Pulmonary function as a predictor of lung cancer mortality in continuing cigarette smokers and in quitters

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Background Forced expiratory volume in 1 second (FEV1) may be useful for identifying smokers at higher risk of lung cancer. We examined the association of FEV1 with lung cancer mortality (LCM) among cigarette smokers in the Multiple Risk Factor Intervention Trial (MRFIT).

Methods In all, 6613 MRFIT baseline smokers alive at trial end in 1982 had acceptable FEV1 measures and complete smoking history; men were classified as during-trial long-term quitters (N = 1292), intermittent quitters (1961), and never quitters (3360). Proportional hazards models for LCM were fit with quintiles of average FEV1, adjusted for age, height, race, smoking history, and other risk factors.

Results For long-term, intermittent, and never quitters respectively, mean baseline cigarettes/day was 28, 32, and 35; trial-averaged FEV1 was 3201, 3146, and 3082 ml; and average decline in FEV1 was –46.0, –54.6, and –62.5 ml/year. With median post-trial mortality follow-up of 18 years, there were 363 lung cancer deaths. Age-adjusted LCM rates varied across FEV1 quintiles from 50 (lowest quintile) to 11 (highest quintile), 58 to 11, and 76 to 20, per 10 000 person-years, for long-term quitters, intermittent quitters, and never quitters, respectively. Multivariate adjusted hazard ratios for 100 ml higher FEV1 were 0.92 [P = 0.004], 0.95 [P = 0.003], and 0.95 [P < 0.0001] respectively.

Conclusions These results demonstrate the strong predictive value of FEV1 for lung cancer among cigarette smokers independent of smoking history; results did not differ by during-trial quit status. FEV1 may be a biological marker for smoking dose or it may be that genetic susceptibilities to both decreased FEV1 and lung cancer are associated.

Keywords Lung diseases, lung neoplasms, respiratory function tests, forced expiratory volume, smoking, risk factors, risk assessment

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Poor clinical outcomes after a diagnosis of lung cancer have generated considerable interest in both early detection of lung cancer (and hopefully improved subsequent survival) and chemoprevention to reduce the risk of incident lung cancer among current and former cigarette smokers. The utilization of new screening techniques, and probably of chemopreventive agents, could be greatly enhanced by improved methods to identify higher risk groups of smokers and ex-smokers for developing lung cancer. The identification of high-risk individuals could reduce the number of smokers and ex-smokers to be screened for lung cancer, and could enhance the potential benefits versus likely adverse side-effects of chemopreventive agents.
Screening methods to detect lung cancer, recently reviewed, using chest X-ray and sputum cytology have demonstrated little benefit in reducing lung cancer mortality (LCM) in clinical trials. Newer methods using computerized axial tomography (CT) of the lung are being evaluated and preliminary data suggest that earlier detection of lung cancer may be feasible. Other screening methods to identify those cigarette smokers at higher risk for lung cancer include the evaluation of genetic markers of the metabolism of cigarette carcinogens, and/or host susceptibility, and clinical measures such as symptoms of chronic bronchitis or decreased pulmonary function. 

A previous investigation of lung cancer and pulmonary function (as measured by FEV$_1$) in the Multiple Risk Factor Intervention Trial (MRFIT) cohort examined the association of FEV$_1$ with LCM among smokers at 7.5 years of post-trial mortality follow-up. A single measure of FEV$_1$ was a significant predictor of LCM with a multivariate adjusted hazard ratio (HR) of 0.49 per 1 litre higher FEV$_1$ (P = 0.001); the adjustment included multiple measures of smoking dose. In other work, Townsend and colleagues examined the associations between FEV$_1$ and during-trial smoking cessation, concluding that quitters, compared with continuing smokers, had smaller decreases in FEV$_1$ across the MRFIT trial years. The LCM in the MRFIT cohort of smokers examined relative to smoking dose demonstrated an increased risk over 10 years of 30% for every 10 cigarette/day increase (HR = 1.30, P < 0.001), and relative to the randomized intervention groups demonstrated equivalent risk over 15.8 years (HR = 1.17, P > 0.05). With almost five times as many lung cancer deaths now than in the original MRFIT exploration of FEV$_1$, we can re-examine with greater power both the overall association among smokers between FEV$_1$ and LCM and whether or not that association differs according to during-trial smoking cessation.

**Methods**

**MRFIT trial design**

The MRFIT participants were 12,866 men aged 35–57 years at increased risk for coronary heart disease (CHD) based on levels of serum cholesterol, cigarette smoking, and blood pressure, and free of overt CHD on entry. Men with diastolic blood pressure (DBP) of ≥115 mmHg, with total cholesterol of ≥9.07 mmol/l (350 mg/dl), who had a serious life-shortening disease or who were believed to be unable to participate in the specific interventions were excluded from the trial prior to randomization. Individuals with clinically significant chronic obstructive pulmonary disease, as well as those with documented clinical myocardial infarction or angina pectoris, or electrocardiographic evidence of previous myocardial infarction, were also excluded. Participants for the trial were screened over three visits prior to randomization. At Screen 1, 8,194 of the randomized men (63.7%) reported smoking cigarettes (average 34 cigarettes/day). At Screen 2, serum thiocyanate (a chemical measure of smoking dose) was collected, a physical examination was performed, and pulmonary function (FEV$_1$) was determined. At Screen 3, a detailed smoking history was collected. Of the 12,866 men who were eligible and enrolled in the trial from December 1973 through February 1976, 6,428 were randomized to special intervention (SI) and 6,438 were randomized to usual care (UC). SI men were given dietary advice to lower blood cholesterol, smoking cessation counselling, and hypertension medication using a stepped care approach; UC men were not offered interventions at the clinical centres and were referred back to their usual source of medical care. All participants were asked to return to their MRFIT clinical centre (22 centres in 18 US cities) once a year for 6 years for a comprehensive evaluation, including FEV$_1$ measurement, assessment of risk factors, medical history update, and morbidity status. Results regarding the randomized intervention have been reported elsewhere. Follow-up rates in MRFIT were excellent with fewer than 10% of annual visits missed in each year.

**Pulmonary function**

Pulmonary function (FEV$_1$) was measured at Screen 2 and annually thereafter; techniques and quality control procedures have been described elsewhere. $^{29}$ FEV$_1$ was measured using a 10-l Stead-Wells water-filled spirometer (Stead-Wells, Braintree, MA, USA) and adjusted for ambient room temperature. Standardization of pulmonary function measures and calibration checks were not given high priority at the start of the trial; a rigorous standardization programme was not introduced until several years into the trial. The standardization met standards subsequently developed by the American Thoracic Society and the Epidemiology and Standardization Project. $^{31}$ By Annual Visit 3, approximately 85% of the tracings met the standards. $^{16,32}$

The ‘baseline’ FEV$_1$ measure used in this paper is based on Annual Visit 3 data because of the smaller proportion of acceptable tracings at true baseline (Screen 2) and at Annual Visits 1 and 2. ‘Trial-averaged’ FEV$_1$ is the average of FEV$_1$ determinations at Annual Visits 3, 4, 5, and 6. Average annual change in FEV$_1$ is the slope in FEV$_1$ across Annual Visits 3, 4, 5, and 6.

**Smoking status**

Smoking status is defined in this study based on whether an individual smoked at baseline and at Annual Visits. Never smokers are defined as individuals who reported never smoking at Screen 3. Ex-smokers are defined as those who reported at Screen 3 that they had been a smoker in the past and were not current smokers. Long-term quitters are defined as those participants who reported smoking at Screen 3 and reported not smoking at each of Annual Visits 2, 3, 4, 5, and 6 (regardless of smoking status reported at Annual Visit 1). Never quitters are defined as those participants who reported smoking at Screen 3 and at each of Annual Visits 1 through 6. The intermediate group, intermittent quitters, are defined as those participants who reported smoking at Screen 3 and are neither long-term quitters nor never quitters (i.e. they reported not smoking at one or more of Annual Visits 1 through 6, but not all of 2 through 6). If a participant missed one or more of these visits then only the visits he attended were used in determining smoking status.

**Mortality ascertainment**

During the trial and at termination of active intervention on 28 February 1982, vital status was ascertained by clinic staff through contact with the participant, or with family or friends,
and through searches of publicly accessible files if the participant was thought to be deceased. Causes of death were verified by clinical staff and coded using International Classification of Diseases, Ninth Revision (ICD-9).35-37 Post-trial mortality through December 1990 was determined by matching identifying information, provided by each participant during screening, with US National Death Index (NDI) records.36-38 Death certificates were obtained to ascertain underlying cause of death, coded independently by two nosologists; a third nosologist adjudicated any disagreements. Death dates and corresponding ICD-9 or ICD-1035,39 causes from January 1991 through December 1999 were obtained using the NDI-Plus service. Mortality ascertainment is estimated to be approximately 100% complete using these data sources.38 ICD-9 code 162 and ICD-10 codes C33–C34 were used to identify lung cancer deaths.

Statistical methods
Among the smokers, five groups of participants were created according to quintiles of trial-averaged FEV1. Participant characteristics were summarized within each FEV1 quintile and tested for group differences with ANOVA or χ2 analysis, as appropriate; sub-group differences among the smoking groups were similarly explored. Death rates per 10 000 person-years, age-adjusted by the direct method to the full cohort of MRFIT screenees (N = 361 662), and Kaplan-Meier curves for time from sixth anniversary of randomization to lung cancer death were computed for each quintile. Univariate and multivariate proportional hazards models40 were carried out on time to lung cancer death to test quintile differences; adjusting variables were for known lung cancer risk factors (age at randomization, cigarettes/day, thiocyanate, age at which smoking began, use of filter cigarettes, cigarette tar and nicotine content), MRFIT design variables (DBP, fasting cholesterol, randomized intervention group [SI or UC]), and potential moderators of the FEV1 effect (race, height, body mass index [BMI]); analyses were stratified by clinical centre. These models were repeated using a single FEV1 from Annual Visit 3 and then using quintiles of the average annual change (slope) in FEV1, additionally adjusting for Annual Visit 3 FEV1. Models using trial-averaged FEV1 were run separately within smoking sub-groups (never quitters, intermittent quitters, long-term quitters). The associations of FEV1 with mortality were compared for deaths within 10 years to deaths after 10 years, and separately for the SI compared with the UC men. P-values given are two-tailed; no adjustments for multiple comparisons were made.

Results
Of the 12 866 men randomized to the MRFIT, 430 men were excluded because of death before their sixth anniversary of randomization (52 from lung cancer). 519 for having no valid annual visit FEV1 determinations, and 7 for missing baseline covariate values. Of the remaining 11 910 men, 6913 were current cigarette smokers at Screen 3; an additional 300 were excluded for missing smoking-related covariates (e.g. age began smoking), leaving 6613 men for all analyses. Quintile cutpoints for trial-averaged FEV1 among the 6613 smokers were 2605, 2984, 3306, and 3673 ml. There were during-trial 1292 long-term quitters, 1961 intermittent quitters, and 3360 never quitters. Participant characteristics and lung cancer death rates are shown in Table 1 by FEV1 quintile and smoking status.

Comparing across the five quintiles of FEV1, men in the lower quintiles were older (4 d.f., F-test P < 0.0001), shorter in height (P = 0.0004), smoked more cigarettes at baseline (P = 0.02) and across the trial (P < 0.0001), and had a steeper decline in FEV1 (P < 0.0001) than men in the upper quintiles. No significant differences were found across quintiles for BMI and alcoholic drinks/week at level 0.05.

Comparing across smoking sub-groups, long-term and intermittent quitters smoked significantly fewer cigarettes/day at baseline (2 d.f., F-test P < 0.0001), showed lower thiocyanate values (P < 0.0001), and consumed fewer alcoholic drinks/week (P < 0.0001) than never quitters. Height and cholesterol were not significantly different at level 0.05. Over 6 trial years, average cigarettes/day smoked were 30.5 for never quitters, 15.0 for intermittent quitters, and 0.9 for long-term quitters (P < 0.0001). FEV1 was highest for long-term quitters and lowest for never quitters (P < 0.0001), while FEV1 declined on average 46.0, 54.6, and 62.5 ml per year for the three groups respectively (P < 0.0001).

Over a median 18 years post-trial follow-up, there were 2547 deaths, including 363 from lung cancer. There were 127, 87, 62, 52, and 35 lung cancer deaths in the lowest to highest FEV1 quintiles, corresponding to decreasing age-adjusted death rates of 64.1, 41.4, 30.6, 25.6, and 16.5 deaths per 10 000 person-years respectively (Table 2). Kaplan-Meier curves of survival by FEV1 quintiles showed significant differences (Figure 1; log rank test χ2 = 112.4, d.f. = 4, P < 0.0001). Survival probability began dropping immediately for the lowest quintile, after about 2 years for the second quintile, and not until about 7 years for the third through fifth quintiles. There were 238, 82, and 43 lung cancer deaths among the never, intermittent, and long-term quitters, respectively, with decreasing age-adjusted death rates of 52.6, 27.8, and 21.0 deaths per 10 000 person-years. In contrast, lung cancer death rates among MRFIT self-identified never smokers (N = 1792) and ex-smokers (N = 3205) were 3.6 and 11.5 deaths per 10 000 person-years (11 and 62 deaths), respectively.

Age, race, and height-adjusted proportional hazards regressions showed significantly higher risks of LCM in the lowest FEV1 quintile when compared with each of the second, third, fourth, and fifth quintiles (Table 2). Similar trends were seen in multivariate adjusted models: the hazard ratio (HR) relative to the first quintile was 0.68 for the second quintile (95% CI: 0.51, 0.89, P = 0.0006), 0.48 (95% CI: 0.35, 0.66, P < 0.0001) for the third quintile, 0.42 (95% CI: 0.30, 0.59, P < 0.0001) for the fourth quintile, and 0.32 (95% CI: 0.21, 0.48, P < 0.0001) for the fifth quintile. A test for linear trend (FEV1 as a continuous measure) showed a 5% decrease in risk for every 100 ml higher FEV1 (HR = 0.95, 95% CI: 0.93, 0.96, P < 0.0001).

Proportional hazards regression results across smoking sub-groups showed quintile-specific HR that were very similar to those in the smokers overall (Table 3). There was a slightly weaker linear association of FEV1 with mortality among never quitters (HR per 100 ml higher 0.95, 95% CI: 0.93, 0.97, P < 0.0001) than among long-term quitters (HR = 0.92, 95% CI: 0.88, 0.97, P = 0.03). There was no significant interaction between FEV1 quintile and smoking sub-groups (P = 0.80).

Analyses among all smokers performed separately for the SI and UC groups showed very similar results for quintiles two
### Table 1

Baseline and during-trial characteristics and death rates through 1999 of the 6613 Multiple Risk Factor Intervention Study (MRFIT) smokers, separately by during-trial averaged pulmonary function and during-trial quit status.

<table>
<thead>
<tr>
<th>Quintile 1</th>
<th>Quintile 2</th>
<th>Quintile 3</th>
<th>Quintile 4</th>
<th>Quintile 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Averaged FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>2605 ml</td>
<td>2606–2984 ml</td>
<td>2985–3306 ml</td>
<td>3307–3673 ml</td>
</tr>
<tr>
<td>(Visit 3)</td>
<td>(1108)</td>
<td>(2606–2984)</td>
<td>(2985–3306)</td>
<td>(3307–3673)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quintile 1</th>
<th>Quintile 2</th>
<th>Quintile 3</th>
<th>Quintile 4</th>
<th>Quintile 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Averaged FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>2180 ml</td>
<td>2144 ml</td>
<td>2187 ml</td>
<td>2807 ml</td>
</tr>
<tr>
<td>(Visit 3–6)</td>
<td>(128)</td>
<td>(138)</td>
<td>(120)</td>
<td>(107)</td>
</tr>
</tbody>
</table>

#### Baseline characteristics

- **Age (years)**
  - No. of men: 732
  - Mean: 48.18, (SD: 5.54)
  - Quintile 1: 2605 ml
  - Quintile 2: 2606–2984 ml
  - Quintile 3: 2985–3306 ml
  - Quintile 4: 3307–3673 ml
  - Quintile 5: 3674 ml
- **Black (%)**
  - No. of men: 732
  - Mean: 10, (SD: 0.07)
- **Height (m)**
  - No. of men: 732
  - Mean: 1.73, (SD: 0.07)
- **BMI**
  - No. of men: 732
  - Mean: 27.10, (SD: 3.73)
- **DBP**
  - No. of men: 732
  - Mean: 89.46, (SD: 9.11)
- **Cholesterol (mmol/l)**
  - No. of men: 732
  - Mean: 6.03, (SD: 1.03)
- **FEV<sub>1</sub> (ml)**
  - No. of men: 732
  - Mean: 2281, (SD: 414)
- **Alcoholic drinks/week**
  - No. of men: 732
  - Mean: 14.08, (SD: 12.9)
- **Cigarettes/day**
  - No. of men: 732
  - Mean: 36.15, (SD: 14.6)
- **Age began smoking (years)**
  - No. of men: 732
  - Mean: 17.01, (SD: 3.49)
- **Thiocyanate (µmol/l)**
  - No. of men: 732
  - Mean: 183.6, (SD: 50.7)
- **Tar (mg/cigarette)**
  - No. of men: 732
  - Mean: 18.90, (SD: 4.72)
- **Nicotine (mg/cigarette)**
  - No. of men: 732
  - Mean: 12.36, (SD: 2.88)

#### During-trial characteristics

- **Averaged FEV<sub>1</sub>**
  - No. of men: 732
  - Mean: 2180 ml, (SD: 128)
- **Slope in FEV<sub>1</sub> (ml/year)**
  - No. of men: 732
  - Mean: –72.36, (SD: 117)
- **Averaged cigarettes/day**
  - No. of men: 732
  - Mean: 30.51, (SD: 13.6)

#### Post-trial mortality

- **Lung cancer deaths**
  - No. of men: 732
  - Mean: 81, (SD: 3.4)

a. Forced expiratory volume in 1 second.
b. Body mass index.
c. Diastolic blood pressure.
d. To convert cholesterol to mg/dl, divide by 0.0259.
e. Death rates are per 10 000 person-years, age-adjusted.
Table 2  Lung cancer deaths, mortality rates through 1999, and hazard ratios (HR) for the 6613 Multiple Risk Factor Intervention Study (MRFIT) smokers, by quintiles of trial-averaged forced expiratory volume in 1 second (FEV₁)

<table>
<thead>
<tr>
<th>Quintiles of averaged FEV₁ (ml)</th>
<th>No. of men within quintile</th>
<th>No. of lung cancer deaths</th>
<th>Lung cancer death ratesa</th>
<th>Partially adjusted HRb (95% CI)</th>
<th>P-value</th>
<th>Fully adjusted HRc (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2605</td>
<td>1323</td>
<td>127</td>
<td>64.1</td>
<td>1.00</td>
<td>–</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>2606–2984</td>
<td>1324</td>
<td>87</td>
<td>41.4</td>
<td>0.61 (0.47, 0.81)</td>
<td>0.0005</td>
<td>0.68 (0.51, 0.89)</td>
<td>0.0006</td>
</tr>
<tr>
<td>2985–3306</td>
<td>1321</td>
<td>62</td>
<td>30.6</td>
<td>0.42 (0.31, 0.57)</td>
<td>&lt;0.0001</td>
<td>0.48 (0.35, 0.66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3307–3673</td>
<td>1323</td>
<td>52</td>
<td>25.6</td>
<td>0.34 (0.24, 0.48)</td>
<td>&lt;0.0001</td>
<td>0.42 (0.30, 0.59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥3674</td>
<td>1322</td>
<td>35</td>
<td>16.5</td>
<td>0.23 (0.15, 0.36)</td>
<td>&lt;0.0001</td>
<td>0.32 (0.21, 0.48)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Regression coefficient for linear trend (for 100 ml higher FEV₁) –0.0699 –0.0563

Standard error for regression coefficient 0.0086 0.0090

P-value for regression coefficient <0.0001 <0.0001

a Death rates are per 10 000 person-years, age-adjusted.
b Adjusted for baseline covariates age, race, and height.
c Adjusted for baseline covariates age, race, height, body mass index, baseline number of cigarettes/day, thiocyanate, age at which smoking began, use of filter cigarettes, cigarette tar and nicotine content, alcoholic drinks/week, diastolic blood pressure, fasting cholesterol, and special intervention/usual care group.

Discussion

Among smokers, and after adjustment for smoking-related covariates such as smoking dose and smoking history, there was a strong increasing risk of lung cancer with decreasing pulmonary function, similar to that shown in previous studies.10,16,41–43

This gradient appeared for smokers overall, as well as within the sub-groups defined by during-trial smoking status: never quitters, intermittent quitters, and long-term quitters. We confirmed here that the lung cancer death rates over 18 post-trial years remained much higher among never quitters compared with quitters, and that this occurred even when compared with those quitters with FEV₁ in the highest quintile. There was no significant interaction between pulmonary function and smoking status in their associations with LCM. During-trial long-term quitters did not regain the lung cancer or all-cause mortality through four with similar age-adjusted death rates ranging from 39.2 to 16.7 per 10 000 person-years in the SI men and from 43.3 to 15.0 in the UC men. In the first (lowest) quintile, the death rate was 81.6 among the SI men and 47.5 among the UC men, which resulted in a slightly stronger linear association of FEV₁ with risk of lung cancer death among the SI men (HR per 100 ml higher FEV₁ = 0.93, 95% CI: 0.90, 0.95, P < 0.0001) compared with among the UC men (HR = 0.96, 95% CI: 0.94, 0.99, P = 0.003); the interaction of linear FEV₁ with SI/UC was significant (P = 0.03). When early lung cancer deaths (151 deaths within 10 years after the trial) were examined separately from late deaths (212 deaths after 10 years), there was only a slightly weaker linear association of FEV₁ with earlier deaths (HR = 0.95, 95% CI: 0.93, 0.98, P = 0.0003) than with later deaths (HR = 0.94, 95% CI: 0.92, 0.96, P < 0.0001).

Results among all smokers using a single measure of FEV₁ showed similar results (Table 4) as those using an averaged FEV₁. The multivariate-adjusted HR per 100 ml higher FEV₁ was 0.95 (95% CI: 0.93, 0.97, P < 0.0001). Results among all smokers using the average annual change (slope) in FEV₁ were not as strong, with no significant results for comparisons across quintiles of average annual change (results not shown), but a marginally significant linear trend (HR = 0.89, 95% CI: 0.80, 0.99, P = 0.04). Here the HR represents an 11% decrease in risk associated with a 100-ml higher average annual change (e.g. a participant whose FEV₁ is unchanged in a year compared with a participant whose FEV₁ declines by 100 ml in a year).

To explore whether smoking dose (as measured by trial-averaged cigarettes/day) was a stronger or weaker predictor of LCM than pulmonary function (as measured by trial-averaged FEV₁), we fit a multivariate-adjusted proportional hazards regression model with linear cigarettes/day and linear FEV₁. Both variables were highly significant (P < 0.0001) with a χ² test statistic of 43.4 for cigarettes/day and 38.1 for FEV₁, indicating that cigarettes/day was a slightly stronger predictor; their interaction was not statistically significant (P = 0.11). When examining all-cause death, both variables were again highly significant (P < 0.0001), but in contrast the χ² test statistic was 38.2 for cigarettes/day and 141.0 for FEV₁. Again their interaction was not statistically significant (P = 0.40).
Table 3  Lung cancer deaths, mortality rates through 1999, and hazard ratios (HR) for the 6613 Multiple Risk Factor Intervention Study (MRFIT) smokers, separately for never quitters, intermittent quitters, and long-term quitters, by quintiles of trial-averaged forced expiratory volume in 1 second (FEV\textsubscript{1}).

<table>
<thead>
<tr>
<th>Averaged FEV\textsubscript{1} (ml)</th>
<th>No. of men within quintile</th>
<th>No. of lung cancer deaths</th>
<th>Lung cancer death rates\textsuperscript{a}</th>
<th>Partially adjusted HR\textsuperscript{b} (95% CI)</th>
<th>P-value</th>
<th>Fully adjusted HR\textsuperscript{c} (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never quitters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2605</td>
<td>732</td>
<td>81</td>
<td>76.0</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>2606–2984</td>
<td>708</td>
<td>55</td>
<td>54.2</td>
<td>0.62 (0.44, 0.88)</td>
<td>0.007</td>
<td>0.66 (0.47, 0.94)</td>
<td>0.02</td>
</tr>
<tr>
<td>2985–3306</td>
<td>671</td>
<td>45</td>
<td>45.2</td>
<td>0.51 (0.35, 0.75)</td>
<td>0.0005</td>
<td>0.56 (0.38, 0.82)</td>
<td>0.003</td>
</tr>
<tr>
<td>3307–3673</td>
<td>641</td>
<td>34</td>
<td>37.3</td>
<td>0.41 (0.27, 0.62)</td>
<td>&lt;0.0001</td>
<td>0.45 (0.29, 0.70)</td>
<td>0.0003</td>
</tr>
<tr>
<td>≥3674</td>
<td>608</td>
<td>23</td>
<td>20.1</td>
<td>0.32 (0.19, 0.53)</td>
<td>&lt;0.0001</td>
<td>0.39 (0.23, 0.66)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Regression coefficient for linear trend (for 100 ml higher FEV\textsubscript{1})</td>
<td>-0.0614</td>
<td>-0.0520</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard error for regression coefficient</td>
<td>0.0111</td>
<td>0.0114</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value for regression coefficient</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Intermittent quitters       |                          |                          |                              |                                  |         |                  |         |
| ≤2605                       | 378                      | 31                       | 57.6                         | 1.00                            |         | 1.00             |         |
| 2606–2984                   | 369                      | 20                       | 30.4                         | 0.57 (0.32, 1.02)              | 0.06    | 0.64 (0.36, 1.15) | 0.14    |
| 2985–3306                   | 386                      | 11                       | 18.5                         | 0.29 (0.14, 0.59)              | 0.0007  | 0.34 (0.17, 0.70) | 0.003   |
| 3307–3673                   | 412                      | 11                       | 19.1                         | 0.26 (0.12, 0.55)              | 0.0004  | 0.31 (0.15, 0.67) | 0.003   |
| ≥3674                       | 416                      | 9                        | 10.8                         | 0.21 (0.09, 0.50)              | 0.0004  | 0.29 (0.12, 0.70) | 0.006   |
| Regression coefficient for linear trend (for 100 ml higher FEV\textsubscript{1}) | -0.0665 | -0.0563 |         |         |         |                  |         |
| Standard error for regression coefficient | 0.0180 | 0.0191 |         |         |         |                  |         |
| P-value for regression coefficient | 0.0002 | 0.003  |         |         |         |                  |         |

| Long-term quitters          |                          |                          |                              |                                  |         |                  |         |
| ≤2605                       | 213                      | 15                       | 49.5                         | 1.00                            |         | 1.00             |         |
| 2606–2984                   | 247                      | 12                       | 25.6                         | 0.73 (0.34, 1.59)              | 0.43    | 0.75 (0.34, 1.66) | 0.47    |
| 2985–3306                   | 264                      | 6                        | 13.6                         | 0.30 (0.12, 0.80)              | 0.02    | 0.31 (0.12, 0.84) | 0.02    |
| 3307–3673                   | 270                      | 7                        | 12.5                         | 0.36 (0.14, 0.95)              | 0.04    | 0.40 (0.15, 1.11) | 0.08    |
| ≥3674                       | 298                      | 3                        | 10.5                         | 0.14 (0.04, 0.55)              | 0.005   | 0.17 (0.04, 0.68) | 0.01    |
| Regression coefficient for linear trend (for 100 ml higher FEV\textsubscript{1}) | -0.0860 | -0.0790 |         |         |         |                  |         |
| Standard error for regression coefficient | 0.0250 | 0.0272 |         |         |         |                  |         |
| P-value for regression coefficient | 0.0006 | <0.0001 |         |         |         |                  |         |

\textsuperscript{a} Death rates are per 10,000 person-years, age-adjusted.
\textsuperscript{b} Adjusted for baseline covariates age, race, and height.
\textsuperscript{c} Adjusted for baseline covariates age, race, height, body mass index, baseline number of cigarettes/day, thiocyanate, age at which smoking began, use of filter cigarettes, cigarette tar and nicotine content, alcoholic drinks/week, diastolic blood pressure, fasting cholesterol, and special intervention/usual care group.

Table 4  Lung cancer deaths, mortality rates through 1999, and hazard ratios (HR) for the 6613 Multiple Risk Factor Intervention Study (MRFIT) smokers, by Annual Visit 3 forced expiratory volume in 1 second (FEV\textsubscript{1}) measures using the trial-averaged FEV\textsubscript{1} quintile cutpoints from Table 2.

<table>
<thead>
<tr>
<th>Annual visit 3 FEV\textsubscript{1} (ml)</th>
<th>No. of men within quintile</th>
<th>No. of lung cancer deaths</th>
<th>Lung cancer death rates\textsuperscript{a}</th>
<th>Partially adjusted HR\textsuperscript{b} (95% CI)</th>
<th>P-value</th>
<th>Fully adjusted HR\textsuperscript{c} (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2605</td>
<td>1036</td>
<td>96</td>
<td>62.9</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>2606–2984</td>
<td>1066</td>
<td>66</td>
<td>39.3</td>
<td>0.62 (0.45, 0.85)</td>
<td>0.0005</td>
<td>0.67 (0.49, 0.93)</td>
<td>0.0006</td>
</tr>
<tr>
<td>2985–3306</td>
<td>1139</td>
<td>68</td>
<td>38.0</td>
<td>0.57 (0.41, 0.79)</td>
<td>&lt;0.0001</td>
<td>0.65 (0.47, 0.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3307–3673</td>
<td>1315</td>
<td>55</td>
<td>27.9</td>
<td>0.39 (0.28, 0.56)</td>
<td>&lt;0.0001</td>
<td>0.49 (0.34, 0.70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥3674</td>
<td>1429</td>
<td>41</td>
<td>15.4</td>
<td>0.27 (0.18, 0.41)</td>
<td>&lt;0.0001</td>
<td>0.37 (0.24, 0.55)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Regression coefficient for linear trend (for 100 ml higher FEV\textsubscript{1})</td>
<td>-0.0647</td>
<td>-0.0528</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard error for regression coefficient</td>
<td>0.0089</td>
<td>0.0093</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value for regression coefficient</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Death rates are per 10,000 person-years, age-adjusted.
\textsuperscript{b} Adjusted for baseline covariates age, race, and height.
\textsuperscript{c} Adjusted for baseline covariates age, race, height, body mass index, baseline number of cigarettes/day, thiocyanate, age at which smoking began, use of filter cigarettes, cigarette tar and nicotine content, alcoholic drinks/week, diastolic blood pressure, fasting cholesterol, and special intervention/usual care group.
advantage of never smokers or even ex-smokers; however, we do not know smoking status throughout the post-trial mortality follow-up. A single FEV$_1$ measure from Annual Visit 3 (instead of a 4-year average) showed similar trends in LCM across quintiles. Thus one FEV$_1$ determination could be explored as a useful annual screening tool in smokers for lung cancer, similar to the current use of blood pressure, cholesterol, and other blood lipids for cardiovascular disease.

We used proportional hazards multiple regression with FEV$_1$ (controlling for age, height, and race) rather than with percentage predicted FEV$_1$ (based on normative equations dependent on age, height, and race). Our approach does not require an internal or external comparison group from which the normative equations are derived, and it can reduce the variance of estimated effects because no additional variability is introduced with the use of a normative equation. Our approach allows independent estimation of the effects of and also direct adjustment for age, height, and race. For MRFIT baseline never smokers and ex-smokers, smoking status reported at subsequent Annual Visits was not used: re-defining those never and ex-smokers who smoked during the trial did not affect our results.

The more recent application of CT scan to the early detection of lung cancer has once again raised hopes of diagnosis at a stage of development that permits survival to be favourably affected. Given the relatively low incidence (even in heavy smokers) and the long latency of lung cancer, a definitive randomized trial of CT scan screening would need to be both large and long-term, and thus expensive: the US National Cancer Institute is currently funding CT scan studies (http://researchportfolio.cancer.gov). Additional predictors of lung cancer such as pulmonary function, over and above the rate and duration of cigarette smoking, could be valuable in identifying those smokers most likely to develop lung cancer to enable a smaller, more economical randomized screening trial.

A basic problem with CT of the lungs (and other potential early detection methods) is the relatively low positive predictive value of a CT-identified lesion. Such a lesion usually leads to further diagnostic testing which is both expensive and of potential risk for the patient, i.e. thoracotomy and biopsy. Incorporating additional screening via FEV$_1$ could improve the positive predictive value of the CT screening. In this study, the lung cancer death rate among smokers in the lowest quintile of FEV$_1$ was 64.1 per 10 000 person-years and 16.5 per 10 000 person-years in the highest FEV$_1$ quintile. Assuming a 10-year follow-up, sensitivity of 80%, and specificity of 95%, then the positive predictive value of a CT-identified lesion would be about 52% for those with low FEV$_1$ and only 21% for those with the highest FEV$_1$. In other words, about one in every two lesions identified in those with low FEV$_1$ would be a cancer as opposed to only one in five for those with the highest FEV$_1$. It is important to note that the FEV$_1$ values in this study were not low enough to cause significant disability; participants with very low FEV$_1$ or a history of chronic pulmonary disease were excluded from the original MRFIT trial.

In the absence of a preventive or therapeutic intervention of proven efficacy for lung cancer (other than smoking cessation) the implications for public health practice are thus limited to using the FEV$_1$ as an additional indicator of risk, perhaps useful for exclusion criteria or risk stratification in clinical trials of lung cancer, and, potentially, as a further incentive to quit smoking.

In this paper, we presented evidence that a well-established and inexpensive measurement, the FEV$_1$, is a strong predictor of lung cancer mortality (and of all-cause mortality) independent of smoking dose. This strong association held true among various sub-groups of smokers defined according to their 6-year smoking cessation pattern. There are two primary hypotheses regarding the mechanism by which FEV$_1$ might affect lung cancer occurrence. The first is that the increased risk of lung cancer seen here among smokers with decreased pulmonary function could be attributed to a genetic susceptibility to both decreased lung function and lung cancer (i.e. host susceptibility among smokers). The second is that lung function may be an additional marker of the biological (carcinogenic) effects of smoking exposure beyond measures of duration, dose, and characteristics of cigarette smoking. Using the combination of FEV$_1$ and smoking status may identify smokers at unusually high risk of lung cancer.

Acknowledgements

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**KEY MESSAGES**

- Results from the Multiple Risk Factor Intervention Trial showed that pulmonary function was a strong predictor of lung cancer mortality (LCM) in smokers, independent of smoking history and of during-trial quit status.

- Overall there was a 5% decrease in LCM risk for every 100 ml higher forced expiratory volume in 1 second (FEV$_1$) ($P < 0.0001$).

- Pulmonary function should be considered as a risk stratification variable in clinical trials of lung cancer screening methods in order to identify sub-groups of smokers at higher risk of LCM.
References


