The Smoking Battle

- Individual Freedom
- Profit
- Enjoyment
- Economic Factors
- Health Dangers
- Secondary Smoke
- Addiction
Uaxactun, Guatemala: A pottery vessel depicts a Mayan smoking a roll of tobacco leaves tied with a string.

Columbus discovers smoking.

Tobacco introduced to Europe.

European doctors recommend tobacco for toothache, migraine, worms, halitosis, lockjaw & cancer.

England. A publication (“Worke of Chimney Sweepers”) states that illness in chimney sweeps is caused by soot and that tobacco may have similar effects.
1614

1st cigarette: Beggars in Spain patch together tobacco from used cigars, and roll them in paper (papeletes).

1624

Pope threatens excommunication for snuff users; sneezing is thought too close to sexual ecstasy.

1632

Massachusetts: public smoking is forbidden.

1634

Russia: Czar Alexis creates penalties for smoking:
- 1st offense: whipping, a slit nose, & transportation to Siberia.
- 2nd offense: execution.

1724

Pope Benedict XIII learns to smoke & repeals smoking bans.
England. John Hill warns snuff users they are vulnerable to cancers of the nose. *Dr. Percival Pott* notes cancer of the scrotum in chimney sweeps & theorizes a connection between cancer and exposure to soot.

Matches are invented, making smoking more convenient.

England. A running debate on smoking in the Lancet. The argument runs as much along moral as medical lines, with little substantiation.

USA. The Civil War: Tobacco is given with rations by both North and South.
1864 1st American cigarette factory opens & produces almost 20 million cigarettes.

1912 First strong connection made between lung cancer and smoking. A monograph by Dr. I. Adler strongly suggests that lung cancer is related to smoking.

1914 US Lung cancer death rate is **0.6** per 100,000.

1917 WORLD WAR I. Virtually an entire generation returns from the war addicted to cigarettes.

1919 Medical student Alton Ochsner observes lung cancer surgery—something, he is told, he may never see again.
US Lung cancer death rate is 1.7 per 100,000

Statistician Frederick Hoffman finds "... no definite evidence that smoking ..." causes lung cancer.

US lung cancer death rate in males is 3.8 per 100,000.

Zippo lighter invented by George G. Blaisdell
1933 Chesterfield runs ads in the NY State Journal of Medicine with claims like, "Just as pure as the water you drink . . . and practically untouched by human hands."

1936 Alton Ochsner (17 yrs later) sees 8 cases of lung cancer in six months--all smokers who began in WW I.

1941 An article by Dr. Michael DeBakey cites a correlation between the increased sale of tobacco & the increasing prevalence of lung cancer.
As part of the war effort, Roosevelt makes tobacco a protected crop. Cigarettes are included in GI's C-Rations. Tobacco companies send millions of free cigarettes to GI's. By the end of the war, cigarette sales are at an all-time high.
Smoking is actually good for you! And there’s proof!

Camels Steady Your Nerves
Camels Boost Your Energy

WORN OUT... and then he smoked a Camel!

"DOG-TIRED" AFTER WORK... with a long evening ahead... and dinner time still an hour away! Just one of the many times during the day when you will want to light up a Camel—for recovering your flow of helpful energy. You'll like Camel—a smoothest blend of costlier tobaccos!

FIND...

Important Facts for Smokers Discovered by Science!

Let CAMELS increase your flow of ENERGY

Tired? Light a Camel. And as you enjoy its cool, pleasing fragrance, you feel a new flow of energy—a quick and delightful "energizing effect."

You've probably noticed this yourself and wondered how it happened. The "lift" you get from Camels is a release of your own natural energy... made easy and harmlessly available.

So when you're feeling "all in" try a Camel. That tired feeling slips away. Camels have helped your own body to help itself.

You can smoke just as many of these delightful Camels as you want. And you need never worry about your nerves. For Camel's costlier tobaccos never get on your nerves.

CAMELS Costlier Tobaccos never get on your Nerves

"Get a LIFT with a Camel!"
Smoking camels stimulates the natural flow of digestive fluids... increases alkalinity.
Camels Improve Your Disposition

For more pure pleasure... have a Camel

No other cigarette is so rich-tasting, yet so mild!
Doctors and Nurses Smoke
"I’m going to grow a hundred years old!"

"and possibly she may… the amazing strides of medical science have added years to life expectancy."

More Doctors Smoke Camels (and they’re smart!)
Give your throat a vacation.
Smoke a FRESH cigarette!!
All the Cool, Important People Smoke!

Steve McQueen smoked.

Fred & Wilma smoked.

Wanted Dead or Alive??

McQueen died from lung cancer...

but they didn’t die, which proves that smoking isn’t always bad for you.
"My cigarette is the MILD cigarette... that's why Chesterfield is my favorite"

Ronald Reagan

STARRING IN
"THE VOICE OF THE TURTLE"
A WARNER BROS. PRODUCTION

W. O. Crombie

Copyright 1940, American Tobacco Co.
A GIFT OF PLEASURE

My spirit—the spirit of Christmas-giving—is abroad in the land. A gift that expresses that spirit, and brings pleasure to every home, both great and small, is rare indeed. Such a gift, my friends, in LUCKY STRIKE.

Santa Claus

Luckies—a light smoke
OF RICH, RIPE-BODIED TOBACCO—"IT'S TOASTED"
Lung cancer has grown 5 times faster than other cancers since 1938; behind stomach cancer, it is now the most common form of the disease.

44-47% of all adult Americans smoke; over 50% of men, and about 33% of women.

Lung cancer death rate in white males is 31.0 in 100,000, resulting in 29,000 deaths.
Lung cancer has grown 5 times faster than other cancers since 1938; behind stomach cancer, it is now the most common form of the disease.

44-47% of all adult Americans smoke; over 50% of men, and about 33% of women

Lung cancer death rate in white males is 31.0 in 100,000, resulting in 29,000 deaths.

Several important epidemiological studies provide the first powerful links between smoking and lung cancer
It is 1950…

and you are witnessing an epidemic of lung cancer. Some people believe smoking is involved, but most believe it is due to industrialization, autos, and tarred roads.

Is there an association between smoking and lung cancer?

1) What sort of study would you do?

2) How would you do it?
Doll & Hill Case-Control Study

Setting: 20 participating hospitals in London (1948-49)

Restricted: to patients <75 y.o.

Cases (identification varied):
  • Based on admission diagnosis
  • Hospital cancer registry
  • Radiotherapy department

Controls:
  • General medical & surgical patients (non-cancer)
  • Matched by age, gender, & hospital

Confirmation of Diagnosis:
  At time of discharge or death
Doll & Hill Case-Control Study:

Data Collection:
- 4 full-time interviewers
- Standardized questionnaire

Definition of a “smoker”: smoked $\geq 1$ cig/day for $\geq 1$ yr.

Detailed smoking history:
- Age of start/stopping
- Amount before onset of illness
- Maximum; major changes in habit
- Type: pipe, cigarette, cigar
### Doll & Hill Case-Control Study

#### Males

<table>
<thead>
<tr>
<th>Lung CA Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Smoker</td>
<td>647</td>
</tr>
<tr>
<td>- Smoker</td>
<td>2</td>
</tr>
</tbody>
</table>

**OR = \(\frac{(647)(27)}{(622)(2)} = 14\)**

p = .0000006; 95% CI: 4.7-42

#### Females

<table>
<thead>
<tr>
<th>Lung CA Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Smoker</td>
<td>41</td>
</tr>
<tr>
<td>- Smoker</td>
<td>19</td>
</tr>
</tbody>
</table>

**OR = \(\frac{(41)(32)}{(28)(19)} = 2.5\)**

p = .016; 95% CI: 1.2-5.2
Doll & Hill Case-Control Study: Validity?

• Use of hospital controls?

• Selection bias?

• Observation bias?
  ➢ Recall bias
  ➢ Misclassification
  ➢ Interviewer bias
Questions That Arose

• Can the association be confirmed?

• What is the incidence?
  Relative risk?
  Risk difference?

• What other diseases are caused by smoking?

• What if you quit?
United Kingdom, 1951: Postal questionnaires sent to all registered physicians

Restricted to 34,439 males who responded. (There were few smokers among the 6,194 females.)

Prospective Cohort Study:
- Demographics, smoking habits, other factors
Doll & Hill Cohort Study

Cause of Death:
- Automatic notification from Office of Population Census and Surveys
- Monitored obituaries of *BMJ*
- Correspondence with next of kin, friends, etc.
- 1% cause unknown

Completeness of Follow up:
- 1971: vital status and place of residence for 99.7%
- 1990: complete in 94% of those known to have died
### Doll & Hill Cohort Study:

**Annual Mortality per 100,000 men**  
*Neoplastic Diseases*

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Never</th>
<th>1-14</th>
<th>15-24</th>
<th>&gt;24</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Resp.</td>
<td>1</td>
<td>12</td>
<td>18</td>
<td>48</td>
<td>48.0</td>
</tr>
<tr>
<td>Lung</td>
<td>14</td>
<td>105</td>
<td>208</td>
<td>355</td>
<td>25.4</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4</td>
<td>17</td>
<td>33</td>
<td>45</td>
<td>11.3</td>
</tr>
<tr>
<td>Pancreas</td>
<td>16</td>
<td>30</td>
<td>29</td>
<td>49</td>
<td>3.0</td>
</tr>
<tr>
<td>Bladder</td>
<td>13</td>
<td>29</td>
<td>29</td>
<td>37</td>
<td>2.9</td>
</tr>
<tr>
<td>Stomach</td>
<td>26</td>
<td>40</td>
<td>46</td>
<td>44</td>
<td>1.7</td>
</tr>
<tr>
<td>Colon</td>
<td>36</td>
<td>49</td>
<td>39</td>
<td>52</td>
<td>1.4</td>
</tr>
<tr>
<td>Rectum</td>
<td>10</td>
<td>13</td>
<td>19</td>
<td>44</td>
<td>4.4</td>
</tr>
</tbody>
</table>
## Doll & Hill Cohort Study:

### Annual Mortality per 100,000 men
(Respiratory and Vascular Diseases)

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Never</th>
<th>1-14</th>
<th>15-24</th>
<th>&gt;24</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulm. TB</td>
<td>4</td>
<td>7</td>
<td>9</td>
<td>20</td>
<td>5.0</td>
</tr>
<tr>
<td>Emphysema</td>
<td>10</td>
<td>86</td>
<td>112</td>
<td>225</td>
<td>22.5</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>71</td>
<td>113</td>
<td>154</td>
<td>169</td>
<td>2.4</td>
</tr>
<tr>
<td>Ischemic ht dis.</td>
<td>572</td>
<td>802</td>
<td>892</td>
<td>1025</td>
<td>1.8</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>15</td>
<td>38</td>
<td>74</td>
<td>81</td>
<td>5.4</td>
</tr>
<tr>
<td>Arteriosclerosis</td>
<td>22</td>
<td>31</td>
<td>38</td>
<td>72</td>
<td>3.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32</td>
<td>28</td>
<td>51</td>
<td>60</td>
<td>1.9</td>
</tr>
<tr>
<td>Stroke</td>
<td>253</td>
<td>344</td>
<td>388</td>
<td>447</td>
<td>1.8</td>
</tr>
</tbody>
</table>
24 causes of death were significantly associated with cigarette smoking.

Those who quit before 35 y.o. had life expectancy similar to non-smokers.

Even quitting in middle age increased life expectancy.

Earlier studies “...underestimated the hazards of long term use of tobacco. It now seems that about half of all regular cigarette smokers will eventually be killed by their habit.”
Case-Control

Prospective Cohort

**Advantages**
- Inexpensive
- Efficient
- Good for testing many risks
- Good for rare diseases

**Disadvantages**
- Subject to selection bias
- Can’t determine incidence

**Advantages**
- Less selection bias
- Determines incidence
- Can look at many endpoints
- Good for unusual risks

**Disadvantages**
- Can be expensive
- Can be time consuming
Testimony to OSHA by the tobacco industry
Does Smoking “Cause” Lung Cancer?

What is a “cause”?

Merriam-Webster Dictionary: Something that brings about a result; a person or thing that is the agent of bringing something about.

K.J. Rothman: An event, condition or characteristic without which the disease would not have occurred.

M. Susser: Something that makes a difference.
How does one demonstrate causation?
Theories of Causation

1. Divine retribution; God’s punishment for sins

2. Imbalance in body “humors”

3. Miasmas: disease transmitted by toxic vapors or gases. Bad odors were equated with disease.

4. Germ theory of disease (Pasteur, 1878)
Koch’s Postulates (1882):

- The organism must be present in every case of disease.
- The organism must be isolated and grown in culture.
- The organism must cause a specific disease when given to an animal.
- The organism must be recovered from the animal.

Sought specific causes for specific diseases.
Brought order out of chaos, especially for infectious diseases.

However, cause cannot be established simply by Koch’s rules.
Theories of Causation

1. Divine retribution; God’s punishment for sins

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4. Germ theory of disease (Pasteur, 1878)

5. Multifactorial Causes
   • “Germs”: bacteria, viruses, protozoa, rickettsia
   • Toxins
   • Radiation
   • Genetic
   • Nutritional
   • Behaviors (exercise)
Webs of Causation

The likelihood of a given disease may be influenced by many factors.

Smoking
Radon
Secondary smoke
Asbestos
Coal dust
Pollution
Immunity
Genetics

One risk factor may contribute to many diseases.

Lung cancer
Smoking
Emphysema
Chronic bronchitis
Heart disease
Bladder cancer
Usually, many factors act together (or interact) in a complex way to produce disease.

**Example**: atherosclerotic heart disease (diet, exercise, smoking, stress, hypercholesterolemia, hypertension, chronic inflammation, genetics).
Think About Proximate vs. Distal Causes

LOOKING FOR Causes in all the WRONG PLACES

THERE IS AN OLD JOKE about a fellow who, late one dark night, drops his keys in the middle of a parking lot. He moves some distance over to the side of the lot and begins a fruitless search for them under a bright street light. When asked why he was not looking where he actually dropped them, he replied, “but this is where the light is.”

POVERTY
ACCESS TO CARE
ENVIRONMENTAL EXPOSURE
RACISM

WHY IS HE LOOKING AT RISK FACTORS AND BEHAVIORS WHEN THE KEY LIES IN SOCIAL DETERMINANTS?

LOOKING IN A DIFFERENT PLACE FOR THE KEY
A disease with 3 sufficient causes (each with 5 components)

- Component “A” is necessary because it is a component of each sufficient cause.
Absence of anti-retrovirals
Exposure to person with HIV
Engaging in risky sexual behavior
Even if infected the bacteria generally stay latent (dormant); only 10% of people infected with TB will ever come down with the active disease.

The remaining 90% will have a positive PPD test (skin test) or small abnormalities on their chest x-ray, but they will not be able to spread TB to others.

Latent infections can eventually become active, however, so even people without symptoms should be treated if their PPD test changes from negative to positive.
The residue of a successful encounter with TB is a small peripheral scar (<1 cm diameter) in the lower half of the lung. Together with a similar scar in a hilar lymph node, it is known as the Ghon complex.
Exposure to TB bacillus is necessary, but not sufficient.
What **Caused** His TB?

- Infectious Agents (TB; HIV)
- Poverty
- Nutrition
- Decreased Immunity
- Genetics
- Behavior & Lifestyle (IV drugs; sexual behavior)
Definition of a Cause from an Epidemiologic Perspective

Anything that alone, or in conjunction with other factors, affects the likelihood of an outcome.
TB is caused by *Mycobacterium tuberculosis*

But, occurrence of disease is also determined by less specific, more remote causes or risk factors.

Effects of war, crowding, malnutrition, environmental & occupational exposures, heredity?
What Causes Cancer?

- Heredity
- Chemicals
- Radiation
- Viruses & Bacteria
- Diet
Environmental agents that damage DNA • Chemicals • Radiation • Viruses

• Hormones • Chronic Inflammation

Normal cell

Successful repair

DNA damage

Failed repair

Mutations in somatic cells

Activation of growth-promoting oncogenes

Impaired apoptosis

Inactivation of tumor suppressor genes

Altered gene products (proteins); abnormal structural & regulatory proteins

Malignant tumor

Inherited mutations in genes affecting: • DNA repair • Cell growth • Apoptosis
Inherited Defect in DNA Repair

Defective Apoptosis from tobacco carcinogen

Mutated proto-ongene from tobacco carcinogen

Mutated Anti-oncogene from Radon

High BMI
Establishing Cause

First, there must be a valid association.

Have you eliminated alternative explanations for an apparent association?
  - Chance
  - Bias
  - Confounding

But, even if you have a valid association, not all associations are causal.
**Example:** A rooster crows each morning at sunrise, (an association), but the crowing doesn’t causes the sun to rise.

**Example:** breast cancer is associated with:
- Being born in North America or Europe
- High socioeconomic status
- Having never married
- Higher in Jewish religion; lower in Mormons

Are these **causes** of breast cancer?
A Correlational Study
(Ecologic Study)

**Average Meat consumption (in many people)**
Hill’s Criteria

A Judgment of Causality is Strengthened by:

- A strong association
- Biologic credibility of the hypothesis
- Consistency of the findings
- The temporal sequence (risk factor first)
- The presence of a dose-response relationship
- Results of clinical experiment
Example: A 19-times greater incidence of lung cancer in smokers versus non-smokers is more convincing of causal link than the 1.4x greater risk of colon cancer in smokers.

However, by itself, a large RR doesn’t lead to conclusion of causality. (Bias or confounding?)

Also, cannot dismiss possibility of cause-effect relationship with small RR.
Biologic Credibility
(plausibility of mechanism)

Is there a plausible mechanism that could explain this cause-effect relationship?

**Examples:**
1. Cigarettes and lung cancer: Cigarettes contain *many* carcinogenic substances.

2. Low fiber diet and colon cancer: Dietary fiber enhances intestinal motility and dilutes or adsorbs fecal carcinogens.

A plausible mechanism helps, but isn’t essential. Epidemiologic studies often identify cause-effect before mechanism is known. **Examples:** John Snow (cholera), Ignaz Semmelweis, Oliver Wendel Holmes (puerperal fever).
1843: Oliver Wendell Holmes arguing in favor of hand washing to prevent puerperal fever at the Boston Society for Medical Improvement.

Dr. Holmes: “The disease known as puerperal fever is so far contagious, as to be frequently carried from patient to patient by physicians and nurses.”

Dr. Charles Meigs: “I prefer to attribute this disease to accident, or Providence, of which I can form a conception, rather than to contagion of which I cannot form any clear ideas....”
Thinking of the causes of health and disease as exclusively cellular and biochemical processes restricts possibilities for useful interventions.

So… if washing your hands prevents postpartum sepsis, go for it … even if you don’t know the mechanism.
Consistency of the Findings (Coherence)

• Does cause-effect relationship conflict with current knowledge of the biology of the disease?

• Are the findings consistent with laboratory evidence? (However, lab models frequently differ from human.)

• Have other studies arrived at similar conclusions in different persons, places, times, & circumstances?

**Example:**
Many studies indicate a link between smoking and disease.

Coherence supports cause-effect, but lack of coherence does not nullify.
A factor must precede an outcome in order to be a cause of it. (A *sine qua non* for causality)

A factor or behavior might co-occur or even result from a disease rather than be a cause of it.

**Examples:** Cause or effect?
1. Low beta-carotene levels in patients with cancer.
2. Decreased physical activity in people with heart disease.

Prospective cohort studies & randomized clinical trials provide best evidence that the cause precedes the effect.
Presence of a Dose-Response Relationship (Biological Gradient)

In many biological models, more exposure means greater risk.

**Example:** Smoking & lung cancer:
Lung cancer rates rise with the # of cigarettes per day smoked.

But, some exposures have a threshold effect: below a certain level there is low risk; above that there is high risk, but no gradient in between.

Dose-response provides support, but lack does not nullify.
Results of Clinical Experiment

Does an intervention aimed at preventing or removing the exposure result in less disease?

**Examples:**
1. Does smoking cessation lower rates of lung cancer?
2. Does reduction of serum cholesterol lower risk of myocardial infarction?

Most epidemiology studies are observational. RCT is closest to a lab experiment.
Given the complexity of disease:

1. Is it ever possible to prove causality with absolute certainty?

2. Is it possible to isolate a single cause for a given person’s lung cancer?

3. Is absolute proof required for legal or political action?

- Preponderance of evidence
- Reasonable doubt
Does exposure to environmental tobacco smoke cause heart disease and lung cancer?

To what extent should smoking be banned?
• 1966: Health warnings on Cigarette Packs begin

• 1975: Military stops distribution of free cigarettes in rations.

• 1987: Department of Health and Human Services goes smoke-free.


• 1995: FDA declares nicotine a drug

• 1999: Tobacco settlements; tobacco education & control programs
“After decades of downplaying smoking’s dangers, cigarette makers plan to argue before the Supreme Court this week that the Food and Drug Administration has no right to police the industry because tobacco products are too deadly for the FDA to regulate.

In a landmark case with sweeping public health implications, the $50 billion industry is keeping its Marlboro Man image out of the courtroom and expressing a new corporate motto that is emblazoned on Philip Morris’s Web site: ‘There is no “safe” cigarette.’

The turnabout is pivotal to the industry’s attempt to thwart the FDA, which claimed jurisdiction over tobacco products in 1996 after concluding that nicotine is a drug and cigarettes are drug-delivery devices.”
<table>
<thead>
<tr>
<th>Year</th>
<th>% Men</th>
<th>% Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>1965</td>
<td>51.9</td>
<td>33.9</td>
</tr>
<tr>
<td>1970</td>
<td>44.1</td>
<td>31.5</td>
</tr>
<tr>
<td>1976</td>
<td>41.9</td>
<td>32.0</td>
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<tr>
<td>1980</td>
<td>37.6</td>
<td>29.3</td>
</tr>
<tr>
<td>1985</td>
<td>32.6</td>
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<td>1990</td>
<td>28.4</td>
<td>22.8</td>
</tr>
<tr>
<td>1991</td>
<td>28.1</td>
<td>23.5</td>
</tr>
</tbody>
</table>
Evaluating or Designing a Study

• What was the objective/goal?
• Outcomes? (How defined/measured?)
• Exposures? (accurately measured?)

• Type of study?

• What is the study population? Selection criteria?
  Selection bias?

• How was data collected? Information bias?
  ➢ Adequate sample size? Chance? Precision of estimate?
  ➢ Bias
  ➢ Confounding (control?)

• Conclusion? Balanced discussion?

• Can the conclusions be generalized to other groups?