A personal journey in the NCI intramural program.....

**Goal to identify hereditary component of lung cancer**

3 lines of evidence available in the late 1980's

- Family History
- Lung Cancer
- ~OR=2

Tokuhata and Lilienfeld 1983

- Pedigrees

- Pharmacogenetics
A Population Perspective on Lung Cancer and Smoking

- Descriptive Epidemiology
- Molecular Epidemiology
- Integrative Epidemiology
- Genomics
  - Smoking
  - Lung Cancer
- Importance of Key Subgroups
- Summary
A Population Perspective on Lung Cancer and Smoking

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The lung cancer challenge....

1- Drives overall cancer mortality in the US and worldwide
2- Treatment and screening pose challenges
3- Lung cancer is paradigm for genetics of complex disease
4- Clearest example of environment and gene in cancer
5- The clearest example of a genetically influenced behavior associated with the leading public health problem in the world

### 2009 Estimated US Cancer Deaths*

<table>
<thead>
<tr>
<th>Site</th>
<th>Men 292,540</th>
<th>Women 269,800</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>30%</td>
<td>26%</td>
</tr>
<tr>
<td>Prostate</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td>25%</td>
</tr>
<tr>
<td>All other sites</td>
<td>25%</td>
<td>25%</td>
</tr>
</tbody>
</table>

### Trends in Five-year Relative Survival (%) * Rates, US, 1975-2004

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>50</td>
<td>54</td>
<td>66</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>75</td>
<td>79</td>
<td>89</td>
</tr>
<tr>
<td>Colon</td>
<td>52</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>Leukemia</td>
<td>35</td>
<td>42</td>
<td>51</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>13</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Melanoma</td>
<td>82</td>
<td>87</td>
<td>92</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>48</td>
<td>53</td>
<td>65</td>
</tr>
<tr>
<td>Ovary</td>
<td>37</td>
<td>40</td>
<td>46</td>
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<tr>
<td>Pancreas</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Prostate</td>
<td>69</td>
<td>76</td>
<td>99</td>
</tr>
<tr>
<td>Rectum</td>
<td>49</td>
<td>57</td>
<td>67</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>74</td>
<td>78</td>
<td>81</td>
</tr>
</tbody>
</table>
Traditional epidemiology

E  →  D

Exposure  Disease

Tobacco  Lung Cancer
Molecular epidemiology

Adding biomarkers allows us to investigate genes and mechanisms.
PLCO Trial: Study Design

- Screening Centers: 10
- Coordinating Center
- Participants: 154,935
- Gender: 50:50
- Age: 55-74 years
- Recruitment: 1993-2001
- Screening: 1993-2006
- Baseline questionnaire
- Dietary questionnaires
- Follow-up:
  - Annual surveys
  - Monitoring and QA
  - Mortality searches
  - Interim analyses regularly
- 847 lung cancer cases and 847 controls participate in GWAS

http://prevention.cancer.gov/programs-resources/groups/ed/programs/plco
EAGLE (Environment and Genetics in Lung Cancer Etiology)

Study protocol
Environment And Genetics in Lung cancer Etiology (EAGLE) study: An integrative population-based case-control study of lung cancer
Maria Teresa Landi¹, Dario Consonni², Melissa Rotunno¹, Andrew W Bergen¹, Alisa M Goldstein¹, Jay H Lubin¹, Lynn Goldin¹, Michael Alavanja¹, Glen Morgan³, Amy F Subar³, Ilona Linnoila⁴, Fabrizio Previdi², Massimo Corno², Maurizia Rubagotti², Barbara Marinelli², Benedetta Albetti², Antonio Colombi², Margaret Tucker¹, Sholom Wacholder¹, Angela C Pesatori¹, Neil E Caporaso¹ and Pier Alberto Bertazzi¹²
Example from EAGLE: molecular epidemiology approach

Epidemiology
‘doneness module’

Biospecimens
Higher frequency of fresh red and processed meat intake increased lung cancer risks

Lam et al, 2009, Cancer Res.
A Population Perspective on Lung Cancer and Smoking

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Instruments

- Fagerstrom Nicotine Dependency
- DSM-IV Nicotine Dependency
- Hospital Anxiety and Depression Scale
- Eysenck Personality Inventory
- CESD- Depression
- Attention Deficit Inventory
- Attitudes and Knowledge about Smoking
- Intention to Quit Smoking

Integrative epidemiology

- Exposure
- Internal dose
- Early biological effect
- Altered structure or function
- Early disease
- Disease
- Outcome

Behavior

Treatment

Survival

Prognostic and Clinical
A Population Perspective on Lung Cancer and Smoking

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Tobacco Is a Risk Factor for 6 of the World’s 8 Leading Causes of Death

Hatched areas indicate proportions of deaths related to tobacco use.
Trends in Cigarette Smoking Prevalence* (%), by Sex, Adults 18 and Older, US, 1965-2007

*Redesign of survey in 1997 may affect trends.

Strong and consistent evidence for a genetic contribution to smoking from twin studies…

- Genetic 56%
- Shared environment 24%
- Individual environment 20%

Sullivan & Kendler
Nicotine Tobacco Res.
1999;1:S51-S57
Smoking GWAS, 2 cohort studies

Prostate, Lung, Colon Ovary
2,289 male, Caucasian

Nurses Health Professional Study (NHS)
2,282 female, Caucasian

Illumina HumanHap 550K

2 loci are prominent...

Nicotinic receptor
Evidence: very strong

Dopamine pathway
Evidence: requires confirmation

Varenicline (Chantix)
Buproprion

Caporaso et al, 2009
Lung cancer rate drops after smoking cessation but...

...currently most lung cancer in the United States is diagnosed in former smokers!!!
### Lung Cancer GWAS

<table>
<thead>
<tr>
<th>Study/Sample</th>
<th>N. SUBJECTS</th>
<th>LOC</th>
<th>DESIGN</th>
<th>CHIP</th>
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<tbody>
<tr>
<td><strong>NCI Studies</strong></td>
<td></td>
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<tr>
<td>EAGLE</td>
<td>1,920</td>
<td>Italy</td>
<td>Pop c/c</td>
<td>550</td>
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<tr>
<td>ATBC</td>
<td>1,732</td>
<td>Finland</td>
<td>Cohort</td>
<td>610/550</td>
</tr>
<tr>
<td>PLCO</td>
<td>1,390</td>
<td>USA</td>
<td>Cohort</td>
<td>550/610/317+240S</td>
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<tr>
<td>CPS-II</td>
<td>697</td>
<td>USA</td>
<td>Cohort</td>
<td>610/1M/550</td>
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<tr>
<td><strong>NCI TOTAL</strong></td>
<td><strong>5,739</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Meta-analysis</strong></td>
<td></td>
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<td></td>
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<tr>
<td>UK</td>
<td>1,987</td>
<td>ICR Sut</td>
<td>Hosp cases</td>
<td>550</td>
</tr>
<tr>
<td>Central Europe</td>
<td>1,837</td>
<td>East Eur</td>
<td>MC c/c</td>
<td>300-370duo</td>
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<tr>
<td>Texas</td>
<td>1,154</td>
<td>USA</td>
<td>Hosp c/c</td>
<td>317</td>
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<tr>
<td>Iceland</td>
<td>719</td>
<td>Iceland</td>
<td>Pop c/c</td>
<td>550</td>
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<tr>
<td>HCF Germany</td>
<td>506</td>
<td>Germany</td>
<td>Pop c/c, age&lt;50</td>
<td>550</td>
</tr>
<tr>
<td>CARET</td>
<td>397</td>
<td>USA</td>
<td>Clin Trial</td>
<td>370duo</td>
</tr>
<tr>
<td>HUNT2/Tromso</td>
<td>394</td>
<td>Norway</td>
<td>Hosp c/c</td>
<td>370duo</td>
</tr>
<tr>
<td>Canada</td>
<td>332</td>
<td>Toronto</td>
<td>c/c</td>
<td>317</td>
</tr>
<tr>
<td>France</td>
<td>135</td>
<td>Paris+</td>
<td>Hosp c/c</td>
<td>317</td>
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<tr>
<td>Estonia</td>
<td>109</td>
<td>Estonia</td>
<td>hosp c/c</td>
<td>317/370duo</td>
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<td><strong>META TOTAL</strong></td>
<td><strong>7,561</strong></td>
<td></td>
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<tr>
<td><strong>GRAND TOTAL</strong></td>
<td><strong>13,300</strong></td>
<td></td>
<td></td>
<td><strong>19,666</strong></td>
</tr>
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</table>
Lung and Smoking GWAS to date

- Three implicated loci on chromosome 5, 6 and 15.
- Chr15q25 (nicotinic receptor) implicated in smoking

**Selected variants:**

<table>
<thead>
<tr>
<th>Chr15q25</th>
<th>CHRNA5</th>
<th>Caucasian</th>
<th>Asian</th>
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<td>Loc123688</td>
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<td>CHRNA3</td>
<td>rs12914385</td>
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<tr>
<td>CHRNA3</td>
<td>rs1317286</td>
<td>x</td>
<td>x</td>
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<td>Loc123688</td>
<td>rs931794</td>
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<table>
<thead>
<tr>
<th>chr5p15</th>
<th>TERT</th>
<th>Caucasian</th>
<th>Asian</th>
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<tr>
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<td>x</td>
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<tr>
<td>CLPTM1L</td>
<td>rs2736100</td>
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<table>
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<th>Asian</th>
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<td>rs2256543</td>
<td>rs4324798</td>
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</table>
A personal journey in the NCI intramural program....

Goal to identify hereditary component of lung cancer

3 lines of evidence available in the late 1980’s

- Family History
- Pedigrees
- Pharmacogenetics

Lung Cancer
~OR=2
Tokuhata and Lilienfeld 1963
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- Pedigrees
- Pharmacogenetics

- Lung Cancer
  - OR=2
  - Tokuhata and Lilienfeld 1963

Linkage studies
- Bailey-Wilson et al, 2004

Pharmacogenomics
- Caporaso et al, 2008
Sustained effort in the intramural program over time led to breakthroughs......

80’s     90’s     00     KEY ADVANCES

case-control studies

80’s 90’s 00

PLCO

EAGLE

molecular epidemiology
larger studies
integrative epidemiology
technology
consortia efforts
Priorities from Population Perspective:

1. Genomics of Lung Cancer/Smoking

2. Genomics of Outcome

3. Key subgroup: African Americans

4. Key subgroup: Non-smokers