Spirometry, COPD and lung cancer

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New Zealand
## Spirometry for those with smoking and dust exposures

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# Diagnose end organ damage (coronary angiogram or CT chest)
Smoking and lung disease

Lung Cancer

Emphysema

Cigarettes
Smoking and its complications

Respiratory

- COPD
- Lung cancer

Cardiovascular

- CAD
- Stroke
- PVD
Epidemiology of lung cancer

• Smoking (90%)
  – Duration over 30 years or over 30 pk years

• Age (over 50 yo)

• Other factors
  – Exposure to asbestos, radon, radiation and cooking fuels
  – Low consumption of fruit and vegetables (antioxidants)
  – Lower risk in atopics

• Lung function

• Family history

Genetic factors
Decline of Lung Function: Not Homogeneous

Lung function in smokers who get COPD
Segmentation of Lung Function Decline

A 0-20 Pack Years

B 50-60 Pack Years

C 50-60 Pack Years

D COPD

Resistant Smokers

% of Population

% FEV1

% of Population

% FEV1

% of Population

% FEV1

% of Population

% FEV1
Reduced FEV$_1$: linked to all cause mortality

- Low FEV1 (COPD)
  - diagnosed COPD
  - 5x ↑ Lung cancer
  - 5x ↑ heart attack
  - 2-3x ↑ stroke

Smokers
Not Susceptible to Smoke (60%)

Intermediate Smokers (20%)

Onset of symptoms
Severe disability
Death

FEV1 (% of value at age 25 years)

Age (years)
Lung Function and Lung Cancer

Consistently reported risk of 3-6x for lung cancer in smokers with impaired lung function

<table>
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<th>Lung cancer</th>
<th>Age</th>
<th>RR 2.8</th>
</tr>
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<td>↓FEV1</td>
<td>RR 6.4</td>
<td></td>
</tr>
<tr>
<td>Pk yrs</td>
<td>RR 3.1</td>
<td></td>
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</table>

Age

Pack Yrs

↓FEV1

Lung Cancer

1.8  2.2  1.4

5.3  2.4
COPD prevalence is increased in lung cancer independent of age, sex and smoking history

R.P. Young*, R.J. Hopkins*, T. Christmas#, P.N. Black†, P. Metcalf† and G.D. Gamble*
Lifetime risk: COPD and lung cancer

Lung cancer develops in

6/20 with COPD (30%)
4/80 with normal lung function (5%)

Young RP, et al.
ERJ, On line Feb 5\textsuperscript{th}, 2009
Smoking, lung function and lung cancer

Smoking

20-30% of smokers develop impaired lung function (COPD)

COPD

65-75% of lung cancer patients have COPD

Lung Cancer

Parallel:
Obesity predisposes to diabetes
Lung Cancer Risk climbs steeply with age

10 Year Mortality for Lung Cancer by Smoking Status

Deaths per 100 Men

Incidence ≈ Mortality

Age (Years)

Smoker-life long
Smokers-quit aged 50 yo
smokers-quit aged 70 yo
Nonsmokers
Smokers-quit aged 60 yo
Risk spectrum for lung cancer risk

Genetic make up
Smoking exposure dose
Asbestos exposure
Advancing age
Advancing COPD

Lifelong non-smokers Ex-smokers Smokers

Lowest risk Highest risk
Lung cancer and age distribution

Age distribution of lung cancer cases
*(n=446)*

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<th>Age bands (years)</th>
<th>Frequency (%)</th>
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<tr>
<td>40-49</td>
<td>21%</td>
</tr>
<tr>
<td>50-54</td>
<td>52%</td>
</tr>
<tr>
<td>55-59</td>
<td>26%</td>
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<tr>
<td>60-64</td>
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<tr>
<td>65-69</td>
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<tr>
<td>70-74</td>
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<tr>
<td>75-79</td>
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</tr>
<tr>
<td>80-84</td>
<td></td>
</tr>
<tr>
<td>85+</td>
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Inflammation and cardio-pulmonary disease

- Smoking
  - Inflammation
    - Normal repair
    - Tissue inflammation and remodeling
      - Lung airways and matrix remodeling with COPD
      - Lung epithelial remodeling with carcinogenesis
      - Vascular remodeling with accelerated atherosclerosis
Proposed Pathogenesis of COPD

Small Airway Lumen

- Cigarette Smoke
  - Nicotine
  - Oxidants (ROS)
  - Heavy Metals
  - LPS
  - Goblet Cell Hyperplasia
  - Carcinogens (Nitrosamines)
  - Products of Combustion (PAH)
  - Particulate Matter

Airway Wall

- BEC
- IL-8
- PMN Influx
- MPO
- Oxidant Load (Exogenous, Endogenous)
- Acquired Antiprotease Deficiency
- Matrix Remodelling and Impaired Repair (↓ Elastin, ↑ Collagen)
- Smooth Muscle Proliferation
- VEGF
- Apoptosis
- Lymphocytes

Pulmonary Circulation

- Cytokines (IL-8, IL-6, TNFα, IL-1β, GMSCF, TGFβ1)
- MØ Influx
- MMP 1,2,9,12,15
- Oxidants

Systemic Circulation

- TNFα
- CRP
- IL-6
- Systemic Inflammation

- Arteries
  - Atherosclerosis
  - Plaque rupture
- Muscle
  - Wasting
  - Fatigue
- Liver
  - CRP
  - αAT
  - IL-6
- Bone
  - Osteoporosis

Young RP, et al. (submitted)
Proposed Pathogenesis of Lung Cancer

Airway Lumen
- Cigarette Smoke
  - Nicotine
  - Oxidants (ROS)
  - Heavy Metals
  - LPS
- Carcinogens (Nitrosamines)
- Products of Combustion (PAH)
- Particulate Matter

Epithelial Cell
- HMGCoA
- Statins
- Mevalonate Pathway
- Cholesterol
- Prenylation of GTPases
- Intracellular Signalling
  - Ras
  - Rho
  - Rac
- E-cadherin
  - Bcl2
  - SMAD
- ↑ Cell Proliferation
- ↓ DNA repair capacity
- DNA damage
  - ↑ oncogenes
  - ↓ tumor suppressor genes
  - ↑ DNA adducts
- Mevalonate Pathway
- ↑ NFkB
- ↑ API
- Epithelial Mesenchymal Transition
  - ↓ cell adhesion
  - change in polarity
  - ↑ motility / migration
  - mesenchymal gene expression
- Lung Cancer

Mesenchyme (ECM)
- Cytokine driven inflammation
- Matrix remodeling
  (MMP: fibrosis, emphysema)
- Oxidant Load
  (ROS, MPO in PMN)
- FGF, MMP3
- Impaired Repair
  - Lung Fibrosis
  - Emphysema
- Atherosclerosis
  - Plaque Instability
- TGFβ3
- TGFβ1
- Young RP, et al. (submitted)
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# Diagnose end organ damage (coronary angiogram or CT chest)
Pool of many SNPs each conferring a modest effect through modifying the body’s response to smoke in the lungs

Genes altering metabolism of the smoke derived toxins
Anti-oxidant response genes
Genes controlling DNA repair
Genes controlling apoptosis and/or inflammation *
Genes controlling nicotine addiction *
Genes controlling matrix remodeling
Genes controlling airway fibrosis
Genes controlling nicotine addiction *

Smoking

Genetic susceptibility to lung cancer

Many genetic variants
Interaction with smoking
Affect many different pathways
Overlap between genes conferring COPD and lung cancer

nAChR gene* locus associated with lung cancer, COPD and nicotine addiction

COPD
Lung Cancer
Lung Cancer Susceptibility Score

- Educational tool to personalise risk and raise awareness of lung cancer
- Refines existing risk derived from smoking exposure
- Based on age, FHx of lung cancer, COPD and SNP markers
- Target 40+ yr old who are smokers and ex-smokers (last 10 years)
- Aim to motivate smoker to quit or ex-smoker to avoid relapse
- Referenced against the “average” smoker’s risk
- Shows risk reduction with quitting

No one is lower than average risk for lung cancer
Epidemiology of lung cancer

- Smoking (90%)
  - Duration over 30 years or over 30 pk years

- Age (over 50 yo)

- Other factors
  - Asbestos, radon, radiation, cooking fuels
  - Low consumption of fruit and vegetables (antioxidants)
  - Lower risk in atopics

- Lung function

- Family history
April 2008 – “Lung cancer” gene discovered

Headlines
- NY times
- Herald Tribune
- Financial Times
- NZ Herald

LETTERS

A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25


LETTERS

A variant associated with nicotine dependence, lung cancer and peripheral arterial disease

Thorgeir E. Thorgeirsson1, Frank Geller2, Patrick Sulem3, Thorunn Rafnar4, Anna Wista2,3, Kristinn F. Magnusson1, Andrei Manolescu2, Gudmar Thorleifsson1, Hreinn Stefansson1, Andres Ingason3, Simon N. Stacey5, Jon T. Bergholst1, Steinunn Thorlarsdottir1, Julius Gudmundsson1, Thorlfur Jonsson1, Margret Jakobsdottir5, Jona Saemundsdottir1, Olof Olafsdottir1, Larus J. Gudmundsson1, Gyda Bjornsdottir1, Kristjana Kristjansdottir1, Halla Skuladottir1, Helgi J. Saeksson1, Tomas Gudbjartsson1, Gregory T. Jones1, Thomas Mueller1, Anders Gottsater9, Andrea Fav1, Katja K. Aben10,11,12,13 Femme de Vegt5, Peter F. A. Mulders14, Dolores Ibañez9, Maria J. Vidal15, Laura Asin16, Berta Saéz17, Laura Munillo19, Thorsteinn Blondal19, Halldor Kolbeinsisson1, Jon G. Stefansson5, Ingunn Hansdottir17, Valgerdur Runarsdottir17, Roberto Pola11,21 Bengt Lindblad18, Andre M. van Rij5, Benjamin Dieplinger1, Meinhard Haiml19, Jose I. Mayordomo16,17,18,19, Lambertus A. Klemenc12,13,14, Stefan E. Matthiasson19, Hogni Oskarsson19, Thorarinn Thorarinsson20, Daniel F. Gudbjartsson1, Jeffrey R. Gutcher1, Steinn Jonsson1, Unmur Thorsteinsdottir14,17, Augustine Kong1 & Karl Stefansson1,2

Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1

Christopher I Amos1, XiFeng Wu2, Peter Broderick2, Ivan P Gorlov3, Jian Gu4, Timothy Eisen5, Qiong Dong6, Qiong Zhang6, Xiangjun Gu6, Jayaram Vijayakrishnan6, Kate Sullivan6, Athena Matsakis6, Yufei Wang7, Gordon Mills8, Kimberly Doherty8, Ya-Yu Tsai8, Wei Vivien Chen2, Sanjay Sethi2, Margaret R Spirit18 & Richard S Houlston2,6
Lung cancer gene associated with COPD: triple whammy or possible confounding effect?

R.P. Young*, R.J. Hopkins*, B.A. Hay*, M.J. Epton†, P.N. Black* and G.D. Gamble*

**Nicotinic acetylcholine receptor SNP**
- Chromosome 15q25 (GWAS)
- Associated with lung cancer, COPD and nicotine addiction
- Nicotine up-regulates inflammation in the lung
- SNP appears to be involved in modifying this inflammatory effect
- SNPs associated with both diseases
<table>
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<tr>
<th>Primay Cohorts</th>
<th>GG</th>
<th>GA</th>
<th>AA</th>
<th>OR* (95% CI)</th>
<th>P value*</th>
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<tr>
<td>Controls N=475</td>
<td>225 (47%)</td>
<td>205 (43%)</td>
<td>45 (9%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>COPD N=445 (97%)</td>
<td>166 (37%)</td>
<td>219 (49%)</td>
<td>60 (14%)</td>
<td>1.5 (1.0-2.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Lung cancer N=437 (96%)</td>
<td>170 (39%)</td>
<td>199 (46%)</td>
<td>68 (16%)</td>
<td>1.8 (1.2-2.7)</td>
<td>0.005</td>
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**Subgroup Analyses**

| COPD and LC+COPD, N=706 | 252 (36%)| 344 (49%)| 110 (16%) | 1.8 (1.2-2.6) | 0.002    |
| LC + COPD*, N=261 | 86 (33%)| 125 (48%)| 50 (19%) | 2.3 (1.4-3.6) | 0.0002   |
| LC only, N=168 | 81 (48%)| 69 (41%)| 18 (11%) | 1.2 (0.6-2.1) | 0.64     |

Genotypes for the α5 subunit of the nAChR gene (Young RP, et al. ERJ Nov 2008)
Clinical utility of spirometry

Reduced FEV$_1$ (compared to normal lung function)

- Predicts increased risk of coronary artery disease
- Predicts increased risk of lung cancer
- Predicts increased risk of stroke
- Predicts increased risk of peripheral arterial disease
Smoking, lung function and mortality

Smoking → Inflammation → Normal repair

FEV1

Tissue remodeling

Lung airways and matrix remodeling with COPD

Lung epithelial remodeling with carcinogenesis

Vascular remodeling with accelerated atherosclerosis
FEV<sub>1</sub> = “barometer” of a person’s tendency (or susceptibility) to exaggerated airway inflammation and adverse remodeling.
Clinical implications of detecting COPD

• Increased cardiovascular and lung cancer risk and urgent need for aggressive smoking cessation
• Inclusion of COPD in lung cancer risk models
• Consideration of statin therapy in increased cardiovascular risk
• Initiation of usual inhaler therapy for symptom control
Smoking and its complications

Smoking → COPD

COPD → CAD

COPD → Lung cancer

COPD → Stroke

COPD → PVD