

# Spontaneous Smoking Cessation Before Lung Cancer Diagnosis

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**Introduction:** We have observed that many patients with lung cancer stop smoking before diagnosis, usually before clinical symptoms, and often without difficulty. This led us to speculate that spontaneous smoking cessation may be a presenting symptom of lung cancer.

**Methods:** Patients from the Philadelphia Veterans Affairs Medical Center with lung cancer and for comparison, prostate cancer and myocardial infarction underwent a structured interview about their smoking habits preceding diagnosis. Severity of nicotine addiction was graded using the Fagerström Test for Nicotine Dependence. Among former smokers, dates of cessation, onset of symptoms, and diagnosis were recorded. Difficulty quitting was rated on a scale of 0 to 10. Distributions of intervals from cessation to diagnosis were compared between groups.

**Results:** All 115 patients with lung cancer had been smokers. Fifty-five (48%) quit before diagnosis, and only six of these (11%) were symptomatic at quitting. Patients with lung cancer who quit were as dependent on nicotine, when smoking the most, as those who continued to smoke, unlike the other groups. Despite this, 31% quit with no difficulty. The median interval from cessation to diagnosis was 2.7 years for lung cancer, 24.3 years for prostate cancer, and 10.0 years for patients with myocardial infarction.

**Conclusions:** These results challenge the notion that patients with lung cancer usually quit smoking because of disease symptoms. The hypothesis that spontaneous smoking cessation may be a presenting symptom of lung cancer warrants further investigation.

**Key Words:** Lung neoplasms, Prostate cancer, Myocardial infarction, Smoking cessation, Veterans.

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Lung cancer accounts for 27.6% of cancer deaths in the United States,<sup>1</sup> and most cases are caused by smoking. Although not widely recognized, it is well documented in cohort<sup>2–5</sup> and case-control studies<sup>6–8</sup> that the risk of lung cancer among former smokers exceeds that of continuing smokers for several years after smoking cessation. It has been assumed that these smokers quit because of symptoms of their cancer (the “quitting ill” effect).<sup>4</sup> However, we have observed that many patients with lung cancer stop smoking spontaneously before diagnosis, sometimes without making a conscious decision to do so, and usually before the onset of symptoms. In a series of 178 patients with lung cancer seen by Dr. Campling at the Kingston Regional Cancer Centre (KRCC) in Canada from 1992 to 1994 (122 small cell lung cancer [SCLC] and 56 non-small cell lung cancer [NSCLC]), 174 had been smokers. Fifty-nine percent had stopped smoking before diagnosis, and 65% of these were asymptomatic from their cancer at the time of cessation<sup>9</sup> (and unpublished results). These observations led us to speculate that, in some cases, spontaneous smoking cessation may be a presenting symptom of lung cancer, possibly caused by tumor secretion of a substance interfering with nicotine addiction. The purpose of this study was to confirm and extend our clinical observations.

This is primarily a descriptive study of the incidence and circumstances of smoking cessation before the diagnosis of lung cancer. Patients with lung cancer from the Philadelphia Veterans Affairs Medical (PVAMC) underwent a structured interview with particular attention to the timing of smoking cessation in relationship to onset of symptoms. In addition, for comparison, we interviewed patients with prostate cancer and myocardial infarction (MI). We expected that for prostate cancer and MI, smoking cessation would reflect what is seen in the general population, but this would not be the case for lung cancer. We compared lifetime tobacco exposure and severity of nicotine addiction among current and former smokers in the three groups. Among former smokers, we compared the distribution of intervals from cessation to diagnosis between groups. To determine whether our results for veterans with lung cancer also apply to other patients with lung cancer, we compared intervals from cessation to diagnosis in the series of patients with lung cancer seen at the KRCC with those in the Veterans Affairs (VA) study.

## METHODS

### Patients

Veterans from the PVAMC were recruited from June 2004 until August 2006. Eligibility criteria included a diag-

nosis of lung cancer, prostate cancer, or MI and availability for an interview. Patients were identified from outpatient clinic lists and a weekly lung tumor board. They were not selected according to their smoking status. Surveys were administered by trained interviewers who were blind to the hypothesis. The study was approved by the Institutional Review Boards of the PVAMC and the University of Pennsylvania, and all patients signed informed consent.

### Procedures and Measurements

Participants were asked whether they had any symptoms before diagnosis, and if so, what these symptoms were, and when they began. A cigarette smoker was defined as anyone who had smoked at least 100 cigarettes in their lifetime. All smokers were asked whether they currently smoked, and if not, when they quit. Subjects who had ever smoked were asked how old they were when they started, how much they currently smoked, the most they had ever smoked, and the number of years they smoked at least a pack a day. The severity of nicotine addiction when smoking the most was assessed using the Fagerström Test for Nicotine Dependence (FTND).<sup>10</sup> Subjects were also asked about consumption of other tobacco products, and those who had smoked only cigars or pipes on a daily basis were classified as ever smokers.

Among subjects who had stopped smoking before diagnosis, their difficulty quitting and severity of withdrawal symptoms were each recorded on a scale of 0 to 10, with 10 being most severe. Patients who continued to smoke were asked whether they had cut down within 1 year of diagnosis, and if so, by how much. Subjects were also asked whether their weight had changed in the year before diagnosis, and if so, by how much.

The type of cancer (lung or prostate) and date of diagnosis of cancer or MI were obtained from medical records. For lung cancer, the histological subtype was recorded as SCLC or NSCLC. The NSCLC cases were categorized as adenocarcinoma, squamous cell, large cell anaplastic, or other. Cancer stage was classified according to the American Joint Committee on Cancer Staging System.<sup>11</sup> Clinical records of those patients who had quit smoking before diagnosis were reviewed to confirm their self-report of whether they were symptomatic at the time of smoking cessation.

### Biochemical Validation of Smoking Status

After completing the interview, subjects were asked to provide a saliva sample. Specimens obtained from patients with lung cancer who claimed to be former smokers were sent for cotinine analysis by gas chromatography-mass spectrometry.<sup>12</sup> Samples were analyzed by the Clinical Pharmacology Laboratory, San Francisco General Hospital. Abstinence was confirmed by a level of less than 15 ng/ml.<sup>13</sup>

### KRCC Patients

In the series of 178 patients with lung cancer seen at the KRCC from 1992 to 1994, four had never smoked, 71 were current, and 103 were former smokers at diagnosis. These patients were asked whether they had ever smoked, and if

they had quit, the approximate interval between cessation and diagnosis. Intervals from cessation to diagnosis were recorded for all former smokers.

### Statistics

Data were entered in an access database and analyzed using SAS software (SAS Institute, Inc., Cary, NC). Descriptive statistics were used to summarize the data. For comparisons between groups, the  $\chi^2$  test was used for categorical variables, and the Kruskal-Wallis test was used for continuous variables. A *p* value of less than 0.05 was considered significant.

The Kaplan-Meier method was used to examine the distribution of intervals from cessation to diagnosis.<sup>14</sup> The initial event was a diagnosis of lung cancer, prostate cancer, or MI, and the time to event was the cessation to diagnosis interval, which was derived retrospectively by former smokers recalling when they quit. We also used the Kaplan-Meier method to compare intervals from cessation to diagnosis among former smokers from the VA and the KRCC, and between former smokers with SCLC and NSCLC. In the same manner, we examined the intervals from symptoms to diagnosis among the VA patients with lung cancer. The log-rank test was used for comparisons between groups.

## RESULTS

### Participants

During the recruitment period, 122 patients with lung cancer were approached about the study, and 115 agreed to participate. We also recruited 101 patients with prostate cancer and 99 patients with MI. Only subjects who were aware that they had an MI were approached. Table 1 summarizes the patient characteristics. There were no major differences in socioeconomic variables such as education, income, employment, or marital status between the three diagnostic groups or between current and former smokers within the groups (data not shown).

### Comparison of Current and Former Smokers

Across all groups, former smokers were older than current smokers. This was most striking for lung cancer with a median difference of 10 years. For both lung cancer and prostate cancer, there was no significant difference in tumor stage distribution between current and former smokers. For lung cancer, there was no significant difference in histologic subtype distribution of current and former smokers (Table 2).

For prostate cancer and MI, the lifetime tobacco exposure was much less for former than current smokers, as expected. In contrast, for lung cancer, there was no difference in lifetime tobacco exposure between current and former smokers. For severity of nicotine addiction, subjects were asked to base their answers on the time in their lives when they were smoking most heavily. For both prostate cancer and MI, former smokers had lower FTND scores than current smokers. In contrast, for lung cancer, the median FTND score was high (7.0) for both current and former smokers.

Among current smokers with lung cancer, 38% reduced their tobacco consumption by  $\geq 50\%$  within the year before

**TABLE 1.** Characteristics of Study Patients

| Variables        | Number (%)        |                        |                       |
|------------------|-------------------|------------------------|-----------------------|
|                  | Lung Cancer       | Prostate Cancer        | Myocardial Infarction |
| Number           | 115 (36.5)        | 101 (32.1)             | 99 (31.4)             |
| Age at diagnosis |                   |                        |                       |
| Mean ( $\pm$ SD) | 63.4 ( $\pm$ 9.5) | 66.7 ( $\pm$ 8.1)      | 54.6 ( $\pm$ 10.3)    |
| Median           | 62.1              | 66.8                   | 54.9                  |
| Range            | 38–86             | 49–83                  | 28–82                 |
| Race             |                   |                        |                       |
| White            | 65 (56.5)         | 44 (43.6)              | 59 (59.6)             |
| Black            | 49 (42.6)         | 54 (53.5)              | 35 (35.4)             |
| Hispanic         | 0                 | 0                      | 5 (5.1)               |
| Other            | 1 (0.9)           | 3 (3)                  | 0                     |
| Gender           |                   |                        |                       |
| Male             | 113 (98.2)        | 101 (100)              | 97 (98)               |
| Female           | 2 (1.7)           | N/A                    | 2 (2)                 |
| Stage            |                   |                        |                       |
| I                | 19 (16.5)         | 2 (2)                  | N/A                   |
| II               | 9 (7.8)           | 80 (79.2)              |                       |
| III              | 39 (33.9)         | 9 (8.9)                |                       |
| IV               | 48 (41.7)         | 10 (9.9)               |                       |
| Smoking status   |                   |                        |                       |
| Never            | 0                 | 21 (20.8)              | 15 (15.2)             |
| Current          | 60 (52.2)         | 32 (31.7) <sup>a</sup> | 58 (58.6)             |
| Former           | 55 (47.8)         | 48 (47.5) <sup>a</sup> | 26 (26.3)             |

<sup>a</sup> Five subjects, all with prostate cancer were categorized as ever smokers based on daily pipe smoking (one former smoker) or cigar smoking (one current and three former smokers).

N/A, not applicable.

diagnosis. Only 17% of current smokers with prostate cancer and 4% with MI reduced consumption during this interval.

We considered whether smoking cessation could be a manifestation of generalized loss of appetite. However, for lung cancer there was no difference between current and former smokers in weight loss before diagnosis (Table 2). Furthermore, 36.4% of former smokers with lung cancer gained weight when they quit (Table 3).

### Comparison of Former Smokers

The median interval from cessation to diagnosis was much shorter for lung cancer (2.7 years) than prostate cancer (24.3 years) or MI (10.0 years). Lifetime tobacco exposure was much higher for former smokers with lung cancer than the other groups. The severity of addiction, when smoking the most, was also much higher among former smokers with lung cancer (Table 3).

The median difficulty quitting was 3.0 for lung cancer, 1.0 for prostate cancer, and 0.5 for MI. These values must be interpreted relative to severity of nicotine addiction. For example, although former smokers with prostate cancer had little difficulty quitting, they were usually not severely addicted (median FTND = 3.0). For prostate cancer, there was a significant correlation between difficulty quitting and severity of addiction ( $R = 0.40$ ,  $p = 0.01$ ). In contrast, for lung

cancer and MI, there was no correlation ( $R = 0.13$ ,  $p = 0.36$  for lung cancer and  $R = -0.03$ ,  $p = 0.87$  for MI).

Smoking cessation rates in the three groups were stratified by severity of nicotine addiction. Among subjects with moderate to high levels of addiction (FTND  $\geq 5$ ), the proportion who quit before diagnosis was higher for lung cancer (45.2%) than for prostate cancer (36.8%) or MI (20%) ( $p = 0.007$ ).

Among former smokers with lung cancer, 31% reported quitting with no difficulty (0 on a scale of 0–10), and their median FTND score was 5. Among former smokers with prostate cancer, 48% quit with no difficulty, but their median FTND was only 1. Among former smokers with MI, 50% quit with no difficulty, and their median FTND was 4. One would expect that those most severely addicted to nicotine would have the most difficulty quitting. This was the case for the former smokers with prostate cancer but not lung cancer or MI. Even among the subjects with prostate cancer, there were a number of “outliers” who quit smoking with no difficulty despite a high-FTND score. One of these patients, who quit smoking 4.5 years before diagnosis of prostate cancer, with an FTND score of 8 and difficulty quitting of 0, recently received a diagnosis of lung cancer, 8.6 years after cessation.

### Cotinine Levels

Samples from patients with lung cancer who claimed to be former smokers were sent for analysis. Cotinine levels were below limits of quantitation for all but one patient, who had a cotinine of 58 ng/ml, consistent with his self-reported status of being on nicotine replacement.

### Intervals from Cessation to Diagnosis

The distribution of intervals from cessation to diagnosis in the three groups is shown in Figure 1. The results are displayed as intervals from cessation to diagnosis, with the time of diagnosis set as  $t = 0$  and intervals before diagnosis set as positive. The intervals from cessation to diagnosis were much shorter for lung cancer than the other two groups. Furthermore, there was a striking difference in the shape of the curves for lung cancer compared with the other groups. We found for prostate cancer and MI that the hazard of smoking cessation was highest at the longest intervals before diagnosis. In contrast, for lung cancer, the hazard of smoking cessation rose at an increasing rate approaching diagnosis (data not shown).

### Symptoms Before Diagnosis

Among all patients with lung cancer, 62% reported symptoms before diagnosis. Of the 55 former smokers with lung cancer, 28 (51%) reported symptoms of their cancer before diagnosis. Of these 28 patients, only six (11% of all 55 former smokers) quit smoking after the onset of symptoms. Clinical records of those patients who quit before diagnosis were reviewed and in all cases confirmed their self-report.

In Figure 2, intervals from symptoms to diagnosis were compared with intervals from cessation to diagnosis for patients with lung cancer. The intervals from symptoms to diagnosis were much shorter (median, 2.3 months) than the intervals from smoking cessation to diagnosis (median, 2.7 years). The six

**TABLE 2.** Comparison of Current vs. Former Smokers

| Variables                            | Number (%)          |                    |                       |                     |                    |                       |                       |                    |   |
|--------------------------------------|---------------------|--------------------|-----------------------|---------------------|--------------------|-----------------------|-----------------------|--------------------|---|
|                                      | Lung Cancer         |                    |                       | Prostate Cancer     |                    |                       | Myocardial Infarction |                    |   |
|                                      | Current<br>(n = 60) | Former<br>(n = 55) | <i>p</i> <sup>a</sup> | Current<br>(n = 32) | Former<br>(n = 48) | <i>p</i> <sup>a</sup> | Current<br>(n = 58)   | Former<br>(n = 26) | <i>p</i> <sup>a</sup>   |
| Age at diagnosis                     |                     |                    |                       |                     |                    |                       |                       |                    |   |
| Mean                                 | 59.7                | 67.5               | <0.0001               | 61.1                | 69.0               | <0.0001               | 52.7                  | 56.6               | NS  |
| Median                               | 57.8                | 68.0               | <0.0001               | 61.6                | 69.0               | <0.0001               | 54.3                  | 57.2               | NS  |
| Stage                                |                     |                    |                       |                     |                    |                       | N/A                   | N/A                |   |
| I                                    | 8 (13.3)            | 11 (20.0)          | NS                    | 2 (6.3)             | 0                  | NS                    |                       |                    |   |
| II                                   | 4 (6.7)             | 5 (9.1)            |                       | 23 (71.9)           | 38 (79.2)          |                       |                       |                    |   |
| III                                  | 26 (43.3)           | 13 (23.6)          |                       | 5 (15.6)            | 3 (6.3)            |                       |                       |                    |   |
| IV                                   | 22 (36.7)           | 26 (47.3)          |                       | 2 (6.3)             | 7 (14.6)           |                       |                       |                    |   |
| Histology                            |                     |                    |                       | N/A                 | N/A                |                       | N/A                   | N/A                |   |
| Small cell                           | 13 (21.7)           | 8 (14.6)           | NS                    |                     |                    |                       |                       |                    |   |
| Adeno                                | 14 (23.3)           | 19 (34.6)          |                       |                     |                    |                       |                       |                    |   |
| Squamous                             | 10 (16.7)           | 13 (23.6)          |                       |                     |                    |                       |                       |                    |   |
| Large cell                           | 2 (3.3)             | 0                  |                       |                     |                    |                       |                       |                    |   |
| Other                                | 21 (35.0)           | 15 (27.3)          |                       |                     |                    |                       |                       |                    |   |
| Lifetime tobacco exposure            |                     |                    |                       |                     |                    |                       |                       |                    |   |
| Years smoked                         |                     |                    |                       |                     |                    |                       |                       |                    |   |
| Mean                                 | 43.8                | 43.9               | NS                    | 44.1                | 27.1               | <0.001                | 38.2                  | 25.9               | <0.001  |
| Median                               | 42.8                | 44.0               |                       | 44.4                | 30.2               |                       | 41.3                  | 27.8               |   |
| Maximum cigarettes/d                 |                     |                    |                       |                     |                    |                       |                       |                    |   |
| Mean                                 | 37.2                | 32.6               | NS                    | 31.7                | 19.4               | <0.001                | 34.7                  | 32.0               | NS  |
| Median                               | 40.0                | 30.0               |                       | 30.0                | 15.0               |                       | 30.0                  | 25.0               |   |
| Years >1 pack per day                |                     |                    |                       |                     |                    |                       |                       |                    |   |
| Mean                                 | 33.2                | 30.1               | NS                    | 28.5                | 8.3                | <0.001                | 26.5                  | 13.4               | 0.002   |
| Median                               | 37.0                | 30.0               |                       | 35.0                | 0                  |                       | 30.0                  | 7.5                |   |
| Severity of addiction                |                     |                    |                       |                     |                    |                       |                       |                    |   |
| FTND                                 |                     |                    |                       |                     |                    |                       |                       |                    |   |
| Mean                                 | 6.6                 | 5.9                | NS                    | 6.2                 | 3.4                | 0.0001                | 6.2                   | 4.4                | 0.003   |
| Median                               | 7.0                 | 7.0                | NS                    | 7.0                 | 3.0                | 0.0002                | 6.5                   | 4.0                | 0.01  |
| Reduction in smoking                 |                     |                    |                       |                     |                    |                       |                       |                    |   |
| Cut down 50% or more                 | 19/50 (38.0%)       | N/A                | N/A                   | 5/29 (17.2%)        | N/A                | N/A                   | 2/50 (4.0%)           | N/A                | <i>p</i> < 0.0001<br>(comparison<br>between<br>three<br>groups) |
| No. of quit attempts                 |                     |                    |                       |                     |                    |                       |                       |                    |   |
| Mean                                 | 9.1                 | 4.2                | 0.05                  | 5.7                 | 4.9                | NS                    | 4.6                   | 3.1                | NS  |
| Median                               | 3.0                 | 3.0                | NS                    | 3.0                 | 2.0                | NS                    | 3.0                   | 2.0                | NS  |
| Weight loss in year before diagnosis | 20/59 (33.9%)       | 15/55 (27.3%)      | NS                    | 7/32 (21.9%)        | 4/48 (8.3%)        | NS                    | 3/58 (5.2%)           | 0/26 (0%)          | NS  |

<sup>a</sup> Chi-square test for categorical variables, and Kruskal-Wallis test for continuous variables.

N/A, not applicable; NS, not significant; FTND, Fagerström Test for Nicotine Dependence.

patients with lung cancer who had symptoms at the time of smoking cessation are highlighted.

### Comparison with KRCC Patients

To determine whether our results in a group of veterans with lung cancer can be generalized to the civilian lung cancer population, we reexamined the data from our study done at the KRCC. Of the 178 patients included in that study, only four were never smokers, and 103 were former smokers at diagnosis. Because all former smokers with lung cancer in the VA study

were men, we compared the distribution of intervals from cessation to diagnosis for all male subjects in the KRCC (*n* = 67) and VA studies (*n* = 53, excluding two subjects who had quit 52 and 49 years before diagnosis). There was no significant difference between the two groups (Figure 3).

### Comparison of SCLC with NSCLC

The VA study included 21 patients with SCLC, and only eight of these were former smokers. These numbers were too small for robust comparisons of intervals from



**TABLE 3.** Comparison of Former Smokers

| Variables   | Lung Cancer<br>(n = 55) | Prostate Cancer<br>(n = 48) | Myocardial Infarction<br>(n = 26) | p <sup>a</sup> |
|---|-------------------------|-----------------------------|-----------------------------------|----------------|
| Interval from cessation to diagnosis (yr)   |                         |                             |                                   |                |
| Mean  | 7.6                     | 23.4                        | 12.7                              | <0.0001        |
| Median  | 2.7                     | 24.3                        | 10.0                              | <0.0001        |
| Lifetime tobacco exposure   |                         |                             |                                   |                |
| Years smoked  |                         |                             |                                   |                |
| Mean  | 43.9                    | 27.1                        | 25.9                              | <0.0001        |
| Median  | 44.0                    | 30.2                        | 27.8                              | <0.0001        |
| Maximum cigarettes/d  |                         |                             |                                   |                |
| Mean  | 32.6                    | 19.4                        | 32.0                              | 0.002          |
| Median  | 30.0                    | 15.0                        | 25.0                              | 0.0002         |
| Years >1 pack per day   |                         |                             |                                   |                |
| Mean  | 30.1                    | 8.3                         | 13.4                              | <0.0001        |
| Median  | 30                      | 0                           | 7.5                               | <0.0001        |
| Severity of addiction   |                         |                             |                                   |                |
| FTND  |                         |                             |                                   |                |
| Mean  | 5.9                     | 3.4                         | 4.4                               | 0.0002         |
| Median  | 7.0                     | 3.0                         | 4.0                               | 0.0005         |
| Quitting information  |                         |                             |                                   |                |
| Difficulty quitting (out of 10)   |                         |                             |                                   |                |
| Mean  | 3.4                     | 2.2                         | 2.1                               | NS             |
| Median  | 3.0                     | 1.0                         | 0.5                               | NS             |
| Number of quit attempts in past   | n = 54                  | n = 40                      | n = 26                            |                |
| Mean  | 4.2                     | 4.9                         | 3.1                               | NS             |
| Median  | 3.0                     | 2.0                         | 2.0                               | NS             |
| Proportion of subjects with FTND ≥5 who stopped smoking (denominator includes current and former smokers) | 38/84 (45.2%)           | 14/38 (36.8%)               | 12/60 (20%)                       | 0.007          |
| Quit with no difficulty (0/10)  | 17/55 (31%)             | 20/42 (48%)                 | 13/26 (50%)                       | NS             |
| Median FTND of those who quit with no difficulty  | 5                       | 1                           | 4                                 | NS             |
| Severity of withdrawal symptoms (out of 10)   |                         |                             |                                   |                |
| No withdrawal symptoms (0/10)   | 20/51 (39%)             | 20/40 (50%)                 | 13/26 (50%)                       |                |
| Mean  | 2.8                     | 1.9                         | 2.4                               | NS             |
| Median  | 2.0                     | 0.5                         | 0.5                               | NS             |
| Weight gain at cessation  | 20/55 (36.4%)           | 20/42 (47.6%)               | 19/26 (73.1%)                     |                |

<sup>a</sup> Chi-square test for categorical variables, and Kruskal-Wallis test for continuous variables.

NS, not significant; FTND, Fagerström Test for Nicotine Dependence.

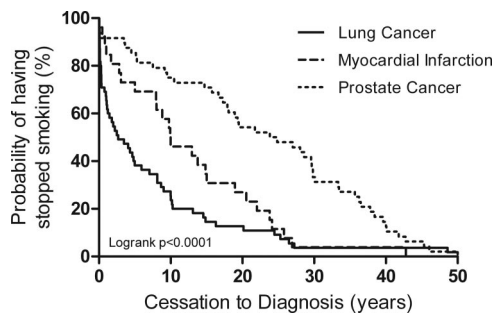
cessation to diagnosis between the two major histologic types of lung cancer, SCLC and NSCLC. Therefore, we combined the VA and male KRCC data sets (55 SCLC and 67 NSCLC). The median interval from cessation to diagnosis was much shorter for SCLC (6 months) than for NSCLC (3.5 years). When subjects who had quit smoking more than 5 years before diagnosis were excluded, the difference in distribution of intervals from cessation to diagnosis for SCLC compared with NSCLC was significant ( $p = 0.005$  by log rank).

## DISCUSSION

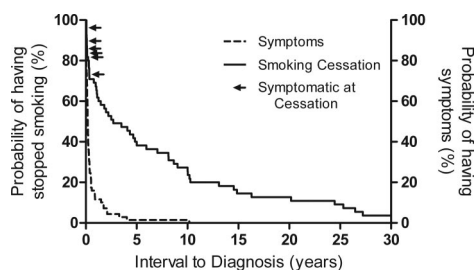
This study confirms our clinical observation that patients with lung cancer frequently stop smoking before diagnosis, usually before clinical symptoms, and often with very

little effort. All patients with lung cancer in this study had smoked in their lives, and 48% of them had stopped before diagnosis. Only 11% of these were symptomatic when they quit. These results challenge the belief that patients with lung cancer usually stop smoking because of disease symptoms.

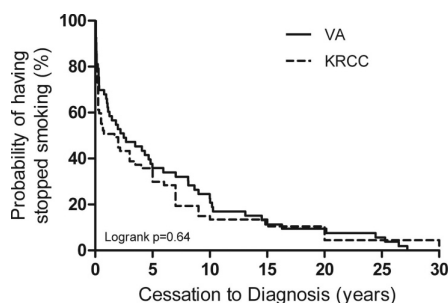
For prostate cancer and MI, former smokers had smoked less heavily and were less severely addicted than continuing smokers, as expected. In contrast, for lung cancer, there was no difference between current and former smokers in lifetime tobacco exposure or severity of addiction when smoking most heavily. Despite this, 31% of them quit with no difficulty. Even among continuing smokers with lung cancer, 38% had reduced their tobacco use by ≥50% in the year before diagnosis, suggesting a spontaneous decrease in their



**FIGURE 1.** Kaplan-Meier distribution of intervals from cessation to diagnosis for lung cancer, myocardial infarction (MI), and prostate cancer. The difference between the groups was highly significant ( $p < 0.0001$ ).



**FIGURE 2.** Comparison of intervals from symptoms to diagnosis and from cessation to diagnosis for patients with lung cancer. Survival curves were generated using the Kaplan-Meier method. The probability of having stopped smoking is shown on the left y axis and the probability of having symptoms is shown on the right y axis. Those patients who were symptomatic at quitting are identified with arrows.



**FIGURE 3.** Kaplan-Meier distribution of intervals from cessation to diagnosis for patients with lung cancer from the Veterans Affairs (VA) and the Kingston Regional Cancer Centre (KRCC). There was no significant difference between the two groups ( $p = 0.64$ ).

desire for nicotine. For patients with lung cancer, we did not find any correlation between smoking cessation and weight loss, indicating that smoking cessation is not usually a manifestation of anorexia associated with cancer.

A causal relationship between lung cancer diagnosis and prior symptoms is generally accepted. We suggest that there may also be a causal relationship between the presence of lung cancer and smoking cessation and that smoking

cessation may itself be a symptom in some lung cancer cases. Two groups have argued that lung cancers may be triggered by smoking cessation.<sup>15,16</sup> However, initiation and promotion of lung cancer is a process that develops over many years. With a median interval from cessation to diagnosis of 2.7 years, the majority of former smokers with lung cancer in this study likely harbored their cancer at the time of cessation. Furthermore, the uncharacteristic ease of quitting in some of the lung cancer cases suggests that another process is involved. Thus, the notion that ongoing smoking protects from lung cancer is untenable.

A more plausible explanation is that some lung cancers may somehow lead to smoking cessation. The most widely held belief is that smokers quit because of cancer symptoms.<sup>4,5</sup> However, we have shown that most patients with lung cancer do not quit for this reason. We speculate that some lung cancers may produce a factor that blocks or emulates the effects of nicotine. For example, there are a variety of noncompetitive endogenous modulators of nicotinic responses, including histamine, neurokinins, and other tachykinins,<sup>17–19</sup> which are produced by some lung cancers.<sup>20,21</sup> Alternatively, substances that modulate dopamine release within the mesolimbic system could be antiaddictive. Certain endogenous opioids (e.g., dynorphins), which are known to be produced by some lung cancers,<sup>22,23</sup> could possibly play such a role. A recent study showed that neurologic damage involving the insula, a region of the brain implicated in regulation of conscious cravings, can result in “disruption of smoking addiction.”<sup>24</sup> This effect may be mediated through insular hypocretin transmission.<sup>25</sup> Whether spontaneous smoking cessation in patients with lung cancer could be caused by such a factor is another intriguing possibility.

The marked difference in age between current and former smokers was unexpected, although it has been previously reported.<sup>26,27</sup> In all three diagnostic groups, the median age of current smokers was much less than that of former smokers. The difference was most striking for lung cancer (10.2 years) and prostate cancer (7.4 years) but less marked for MI (2.8 years). One possible explanation for this difference is that current smokers may have higher rates of competing causes of mortality than former smokers. Although the risk of lung cancer goes up for a number of years after smoking cessation, as outlined earlier, the risk of other illnesses, in particular cardiovascular diseases, goes down rapidly.<sup>28,29</sup>

Excess competing mortality among continuing smokers is unlikely to be the only explanation for the large age difference between current and former smokers with lung cancer and prostate cancer. With a median interval of 2.7 years from cessation to diagnosis, it is likely that the majority of former smokers with lung cancer harbored their cancer at the time of quitting. The sudden removal of the growth-promoting effects of nicotine and other components of tobacco smoke,<sup>22,30–33</sup> as well as angiogenic effects of nicotine,<sup>34,35</sup> may have delayed the presentation of cancer among the former smokers. Nevertheless, it is difficult to explain the fact that the age difference between current and former

smokers with lung cancer far exceeds the median interval from cessation to diagnosis in this group of patients.

With a median interval of 24.3 years from cessation to diagnosis, the majority of former smokers with prostate cancer likely developed their cancer after they stopped smoking. Although smoking is not considered a cause of prostate cancer, it is possible that continued smoking could promote the growth of established tumors, leading to earlier presentation in current compared with former smokers.

Our study has a number of limitations. Because it is a preliminary report, the number of patients in each group is small. The three groups were not matched for age, sex, or demographic factors, thereby limiting comparisons between groups. Furthermore, because the subjects underwent a single interview, we have no information on their smoking status after diagnosis.

Although we noted whether the subjects had symptoms of their disease when they quit, we did not record the date of first radiologic abnormality or suspicion of lung cancer. Thus, some patients may have quit because they suspected they had lung cancer, even in the absence of symptoms. Furthermore, because subjects were identified at the time of diagnosis and then asked to recall their past smoking habits, our results may be biased from retrospective recall. Although the reliability of retrospective assessment of nicotine dependence is good,<sup>36</sup> a prospective study will be required to eliminate this potential bias.

It may be difficult for patients with lung cancer and their physicians to ascertain the exact time of onset of symptoms. These patients often have longstanding pulmonary symptoms due to many years of smoking. We believe that patients with lung cancer themselves are in the best position to judge when a new symptom or a change in a chronic symptom could be identified as the initial symptom of their cancer. Thus, we have relied on the subject's self-report of whether and when they had symptoms of their disease.

Our study also has a number of strengths. Our hypothesis is novel and has many clinical and biological implications. Our reanalysis of the KRCC dataset confirms that our results are applicable to the general population of patients with lung cancer. The fact that in all former smokers with lung cancer, the cotinine levels confirmed self-reported smoking status indicates that the smoking histories are reliable.

Further investigation will include a prospective cohort study to determine the outcome of subjects in the general population who have quit smoking, especially without difficulty. To determine the true risk of lung cancer after smoking cessation, smoking status must be determined relative to time of diagnosis.

We believe that long-term heavy smokers who quit, especially without difficulty, are at risk for having or developing lung cancer. Our study could be dangerously misinterpreted to suggest that those who have smoked heavily for most of their lives might be better off to continue smoking. This is clearly not the case. All smokers, especially heavy smokers, must be strongly encouraged to stop.

The simple observation that many patients with lung cancer quit smoking without difficulty before diagnosis has many implications. Recognition of this phenomenon as a presenting symptom of lung cancer could result in earlier diagnosis of this common, highly lethal cancer, which is curable only when diagnosed at an early stage. An understanding of the biological basis of this phenomenon could lead to new strategies for smoking cessation.

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