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# Familial Risk of Lung Carcinoma in the Icelandic Population

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LUNG CARCINOMA IS THE LEADING cause of death from cancer among men and women in many Western countries.<sup>1</sup> Mortality due to lung carcinoma in the United States exceeds the death rate from breast, prostate, and colon cancer combined.<sup>2</sup> Treatment results for lung carcinoma have remained disappointing and only marginal gains have been made during the last 30 to 40 years. Five-year survival is now approaching 14% given the best available diagnostic and treatment modalities.<sup>3</sup>

The dominant role of tobacco smoke as a causative factor in lung carcinoma is well established. Most studies report that more than 90% of patients with lung carcinoma are smokers.<sup>1</sup> Previous epidemiological case-control studies have shown an approximately 2-fold increase in the development of lung carcinoma in first-degree relatives of patients with lung carcinoma, after controlling for confounding fac-

See also pp 2984 and 3026.

**Context** The dominant role of tobacco smoke as a causative factor in lung carcinoma is well established; however, an inherited predisposition may also be an important factor in the susceptibility to lung carcinoma.

**Objective** To investigate the contribution of genetic factors to the risk of developing lung carcinoma in the Icelandic population.

**Design, Setting, and Participants** Risk ratios (RRs) of lung carcinoma for first-, second-, and third-degree relatives of patients with lung carcinoma were estimated by linking records from the Icelandic Cancer Registry (ICR) of all 2756 patients diagnosed with lung carcinoma within the Icelandic population from January 1, 1955, to February 28, 2002, with an extensive genealogical database containing all living Icelanders and most of their ancestors since the settlement of Iceland. The RR for smoking was similarly estimated using a random population-based cohort of 10541 smokers from the Reykjavik Heart Study who had smoked for more than 10 years. Of these smokers, 562 developed lung cancer based on the patients with lung cancer list from the ICR.

**Main Outcome Measures** Estimation of RRs of close and distant relatives of patients with lung carcinoma and comparison with RRs for close and distant relatives of smokers.

**Results** A familial factor for lung carcinoma was shown to extend beyond the nuclear family, as evidenced by significantly increased RR for first-degree relatives (for parents: RR, 2.69; 95% confidence interval [CI], 2.20-3.23; for siblings: RR, 2.02; 95% CI, 1.77-2.23; and for children: RR, 1.96; 95% CI, 1.53-2.39), second-degree relatives (for uncles/aunts: RR, 1.34; 95% CI, 1.15-1.49; and for nephews/nieces: RR, 1.28; 95% CI, 1.10-1.43), and third-degree relatives (for cousins: RR, 1.14; 95% CI, 1.05-1.22) of patients with lung carcinoma. This effect was stronger for relatives of patients with early-onset disease (age at onset  $\leq$  60 years) (for parents: RR, 3.48; 95% CI, 1.83-8.21; for siblings: RR, 3.30; 95% CI, 2.19-4.58; and for children: RR, 2.84; 95% CI, 1.34-7.21). The hypothesis that this increased risk is solely due to the effects of smoking was rejected for all relationships, except cousins and spouses, with a single-sided test of the RRs for lung carcinoma vs RRs for smoking.

**Conclusions** These results underscore the importance of genetic predisposition in the development of lung carcinoma, with its strongest effect in patients with early-onset disease. However, tobacco smoke plays a dominant role in the pathogenesis of this disease, even among those individuals who are genetically predisposed to lung carcinoma.

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tors, such as smoking and age, suggesting a genetic predisposition.<sup>4-7</sup>

Similar risk has also been observed for relatives of patients with lung carcinoma in larger registry-based studies utilizing the Utah Population and Cancer Registry Database<sup>8,9</sup> and the Swedish Family-Cancer Database.<sup>10-12</sup>

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These registry-based studies are more meaningful as they are less prone to sampling bias, resulting from proband identification and oversampling of families with several affected members.<sup>13</sup> However, none of these larger studies were controlled for smoking. It is important to control for smoking for 2 reasons. First, it is possible that the increased incidence of lung carcinoma in first-degree relatives is due to shared environment (second-hand smoke or other environmental factors), as demonstrated by increased lung cancer risk for spouses of patients with lung cancer in 1 of the Swedish studies.<sup>12</sup> Second, the familiarity of lung cancer could be entirely due to the familiarity of nicotine addiction and smoking.

In our study, we estimated the familiarity of lung carcinoma in the Icelandic population by linking together records from the Icelandic Cancer Registry (ICR)<sup>14,15</sup> of all cases of lung carcinoma diagnosed in Iceland from January 1, 1955, to February 28, 2002, with a nationwide genealogical database containing all living Icelanders and the majority of their ancestors since the settlement of Iceland in 870 AD. This allowed us to examine all relationships among all of the lung carcinoma cases registered in the ICR and to estimate risk for lung carcinoma development beyond first-degree relatives of patients with lung carcinoma, thus reducing the effects of shared environment. Furthermore, by using information on smoking history from the Reykjavik Heart Study,<sup>14</sup> we estimated the familiarity of smoking, and compared the risk ratio (RR) of lung carcinoma with the RR of smoking to examine whether there is a genetic component to the risk of lung carcinoma.

## METHODS

### Study Population

The study population included all patients diagnosed with lung carcinoma in Iceland from January 1, 1955, to February 28, 2002. These cases were all registered in the ICR.<sup>14,15</sup> Lung carcinoma was defined as a malignant neoplasm of epithelial origin accord-

ing to the World Health Organization histological classification.<sup>16</sup> Carcinoid tumors as well as tumors of lymphoid and mesenchymal origin were excluded from our analysis. Information in the ICR includes year of diagnosis, year of death, Systematized Nomenclature of Medicine code, *International Classification of Diseases, 10th Revision (ICD-10)*, and mode of lung carcinoma verification. During this 47-year period, 2756 patients with lung carcinoma were identified (1504 men and 1252 women). Histological and cytological verification was available for 2516 patients with lung carcinoma; the remaining 240 patients were diagnosed clinically.

A random collection of 10541 adult smokers from the Icelandic population was obtained from the Icelandic Heart Association. These were individuals who had been randomly selected to take part in a nationwide study of cardiovascular risk factors (the Reykjavik Heart Study) during the years 1967 to 2002 and had answered a questionnaire on entry, which included information about their smoking habits. All individuals who had smoked for more than 10 years were defined as smokers. Of the 10541 smokers in the study, 562 developed lung carcinoma. Because we had smoking information only on a small proportion of all patients with lung carcinoma and their relatives, we could not calculate lung carcinoma RR directly, taking smoking into account. Instead, we used the random sample of smokers to estimate the familiarity of smoking.

All data were encrypted through a process approved by the Data Protection Commission of Iceland before being sent to our laboratory for analysis.<sup>17</sup> The study was approved by the National Bioethics Committee of Iceland and the Data Protection Commission of Iceland.

### Genealogical Database

We have built a computerized database of genealogical information in Iceland, including the names of all 284000

living Icelanders and their deceased ancestors.<sup>18</sup> Currently, more than 685000 individuals are registered in the database. Control groups were assembled to match the patients with lung carcinoma group according to year of birth, sex, and number of ancestors within the database in the preceding 5 generations. The Data Protection Commission of Iceland reversibly encrypted the data along with the genealogical database, before making it available to our laboratory.<sup>17</sup>

### RR Calculation

To evaluate familial risk of lung carcinoma in the Icelandic population, we calculated RRs of close and distant relatives of the probands.<sup>18</sup> The RR for relatives of patients with lung carcinoma were defined as the risk of lung carcinoma in the relatives of affected individuals divided by the prevalence in the general population. In other words, if  $P$  denotes the event in which the proband is affected and  $R$  denotes the event in which the relative is affected, the RR is defined as

$$\frac{P(R|P)}{P(R)}$$

When calculating the risk of lung carcinoma in relatives, we restricted our analyses to relatives born during the period covering the lifespan of the group of patients in question. We used the same restriction according to year of birth in estimating the risk in the general population for the given RR.

The RR of smoking was evaluated in a similar way as the RR of lung carcinoma using the list of the 10541 smokers and the Icelandic genealogical database. The RR for smoking together with the RR for lung carcinoma allows for a statistical test on the effects of smoking on lung carcinoma.

### Statistical Analysis

Let  $r$  be the number of relatives of probands (counting multiple times individuals who are relatives of multiple probands<sup>19</sup>),  $a$  the number of relatives of probands that are affected (again possibly counting the same individual more

than once),  $n$  the size of the population, and  $x$  the number of affected individuals in the population. If  $P(R)$  and  $P(R|P)$  can reasonably be assumed to be constant in the population, then respectively  $x/n$  and  $a/r$  are estimates of these probabilities. Given the estimates, RR is consistently estimated by

$$\frac{a/r}{x/n}$$

Assuming the population may be split into  $N$  subpopulations, within each of which  $P(R)$  and  $P(R|P)$  can reasonably be assumed to be constant, although they may vary between subpopulations, and assuming RR is the same in all subpopulations, it is consistently estimated by any weighted sum of the estimates for the  $N$  subpopulations. We chose to select weights such that the efficiency of the estimator is at maximum for RR equal to 1. Making the simplifying assumption that the relatives are independent (although this assumption is obviously wrong, it only affects efficiency, not validity), the optimal weight for group  $j$  is

$$w_j = \frac{x_j r_j}{n_j - x_j}$$

(this is the inverse of the variance of the estimate for RR in subpopulation  $j$ ), where the meaning of  $a$ ,  $r$ ,  $x$ , and  $n$  is the same as above, restricted to the subpopulation  $j$ , except that all affected individuals in the population are still taken as probands and not just the individuals in the subpopulation. Given these weights, our estimate of RR is

$$\frac{\sum_{j=1}^N w_j \frac{a_j/r_j}{x_j/n_j}}{\sum_{j=1}^N w_j} = \frac{\sum_{j=1}^N \frac{a_j n_j}{n_j - x_j}}{\sum_{j=1}^N \frac{r_j x_j}{n_j - x_j}}$$

In our analysis, potential differences in  $P(R)$  and  $P(R|P)$  between subpopulations stem from time-dependent censoring of affection statuses and possibly sex-specific differences. Therefore, we have taken  $j$  to run over groups of relatives born in the same 5-year period and of the same sex. The patients with lung carcinoma in our analysis

were born between the years 1868 and 1977, yielding 44 subpopulations.

In the case of smoking, our list is only a random sample of all the smokers. By applying the same method to estimate RR with this partial list,  $a_j/r_j$  is an underestimate of  $P(R|P)$  and  $x_j/n_j$  is an underestimate of  $P(R)$ . However, since these estimates should be off by the same factor,  $(a_j/r_j)/(x_j/n_j)$  continues to be a valid estimate of RR.

Because a person can both be a proband and a relative of 1 or more other probands,  $a_j$  does not have a binomial distribution. In general, for stratum  $j$ ,  $a_j/r_j$  can be considered as a weighted average of many unbiased but correlated estimates of  $P(R|P)$ . It follows that  $(a_j/r_j)/(x_j/n_j)$  is a ratio of 2 unbiased estimates and a consistent estimate of RR. Our overall estimate of RR is a weighted average of the estimates obtained from the various strata and is itself a consistent estimate. However, appropriate simulations, instead of purely analytical calculations, are needed to study its sampling variation. To assess the significance of the RR obtained for a given group of patients, we compared their observed values with the RR computed for 1000 independently drawn and matched groups of control individuals. Each patient was matched to a specific control individual in each control group. The control individuals were drawn at random from the genealogical database and had the same year of birth, the same sex, and the same number of ancestors recorded in the database, as did the patients to whom they were matched. A reported  $P=.05$  for the RR would indicate that 50 of the 1000 matched control groups had values as large or larger than that for the patient's relatives or spouses. When none of the values computed for the control groups were larger than the value for the patient's relatives or spouses, we report  $P<.001$ . Using a variance stabilizing square root transform, an approximate confidence interval (CI) may be constructed based on the control distribution.<sup>19</sup>

**Relationship Between RR of Smoking and Lung Carcinoma Under Certain Assumptions**

We show that, assuming that the familial clustering of lung carcinoma is entirely explained by the familial clustering of smoking, the RR of smoking must be greater than that of lung carcinoma. Mathematically, when we say "the familial clustering of lung carcinoma is entirely explained by the familial clustering of smoking," we mean that the 4 random variables, proband lung carcinoma status, proband smoking status, relative smoking status, and relative lung carcinoma status, form a Markov Chain. For example, this means that relative lung carcinoma status is conditionally independent of proband lung carcinoma status, given the smoking status of either the proband or the relative.

Let  $P_{LC}$ ,  $P_S$ ,  $R_S$ , and  $R_{LC}$  denote the events that the proband has lung carcinoma, the proband smokes, the relative smokes, and the relative has lung carcinoma, respectively. Given that these events are all positively correlated and if we make the Markov assumption described above, then

$$(1) \quad P(R_{LC}|P_{LC}) \leq P(R_{LC}|P_S)$$

and

$$(2) \quad P(P_S|R_{LC}) \leq P(P_S|R_S)$$

We want to prove that

$$(*) \quad [P(R_{LC}|P_{LC})/P(R_{LC})] \leq [P(R_S|P_S)/P(R_S)]$$

Because of (1), to prove (\*), it is sufficient to show that

$$(**) \quad [P(R_{LC}|P_S)/P(R_{LC})] \leq [P(R_S|P_S)/P(R_S)]$$

Applying Bayes' Rule, the left-hand side of (\*\*) can be rewritten as

$$(3) \quad P(P_S|R_{LC})/P(P_S)$$

and the right-hand side of (\*\*) can be rewritten as

$$(4) \quad P(P_S|R_S)/P(P_S)$$

It follows from (2) that (3)  $\leq$  (4). Hence, (\*\*) and (\*) hold. It is also worth noting that equality holds in (\*) if and only if (1) and (2) are both equalities. The latter is true if and only if

$P(P_S|P_{LC}) = 1$  and  $P(R_S|R_{LC}) = 1$ . In other words, equality holds in (\*) if and only if an individual must smoke to get lung carcinoma.

**RESULTS**

When the 2756 patients with lung carcinoma were matched to the Icelandic genealogical database, 274 affected sibling pairs, 296 affected avuncular pairs, and 724 affected cousin pairs were observed.

Estimates of the RR for relatives of the 2756 patients are shown in TABLE 1. Parents, siblings, and children (first-degree relatives) had RRs of 2.69 (95% CI, 2.20-3.23), 2.02 (95% CI, 1.77-2.23), and 1.96 (95% CI, 1.53-2.39), respectively. The RRs for uncles/aunts and nephews/nieces (second-degree relatives) and for cousins (third-degree relatives) were less than that of first-degree relatives but were also significantly increased. The RR for spouses was also sig-

nificantly increased, although less than that for first-degree relatives.

To determine whether the risk of developing lung carcinoma is greater for relatives of patients with early-onset vs late-onset disease, we calculated the RR for relatives of patients diagnosed with lung carcinoma at 60 years or younger (Table 1). For all groups of relatives analyzed, the risk was greater for relatives of patients with early-onset disease than for relatives of all patients with lung carcinoma. Thus, the risk for second-degree relatives (RR, 1.96; 95% CI, 1.35-2.78, for uncles/aunts; and RR, 1.94; 95% CI, 1.32-2.72, for nephews/nieces) of patients with early-onset disease is similar to the risk for children and siblings (RR, 1.96; 95% CI, 1.53-2.39; and RR, 2.02; 95% CI, 1.77-2.23, respectively) of all patients with lung carcinoma.

All 4 major histological types of lung carcinoma (adenocarcinoma and small

cell, large cell, and squamous cell carcinoma) are significantly associated with smoking, and the risk of developing lung carcinoma increases with number of cigarettes smoked and the duration of smoking. However, the strength of this relationship varies between the histological types with adenocarcinoma displaying the weakest overall relationship to smoking.<sup>20,21</sup> Due to this difference, we calculated the risk of lung carcinoma development for relatives and spouses for adenocarcinoma separately from the other major histological types of lung carcinoma (ie, small cell, large cell, and squamous cell carcinomas) (TABLE 2). No significant difference in lung carcinoma risk was detected between relatives and spouses of patients with lung carcinoma from these 2 histological groups. However, the risk for spouses of patients with adenocarcinoma of the lung was only half of that of spouses of the combined group of

**Table 1.** Estimation of Risk Ratio of Lung Carcinoma for Relatives and Spouses of Icelandic Patients With Lung Carcinoma

| Relationship   | All Lung Carcinoma Patients (n = 2756)* |                  |          | Lung Carcinoma Patients, Age at Onset ≤60 y (n = 793)† |                  |          |
|----------------|---|------------------|----------|--|------------------|----------|
|                | No. of Relatives‡                       | RR (95% CI)      | P Value§ | No. of Relatives‡                                      | RR (95% CI)      | P Value§ |
| Parents        | 4874                                    | 2.69 (2.20-3.23) | <.001    | 1489   | 3.48 (1.83-8.21) | <.001    |
| Siblings       | 11 081                                  | 2.02 (1.77-2.23) | <.001    | 3130   | 3.30 (2.19-4.58) | <.001    |
| Children       | 8748                                    | 1.96 (1.53-2.39) | <.001    | 2416   | 2.84 (1.34-7.21) | .007     |
| Uncles/aunts   | 20 348                                  | 1.34 (1.15-1.49) | <.001    | 6779   | 1.96 (1.35-2.78) | <.001    |
| Nephews/nieces | 29 134                                  | 1.28 (1.10-1.43) | <.001    | 8577   | 1.94 (1.32-2.72) | <.001    |
| Cousins        | 49 275                                  | 1.14 (1.05-1.22) | .002     | 18 006   | 1.32 (1.03-1.69) | .02      |
| Spouses        | 2909                                    | 1.75 (1.29-2.33) | <.001    | 895  | 1.91 (0.71-5.68) | .06      |

Abbreviations: CI, confidence interval; RR, risk ratio.

\*All patients with lung carcinoma who were registered in the Icelandic Cancer Registry (ICR) from 1955-2002.

†All patients with lung carcinoma who were registered in the ICR from 1955-2002 with age at onset of 60 years or younger.

‡Numbers given for relatives are unique counts.

§Reported P<.001 indicates that none of the 1000 matched control groups had RR values as large or larger than that for the patients' relatives or spouses.

**Table 2.** Estimation of Risk Ratio of Lung Carcinoma for Relatives and Spouses of Icelandic Patients With Adenocarcinoma vs Small Cell, Large Cell, and Squamous Cell Carcinoma

| Relationship   | Adenocarcinoma (n = 829)* |                  |         | Small Cell, Large Cell, and Squamous Cell Carcinoma (n = 1118)* |                  |         |
|----------------|---------------------------|------------------|---------|---|------------------|---------|
|                | No. of Relatives†         | RR (95% CI)      | P Value | No. of Relatives†   | RR (95% CI)      | P Value |
| Parents        | 1559                      | 2.12 (1.01-3.80) | .02     | 2064  | 2.47 (1.36-4.55) | <.001   |
| Siblings       | 3565                      | 2.61 (1.77-3.66) | <.001   | 4758  | 2.18 (1.64-2.74) | <.001   |
| Children       | 2672                      | 1.65 (0.67-3.22) | .13     | 3507  | 1.81 (0.91-3.56) | .05     |
| Uncles/aunts   | 6978                      | 1.67 (1.16-2.36) | .004    | 8881  | 1.91 (1.40-2.40) | <.001   |
| Nephews/nieces | 9962                      | 1.57 (1.05-2.19) | .02     | 12 885  | 1.77 (1.35-2.22) | <.001   |
| Cousins        | 18 437                    | 1.10 (1.05-1.33) | .31     | 22 593  | 1.22 (1.06-1.48) | .004    |
| Spouses        | 857                       | 1.08 (0.20-4.15) | .38     | 1198  | 2.23 (1.14-4.09) | .008    |

Abbreviations: CI, confidence interval; RR, risk ratio.

\*Patients with adenocarcinoma, small cell, large cell, and squamous cell carcinoma who were registered in the Icelandic Cancer Registry from 1955-2002.

†Numbers given for relatives are unique counts.

small cell, large cell, and squamous cell lung carcinoma. Although this difference was large, it was not significant as the CI for the spouses of patients with adenocarcinoma lung cancer was wide due to low number of spouses in that cohort.

It has been proposed that nicotine addiction (smoking) is at least in part inherited. We thus calculated the risk of smoking for relatives and spouses of smokers using a random list of 10541 individuals who had smoked at least 1 package of cigarettes per day for more than 10 years. As shown in TABLE 3, the risk of having smoked for more than 10 years is significant for first-, second-, and third-degree relatives of smokers. The risk was, however, highest for spouses of smokers (RR, 2.39; 95% CI, 2.28-2.48), suggesting that in addition to genetic factors, environmental factors and/or nonrandom mating have a substantial effect on smoking habits.

Prolonged exposure to tobacco smoke precedes the development of lung carcinoma in the vast majority of patients with lung carcinoma. We demonstrate mathematically that if the familiarity of lung carcinoma is entirely explained by the familiarity of smoking, the risk for smoking (Table 3) must be higher than that of lung carcinoma (Table 1). Therefore, if the RR of lung carcinoma is actually higher than the RR of smoking, it would be a rejection of the null hypothesis that lung carcinoma is entirely due to smoking. Based on a single-sided test of the RRs for lung carcinoma vs RRs for smoking, the null hypothesis was rejected beyond the nuclear family (TABLE 4). This was evident by significantly higher RRs for lung carcinoma than for smoking for all relationships except for cousins. In contrast, the RR for smoking of spouses was significantly higher than the RR for lung carcinoma.

Taken together, our data on the nationwide evaluation of lung carcinoma familiarity in Iceland demonstrates that heritable factors are indeed involved in the etiology of lung carcinoma. Furthermore, this genetic pre-

disposition goes beyond the predisposition to smoking.

**COMMENT**

We investigated the role of genetic factors in the development of lung carcinoma by linking together information on all lung carcinoma cases diagnosed within the Icelandic population from January 1, 1955, to February 28, 2002, with an extensive genealogical database covering all Icelanders living during this time and most of their ancestors. Using these data, we found that there is a familial predisposition to the development of lung carcinoma, as RR estimates for first-, second-, and third-degree relatives of patients with lung carcinoma were all significantly increased. This effect was strongest for relatives of patients with early-onset lung carcinoma, in accordance with previous articles.<sup>22</sup> Significantly increased RR for spouses of patients with lung carcinoma also indicates the presence of shared environmental factors and/or nonrandom mating.

The nationwide genealogy database used in our study provided a means for uncovering the familial component by revealing more connections between patients, missed in most other populations. The first-degree relatives (siblings, children, and parents) of patients with lung carcinoma (early- and late-onset) are at a 2- to 3.5-fold increased risk of developing lung carcinoma than the general population. However, members of

a nuclear family share environment, as evidenced by the 1.75-fold risk of lung carcinoma development in spouses. Thus, this RR increase in first-degree relatives of patients with lung carcinoma is the result of a combination of environmental, genetic factors, or both. Using genealogy, our study goes further than other reported studies by demonstrating that this familial factor extends beyond the nuclear family as evidenced by significantly increased RR for second- and third-degree relatives of patients with lung carcinoma. In the more distant relationships, shared environmental factors are likely to be of less significance, providing a stronger evidence for genetic factors given that RR is in excess.

We had smoking information only for a proportion of our nationwide cohort of patients with lung carcinoma and therefore could not estimate RR di-

**Table 3.** Estimation of Smoking Risk Ratio for Relatives and Spouses of Smokers (n = 10 541)\*

| Relationship   | No. of Relatives† | RR (95% CI)‡     |
|----------------|-------------------|------------------|
| Parents        | 14 343            | 1.94 (1.70-2.17) |
| Siblings       | 30 299            | 1.42 (1.38-1.46) |
| Children       | 27 374            | 1.52 (1.31-1.70) |
| Uncles/aunts   | 42 898            | 1.16 (1.08-1.22) |
| Nephews/nieces | 70 144            | 1.17 (1.12-1.23) |
| Cousins        | 86 249            | 1.14 (1.12-1.16) |
| Spouses        | 10 946            | 2.39 (2.28-2.48) |

Abbreviations: CI, confidence interval; RR, risk ratio.  
 \*Smokers were defined as those individuals who had smoked at least 1 package of cigarettes per day for more than 10 years and were randomly gathered by the Icelandic Heart Association.  
 †Numbers given for relatives are unique counts.  
 ‡For all comparisons, P < .001.

**Table 4.** Single-Sided Comparison of Risk Ratio of Lung Carcinoma for Relatives and Spouses of Icelandic Patients With Lung Carcinoma With the Risk Ratio of Smoking for Relatives and Spouses of Icelandic Smokers

| Relationship   | All Lung Carcinoma Patients (n = 2756)   |          | Lung Carcinoma Patients, Age at Onset ≤60 y (n = 793) |          |
|----------------|--|----------|---|----------|
|                | Δ RR of Lung Carcinoma - Δ RR of Smoking | P Value* | Δ RR of Lung Carcinoma - Δ RR of Smoking              | P Value* |
| Parents        | 0.75                                     | .003     | 1.55  | .08      |
| Siblings       | 0.60                                     | <.001    | 1.87  | .002     |
| Children       | 0.44                                     | .04      | 1.32  | .10      |
| Uncles/aunts   | 0.18                                     | .02      | 0.80  | .01      |
| Nephews/nieces | 0.11                                     | .007     | 0.77  | .01      |
| Cousins        | -0.011                                   | .61      | 0.18  | .08      |
| Spouses        | -0.64                                    | >.99     | -0.48   | .74      |

Abbreviation: RR, risk ratio.  
 \*For P < .001, for no pair of controls was the RR for smoking higher than the RR for lung carcinoma.

rectly taking smoking into account. However, we demonstrated mathematically that single-sided comparison of the RR for smoking to that of lung carcinoma in relatives and spouses of smokers and patients with lung carcinoma, respectively, can be used to determine whether lung carcinoma is entirely due to smoking. When that comparison is applied, the risk for lung carcinoma is significantly higher than the risk for smoking beyond the first-degree relatives of patients with lung carcinoma, demonstrating that increased risk for relatives of patients with lung carcinoma is not solely due to smoking. In contrast, this effect for spouses is opposite (the RR for smoking is higher than for lung carcinoma). These results suggest that the increased risk for lung carcinoma among spouses may be solely due to tobacco exposure. Furthermore, and more importantly, these data also demonstrate that the increased risk for close and distant relatives of patients with lung carcinoma is not solely due to tobacco smoke exposure. Similar conclusion was also reached in a study in which survival models were applied in a case-control analysis of lung carcinoma (ie, the familial aggregation of lung carcinoma could not be fully explained by the familial aggregation of smoking).<sup>23</sup> Based on previous theoretical analysis by Khoury et al,<sup>24</sup> it is unlikely that other unknown environmental factors could explain fully the increased familial risk in lung carcinoma, implying an underlying genetic predisposition in lung carcinoma.

When we compared the risk of lung carcinoma for spouses and relatives of patients with adenocarcinoma to that of spouses and relatives of patients with other histological types of lung carcinoma, the greatest difference (more than half, although not significant) was observed between the spouses of these 2 groups. This suggests a weaker environmental influence for adenocarcinoma than for the 3 other major histology types of lung carcinoma. These data concur with epidemiological studies that have demonstrated a weaker association between smoking and adeno-

carcinoma vs other histological types of lung carcinoma.<sup>20,21</sup>

Comparison of the concordance of cancer between monozygotic and dizygotic pairs of twins has been used to quantify the extent to which an observed familial pattern is due to genetic or shared environmental factors.<sup>25</sup> However, these studies are limited because twins are rare and few twin registries go far enough back in time for cancer assessment.<sup>26</sup> The largest of these studies have suggested a limited heritability of lung carcinoma, although none reached statistical significance.<sup>25</sup>

In previous epidemiological studies on lung carcinoma using segregation analysis, a codominant model of inheritance best fitted the data, suggesting that a rare major autosomal gene plays a role in the development of lung carcinoma.<sup>27</sup> Other studies have suggested that a number of low-penetrance, high-frequency polymorphisms are likely to account for a proportion of lung carcinoma risk.<sup>28</sup> Polymorphisms in these genes could explain individual differences in susceptibility to tobacco carcinogens and are likely to include genes involved in decreasing or increasing the activity of carcinogens (eg, *CYP1A*, *CYP2E*, and *GSTM1*) and genes involved in monitoring and repairing tobacco carcinogen-induced DNA damage (eg, *p53* and *ERCC1*).<sup>29-31</sup> Our results of RR calculation cannot discriminate between different models of inheritance. Recently, a major lung cancer susceptibility locus was mapped to chromosome 6q23-25 using multigenerational densely-affected families.<sup>32</sup> The characteristics of this locus are consistent with a dominant or codominant major locus. Information gained from epidemiological and genetical studies such as our study may be of particular importance in allowing for risk stratification with respect to lung carcinoma. Further information gained from linkage and association studies may give additional value in this respect.

In conclusion, to our knowledge, this study is the first population-based study using a comprehensive and extensive genealogy database, taking into account the effects of smoking, which demon-

strates a familial nature of lung carcinoma that strongly suggests a genetic predisposition to the disease. However, although the results presented here support a role for genetics in the risk of lung carcinoma, it should be emphasized that tobacco smoke plays a dominant role in the pathogenesis of this disease, even among those individuals who are genetically predisposed to lung carcinoma.

**Author Contributions:** Drs Jonsson and Stefansson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** S. Jonsson, Thorsteinsdottir, Kristjansson, Arnason, Hallgrímsson, Gulcher, Amundadóttir, Stefansson.

**Acquisition of data:** S. Jonsson, Isaksson.

**Analysis and interpretation of data:** S. Jonsson, Thorsteinsdottir, H. Jonsson, Kong, Gudbjartsson.

**Drafting of the manuscript:** S. Jonsson, Thorsteinsdottir.

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**Obtained funding:** Stefansson.

**Administrative, technical, or material support:** S. Jonsson, Thorsteinsdottir, Kristjansson, Arnason, Isaksson, Gulcher, Amundadóttir, Stefansson.

**Study supervision:** S. Jonsson, Thorsteinsdottir.

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**Role of the Sponsor:** deCODE Genetics participated in the design and conduct of the study, the collection, analysis, and interpretation of the data, and the preparation, review, and approval of the manuscript. **Independent Statistical Analysis:** Kristján Jonsson, PhD, Associate Professor, Department of Mathematics, Faculty of Science, University of Iceland, was given access to the complete data, including genealogical data and lung cancer and smoking data, after coding of personal identification numbers. Dr Jonsson completed a thorough check of the methods and data analysis, and confirmed that the results reported in the submitted manuscript are both statistically correct and in accordance with the data.

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It has never been my object to record my dreams, just to realize them.

—Man Ray (1890-1976)



ming sperm.”<sup>1</sup> This description is supremely felicitous, as the Veil Nebula is, in fact, the tattered remnants of a supernova—an exploding star.

But there is a far deeper connection. The universe started with little other than hydrogen and helium, and none of the heavy elements of our familiar world and ourselves. The heavier elements up through iron are produced inside massive stars much heavier than the sun, by thermonuclear fusion during the stable portions of their lives. When such stars reach the end of their useable nuclear fuel, they become unable to sustain their own weight, collapse, and rebound in a titanic explosion. This blast, occupying the last few seconds of the star's existence, synthesizes the elements heavier than iron and blows the entire star, aside from the core, into free space, where the heavy elements enrich the hydrogen and helium of the pristine interstellar medium. The next generation of stars and planetary systems born of the enriched gas thereby possesses the heavy elements required for the formation of solid planets and for life. Thus are we all, as astrophysicists and songwriters are wont to say, stardust. In this sense, the supernova actually is how “life begins.”

The portion shown in the (much overexposed) photograph in the painting is called the Western Veil and is part of a larger complex called the Cygnus Loop, which is about 15000 years old, 2500 light years away, 4 times the apparent diameter of the full moon, but very faint. Examined at leisure through a large telescope, under dark and transparent skies, the Veil Nebula is a complex, subtle, and sublime sight. Excellent photographs of the Veil Nebula can be found at the Web site of the National Optical Astronomy Observatories.<sup>2</sup>

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## Rhesus Pieces

**To the Editor:** I read with interest the analysis of the stylistic aspects of the artwork of Wassily Kandinsky,<sup>1</sup> but felt that the geometric analysis regarding *Untitled Improvisation III* on the cover of the September 15, 2004, issue of *JAMA* sacrificed the whole at the expense of its parts, and in so doing Kandinsky makes a monkey out of all of us. Just take a second look and see if you don't agree.

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1. Southgate MT. The Cover. *JAMA*. 2004;292:1274.

## CORRECTIONS

**Data Error:** In the Editorial titled “Stenting Small Coronary Arteries: Works in Progress” published in the December 8, 2004, issue of the *JOURNAL* (2004;292:2777-2778), an incorrect number was published. On page 2777 at the bottom of the first column, the percentage of patients in the sirolimus stent group with diabetes mellitus should read 19% (not 9%).

**Error in Table:** In the Original Contribution entitled “Familial Risk of Lung Carcinoma in the Icelandic Population” published in the December 22/29, 2004, issue of *THE JOURNAL* (2004;292:2977-2983), there was an error in Table 4. On page 2981, the second and fourth column headings, “ $\Delta$  RR of Lung Carcinoma –  $\Delta$  RR of Smoking” should have read “RR of Lung Carcinoma – RR of Smoking.”

**Funding Omissions:** In the Original Contribution titled “Menopause and Hypothalamic-Pituitary Sensitivity to Estrogen” published in the December 22/29, 2004, issue of the *JOURNAL* (2004;292:2991-2996), the funding statement was incomplete. The paragraph should read:

**Funding/Support:** The Study of Women's Health Across the Nation (SWAN) was funded by the National Institute on Aging, the National Institute of Nursing Research, and the NIH Office of Research on Women's Health.

In addition, the NIH Program Office paragraph was incomplete. It should read:

**NIH Program Office:** National Institute on Aging, Bethesda, Md: Sherry Sherman, 1994-present; Marcia Ory, 1994-2001; National Institute of Nursing Research, Bethesda, Md: Yvonne Bryan, 2004-present; Janice Phillips, 2002-2004; Carole Hudgings, 1997-2002.