developing lung cancer in female non-smokers, multiple logistic regression methods for estimating covariate effects and maximum likelihood segregation analyses were performed using data from 216 female non-smoking lung cancer probands (2328 individuals) in a population-based case–control study. Having a family history of lung cancer was found to be a significant predictor of lung cancer for non-smoking females (Adjusted Odds Ratio (OR) = 5.7, 95% Confidence Interval (CI) = 1.9–16.9). Having a female relative with lung cancer (adjusted OR = 14.4, 95% CI = 2.7–75.5) was more strongly associated with the lung cancer risk than was having a male relative with lung cancer. This association was stronger for probands aged less than 60 years at onset (adjusted OR = 11.2, 95% CI = 2.2–56.9). All of the Mendelian models fitted the data significantly better than the sporadic (no major type) model or the environmental model ($P < 0.00l$). The Mendelian codominant models provided the best fit of the data for the early onset probands and showed a stronger effect for a major susceptibility locus for non-smoking lung cancer probands. The results of this study provide evidence that a rare autosomal codominant gene may influence the risk lung cancer in non-smoker and is responsible for the familial aggregation observed in non-smoking lung cancer patients.

Keywords: Female lung cancer; Family aggregation; Segregation analysis

1. Introduction

The role of environmental factors in the aetiology of lung cancer is well known. Tobacco smoke, in particular has long been established as a causal factor [1]. Taiwanese women, like Chinese women in other countries, have a relatively high lung cancer incidence despite the fact that very few smoke [2]. Inherited susceptibility to lung cancer is one of a number of possible risk factors that could account for this. One problem encountered when attempting to judge the importance of genetic factors is the difficulty in determining how much of the observed familial aggregation of lung cancer cases can be explained by shared environmental factors and how much is due to genetic predisposition. A previous study [3] has examined the familial aggregation of lung cancers and indicated that a parental history of lung cancer resulted in an Odds Ratio (OR) for lung cancer of over five after adjustment for demographic variables and smoking history. Several studies from Mainland China [4,5] and the United States [6–8] indicated that having a first-degree relative with lung cancer was significantly associated with an increased risk of lung cancer among non-smokers aged 40–59 years but not for those over 60 years of age. Several recent familial segregation analyses suggest that there might be a gene influencing the

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incidence of lung cancer that was related to the family history of lung cancer among first-degree relatives and may associated with an increased risk for early-onset cancer [9,10].

The failure to control for several environmental risk factors, while examining familial clustering was a major weakness in many previous studies. These include exposure to environmental tobacco smoke and the exposure to cooking fumes both of which have recently been confirmed to contain several carcinogens [11,12] for lung cancer. The purpose of this study was to examine the family aggregation of lung and other cancers of the organs in relatives of female non-smoking lung cancer patients, while controlling for as many potential confounders as possible. Furthermore, we wanted to distinguish the role of genetic predisposition in the observed familial aggregation from the role of environmental factors, and therefore a complex segregation analysis was performed to determine the effect of any genes influencing the cancer risk using pedigree data constructed from this study.

2. Patients and methods

This was a population-based case–control study for which the probands were matched for age (1:1 ratio). Data was collected for these patients, their spouses and all of their first-degree blood relatives (parents, full siblings and children). Cases consisted of 125 female non-smoking patients with lung cancer who presented at the Kaohsiung Medical University (KMU) Hospital and Chi Mei Medical Center (CMMC) during the period from January 1992 to July 2002. Of these, complete data was obtained for 108 (86.4%) patients, 108 of their spouses and 1164 first-degree blood relatives. Control subjects were 108 female patients who presented at the same hospital for problems unrelated to respiratory ailments or any type of cancer. Data was also collected for their 108 spouses and 1164 first-degree blood relatives. The structured questionnaires of the cases and controls were collected, mainly through face-to-face interviews. The response rate from interviewing the spouses and the relatives for the cases was 84.7%, and that for the controls was 85.1%. The rate for interviewing face-to-face was 89.2% and by telephone was 10.8% for the spouses and the relatives of cases, and the rate for controls, face-to-face was 91.5% and by telephone was 8.5%. Data collected for the cases, controls and their relatives included demographic, life-style and medical history variables. Six public health and medical experts were called upon to analyse the items in the questionnaire and to oversee the content coverage and adequacy. Answers to the questionnaire were re-tested using 150 people 4 weeks after the first interview. The reliability coefficients in continuous and ordinary variables ranged from 0.81 to 0.92; the percentage of consistency in the categorised variables varied from 0.83 to 0.92, giving an acceptable agreement for the answers given four weeks after the first interview.

Two types of multiple logistic regression models were fit to the data. Conditional logistic regression analysis was used to estimate the ORs for comparisons involving the probands assessing the effect of a family history of lung cancer on the lung cancer risk. Logistic regression models treated lung cancer or other cancers among the first-degree relatives of the cases and controls as the outcome variable to assess the effect of having a female relative with lung cancer on an individual risk of lung cancer and other types of cancer. Other variables which were found to be associated with the lung cancer risk, including demographic, life-style and medical history variables, were added to the above multiple logistic regression model. Covariates were retained in the final models if they were significant at the level of $P<0.05$.

To evaluate the role of Mendelian inheritance in the familial clustering of cancer, we performed a complex segregation analysis, using maximum likelihood procedures that test for the transmission model that best fits the observed pedigree data [13–15]. All analyses were performed using the program REGTL from the software package S.A.G.E. (Statistical Analysis for Genetic Epidemiology) [16]. The possible segregation of a major locus affecting disease risk is allowed for by letting the parameters of the age of onset distribution depend on an unobserved factor u (u = AA, AB, BB).

Several parameters can be estimated using REGTL, including the frequency of the allele (A) conferring a greater disease risk, τu, the probabilities of transmitting the allele A from parent to offspring; parameters of the age of onset distribution (age coefficient α and baseline parameter β); parameters representing the effect of one or more covariates $\varepsilon 1$–$\varepsilon 10$; and the proportion of the population who are susceptible, γ, which can depend on gender or unmeasured environmental factors. For the model type used in this analysis, major type was assumed to affect cancer only through the age of onset, with susceptibility being the result of unmeasured environmental factors.

We first generated a sporadic model with an overall mean and variance of age of onset and susceptibility. This model assumes no major type and that cancer risk is affected only by unmeasured environmental factors. Covariates that were found to affect the cancer risk in an ordinary logistic regression model were added sequentially and those that were found to significantly improve the likelihood were retained in the subsequent models. An environmental model which assumes that there is no major type transmitted from parent to offspring, but that unmeasured environmental factors result in two different distributions of age of onset in the population. The best possible genetic model (dominant,

recessive or co-dominant) was then determined. The Mendelian dominant model assumes $\beta AA = \beta AB$ implying that a single copy of the A allele is sufficient to increase the risk of cancer at an earlier age. The recessive model assumes that $\beta AB = \beta BB$ and that two copies of the A allele are necessary for an earlier age of onset. The additive co-dominant model assumes that $\beta AA < \beta AB < \beta BB$ and that βAB is exactly halfway between the other two types. Finally, the transmission parameters were tested by comparing the general model with unrestricted transmission parameters to the Mendelian and the environmental models. The maximum likelihood ratio test was used to compare the likelihood of the general model with those of the other models. The natural logarithm of this ratio multiplied by -2 can be used to test the statistical significance of differences in the likelihood of two models and follows an asymptotic Chi-squared distribution with degrees of freedom equal to the difference in the number of parameters estimated. A P value of less than 0.05 indicates that a sub-model can be rejected, In addition, to correct for ascertainment via probands, the likelihood of the data under each model was conditioned on the likelihood of the phenotype of the proband. Since the likelihood ratio test (LRT) requires that one of the two models being compared be a sub-model of the other one, Akaikes Information Criteria (AIC) equal to -2*log-likelihood $+(2)$*(number of parameters estimated) was also used to compare the models, since this method can be used to compare any two models. The model with the smallest AIC is considered to provide the best fit of the data.

3. Results

Data on the reported family history of lung cancer in first-degree relatives of the cases and controls is presented in Table 1. The prevalence of a history of lung cancer in at least one first-degree relative was 23.1% (25/108) for the lung cancer cases and 6.5% (7/108) for the control group. The adjusted OR for any family history of lung cancer was 5.7 (95% Confidence Interval (CI) = 1.9–16.9). Having a history of lung cancer in a female relative (adjusted OR = 14.4, 95% CI = 2.7–75.5) was much more strongly associated with the lung cancer risk than was having a male relative with lung cancer (adjusted OR = 1.8, 95% CI = 0.4–7.4). The prevalence of lung cancer was particularly high in mothers of cases than for the controls (13% versus 2%, $P < 0.05$). The cases that were diagnosed before the age of 60 years were more likely to have a family history of lung cancer (16/48 = 33%) than were those diagnosed after the age of 60 years (9/60 = 15%) and this difference was statistically significant ($P = 0.014$). Logistic regression analysis, stratified by age of onset, showed that family history of lung cancer was a stronger predictor of the lung cancer risk among the early onset group (adjusted OR = 11.2, 95% CI = 2.2–56.9) than for the older group (adjusted OR = 2.8, 95% CI = 0.7–10.9).

Table 1
Risk of lung cancer for female non-smokers by family history of lung cancer in Taiwan, 1992–2002

	Cases	Controls	AOR[a]	95% CI
Any family history of lung cancer				
No	83	101	1.0	
Yes	25	7	5.7	(1.9–16.9)*
Family member with history of lung cancer				
Mother	14	2	12.3	(2.2–68.7)*
Father	7	3	2.6	(0.5–12.6)
Brother/sister	5	2	2.4	(0.2–24.6)
Gender of affected relative:				
Female	18	2	14.4	(2.7–75.5)*
Male	8	5	1.8	(0.4–7.4)
Age of onset (years)				
<60	16	3	11.2	(2.2–56.9)*
⩾60	9	4	2.8	(0.7–10.9)

95% CI, 95% Confidence Interval. *$P < 0.05$.

[a] Odds Ratio adjusted for education, passive smoking, years of cooking, history of tuberculosis and family history of other cancers.

Data on the prevalence of a family history of non-lung cancer for the cases and controls is presented in Table 2. A family history of non-lung cancer was nearly as strong a predictor of the lung cancer risk as a history of lung cancer (adjusted OR = 4.9, 95% CI = 1.8–13.1). In direct contrast to the findings for a family history of lung cancer, a history of non-lung cancer in male relatives was much more strongly associated with the lung cancer risk in the index cases than was a history of non-lung cancer in female relatives (adjusted OR = 10.8, 95% CI = 2.5–46.3). A family history of non-lung cancer was also a stronger predictor for the late onset cases (adjusted OR = 6.3, 95% CI = 2.0–20.4) than for the early onset cases (adjusted OR = 2.5, 95% CI = 0.7–8.9).

The results for the analyses that treated lung cancer, non-lung cancer and any cancer among the relatives of the index cases as outcome variables are shown in Table 3. Among the 1164 first-degree blood relatives of the cases, 26 (2.2%) had a reported diagnosis of lung cancer, and 41 (3.5%) had a diagnosis of a non-lung cancer. For the 1164 first-degree relatives of the controls, these numbers were 7 (0.6%) and 21 (1.8%), respectively. The strongest effects were for lung cancer in any female relatives (adjusted OR = 8.8, 95% CI = 2.0–38.7) and mothers (adjusted OR = 7.5, 95% CI = 1.7–34.2) and non-lung cancer in brothers (adjusted OR = 7.3, 95% CI = 1.6–33.5). Lung cancer was the most prevalent type for both cases and controls followed by liver cancer and stomach cancer. All three of these were more prevalent in the relatives of the cases, with the excess of lung cancer being primarily from the

Table 2
Family history of non-lung cancer and lung cancer risk for female non-smokers in Taiwan, 1992–2002

	Cases	Controls	AOR[a]	95% CI
Any family history of non-lung cancer				
No	75	93	1.0	
Yes	33	15	4.9	(1.8–13.1)*
Family member with history of non-lung cancer				
Mother	7	4	1.9	(0.4–9.3)
Father	11	5	4.4	(1.0–19.2)*
Sister	6	7	0.8	(0.2–2.7)
Brother	12	2	12.1	(1.4–100.6)*
Gender of affected relative				
Female	15	10	1.7	(0.6–4.4)
Male	23	7	10.8	(2.5–46.3)*
Age of onset (for proband) (years)				
<60	13	6	2.5	(0.7–8.9)
$\geqslant 60$	20	9	6.3	(2.0–20.4)*

*$P<0.05$.
[a] Odds Ratio adjusted for education, passive smoking, years of cooking, history of tuberculosis, and family history of lung cancer.

female relatives and the excess of liver and stomach cancers from the males.

Of the 216 families of case and controls, 58 families totalling 770 individuals were used in the complex segregation analysis. The families included in the segregation analysis were those with more than one member with a history of cancer. The distribution of cancer sites among the relatives was investigated. Pack-years of smoking, education and environmental tobacco smoke exposure were added to the sporadic model. Only pack-years of smoking in the relatives was found to significantly improve the likelihood of the model, and, hence, it was retained in all subsequent models and the other covariates were not.

The results of the fitting of the Mendelian type affects the lung cancer risk through an earlier age of onset and these are shown in Table 4. All of the Mendelian models fit the data significantly better than the sporadic (no major type) model or the environmental model ($P<0.001$), providing evidence that a major factor transmitted from parent to offspring was involved.

Table 3
Risk of cancer for relatives of non-smoking female cases and controls in Taiwan, 1992–2002

	Lung cancer			Other cancers			Any cancer		
	Yes	No	AOR[a] (95% CI)	Yes	No	AOR[b] (95% CI)	Yes	No	AOR[c] (95% CI)
All relatives									
Cases	26	1138	3.7 (1.6–8.5)*	41	1123	2.1 (1.2–3.6)*	67	1097	2.6 (1.6–4.1)*
Controls	7	1157		21	1143		28	1136	
Female relatives									
Cases	18	568	8.8 (2.0–38.7)*	19	567	1.3 (0.7–2.7)	37	549	2.3 (1.3–4.3)*
Controls	2	536		14	524		16	522	
Male Relatives									
Cases	8	570	1.6 (0.5–5.1)	22	556	3.7 (1.6–8.9)*	30	548	2.9 (1.5–5.9)*
Controls	5	621		7	619		12	614	
Fathers									
Cases	7	101	2.3 (0.6–9.4)	10	98	2.1 (0.7–6.3)	17	91	2.3 (0.9–5.6)
Controls	3	104		5	102		8	99	
Mothers									
Cases	14	94	7.5 (1.7–34.2)*	7	101	1.7 (0.5–6.3)	21	87	4.0 (1.5–10.4)*
Controls	2	106		4	104		6	102	
Brothers									
Cases	1	230	0.5 (0.1–6.2)	11	220	7.3 (1.6–33.5)*	12	219	3.5 (1.1–11.0)*
Controls	2	272		2	272		4	270	
Sisters									
Cases	4	233	–[d]	10	227	1.1 (0.5–2.9)	14	223	1.5 (0.6–3.7)
Controls	0	213		9	204		9	204	
Children									
Cases	0	480	–[d]	3	477	2.6 (0.3–25.8)	3	477	2.7 (0.3–26.9)
Controls	0	462		1	461		1	461	

*$P<0.05$.
[a] OR adjusted for pack-years of smoking, age and years of cooking.
[b] OR adjusted for gender, age, years of cooking and education.
[c] OR adjusted for gender, age, pack-years of smoking, years of cooking and education.
[d] Adjusted OR could not be estimated.

Table 4
Parameter estimates from segregation analysis of cancer at any site in 58 families from Taiwan

Parameter	General model	No major type	Dominant	Recessive	Codominant (additive)	Codominant (decreasing)	Environmental factors
q_A[a]	0.29		0.05	0.23	0.23	0.16	0.13
τAA	1.0		[1.0]	[1.0]	[1.0]	[1.0]	
τAB	0.0		[0.5]	[0.5]	[0.5]	[0.5]	
τBB	0.0		[0.0]	[0.0]	[0.0]	[0.0]	
βAA	−12.92	−17.12	−14.40	−13.73	−13.76	−13.11	−15.02
βAB	−16.23	$=\beta$AA	$=\beta$AA	−17.34	−16.52	−16.21	$=\beta$AA
βBB	−17.75	$=\beta$AA	−17.47	$=\beta$AB	−19.29	−18.03	−17.78
α	0.24	0.18	0.22	0.22	0.26	0.24	0.21
ε_{smk}[b]	0.0091	0.013	0.014	0.012	0.013	0.015	0.0097
γ	0.7	0.67	0.64	0.65	0.67	0.64	0.69
No. of parameters	10	4	6	6	6	7	6
−2lnL	1058.7	1092.8	1072.4	1071.5	1067.2	1067.9	1095.3
LRT		34.1	14.7	12.8	8.5	9.2	36.6
Df	0	6	4	4	4	3	4
P value		$P<0.001$	$0.001<P<0.01$	$0.001<P<0.01$	$0.035<P<0.05$*	$0.01<P<0.025$	$P<0.001$
AIC	1078.7	1100.8	1084.4	1083.5	1079.2	1081.9	1107.3

*The most fitting model with the smallest AIC value. Df, degrees of freedom; −2lnL, −2*log-likelihood; LRT, likelihood ratio test; AIC, Akaikes Information Criteria.

[a] q_A denotes the frequency of component (allele) A. See Methods for definitions of other parameters.

[b] ε_{smk} denotes the covariate for pack-years of smoking.

According to the AIC value, the codominant additive model was the best fitting of the Mendelian models, closely followed by the recessive and dominant models. The Mendelian codominant models with significant modifying effects and was judged the most fit model on the data for early onset probands, showed a stronger effect of the major susceptibility locus for non-smoking lung cancer probands. However, the Mendelian models were all rejected when compared with the general model (with unrestricted transmission probabilities) for another late onset probands. This provides evidence that a major factor was transmitted in a Mendelian manner and suggests that one or more potential autosomal genes affect female early onset non-smoking lung cancer probands. Heterogeneity was also found between the early onset (<60 years) and late onset ($\geqslant 60$ years) subjects when fitting the best model. Gender-specific type effects and susceptibility parameters were tried in each of the models, but in all cases were found to result in a non-significant improvement in the models.

4. Discussion

In this study, we attempted to control for as many environmental risk factors as possible for both the probands and their relatives in order to understand better the causes of the observed family aggregation. The possibility that the family aggregation results from genetic factors is supported by several findings from this study. The positive association between family history and lung cancer risk remains after adjusting for several environmental risk factors and despite the fact that both the numbers and the ages of the first-degree relatives were similar for the cases and controls. In addition, the lung cancer risk was not elevated for the spouses of cases even though they likely shared living environments and had similar diets for much of their adult lives.

The results of our study also suggest that having a female relative with lung cancer, particularly a mother, is a stronger predictor of the lung cancer risk compared with having a male relative with lung cancer. Previous studies [6–8,17] have indicated that having a first-degree relative with lung cancer was significantly associated with lung cancer among non-smokers. The reasons for the apparently stronger association between lung cancer risk and lung cancer history in female relatives are unknown. Since certain cooking habits have been implicated as an important risk factor for lung cancer among Chinese women [2,4,5], one possibility is that genetic factors might influence the susceptibility to carcinogens in cooking fumes. Years of cooking are already in the regression model and seemed to have no significant effect, unless through a highly-penetrating gene that strongly interacts with environmental exposure such as cooking fumes. In excess of 10 carcinogenic chemicals were identified in cooking fumes and these were shown to interact with one another [18–25]. The possible effects on the incidence of lung cancer from the carcinogenic chemicals derived from the cooking fumes in the model need to be evaluated further. The occupational

distributions for the cases and controls were very similar.

Our analysis showed that cases with an earlier age of onset (before the age of 60 years) were more likely to have a family history of lung cancer than those who were diagnosed after the age of 60 years. This finding is consistent with two other studies restricted to non-smokers [9,10] and a segregation analysis [26] that found evidence for a gene influencing the earlier age of onset of lung cancer, and would seem to provide support for a genetic hypothesis. Since genetic susceptibility to cancer would involve either a specific germ line mutation, which creates a situation in which one step in the cancer development process has been determined, or possession of an allele or alleles that induce a greater susceptibility to environmental carcinogens, inherited cancers will usually have an earlier onset than sporadic cases.

A strong positive association between a family history of non-lung cancer and the risk of lung cancer in female non-smokers was also found in our study. Although the other study, restricted to female non-smokers, found no such association [8], our finding is consistent with several studies that have shown a correlation between lung cancer and a family history of the nasal cavity, larynx, uterus, cervix and ovary cancers among lung cancer patients [17,27,28]. Interestingly, the excess of non-lung cancers occurred mostly in male relatives of the cases and the association was stronger for cases with a late onset of cancer than for those with an early onset. A possible explanation for this is that since the roles and lifestyles of males and females in Taiwan are very different, they are exposed to different environmental hazards. If genetic factors influencing the susceptibility to cancer at several different sites exist, it would be expected that inherited susceptibility to cancer would manifest differently (i.e. at different cancer sites) depending on gender. The excess of non-lung cancers among the relatives of cases was largely accounted for by cancers of the liver, stomach, colon and intestine, which primarily affect Taiwanese males.

Our study found statistical evidence of a major factor, transmitted from parent to offspring, which affects the age of onset of cancer. The Mendelian codominant model was the best fitting of the models for all proband ages, and the same model was consistent with significant modifying effects in the families of early onset probands and showed a stronger effect of a major susceptibility locus for non-smoking lung cancer probands. The existence of a familial aggregation of cancer is fairly well established, but the aetiology of this aggregation is more difficult to establish, since both hereditary and environmental factors are shared by family members. Previous segregation analysis studies [26] have found evidence for a gene affecting the risk of one or more types of cancer. Several studies have found associations between the *DraI* polymorphism of the *P450IIE1* gene [29], having both the *GSTM1* null and *CYP1A1 Mspl* heterozygous genotypes [30], and a Myeloperoxidase polymorphism [31] and lung cancer risk. Since several of these factors are involved in the metabolism of carcinogens, they could also affect the risk of other cancers. The likelihood that many genes could affect cancer risk raises the possibility that the major factor could have several risk-enhancing alleles at different loci. Another possibility is that the major factor represents an unmeasured environmental factor that increases cancer risk and is passed from parent to offspring. For instance, certain dietary habits are known to increase cancer risk [32], and these habits may run in families.

Our results showed for the first time the strong effect of family history in a female relative and a strong effect for early onset patients, even when many environmental risk factors were controlled for. We also showed evidence of a major genetic effect in families of early onset female non-smokers. Evidence of a major Mendelian factor leading to an earlier onset of cancer was found and might be interpreted as meaning that alleles leading to a greater cancer susceptibility exist in this population. Identifying and testing specific markers using a linkage analysis to confirm the gene involved in the development and progression of lung cancer should be a high future priority.

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