Lung Cancer Without Cigarettes

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Objectives:
- Review cigarette causes of lung cancer
- Discuss potential for genetic predisposition
- Discuss and review Radon
FIGURE 1. Annual adult per capita cigarette consumption and major smoking and health events — United States, 1900–1998

USA Cancer Death Rates

## Lung Cancer Risk

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Single most important causal determinant of individual and population risk, most valuable indicator of clinical risk</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Active smoking of cigarettes and other tobacco products: Individual risk increases with greater number of cigarettes smoked per day and greater number of years of smoking. Population risk increases with the prevalence of current smokers because population prevalence predicts lung cancer occurrence with a latency period of about 20 y.</td>
</tr>
<tr>
<td><strong>B. Other risk factors causally associated with lung cancer</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Secondhand smoke exposure  Ionizing radiation, including radon  Occupational exposures, eg, arsenic, chromium, nickel, asbestos, tar, and soot  Indoor and outdoor air pollution</td>
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<tr>
<td><strong>C. Additional clinical risk indicators</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>The risk factors noted above, plus:  Older age  Male sex, particularly among those of African American ancestry  Family history of lung cancer  Acquired lung disease, eg, COPD, TB, pneumoconioses, idiopathic pulmonary fibrosis, and systemic sclerosis  Occupational exposures, such as to silica dust  HIV infection</td>
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<tr>
<td><strong>D. Examples of associations with consistent evidence but causal role not presently established</strong></td>
<td>Fruit and vegetable intake (decreased risk)  Physical activity (decreased risk)  Marijuana smoking (not associated with risk)</td>
</tr>
</tbody>
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<sup>a</sup> Single most important causal determinant of individual and population risk, most valuable indicator of clinical risk.

<sup>b</sup> Other risk factors causally associated with lung cancer.

<sup>c</sup> Additional clinical risk indicators.
Radon

- January 13, 2005, Dr. Richard H. Carmona, the U.S. Surgeon General, issued a national health advisory on radon.
- Radon affects smokers and not-smokers
- #2 cause of lung cancer
Radon is Radiation

• Radon222 – colorless, odorless radioactive gas
  – Present in Soil, Rock and ground water
    • Uranium -238 decay chain
      – Ur-234, thorium-230, radium-226 (long T ½)
  – Geography
  – Collects in closed spaces/atmosphere dispersed
  – Half-life = 3.8 days (α particle decay)

• IARC (International Agency for Research on Cancer) Group 1 Carcinogen
Radon

- Ubiquitous, natural occurring radioactive gas
- House acts as a sump (heat, Bernouli, fans)
Radon Effects

Alpha Decay
- Ionizing form of particle radiation
- Kinetic energy of about 5 MeV
- Low Penetration depth
  - Blunted by a few cm of air or skin

USA: Lung Cancer
20,000 deaths/year
Radon Paths
Units of Radon

- Outdoors = 0.4 pCi/L
- Average house = 1.3 pCi/L
- 4 pCi/L increases lung cancer by 50%
Geographic Variation

EPA Map of Radon Zones

Zone 1   >4 pCi/L
Zone 2   2-4 pCi/L
Zone 3   <4 pCi/L

Legend
- Zone 1
- Zone 2
- Zone 3

Zone designation for Puerto Rico is under development.

The purpose of this map is to assist National, State, and local organizations to target their resources and to implement radon-resistant building codes. This map is not intended to be used to determine if a home in a given zone should be tested for radon. Homes with elevated levels

epa.gov/iaq/radon/2003
Radon Exposure

- Basements
- Ventilation
- Time spent (Bedrooms)
  - Age of subject
- Inversion?
- January is Radon Awareness Month
What can you do about it?
Radon Test Kits

Utah testing: 900 in 2005, 4000 in 2011
Mitigation

How Sub-slab Depressurization Works in a Home

- Suction created by fan draws radon from beneath the concrete slab and safely vents radon outdoors
- Most common type of radon mitigation system
Radiation and Cancer
Radon Occupational Studies

**BEIR VI** (Biologic Effects of Ionizing Radiation)

- 11 studies of miners and lung cancer
  - 68,000 miners, 1.2 million person-years
  - 2700 cancer deaths
- Lung cancer proportional to radon exposure
  - Cigarette smoking interaction
  - Subset @ EPA level = 4 pCi/l - same result

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Radon Residential Studies

22 case control studies
- China (2), Europe (13), North America (7)
19/22 increase lung cancer risk at 2.7pCi/l
- China 1.13, EU 1.08, No America 1.11

If effect is seen at 2.7, then risk is underestimated!

Radon and Lung Cancer Risk

- BEIR 18,600 excess deaths/year
- EPA 21,100 (13.4%) deaths
  - @ 4 pCi/l for lifetime
    - 2.3% risk lung cancer for US population
    - 0.73% for never smoker
    - 4.1% for >100 cigarettes lifetime

- No safe level of radiation

Radon Rat Model of Lung Cancer

1574 rats exposed to radon through rebreathing system.
WLM (working level months)

Epigenetic Carcinogenesis

- CDKN2A + MGMT promoter methylation in Chinese miners
- CDKN2A gene affected by DNA losses in radon-induced lung tumors in rats

Su S, Aberrant promoter methylation of p16(INK4a) and O(6)-methylguanine-DNA methyltransferase genes in workers at a chinese uranium mine. J Occup Health 2006, 48(4):261–266.

Histogram of States and Percent Smokers 2001

Utah 2007: 11.7%
CDC Website
Radon

- Radon advocacy
  - SCR011, radon awareness, Radio, internet, youtube, facebook, TV this year?
- #2 cause of lung cancer
- Despite low smoking prevalence, lung cancer remains #1 cause of cancer mortality
- Radiation is an alkylator
  - All histology, all genotypes
Personalized Oncology

NSCLC

Histology
- Squamous
- Small Cell

Molecular
- EGFR ALK
- Other actionable
- No Actionable Gene defined

Same diagnosis
Same treatment
Over 50% of NSCLC have an Identifiable Driver Mutation

Sequist et al, Ann Oncol 2011; Kris et al, ASCO 2011
EGFR Mutations
Not all created equal

Adapted from Sharma SV et al, Nat Rev Cancer.7:169-81, 2007
T790M at initial therapy

De Novo resistance (38%, 10 of 2)
Acquired resistance 60% - requires rebiopsy

SARMS: Scorpion Amplification Refractory Mutation System
plus: EpCam microfluidic CTC chip

Afatinib vs Pem-Cis in EGFR (+)
Lux Lung 3

HER 1,2,4, dimers, T790M inhibitor
N=345, 75% Asian
PFS 11.1 v 6.9 m HR = 0.58
Ex19/21 13.6 6.9 m HR=0.47

Sequist, et al. JCO, 2013
### Third Generation (mutant specific) EGFR TKIs

- A (relatively) new class of drugs irreversibly inhibits mutant EGFR, in particular EGFR T790M, with much less activity against wild-type EGFR.
- Effective in preclinical tumor models with both EGFR-TKI-sensitizing and T790M resistance mutations.
- References: Cross, D Cancer Discovery 2014; Tjin Tham Sjin R Molecular Cancer Therapeutics 2014,

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Reversible/Irreversible</th>
<th>Company</th>
</tr>
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<tbody>
<tr>
<td>AP26113</td>
<td>EGFR/ALK</td>
<td>Reversible</td>
<td>Ariad</td>
</tr>
<tr>
<td>CO-1686</td>
<td>Mutant EGFR</td>
<td>Irreversible</td>
<td>Clovis</td>
</tr>
<tr>
<td>AZD9291</td>
<td>Mutant EGFR</td>
<td>Irreversible</td>
<td>Astra Zeneca</td>
</tr>
<tr>
<td>EGF816</td>
<td>Mutant EGFR</td>
<td>Irreversible</td>
<td>Novartis</td>
</tr>
<tr>
<td>ASP8273</td>
<td>Mutant EGFR</td>
<td>Irreversible</td>
<td>Astellas</td>
</tr>
</tbody>
</table>

Ref: Yu, Riely, and Lovly Clinical Cancer Research in press

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<thead>
<tr>
<th></th>
<th>WT</th>
<th>Sensitivity (^{(18,19,21)})</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{st})</td>
<td>X</td>
<td>X</td>
<td>0</td>
</tr>
<tr>
<td>2(^{nd})</td>
<td>X</td>
<td>X</td>
<td>?</td>
</tr>
<tr>
<td>3(^{rd})</td>
<td>0</td>
<td>X</td>
<td>X</td>
</tr>
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</table>

Inhibition of WT = Rash, GI
Rocelitinib in T790 +/-

RR = 59%,
PFS= 13.1 m

Hyperglycemia: 38% on hypoglycemic IGF-1R blocked by metabolite

AZD9291 in T790 +/-

RR = 61%,  
PFS = 9.6 m

RR = 21%,  
PFS = 2.8 m

N=253

Osimertinib approved November 15, 2015

EGFRI Retreatment- retrospective

• N=11,
• All prior responders or stable
  – Asian, 3 muts (8 unknown), age 55, 7 never,
  – 8 female, 1\textsuperscript{st} PFS=8.5m
• 2\textsuperscript{nd} EGFRI (3 gefitinib, 8 erlotinib)
  – 1 PR, 7 SD (on tx 4 m); DCR=73%
  – Survival from 2\textsuperscript{nd} =6 (.9-24.6m)
• Control (9 similar except no 2\textsuperscript{nd})
  – OS= 21 vs 12.5

Watanabe et al. BMC Cancer 11:1, 2011
Summary

- NSCLC is no longer an adequate diagnosis
- EGFR and ALK testing in all lung cancer
  - ROS1, RET, BRAF, HER-2, MET-amplified
  - T790M
- Rapidly evolving (new + repurposed)
  - Rebiopsy in EGFR (histology, resistance)
- PD-1/PD-L1 changing Landscape
  - Next wave - Combination Immune Tx