Identification and Characterization of Families with Aggregation of Lung Cancer

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Background: To clarify genetic factors involved in the susceptibility to lung cancer, it is essential to identify families with lung cancer clustering and to characterize the mode of clustering. Since somatic mutations of the p53, RB and p16 genes occur frequently in lung cancer and the replication error phenotype is seen in a subset of lung cancer, it is possible that germ-line mutations of the p53, RB, p16 and mismatch repair genes influence the susceptibility to lung cancer.

Methods: In this work, cases with familial clustering of lung cancer were selected from 1068 families with primary lung cancer cases in analogy with the criteria for hereditary non-polyposis colorectal cancer (HNPCC). Cases with Li-Fraumeni syndrome, familial retinoblastoma, familial melanoma and HNPCC were also searched among these 1068 families.

Results: There were only four families (0.4%) in which more than three relatives were affected by lung cancer. Two successive generations were affected in 36 families (3.4%). Patients with lung cancer before the age of 50 were present in 165 families (15.5%). However, no family conformed to all three criteria. There was only one family with Li-Fraumeni syndrome and no family with familial retinoblastoma, familial melanoma and HNPCC.

Conclusion: Familial aggregation of lung cancer is rare and germ-line mutations of the p53, RB, p16 and mismatch repair genes may not contribute greatly to susceptibility to lung cancer.

Key words: lung cancer – cancer family syndrome – genetic susceptibility – Li-Fraumeni syndrome – hereditary non-polyposis colorectal cancer

INTRODUCTION

Familial aggregation is seen in a variety of human cancers. Recent molecular genetic studies have revealed that such aggregation is partly attributable to inherited genetic defects and, up to the present, a number of genes responsible for susceptibility to cancer have been identified. Familial aggregation of lung cancer has been suggested by statistical analyses (1–5) and by case studies (6–8), although the gene responsible has not yet been identified. To identify genes involved in susceptibility to lung cancer, it is essential to recruit families with lung cancer clustering and characterize the mode of familial clustering. In this study, we attempted to identify families with aggregation of lung cancer among 1068 families by selecting patients with lung cancer as probands. In several hereditary cancer syndromes, such as hereditary non-polyposis colorectal cancer (HNPCC), the mode of genetic transmission is consistent with autosomal dominant inheritance pattern. If there is a hereditary lung cancer, the families with autosomal dominant inheritance pattern could be found. Thus, to identify families with lung cancer clustering, familial cases were selected by criteria in accordance with the Amsterdam criteria of HNPCC as a model.

Tumor suppressor genes and mismatch repair genes are involved in the development of hereditary cancers. The p53, RB and p16 tumor suppressor genes are responsible for Li-Fraumeni syndrome (9,10), familial retinoblastoma (11) and familial melanoma (12), respectively, while somatic mutations of those genes frequently occur in sporadic lung cancers (13–17). Inherited genetic defects in the mismatch repair genes, such as...
hMSH2 and hMLH1, play a causative role in the development of HNPCC tumors (18,19). Genomic instability represented by the replication error (RER) phenotype, which is a characteristic of HNPCC tumors, is present in a subset of sporadic lung cancers (20,21). Hence it is possible that germ-line mutations of those genes also influence the susceptibility to lung cancer. For these reasons, we also searched for cases with Li-Fraumeni syndrome, familial retinoblastoma, familial melanoma and HNPCC among those 1068 families.

The results indicated that familial clustering of lung cancer is rare and that cancer family syndromes with germ-line mutations of p53, RB, p16 and mismatch repair genes are also rare in lung cancer patients. Hence it is suggested that the process of multistage lung carcinogenesis is not greatly influenced by genetic factors.

SUBJECTS AND METHODS

Probands of pathologically verified primary carcinoma of the lung and bronchus (International Classification of Disease, Ninth Revision, site code 162) were identified by reviewing the hospital records between 1962 and 1995 at the National Cancer Center Hospital. Family histories were obtained from hospital records that had been systematically taken on admission in interview. Eligibility for this study was limited to probands whose age, gender and family history for the first- and second-degree relatives were available; 1068 families were eligible for this study.

To examine familial aggregation of lung cancer, we defined three criteria in analogy with the diagnosis of HNPCC (Minimum Criteria, Amsterdam, 1990) (22): (1) at least three relatives should have histologically verified lung cancer and one of them should be a first-degree relative of the other two; (2) at least two successive generations should be affected; and (3) in one of the relatives lung cancer should be diagnosed before age 50. We searched for families with Li-Fraumeni syndrome, familial retinoblastoma, familial melanoma and HNPCC as follows: information about types of cancers among relatives of the 1068 families were obtained from medical records, then cases with component tumors in each cancer family syndrome were identified.

RESULTS

In 991 out of the 1068 families (92.8%), no other relatives were affected by lung cancer. There were 73 families (6.8%) in which two relatives were affected by lung cancers and four families (0.4%) in which three relatives were affected. There was no family in which four or more relatives were affected. Among 77 families in which two or three relatives were affected by lung cancers, two successive generations were affected in 36 families (3.4%). The smoking rate of probands among these 77 families was 75.3% (58/77), while that of the remaining 991 individuals was 71.5% (709/991). Ages at diagnosis ranged from 19 to 97 years in males and from 25 to 87 years in females. Mean ages at diagnosis were 61.6 years in males and 60.7 years in females. Among the 1068 probands, 14.4% (106) of males and 17.7% (59) of females were affected before 50 years of age.

The number of lung cancer families is summarized in Table 1 according to the three criteria. The number of families who met criteria 1, 2 and 3 were 0.4% (4), 3.4% (36) and 15.5% (165), respectively. Six (0.6%) families satisfied two of the three criteria,
Table 1. Number of familial lung cancers selected by three criteria

<table>
<thead>
<tr>
<th>Criteria*</th>
<th>No. of families/1068 lung cancer cases</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>165</td>
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<td>1 and 2</td>
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<td>1</td>
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<td>2 and 3</td>
<td>3</td>
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<tr>
<td>1, 2 and 3</td>
<td>0</td>
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</tbody>
</table>

*See Subjects and Methods for criteria 1, 2 and 3.

Table 2. Cancer family syndrome identified by selecting patients with lung cancer as probands

<table>
<thead>
<tr>
<th>Cancer family syndrome</th>
<th>Responsible gene</th>
<th>No. of families/1068 lung cancer cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>p53</td>
<td>1</td>
</tr>
<tr>
<td>Familial retinoblastoma</td>
<td>RB</td>
<td>0</td>
</tr>
<tr>
<td>Familial melanoma</td>
<td>p16</td>
<td>0</td>
</tr>
<tr>
<td>HNPCC</td>
<td>MSH2, MLH1, PMS1, PMS2</td>
<td>0</td>
</tr>
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DISCUSSION

HNPCC accounts for 3–6% of total colorectal cancers (23). Here we used the criteria in analogy with the Amsterdam criteria of HNPCC to recruit familial lung cancer cases; however, no familial cases were diagnosed from 1068 families with primary lung cancer cases. Hence it is evident that familial clustering of lung cancer occurs much less frequently than that of colon cancer. To perform genetic analysis for susceptibility to lung cancer, it is essential to collect a number of families with lung cancer aggregation. However, the present study indicated that it is difficult to recruit families with lung cancer aggregation simply by reviewing medical records.

There was only one family who met the criteria of Li–Fraumeni syndrome and no family with familial retinoblastoma, familial melanoma and HNPCC. Hence it is suggested that germ-line mutations of p53, RB, p16 and mismatch repair genes are not sufficient to increase susceptibility to lung cancer.

Since smoking is the most important environmental risk factor of lung cancer, familial aggregation of the habit may also cause familial clustering of lung cancer. In this study, the smoking rate of 77 possible familial lung cancer cases was not significantly higher than that of other non-familial sporadic lung cancer cases. This result may suggest that the smoking history of probands do not affect the clustering of lung cancer. However, since smoking data for other family members were not available, further studies will be necessary to clarify the effect of smoking on familial aggregation in familial clustering of lung cancer. Genetic polymorphisms of CYP1A1, CYP2D6, CYP2E1 and glutathione S-transferase (GST) and differences in aryl hydrocarbon hydroxylase (AHH) inducibility have been shown to be associated with susceptibility to lung cancer (24–28). Therefore, to elucidate the involvement of those factors in the familial clustering of lung cancer, it would be worth investigating genetic and phenotypic deviations of those factors in 77 possible familial lung cancer cases.

There have been a number of papers suggesting the involvement of inherited genetic factors in the genesis of lung cancer. Tokuhata and Lilienfeld (1) reported that the incidence of lung cancers among relatives of patients with lung cancer was 2.7 times greater than that among relatives of controls. Ooi et al. (3)
reported that all first-degree relatives of probands had a relative risk of 2.4 compared with their spouse counterparts. Same et al. (5) reported that the personal risk of lung cancer was increased more than fivefold if at least one parent had lung cancer. Segregation analysis further suggested that Mendelian inheritance of a rare major autosomal gene may produce lung cancer at an earlier age of onset (29). However, families of the autosomal dominant inheritance pattern were not detected in this study. Sugimura et al. (30) reported that environment and habitual smoking are more important than genetic factors to the occurrence of multiple primary lung cancer. Braun et al. (31) concluded, in a cohort study of monozygotic and dizygotic twin pairs, that inherited predisposition was not demonstrable in relation to smoking-induced lung cancer diagnosed in men older than 50. Although the present study does not entirely rule out the etiological role of inherited predisposition for the development of lung cancer, it supports the conclusion that genetic factors do not contribute greatly to the development of lung cancer.

Acknowledgments

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References