Association of Family History of Cervical, Ovarian, and Uterine Cancer with Histological Categories of Lung Cancer: The Iowa Women’s Health Study

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Abstract

A family history of cervical, ovarian, or uterine cancer has been shown to be associated with increased lung cancer risk among postmenopausal women. The present report examines the hypotheses that a family history of cervical cancer is positively associated with histological subtypes of lung cancer most strongly associated with smoking and that a family history of ovarian or uterine cancer are positively associated with risk of adenocarcinoma of the lung. Data are from the Iowa Women’s Health Study, a prospective cohort study of 34,480 women ages 55–69 in 1986. Personal smoking histories, use of alcohol, and family history of selected cancers in first- and second-degree relatives were collected at baseline. Follow-up for cancer occurrence was achieved through the State Health Registry of Iowa. After baseline exclusions, a total of 343 incident lung cancers were identified in the cohort at risk through 1994. Women with a family history of cervical cancer in a first-degree relative had a multivariate-adjusted relative risk of lung cancer of 1.6 [95% confidence interval (CI): 0.98–2.6] compared to women without a family history. The risk was particularly high for malignancies most strongly associated with smoking (squamous, small cell, and large cell tumors; relative risk, 2.0; 95% CI, 1.1–3.7). Consistent with our hypotheses, a family history of ovarian cancer was associated with an approximately 2-fold increased risk (multivariate adjusted) of adenocarcinoma of the lung; the association with malignancies more strongly associated with smoking was inverse (relative risk, 0.6; 95% CI, 0.2–2.4). A family history of uterine cancer was not associated with adenocarcinoma, but there was a positive association observed for the most strongly smoking-associated histological types. These results suggest that a family history of cervical cancer is a modest independent risk factor for lung cancers most strongly associated with smoking, and a family history of ovarian cancer is a risk factor for adenocarcinoma of the lung.

Introduction

It is clearly established that the majority of lung cancers are caused by environmental carcinogens, with tobacco smoke accounting for more than 85% of lung cancer deaths (1). There is also evidence that although all histological types of lung cancers are influenced by tobacco exposure, the strength of the association varies by histological type. Small cell, squamous, and large cell carcinomas are more strongly associated with the use of tobacco products than adenocarcinomas (2, 3). Since adenocarcinoma is more common in women (4) and demonstrates the weakest association with smoking (5), other factors, such as hormonal factors, may be influential.

Although environmental factors contribute significantly to lung cancer risk, there is considerable interindividual variation in response (6). Several reports have found that relatives of lung cancer cases are at greater risk of lung cancer than relatives of controls (7–9). Segregation analyses which accounted for the effect of cigarette smoking exposure suggest that the pattern of the disease is consistent with Mendelian factors that influence the age at onset distribution (10). There is reason to suspect that, if inherited susceptibility contributes to risk, it may include cancers other than the lung. Several reports have noted an excess occurrence of smoking-associated cancers among relatives of lung cancer cases (8, 11). The report by Sellers et al. (11) on 337 Louisiana lung cancer families noted an excess risk of female reproductive cancers. This observation was explored in greater detail in the Iowa Women’s Health Study, in which a family history of ovarian cancer and a family history of cervical cancer were associated with increased lung cancer risk among postmenopausal women (12).

There are data to suggest that cervical cancer is associated with tobacco usage (13–15), whereas ovarian and uterine cancers are considered to be influenced by hormones (16, 17). The present report provides additional data on the association of family histories of cervical, ovarian, or uterine cancers with risk of lung cancer. In particular, we hypothesized that a family history of cervical cancer would be positively associated with risk of strongly smoking-associated histological subgroups of lung cancer, and a family history of ovarian or uterine cancer would be positively associated with risk of adenocarcinoma of the lung.
Materials and Methods

Iowa Women’s Health Study Cohort. The Iowa Women’s Health Study is a prospective cohort study which has been described in detail elsewhere (18, 19). Briefly, in 1985, a random sample of women between the ages of 55 and 69 with a valid Iowa driver’s license was identified. Questionnaires were mailed to 99,826 women, of whom 41,836 responded, representing a response rate of 42%. The postmenopausal cohort at risk for developing lung cancer excluded women with missing information and those who reported on the baseline questionnaire that they had a previous history of nonskin cancer. After these exclusions, 37,098 women remained for analysis. Further exclusions were made based on implausible energy intake (<600 or >5,000 kcal/day) or unreliable dietary information (>30 blanks), leaving 34,480 for multivariate analyses, 343 of whom had developed lung cancer during the 9 years of follow-up.

Data Collection. The baseline questionnaire covered a variety of exposures, including self-reported family history of breast, cervical, ovarian, and uterine/endometrium cancers in the respondents’ mothers, maternal and paternal grandparents, maternal and paternal aunts, sisters, and daughters. Women were asked if they had ever smoked at least 100 cigarettes in their lifetime and, if so, the age at initiation (and cessation) and the average numbers of cigarettes usually smoked per day. These data were used to construct pack-years of cumulative tobacco exposure and a variable to denote smoking status (current, former, never). Education was categorized according to completion of high school (less than, equal to, or greater than). Questions regarding usual alcohol consumption over the past year were asked as part of a food-frequency questionnaire. These data were converted to g/day as described previously (20).

Identification of Lung Cancer Cases. Follow-up for lung cancer occurrence was performed through the State Health Registry of Iowa, part of the National Cancer Institute’s SEER\(^2\) Program (21). A computer program was used to match incident lung cancer cases listed in the registry between the years of 1986 and 1994 to the participant’s name, zip code, birth date, and social security number. Lung cancer cases were those coded as International Classification of Diseases for Oncology 162 (22). Histological subtype of lung cancer was abstracted from SEER registry records.

The length of follow-up time in person-years for each participant was determined as the date from which the baseline questionnaire was completed until one of the following events: (a) date of lung cancer diagnosis; (b) date of death (if death occurred in Iowa); (c) date moved out of Iowa; (d) midpoint between last follow-up date and 1994 (if moving date is unknown); and (e) midpoint between last date of contact and date of death (when deaths occurred outside of Iowa). Participants who did not meet these criteria were assumed to be living residents of Iowa and contributed to follow-up through December 31, 1994.

Analyses. A positive family history was defined as a self-report of at least one first-degree (mother, sister, or daughter) or second-degree (grandmother, aunt) relative with a reproductive cancer of interest (cervical, ovarian, or uterine).

Proportional hazards regression (23) was used to compute RRs and CIs and to adjust for potential confounders. Multivariate models included age, smoking status, pack-years smoked, education, and alcohol consumption. Variables for smoking included both smoking status and pack-years to account for the different effect of pack-years on risk in current and former smokers.

Lung cancer cases were partitioned according to four histological subtypes: squamous, small cell, adenocarcinoma, and large cell lung cancers. These histological subtypes were then grouped as strongly or moderately smoking-associated lung cancer. Small cell, squamous cell, and large cell lung cancer subtypes are considered to be more strongly smoking-associated than adenocarcinoma. In analyses based on subgroups of histological types, tumors of mixed or unknown origin (n = 42) were excluded.

Within strongly versus moderately smoking-associated groups, RRs and 95% CIs were calculated for each of the cancer family history variables (family history of cervical, ovarian, or uterine cancer in first- and/or second-degree relatives). The incidence rates for the reference categories in Tables 2 and 4 are the same and were calculated from women who reported no family history of cervical, ovarian, or uterine cancer, as indicated.

Results

Through 9 years of follow-up, a total of 373 incident lung cancers were identified in the cohort at risk. This number was reduced to 343 for multivariate analyses including dietary factors. Established risk factors for lung cancer have been examined in this cohort and reported previously (12, 24, 25); the most recent data available are presented in Table 1. The RRs of lung cancer associated with the family history of cancer variables irrespective of histological cell type are presented in Table 2. Women with a family history of cervical cancer in first-degree relatives had a 2-fold (95% CI: 1.24–3.30) increased age-adjusted risk of lung cancer compared with women without a family history. Adjustment for smoking status, pack-

\(^2\) The abbreviations used are: SEER, Surveillance, Epidemiology, and End Results; CI, confidence interval; RR, relative risk.
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Table 2. Age- and multivariate-adjusted RRs and 95% CIs of lung cancer associated with family history of various cancers in first- and second-degree relatives.

<table>
<thead>
<tr>
<th>Family cancer history</th>
<th>Person-years</th>
<th>Incident lung cancer cases</th>
<th>RR*</th>
<th>95% CI</th>
<th>RR†</th>
<th>95% CI</th>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>First-degree relative</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No 276,505</td>
<td>314</td>
<td>1.00</td>
<td>1.00</td>
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<td></td>
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<tr>
<td>Yes 7,411</td>
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<td>2.02</td>
<td>1.24-3.30</td>
<td>1.59</td>
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<td>Yes 9,726</td>
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<td>1.64</td>
<td>1.02-2.64</td>
<td>1.36</td>
<td>0.84-2.18</td>
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<td>0.61-2.46</td>
<td>1.19</td>
<td>0.59-2.40</td>
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<td>0.75-2.39</td>
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<td>Yes 13,037</td>
<td>20</td>
<td>1.33</td>
<td>0.84-2.09</td>
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<td>0.69-1.71</td>
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<td>1.21</td>
<td>0.82-1.79</td>
<td>1.06</td>
<td>0.72-1.57</td>
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</table>

* Numbers do not sum to 343 because of missing data.
† Adjusted for age.
‡ Adjusted for age, education, smoking status, pack-years, and alcohol.

Table 3. Lung cancer cases and smoking status according to histological subtypes.

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Smoking status</th>
<th>Total</th>
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<tr>
<td></td>
<td>Ever</td>
<td>Never</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Small cell</td>
<td>76</td>
<td>95.0</td>
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<tr>
<td>Squamous cell</td>
<td>63</td>
<td>92.6</td>
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<tr>
<td>Large cell</td>
<td>20</td>
<td>95.2</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>99</td>
<td>75.0</td>
</tr>
<tr>
<td>Total</td>
<td>258</td>
<td>85.7</td>
</tr>
</tbody>
</table>

* Excludes mixed (n = 6) and unspecified (n = 36).
† Includes current and previous smokers.
‡ Percentage of histological subtype.
§ Percentage of total lung cancer cases.

years, education, and alcohol intake reduced the magnitude of the risk estimate to 1.6. Inclusion of data on more distant relatives further lowered the risk estimates. Family histories of ovarian cancer in first-degree relatives only and in either first- or second-degree relatives were associated with increased RRs of lung cancer (1.22 and 1.34, respectively).

The distribution of lung cancer cases according to major histological classification was examined (Table 3). The most common histology was adenocarcinoma followed by similar proportions of small cell and squamous cell types. The least common histology was large cell. As expected, the association between smoking and lung cancer was strongest for small, squamous, and large cell tumors and weakest for adenocarcinoma. Nonetheless, 75% of women with adenocarcinoma of the lung were current or former smokers.

Analyses were then performed in which lung cancers were partitioned into histological subtypes. A family history of cervical cancer in first-degree relatives was positively associated with the age-adjusted risk of strongly smoking-associated lung cancers (Table 4); the RR (2.7) was statistically significant. Following multivariate adjustment, the association with strongly smoking-associated lung cancers was reduced to 2.0 and remained statistically significant. Inclusion of second-degree relatives in the analyses weakened the association of a family history of cervical cancer with risk of lung cancer for both histological groups; only cancers that are strongly associated with smoking remained elevated (RR, 1.8; 95% CI, 1.0–3.26). A family history of ovarian cancer in first-degree relatives was positively associated with moderately smoking-associated lung cancers (adenocarcinoma; Table 4). In women reporting a relative with uterine cancer there was no excess of lung cancers overall (Table 2). However, there was a positive association with lung cancers most strongly associated with smoking (Table 4). This finding was not statistically significant.

Discussion

Women in our study who had a family history of cervical cancer in first- or second-degree relatives had a 1.8-fold in-
increased risk of strongly smoking-associated lung cancers after adjusting for age, education, smoking history, and alcohol consumption. Smoking (1) and alcohol consumption (23, 26) have been previously found to be associated with an increased risk for lung cancer in this cohort. Based on our results, women with a family history of cervical cancer have a moderately increased risk for developing strongly smoking-associated lung cancer histological types independent of personal smoking habits. We were unable to directly assess whether a family history of cervical cancer is due to an underlying genetic susceptibility to tobacco exposure or to shared tobacco consumption behaviors within the family setting (6). However, we believe that shared tobacco consumption habits are unlikely to account for all of the association since an elevated RR persisted after controlling for smoking habits of the study subjects.

Overall, there was no excess of lung cancers reported among women with a family history of uterine cancer. The apparent excess of lung cancers most strongly associated with smoking among these women was unexpected. However, it is not statistically significant. Further investigation with a larger dataset may be warranted.

Immunological (27, 28) and hormonal (5, 29, 30), factors have been suggested to influence the risk for lung adenocarcinomas, and familial patterns have been noted (31–33). Previous studies have found an excess risk of lung cancer among relatives of ovarian cancer cases (34, 35); however, specific lung cancer histological types were not identified. Our findings, with respect to family history of ovarian cancer and risk of adenocarcinoma of the lung, though not statistically significant, are consistent with the hypothesis that a family history of ovarian cancer is a risk factor for this type of lung cancer.

Because of the low prevalence of family history of lung cancers, its contribution to histological types of lung cancer could not be addressed. Several studies have found an increased risk of lung cancer in relatives of lung cancer patients, suggesting that there is a familial component to lung cancer (6). More convincing data are that of Mendelian inheritance of lung cancer susceptibility found through a formal segregation analysis in 337 families ascertained through lung cancer probands (10). The data were consistent with an autosomal codominant inheritance pattern associated with an earlier age of onset for lung cancer. Differences in genetic predisposition may provide an explanation for why more than 80% of smokers live to old age and do not die of smoking-induced lung cancer (36).

Limitations of this study must be considered. There was no attempt to verify cancers in relatives, nor was information collected on age of onset or family size. There is a potential for misclassification for family history variables, and misclassification of any kind has the potential of causing bias. Reporting of family histories of reproductive cancers is imperfect and accuracy is better for first-degree versus second-degree relatives (37). However, this study was prospective, and subjects were free of cancer at baseline; therefore, we do not have reason to believe that there is differential misclassification of family history data by lung cancer status at follow-up. The small number of cases with the various family histories of cancer and the small number of cases within specific histological subtypes are of concern. In addition, it is possible that the ratios of histological subtypes of lung cancer observed in our cohort would differ compared with a younger cohort, so that the association between family history and risk of specific histological categories may differ with age. Histological classifications may be incorrect. There have been reports of significant inter- and intraobserver variability in the classification of cases by histological cell type (38). Histological type distribution can be influenced by the bronchial site of origin (central versus peripheral) of the specimen and the method by which the specimen was obtained (e.g., biopsy, surgery, cytology, or autopsy) and treated (e.g., histochemical staining) to facilitate histological classification (39, 40). The population in Iowa is predominantly Caucasian. Since there may be ethnic differences in allelic frequencies of susceptibility genes, different associations might be observed between family history of cancer and lung cancer in other populations. Finally, although
observed associations with family history of cervical cancer and ovarian cancer were congruent with a priori hypotheses, the relatively small numbers of cases within histological subtypes necessitate the caveat that these findings may be due to chance. A better understanding of the familial history of lung cancer will require more detailed studies.

Acknowledgments
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References
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