CARCINOGENICITY OF AIR POLLUTION

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Disclosures

• Dr. Kipen consults for attorneys regarding asbestos personal injury claims
Outline

• Air Pollution and its burden and effects
• Classification of carcinogens
• Causation
• Lung cancer causation
• What can be done?
“In 2010, household air pollution from solid fuels and outdoor air pollution was responsible for 3.5 and 3.3 million premature deaths respectively, worldwide.”

Premature deaths attributable to outdoor air pollution –

“China: 1.2 million, India: 0.6 million, and US 0.1 million”

- GBD Project findings
PM$_{2.5}$ at the US Embassy Grounds in Beijing: AIRPOCALYPSE
On 10/23/2013 PM$_{2.5}$ reached 1000 µg / m$^3$ in Harbin, Northeast China. Neither the Church, nor Mao were able to resist being obscured.
Beijing’s air pollution spikes to frightening levels as Paris climate talks begin

Published: Nov 30, 2015 2:27 p.m. ET

Smog engulfs Tiananmen Square on Sunday.
Xi’an Airport, Dec 1, 2015
Particulate air pollution

Criteria Air Pollutants

Criteria Pollutants

- Particulate Matter ($\text{PM}_{10}$ and $\text{PM}_{2.5}$)
- Sulfur Dioxide ($\text{SO}_2$)
- Carbon Monoxide ($\text{CO}$)
- Nitrogen Dioxide ($\text{NO}_2$)
- Ozone ($\text{O}_3$)
- Lead ($\text{Pb}$)

Hazardous Air Pollutants (189)
Burden of Air Pollution

• 2015 WHO Air Quality Guidelines: PM$_{2.5}$ 10 mcg/m$^3$

• 2013: US NAAQS: PM$_{2.5}$ 12 mcg/m$^3$

• 2014 92% of World Population in excess

• 2012 3 Million deaths/year attributed to AMBIENT POLLUTION
  • 88% SE Asia and Western Pacific

Chinese Indoor Standard for Healthy Buildings: 35 mcg/m$^3$
Burden of disease attributable to 20 leading risk factors in 2010, expressed as a percentage of global disability-adjusted life years, both sexes
Cardiovascular & Respiratory Outcomes Linked to Air Pollution: epidemiological data

- Heart Attack (Acute Myocardial Infarction)
- Heart Failure (Chronic Congestive Failure)
- Stroke
- Heart Rhythm Disturbances
- Atherosclerosis (Cholesterol Plaques)
- Asthma Incidence & Exacerbation
- COPD Exacerbation
- Lung Cancer
- Reproductive, Metabolic, & Psychiatric conditions
- MORTALITY
- RESPIRATORY, ASCVD, DIABETES, OBESITY HYPOTHESESIZED TO BE SUSCEPTIBLES

Thurston, Kipen et al, ERJ, 2017
Cancer is due to genetic (and epigenetic) interactions with environmental factors

Hamra, GB, et al., EHO, 2014
<table>
<thead>
<tr>
<th>SITE</th>
<th>JAPAN</th>
<th>MIGRANTS BORN JAPAN</th>
<th>MIGRANTS BORN U.S.</th>
<th>U.S. WHITES</th>
</tr>
</thead>
<tbody>
<tr>
<td>STOMACH</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>LARGE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INTESTINE</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>BREAST</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>PROSTATE</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

CANCER CHANGES IN MIGRANTS
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blacks</td>
<td>Whites</td>
</tr>
<tr>
<td>Male Colon</td>
<td>34</td>
<td>349</td>
</tr>
<tr>
<td>Male Liver</td>
<td>272</td>
<td>67</td>
</tr>
<tr>
<td>Male Pancreas</td>
<td>55</td>
<td>200</td>
</tr>
<tr>
<td>Male Lung</td>
<td>27</td>
<td>1546</td>
</tr>
<tr>
<td>Prostate</td>
<td>134</td>
<td>724</td>
</tr>
<tr>
<td>Female Breast</td>
<td>337</td>
<td>1268</td>
</tr>
<tr>
<td>Uterine Cervix</td>
<td>559</td>
<td>507</td>
</tr>
<tr>
<td>Uterine Body</td>
<td>42</td>
<td>235</td>
</tr>
<tr>
<td>Male Lymphosarcoma</td>
<td>133</td>
<td>10</td>
</tr>
</tbody>
</table>

Comparison of cancer incidence rates for Ibadan, Nigeria and blacks and whites in the San Francisco Bay area. (modified Doll and Peto)
### Leading Sites of New Cancer Cases and Deaths – 2015 Estimates

**Estimated New Cases**

<table>
<thead>
<tr>
<th>Male</th>
<th>Estimated New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>220,800 (26%)</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>115,610 (14%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>69,090 (8%)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>56,320 (7%)</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>42,670 (5%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>39,850 (5%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>38,270 (5%)</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>32,670 (4%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>30,900 (4%)</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>25,510 (3%)</td>
</tr>
<tr>
<td>All sites</td>
<td>848,200 (100%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Female</th>
<th>Estimated New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>231,840 (29%)</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>105,590 (13%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>63,610 (8%)</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>54,870 (7%)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>47,230 (6%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>32,000 (4%)</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>31,200 (4%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>24,120 (3%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>23,370 (3%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>23,290 (3%)</td>
</tr>
<tr>
<td>All sites</td>
<td>810,170 (100%)</td>
</tr>
</tbody>
</table>

**Estimated Deaths**

<table>
<thead>
<tr>
<th>Male</th>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>86,380 (28%)</td>
</tr>
<tr>
<td>Prostate</td>
<td>27,540 (9%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>26,100 (8%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>20,710 (7%)</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>17,030 (5%)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>11,510 (4%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,480 (4%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>9,070 (3%)</td>
</tr>
<tr>
<td>All sites</td>
<td>312,150 (100%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Female</th>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>71,660 (26%)</td>
</tr>
<tr>
<td>Breast</td>
<td>40,290 (15%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>23,600 (9%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>19,850 (7%)</td>
</tr>
<tr>
<td>Ovary</td>
<td>14,180 (5%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>10,240 (4%)</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>10,170 (4%)</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>7,520 (3%)</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>6,380 (2%)</td>
</tr>
<tr>
<td>All sites</td>
<td>277,280 (100%)</td>
</tr>
</tbody>
</table>

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.*

Annual Lung cancer incidence: 0.1%
Cancer Burden and Prevention in the U.S. today – The good

- Mortality from all cancer and from the 4 leading cancer sites is declining

*Per 100,000, age adjusted to the 2000 US standard population.*
DEFINING A CAUSE OF A DISEASE

A cause of a disease is an event, condition, or characteristic that preceded the disease event and without which the disease event would not have occurred at all or would not have occurred until some later time.

Concepts of Causality

• Single cause
• Multifactorial
  • Cancer, like all diseases, is cause by complex cascade of events
• Natural history of cancer - multistep cascading process
  • Initiation: Genetic alteration a single cell
  • Promotion: Proliferation and expansion of that cell’s descendents
  • Progression: Stepwise transformation to a neoplasm
• Can a single cause be identified for any one cancer?
  • Everyone who smokes does not get lung cancer
  • People who have never smoked sometimes get lung cancer
How do we infer causality?

• Epidemiological studies are designed to:
  • Ask: Is there an association that exists between an exposure and outcome?
  • Quantitatively express excess risk of outcome for an exposure
    • Measures of association – e.g.: RR, OR

• But is the observed excess risk of outcome caused by the exposure?

• What process(es) do we use to assess and weigh the evidence?
Bradford Hill Guidelines for Causation

1. Temporality
2. Strength (magnitude) of the association
3. Dose-response (biological gradient)
4. Reversibility (cessation of exposure)
5. Consistency with other knowledge
6. Biological plausibility
7. Specificity of the association
8. Analogy
9. Coherence

Bradford Hill Guidelines

• Considerations – NOT a checklist or criteria
• The more aspects fulfilled—the stronger the case for
  E → D
• Weigh the evidence:
  • Key components are challenging in some study designs
    (e.g. Temporality and cross-sectional studies)
  • Others are less relevant for some considerations
    (e.g. Specificity with exposures that cause multiple diseases)
Summarizing the Evidence for Causes of Cancer

Quantitative Summaries
• Meta-analysis
• Pooled Analysis

Qualitative Summaries
• In-depth literature reviews
  • Conducted by experts in the field
  • Use a predetermined scoring system
• For cancer:
  • U.S. National Toxics Program (NTP)
  • U.S. Environmental Protection Agency (EPA)
  • International Agency for Research on Cancer (IARC)
Systematic Reviews: IARC
International Agency for Research on Cancer (also National Toxicology Program and EPA)

• The cancer agency of the World Health Organization
  • Initiated in 1971
  • International expert working groups evaluate the evidence of the carcinogenicity of specific exposures
    • Published in IARC Monographs

• Evaluation of evidence of carcinogenicity
  • Human studies
    • Sufficient, limited, inadequate, suggesting lack of carcinogenicity, no data
  • Animal carcinogenicity studies
    • Sufficient, limited, inadequate, suggesting lack of carcinogenicity, no data
  • Mechanistic data
    • Case-by-case contribution to overall evaluation

http://monographs.iarc.fr/ENG/Monographs/vol89/mono89-4.pdf
# IARC Classification System

<table>
<thead>
<tr>
<th>Group</th>
<th># of Agents</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Known</td>
<td>111</td>
<td>Benzene; Kaposi sarcoma; herpes virus; Chinese-style salted fish; Tobacco; benzene; vinyl chloride; arsenic; asbestos; medications</td>
</tr>
<tr>
<td>2A: Probable</td>
<td>66</td>
<td>Inorganic lead compounds; Shiftwork with circadian disruption;</td>
</tr>
<tr>
<td>2B: Possible</td>
<td>285</td>
<td>Carbon tetrachloride; Dry cleaning (occupational)</td>
</tr>
<tr>
<td>3: Insufficient</td>
<td>505</td>
<td>Caffeine ; Chlorinated drinking-water; Leather goods manufacture</td>
</tr>
<tr>
<td>4: Not</td>
<td>1</td>
<td>Caprolactam (used in the production of nylon)</td>
</tr>
</tbody>
</table>
IARC Group 1 Lung Carcinogens

Metals and others:

• Arsenic and inorganic arsenic compounds
• Beryllium and beryllium compounds
• Cadmium and cadmium compounds
• Chromium (VI) compounds
• Nickel compounds
• Halo Ethers
IARC Group 1 Lung Carcinogens (cont’d)

Dusts and particles:

• Asbestos (all 6 types)
• Silica dust (quartz or crystobalite)
• Outdoor air pollution
• Environmental tobacco smoke
• Diesel engine exhaust
• Welding fumes
Radiation:

• Ionizing radiation

• Radon
IARC Group 1 Lung Carcinogens (cont’d)

Occupations and manufacturing processes:

- Painter
- Coal gasification
- Coke production
- Iron and steel founding
- Aluminum production
- Rubber production industry
- Soot (chimney sweeps)
- Coal tar pitch
Principles of occupational cancer etiology

1. Dose response
2. No safe threshold
3. Latency
4. Interaction
Summary: What Causes Cancer?

Challenges:

• For many cancers, contribution of specific risk factors are unknown
• For cancers where general ‘cause’, is understood, individual susceptibility is poorly understood
• For most cancers, how genes and environment work in concert is poorly understood
• Some potential causes are poorly studied
• Rare occurrence (small numbers) of some cancers makes them challenging to study
Most Common Risk Factors for Cancer

- Older age
- Tobacco use/exposure
  - Tobacco product use, second hand smoke
- Radiation
  - Ultraviolet: natural/artificial
  - Ionizing radiation: radon; diagnostic imaging
- Oncogenic viruses and bacteria
  - Viruses: HBV, HPV, HIV, HTLV-I, HHV8
  - Bacteria: Helicobacter pylori
- Certain hormones
  - Hormone replacement therapy
- Family history of cancer
  - Usually gene environment interactions
- Diet and exercise
  - Diet low in fruits and vegetables
  - Lack of physical activity
  - Excess alcohol
- Overweight/obese
- Chemicals and other substances
  - Occupations
    - Painters, construction workers, chemical industry workers, miners
  - Occupational exposures
    - Asbestos, solvents, vinyl chloride, chromium VI, respirable silica

Epidermoid (Squamous Cell) Type

Low power (H and E): nests of tumor cells separated by fibrous bands. Keratin (horn) pearls present.

High power: nuclear pleomorphism and individual cell keratinization (pink).

Tumor typically located near hilus, projecting into bronchi.

Bronchoscopic view

Cytologic smear from sputum or bronchoscopic scraping. Cells with dark nuclei and cytoplasm strongly pink because of keratin.
What is the evidence for the relationship between air pollution and lung cancer?
Estimated attributable deaths by cancer site for IARC Group 1 carcinogenic agents and occupations, Britain, 2005

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>ICD-10 code</th>
<th>No. of Deaths (95% CI)</th>
<th>% of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>C33-C34</td>
<td>3,946 (3472,4346)</td>
<td>65.9</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>C45</td>
<td>1,937 (1898,1976)</td>
<td>32.4</td>
</tr>
<tr>
<td>Bladder</td>
<td>C67</td>
<td>34 (29, 130)</td>
<td>0.57</td>
</tr>
<tr>
<td>NMSC*</td>
<td>C44</td>
<td>23 (4, 50)</td>
<td>0.38</td>
</tr>
<tr>
<td>Sinonasal</td>
<td>C30-C31</td>
<td>20 (11, 34)</td>
<td>0.33</td>
</tr>
<tr>
<td>Other</td>
<td>-</td>
<td>24</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>5986 (5415, 6612)</td>
<td>100</td>
</tr>
</tbody>
</table>

*Non-melanoma skin cancer

Table 2. Adjusted Mortality Relative Risk (RR) Associated With a 10-µg/m³ Change in Fine Particles Measuring Less Than 2.5 µm in Diameter

<table>
<thead>
<tr>
<th>Cause of Mortality</th>
<th>1979-1983</th>
<th>1999-2000</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause</td>
<td>1.04 (1.01-1.08)</td>
<td>1.06 (1.02-1.10)</td>
<td>1.06 (1.02-1.11)</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>1.06 (1.02-1.10)</td>
<td>1.08 (1.02-1.14)</td>
<td>1.09 (1.03-1.16)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1.08 (1.01-1.16)</td>
<td>1.13 (1.04-1.22)</td>
<td>1.14 (1.04-1.23)</td>
</tr>
<tr>
<td>All other causes</td>
<td>1.01 (0.97-1.05)</td>
<td>1.01 (0.97-1.06)</td>
<td>1.01 (0.95-1.06)</td>
</tr>
</tbody>
</table>

* Estimated and adjusted based on the baseline random-effects Cox proportional hazards model, controlling for age, sex, race, smoking, education, marital status, body mass, alcohol consumption, occupational exposure, and diet. CI indicates confidence interval.

Figure 3. Mortality Relative Risk (RR) Ratio Associated With 10-µg/m³ Differences of PM₂.₅ Concentrations

CPS II CHRONIC

Pope et al., JAMA 2002 287(9): 1132-1141
Figure 1. Fully adjusted hazard ratios (95% confidence interval) for lung cancer mortality in relation to categoric indicators of mean ambient fine particulate matter (PM$_{2.5}$) (1999–2000) concentrations, follow-up 1982–2008, never-smokers, Cancer Prevention Study–II (CPS-II) cohort, United States. The cutpoints between exposure categories were based on the 25th (11.8 µg/m$^3$), 50th (14.3 µg/m$^3$), 75th (16 µg/m$^3$), and 90th (17.9 µg/m$^3$) percentiles. The reference category was less than 11.8 µg/m$^3$. Fully adjusted hazard ratios (95% confidence interval) were plotted at the category midpoint.

DOSE-RESPONSE

Turner et al., 2011 Am J Respir Crit Care Med 184(12): 1374-1381
### Lung Cancer Risk per 10ug PM2.5

#### Study by region

<table>
<thead>
<tr>
<th>Study by region</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>North America</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McDonell et al. 2000</td>
<td>1.39 (0.79, 2.46)</td>
<td>0.66</td>
</tr>
<tr>
<td>Krewski et al. 2009</td>
<td>1.09 (1.05, 1.13)</td>
<td>21.19</td>
</tr>
<tr>
<td>Hart et al. 2011</td>
<td>1.18 (0.95, 1.48)</td>
<td>3.77</td>
</tr>
<tr>
<td>Lipsett et al. 2011</td>
<td>0.95 (0.70, 1.28)</td>
<td>2.22</td>
</tr>
<tr>
<td>Lepeule et al. 2012</td>
<td>1.37 (1.07, 1.75)</td>
<td>3.20</td>
</tr>
<tr>
<td>Hystad et al. 2013</td>
<td>1.29 (0.95, 1.76)</td>
<td>2.14</td>
</tr>
<tr>
<td>Jerrett et al. 2013 (^a)</td>
<td>1.12 (0.91, 1.37)</td>
<td>—</td>
</tr>
<tr>
<td>Puett et al. 2014</td>
<td>1.06 (0.90, 1.24)</td>
<td>6.48</td>
</tr>
<tr>
<td><strong>Subtotal (I^2 = 0.0%, p = 0.490)</strong></td>
<td>1.11 (1.05, 1.16)</td>
<td>39.67</td>
</tr>
<tr>
<td><strong>Europe</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beelen et al. 2008</td>
<td>0.81 (0.63, 1.04)</td>
<td>3.11</td>
</tr>
<tr>
<td>Carey et al. 2013</td>
<td>1.11 (0.86, 1.43)</td>
<td>3.07</td>
</tr>
<tr>
<td>Cesaroni et al. 2013</td>
<td>1.05 (1.01, 1.10)</td>
<td>20.21</td>
</tr>
<tr>
<td>Raaschou-Nielsen et al. 2013</td>
<td>1.39 (0.91, 2.13)</td>
<td>1.17</td>
</tr>
<tr>
<td><strong>Subtotal (I^2 = 50.0%, p = 0.112)</strong></td>
<td>1.03 (0.89, 1.20)</td>
<td>27.56</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cao et al. 2011</td>
<td>1.03 (1.00, 1.07)</td>
<td>21.25</td>
</tr>
<tr>
<td>Katanoda et al. 2011</td>
<td>1.24 (1.12, 1.37)</td>
<td>11.52</td>
</tr>
<tr>
<td><strong>Subtotal (I^2 = 91.0%, p = 0.001)</strong></td>
<td>1.13 (0.94, 1.34)</td>
<td>32.77</td>
</tr>
<tr>
<td><strong>Overall (I^2 = 53.0%, p = 0.010)</strong></td>
<td>1.09 (1.04, 1.14)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Table 2. Estimates for the relationship between a 10-μg/m³ change in PM$_{2.5}$ exposure and lung cancer risk.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>RR (95% CI)</th>
<th>$I^2$ (p-value)</th>
<th>Homogeneity test$^a$</th>
<th>Studies included (by ID)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM$_{2.5}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full meta-estimate</td>
<td>1.09 (1.04, 1.14)</td>
<td>56.4% (0.007)</td>
<td></td>
<td>All</td>
</tr>
<tr>
<td>Continent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>1.11 (1.05, 1.16)</td>
<td>6.5% (0.378)</td>
<td></td>
<td>2, 4, 6, 7, 8, 9, 10</td>
</tr>
<tr>
<td>Europe</td>
<td>1.03 (0.89, 1.20)</td>
<td>50.0% (0.112)</td>
<td></td>
<td>11, 12, 13, 15</td>
</tr>
<tr>
<td>Others</td>
<td>1.13 (0.94, 1.34)</td>
<td>91.0% (0.001)</td>
<td>$p = 0.656$</td>
<td>16, 17</td>
</tr>
<tr>
<td>Exposure assessment method</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed site monitor</td>
<td>1.12 (1.04, 1.21)</td>
<td>77.1% (0.002)</td>
<td></td>
<td>2, 4, 8, 16, 17</td>
</tr>
<tr>
<td>Other</td>
<td>1.06 (1.00, 1.13)</td>
<td>16.2% (0.298)</td>
<td>$p = 0.268$</td>
<td>5, 6, 7, 9, 10, 11, 12, 13, 15</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.18 (1.00, 1.39)</td>
<td>0.0% (0.928)</td>
<td></td>
<td>3, 7, 8, 9, 10, 15</td>
</tr>
<tr>
<td>Former</td>
<td>1.44 (1.04, 2.01)</td>
<td>66.3% (0.031)</td>
<td></td>
<td>3, 8, 9, 15</td>
</tr>
<tr>
<td>Current</td>
<td>1.06 (0.97, 1.15)</td>
<td>0.0% (0.544)</td>
<td>$p = 0.197$</td>
<td>3, 8, 9, 15</td>
</tr>
<tr>
<td>Confounder adjustment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td>1.10 (1.04, 1.17)</td>
<td>61.4% (0.004)</td>
<td></td>
<td>2, 4, 7, 8, 9, 10, 11, 12, 15, 16, 17</td>
</tr>
<tr>
<td>SES/income</td>
<td>1.04 (0.96, 1.12)</td>
<td>24.2% (0.252)</td>
<td></td>
<td>5, 7, 10, 11, 13, 15</td>
</tr>
<tr>
<td>Education</td>
<td>1.07 (1.03, 1.11)</td>
<td>37.7% (0.117)</td>
<td></td>
<td>4, 8, 9, 10, 12, 13, 15, 16,</td>
</tr>
<tr>
<td>Occupation</td>
<td>1.08 (1.05, 1.11)</td>
<td>0.4% (0.420)</td>
<td></td>
<td>4, 6, 7, 9, 10, 13, 15</td>
</tr>
</tbody>
</table>
Bradford-Hill Guidelines

3. Dose-Response

• Definition: The disease rates increase with increases in exposure
  • Presence of a dose-response relationship is strong evidence in support of a causal relationship

**Residential radon and lung cancer**

• N. American and European pooled studies showed clear linear dose-response relationship
• No evidence of a threshold effect
Figure 1. Adjusted RRs [with 95% confidence intervals (CIs)] of lung cancer mortality (A) and IHD, cardiovascular, and cardiopulmonary mortality (B) plotted over estimated daily exposure of PM2.5 (milligrams) and increments of cigarette smoking relative to never smokers (cigarettes/day). Diamonds represent comparative mortality risk estimates (with 95% CIs) for PM2.5 from air pollution from the comparative studies (Dockery et al. 1993; Laden et al. 2006; Miller et al. 2007; Pope et al. 1995, 2002, 2004). Stars represent comparable pooled RR estimates (with 95% CIs) associated with SHS exposure from comparative studies (Teo et al. 2006; U.S. Department of Health and Human Services 2006). The dotted lines represent the nonlinear power function fit through the origin and the estimates (including active smoking, SHS, ambient PM2.5). Estimated doses from different increments of active smoking are dramatically larger than estimated doses from ambient air pollution or SHS; therefore, associations at lower exposure levels (due to ambient air pollution and SHS) are shown as insets with a magnified scale.

Pope et al., EHP, 2011
Bradford-Hill Guidelines

Summary for the association between air pollution and lung cancer

1. Temporality: Yes: Only required component
2. Strength: Probably; Meta analysis desirable
3. Dose-response: Yes: Epidemiology and Rodent
4. Reversibility: No direct evidence although tobacco
5. Consistency: Yes: See meta analyses
6. Biological plausibility: Yes: Rodent and in vitro
7. Specificity: Probably: Also bladder cancer
8. Analogy: Yes: Occupational data
Prophylactic Drugs and Foods

• Oxidative stress, vascular dysfunction, coagulation are likely mechanisms

• Only Mediterranean diet proven to dec CV risk

• All antioxidant and vitamin supplements have failed in RCT’s

• Sulforaphane, statins, fish oil, nitrate-containing foods, aspirin all attractive and untested in terms of air pollution
WHAT CAN WE DO?
Air Cleaner – Honeywell HPA300
Charcoal and HEPA filter
Most effective strategy for managing air pollution is EMISSION CONTROL

- Primary Pollutants and Precursors of Secondary
- Largely a government job through regulation
- Acute Effects vs. Chronic
- Reductions in population exposures are beneficial
  - Mortality, Clinical outcomes
  - Physiologic indicators of risk (Inflammation, Coagulation, Oxidative Stress)

Few direct studies of benefit from Personal Interventions other than biomarkers
Stay Indoors & Limit Outdoor Infiltration

• Developed World: 90% indoors; 70% home
  • Air Exchange Rates determine I/O infiltration
  • Standard guidance from AQI’s (see later)
  • Pollutant infiltration affected by structure, indoor surface materials, air handlers, wind, nature of pollutant, and Window Closing (50% Decrease in infiltration)
Clean the Indoor Air

• In-duct filters dec I/O ratio of PM2.5 from
  • 0.57 (natural ventilation) to 0.35 (conventional in duct filtration)
  • to 0.1 (HEPA)
  • Estimated clinical event benefits have been published
• Portable HEPA (65% dec I/O)
• Costs: energy, noise, wear and tear on system
Conclusions For Air Cleaners

• Air cleaners are effective in reducing indoor pollutant levels
• Most studies did not report occupant behavior restrictions
• Significant reductions in biomarkers of CV risk are found with air filter use
• Interpretation is limited by lack of consistency for a given outcome
• Does this have implications for cancer risk?
DOES AIR POLLUTION CAUSE LUNG CANCER?

• Probably so

• Acute exposure to NJT air pollution causes a decrease in endothelial reactivity in healthy human adults.
Lung cancer mortality rate ratios by asbestos, asbestosis and smoking status, Insulators vs. CPS II

Lung Cancer Rate Ratio

Non-Smokers

Smokers

- A-
- All A
- A+ Asb-
- A+ Asb+

Non-Smokers

Smokers

A+

Asbestos

Asbestosis

Smoking Status

36.8 (30.1-45.0)

28.4 (23.4-34.4)

14.4 (10.7-19.4)

10.3 (8.8-12.2)

7.4 (4.0-13.7)

3.6 (1.7-7.6)

5.2 (3.2-8.5)

1.0

(3.2-8.5)
National Comprehensive Cancer Network (NCCN) recommendations for LDCT lung cancer screening

Criteria #1: ≥ 55 years old
   ≥ 30 pack-years smoking
   < 15 years since smoking cessation

Criteria #2: ≥ 50 years old
   ≥ 20 pack-years smoking
   1 other risk factor for lung cancer
Question 1

• Established risk factors for lung cancer:
  A. Radium Dial Painting
  B. SV40 virus
  C. Pleural plaques (as opposed to asbestos exposure)
  D. Indoor Air Pollution
  E. Arsenic in drinking water
Question 2

Identification of lung carcinogens relies on:

• A. an outdated list of considerations from a British statistician
• B. Epidemiology data
• C. Mechanistic understanding of how the agent acts
• D. B and C
• E. Understanding that cigarette smoking is necessary in addition to other carcinogens