Relationship of Lung Cancer and Emphysema

Lung Cancer Workshop X
May 2, 2013
John Reilly, MD
Are they related? If so, why/how?

- Common things are common.
- Shared risk factors.
- Shared genetic predisposition.
- Shared mechanisms.
According to a recent Nationwide survey:

MORE DOCTORS SMOKE CAMELS THAN ANY OTHER CIGARETTE

DOCTORS in every branch of medicine—113,997 in all—were queried in this nationwide study of cigarette preference. These leading research organizations made the survey. The gist of the query was—What cigarette do you smoke, Doctor?
The brand named most was Camel!
The rich, full flavor and end mildness of Camel’s superb blend of costlier tobaccos seem to have the same appeal to the smoking tastes of doctors as to millions of other smokers. If you are a Camel smoker, this preference among doctors will hardly surprise you. If you’re not—well, try Camels now.

CAMELS Costlier Tobaccos

To celebrate her latest creation, erstwhile milliner Lisa Welsh lit up a cigarette right in the shop.

Unfortunately, she soon found herself working for a mad hatter.

VIRGINIA SLIMS

YOU’VE COME A LONG WAY, BABY.

SURGEON GENERAL’S WARNING: Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.

Found in Mom’s Basement
Significance of the Problem:

• COPD and lung cancer are highly prevalent and conditions with associated morbidity and mortality.

• The most significant risk factor for both COPD and lung cancer in the developed world is cigarette smoking.¹

• An estimated 100 million Americans are current or former smokers.²

Data from American Lung Association 2011 Report: Trends in Chronic Bronchitis and Emphysema Morbidity and Mortality
Alveolar Destruction With Emphysema

Normal

Emphysema

FEV$_1$ 105%
DlCO 50%

FEV$_1$ 95%
DlCO 70%

FEV$_1$ 40%
DlCO 70%
Relationship of CT Density Mask Quantification of Emphysema and % Predicted FEV1

\[ R = -0.19 \]

COPD 5:177-186, 2008
Measuring Emphysema on CT scan: Man vs. Machine

• **Man:**
  - Predictive of response to surgery
  - Somewhat reproducible
  - Not always a scalable solution: slow

• **Machine:**
  - Highly reproducible
  - Very fast
  - Does not recognize ‘patterns’ as well as trained human
Relationship of Lung Cancer and COPD:

- Lung cancer risk has been associated with airflow obstruction.¹⁻⁴
- Lung cancer risk has been associated with presence of emphysema on CT scan.⁵,⁶

<table>
<thead>
<tr>
<th>Airflow obstruction</th>
<th>Radiographic emphysema</th>
<th>Lung cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-IV</td>
<td>Yes</td>
<td>15</td>
</tr>
<tr>
<td>III-IV</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>Yes</td>
<td>32</td>
</tr>
<tr>
<td>II</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>I</td>
<td>Yes</td>
<td>11</td>
</tr>
<tr>
<td>I</td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td>None</td>
<td>Yes</td>
<td>17</td>
</tr>
<tr>
<td>None</td>
<td>No</td>
<td>15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of participants</th>
<th>Outcome</th>
<th>FEV₁ (% predicted)</th>
<th>Emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skirud et al.⁴</td>
<td>226</td>
<td>Incidence</td>
<td>Cancers in 8.8% of cases (FEV₁ &lt;70%) versus 2.0% of controls (FEV₁ &gt;85%); P = 0.024</td>
<td>NA</td>
</tr>
</tbody>
</table>
| Tockman et al.⁵     | 4,395                  | Mortality   | * Cohort 1: RR 4.85 for FEV₁ <60% versus >60%; P = 0.002  
* Cohort 2: RR 2.72 for FEV₁ 60–85% versus >85%; P = 0.043 | NA                                                             |
| Speizer et al.⁷     | 8,427                  | Mortality   | Quartile-based FEV₁ analysis confers cancer risk (RR 2.0–8.27) | NA                                                             |
| Lange et al.⁶       | 13,946                 | Mortality   | * RR 2.1 (95% CI 1.3–3.4) for FEV₁ 40–79% versus >80%   
* RR 3.9 (95% CI 2.2–7.2) for FEV₁ <40% versus >80%       | NA                                                             |
| de Torres et al.¹⁹  | 1,166                  | Incidence   | RR 2.89 (95% CI 1.14–7.27) for FEV₁/FVC ratio <70% versus >70% | Semi-quantitative radiographic emphysema, RR 3.13 (95% CI 1.32–7.44) |
| Wilson et al.¹⁷     | 3,638                  | Incidence   | OR 2.09 (95% CI 1.33–3.27) for any GOLD stage (FEV₁/FVC <70%) | Semi-quantitative radiographic emphysema, OR 3.56 (95% CI 2.21–5.73). After controlling for airflow obstruction, OR 3.14 (95% CI 1.91–5.15) for radiographic emphysema |
| Li et al.²⁰         | 1,015                  | Incidence   | NA                 | Semi-quantitative radiographic emphysema, Any = OR 2.79  
(95% CI 2.05–3.81), >5% = 3.80  
(95% CI 2.78–5.19), >10% = OR 3.33 (95% CI 2.30–4.82) |
| Zulueta et al.²¹    | 9,047                  | Mortality   | NA                 | Semi-quantitative radiographic emphysema, HR 1.7 (95% CI 1.1–2.5); P = 0.013 |
| Maldanado et al.²³  | 1,520                  | Incidence   | Cancer risk conferred by decreasing FEV₁, OR 1.15 (95% CI 1.00–1.32; P = 0.046); and FEV₁/FVC <70%, OR 1.29 (95% CI 1.02–1.62; P = 0.0310) | Automated volumetric determination of radiographic emphysema was not associated with lung cancer risk, OR 1.042 (95% CI, 0.816–1.329; P = 0.743) |

CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; NA, not applicable; OR, odds ratio; RR, relative risk. *All studies controlled for age and cigarette consumption. *The FEV₁ is reported as the percentage that would be predicted for that individual based on parameters that are known to influence the FEV₁, such as gender, age, height and race.
<table>
<thead>
<tr>
<th>Gene</th>
<th>COPD</th>
<th>Lung cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERPINA1</td>
<td>MZ heterozygotes associated with COPD ($P=0.04$)\textsuperscript{151}</td>
<td>A1AT carrier rate (12.3%) exceeded expected control rate ($P=0.002$)\textsuperscript{152}</td>
</tr>
<tr>
<td>MMP1</td>
<td>Combined MMP1 and MMP12 SNPs associated with rapid decline in lung function\textsuperscript{115}</td>
<td>MMP1 promoter SNP associated with lung cancer risk (OR 1.8; 95% CI 1.3–2.4)\textsuperscript{153}</td>
</tr>
<tr>
<td>CYP1A1</td>
<td>Homozygous *2A allele significantly higher in severe COPD ($P&lt;0.01$)\textsuperscript{154}</td>
<td>M1 homozygous genotype found in 4.10% cancers versus 1.69% controls\textsuperscript{155}</td>
</tr>
<tr>
<td>EPHX1</td>
<td>Increased COPD risk for exon 3 variant both as heterozygote (OR 3.0; 95% CI 1.2–7.1) and homozygote (OR 2.4; 95% CI 1.1–5.1)\textsuperscript{156,157}</td>
<td>Lung cancer risk associated with high EPHX activity ($P&lt;0.02$)\textsuperscript{158}</td>
</tr>
<tr>
<td>CRHNA3 and</td>
<td>CHRNA3 and CHRNA5 locus significantly associated with both radiographic emphysema ($P&lt;0.0002$) and airflow obstruction ($P=0.004$)\textsuperscript{38}</td>
<td>CHRNA3 and CHRNA5 locus strongly associated with lung cancer in three independent studies\textsuperscript{40}</td>
</tr>
<tr>
<td>MPO</td>
<td>NA</td>
<td>Reduced risk (OR 0.5; 95% CI, 0.29–0.88) of lung cancer with A/G allele (reduced expression)\textsuperscript{93}</td>
</tr>
</tbody>
</table>

\textit{CHRNA3}, cholinergic receptor, neuronal nicotinic, α-polypeptide 3; \textit{Cl}, confidence interval; COPD, chronic obstructive pulmonary disease; \textit{CYP1A1}, cytochrome P450 subfamily 1, polypeptide 1; \textit{EPHX1}, epoxide hydrolase 1; MMP, matrix metalloproteinase; \textit{MPO}, myeloperoxidase; MZ, individuals that have one normal allele of \textit{SERPINA1} and a commonly encountered abnormal allele designated Z; NA, not applicable; OR, odds ratio; SNP, single nucleotide polymorphism.
Potential Common Mechanisms:

<table>
<thead>
<tr>
<th>Proteinase</th>
<th>Source</th>
<th>Matrix substrates</th>
<th>Promotes emphysema?</th>
<th>Promotes cancer?</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil elastase</td>
<td>PMNs</td>
<td>Elastin, CI, CIII, CIV, laminin, fibronectin and TIMPs</td>
<td>Yes</td>
<td>Yes</td>
<td>122,123</td>
</tr>
<tr>
<td>Proteinase 3</td>
<td>PMNs</td>
<td>Elastin, CIV, laminin and fibronectin</td>
<td>Yes</td>
<td>?</td>
<td>159</td>
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<tr>
<td>Cathepsin S</td>
<td>Macrophages and other cell types</td>
<td>Elastin, CI, CIII, laminin and fibronectin</td>
<td>Yes</td>
<td>Yes</td>
<td>160,161</td>
</tr>
<tr>
<td>Cathepsin L</td>
<td>Macrophages and other cell types</td>
<td>Elastin, CI, CIII, laminin and fibronectin</td>
<td>?</td>
<td>Yes</td>
<td>162</td>
</tr>
<tr>
<td>Cathepsin K</td>
<td>Macrophages and other cell types</td>
<td>Elastin, CI, CIII, laminin and fibronectin</td>
<td>?</td>
<td>?</td>
<td>163</td>
</tr>
<tr>
<td>MMP1</td>
<td>Stromal cells</td>
<td>CI, CIII and A1AT</td>
<td>Yes</td>
<td>Yes</td>
<td>112,114</td>
</tr>
<tr>
<td>MMP2</td>
<td>Stromal cells</td>
<td>Elastin, CI, CIV, laminin, fibronectin and A1AT</td>
<td>?</td>
<td>Yes</td>
<td>164</td>
</tr>
<tr>
<td>MMP3</td>
<td>Stromal cells</td>
<td>Elastin, CIII, CIV, laminin, fibronectin and A1AT</td>
<td>No</td>
<td>Yes</td>
<td>165</td>
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<tr>
<td>MMP8</td>
<td>PMNs</td>
<td>CI, CIII and A1AT</td>
<td>No</td>
<td>No</td>
<td>166</td>
</tr>
<tr>
<td>MMP9</td>
<td>Macrophages, PMNs and other cell types</td>
<td>Elastin, CI, CIV, laminin and A1AT</td>
<td>Yes</td>
<td>Yes</td>
<td>106,107,109</td>
</tr>
<tr>
<td>MMP12</td>
<td>Macrophages</td>
<td>Elastin, CI, CIV, fibronectin, laminin and A1AT</td>
<td>Yes</td>
<td>No</td>
<td>116,119</td>
</tr>
<tr>
<td>MMP13</td>
<td>Stromal cells</td>
<td>CI, CIII and CIV</td>
<td>No</td>
<td>Yes</td>
<td>167</td>
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<tr>
<td>MMP14</td>
<td>Stromal cells and macrophages</td>
<td>CI, CIII, CIV, fibronectin and laminin</td>
<td>?</td>
<td>Yes</td>
<td>168,169</td>
</tr>
</tbody>
</table>

CI, collagen type I; CIII, collagen type III; CIV, collagen type IV; MMP, matrix metalloproteinase; PMNs, polymorphonuclear leukocytes; TIMP, tissue inhibitors of metalloproteinase.
Genetics:
- Process oxidant or noxious stress
- EPHX, CYPs, MPO and NRF2

Cell cycle regulation:
- Avoid apoptosis
- Uncontrolled proliferation

Cytokines:
- NF-κB activation
- Regulate tumour microenvironment

Inflammation:
- Field propagation
- Cytotoxic versus growth promoting

Proteinases:
- Matrix degradation
- Release growth factors
**COPD:**
- Cytotoxic
- Genotoxic
- Matrix degrading

**Cancer:**
- Angiogenic
- Myeloid suppressive
- Growth promoting
Conclusions:

- Weight of evidence supports a greater than chance association of emphysema and lung cancer.
- There are plausible mechanistic hypotheses for this association.
- Changes in lung structure imaged on CT scanning are a marker for increased risk.