Sampling Methods in Scientific Studies

Joshua Naranjo

Department of Statistics,
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Scientific studies may be

- Observational

- Randomized controlled
Scientific studies may be

- Observational
  - descriptive
  - inferential

- Randomized controlled
Scientific studies may be

- Observational
  - descriptive
  - inferential
    - cross-sectional
    - cohort
    - case control

- Randomized controlled
Descriptive Studies

- Collect information to characterize and summarize the health event or problem

  Who? What? Where? When?

- Example: Tractor related deaths in Georgia
Example: Tractor related deaths in Georgia

Figure 1: Deaths associated with tractor injuries, by month of death
Introduction

Types of studies

HRT Story

Descriptive studies
Cross sectional studies
Cohort studies
Case-control studies

Example: Tractor related deaths in Georgia

Figure 1: Deaths associated with tractor injuries, by month of death

Peaks during spring and fall. Due to planting and harvest?
Example: Tractor related deaths in Georgia

Figure 2: Deaths associated with tractor injuries, by time of day
Example: Tractor related deaths in Georgia

Figure 2: Deaths associated with tractor injuries, by time of day

Increasing before lunch. Fatigue?
Example: Tractor related deaths in Georgia

Figure 2: Deaths associated with tractor injuries, by time of day

Increasing before lunch. Fatigue?
Peak at 4-5. Fatigue? Hunger? Darkness?
Example: Tractor related deaths in Georgia

Figure 2: Deaths associated with tractor injuries, by time of day

Increasing before lunch. Fatigue?
Peak at 4-5. Fatigue? Hunger? Darkness?
Children home from school.
Example: Tractor related deaths in Georgia

Figure 3: Deaths associated with tractor injuries, by age

Peak in older age group. Tractor users older? Less likely to survive an accident?
Small peak for school-age group.
Inferential studies test hypotheses using

- Observational study
  - cross-sectional
    - data represent a point in time
  - cohort
    - subjects selected according to exposure
  - case-control
    - subjects selected according to outcome: cases and controls (necessarily retrospective)

- Randomized experiment
Cross-sectional studies are primarily surveys intended to look at prevalence rates and risk factors.

- Example: National Health and Nutrition Examination Survey (NHANES)
- Example: Wisconsin Epidemiologic Study of Diabetic Retinopathy
- Example: Baltimore Eye Survey
Example: NHANES

- to assess the health and nutritional status of adults and children in the US
- combines interviews and physical examinations (including lab tests)
- responsible for producing vital and health statistics for the US
- sample of about 5,000 persons from 15 counties each year
- determine the prevalence of major diseases and risk factors
- the basis for national standards of height, weight, blood pressure, etc.
Major Findings:

- pediatric growth charts
- Federal nutrition recommendations, school lunch programs
- iron fortification of grain and cereal products (1973)
- iodine fortification of salt has virtually eliminated goiter and stillbirths
- Recommended Daily Allowance (RDA) of vitamins and minerals
- vaccine policy (e.g. 1-in-4 females aged 14-59 infected with HPV, 2003-04)
Major Findings:

- prevalence estimates of
  - malnutrition, obesity
  - cholesterol, hypertension
  - diabetes, arthritis, osteoporosis
  - hepatitis, HPV, other infectious diseases
  - dental health, visual health
  - exposures to lead, mercury, asbestos
Smaller, more targeted cross-sectional studies:

- **Wisconsin Epidemiologic Study of Diabetic Retinopathy**
  - studied prevalence of retinopathy among diabetics
  - identified risk factors such as hyperglycemia or hypertension

- **Baltimore Eye Survey**
  - confirmed that rate of primary open-angle glaucoma in black Americans was found to be four to five times higher than whites

- **European Youth Heart Study**
  - physical activity levels should be higher than current guidelines to prevent CVD risk factors.
Cohort studies

- **A cohort** is a group of people who share something in common
  - students enrolled in Stat 5630
  - WMU students 20 years and older
  - adult men and women residents of Framingham, Massachusetts

- the cohort may be chosen according to exposure patterns, but must be identified *before* disease status has been determined (this is crucial)

- determination of disease status may be prospective or retrospective

- allows calculation of relative risk
Cohort studies

• Example: A Cohort Study of Childhood Asthma Followed to Adulthood
  - children born from April 1972 through March 1973 in Dunedin, New Zealand
  - assess risk factors for persistence and relapse

• Example: A Retrospective Cohort Study of Measles, Mumps, and Rubella Vaccination and Autism
  - 537,303 children born in Denmark from January 1991 through December 1998
  - risk of autism was similar in MMR vaccinated and unvaccinated children
Example: Framingham Heart Study
- began in 1948 with 5,209 adults from Framingham, Mass.
- now on its third generation of participants (1971 and 2002)
- assess risk factors for cardiovascular disease

Example: Nurses’ Health Study
- began in 1976, has followed 121,700 female registered nurses
- assess risk factors for cancer and cardiovascular disease
Example: Framingham Heart Study

Major Findings:

1960s  Smoking, high cholesterol and BP increase risk of coronary heart disease (CHD).
       Exercise decreases risk, obesity increases it.
1970s  Elevated BP increases risk of stroke.
1980s  High levels of HDL cholesterol reduces risk of heart disease.
1990s  Framingham Risk Score is published, and correctly predicts 10-year risk of future CHD events.
2000s  Lifetime risk of developing elevated BP is 90%.
       Lifetime risk for obesity is approximately 50%.
       Social contacts are relevant to whether a person is obese.
       Four risk factors for a precursor of heart failure are discovered.
       Some genes increase risk of atrial fibrillation.
       Parent dementia increases risk of poor memory.
**Example: Nurses’ Health Study**

**Major Findings:**

<table>
<thead>
<tr>
<th></th>
<th>Breast Cancer</th>
<th>CHD/Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>No association</td>
<td>Strong positive association</td>
</tr>
<tr>
<td>Oral Contraceptives</td>
<td>Current use increases risk</td>
<td>Current use increases risk</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Increases risk</td>
<td>Reduces CHD risk</td>
</tr>
<tr>
<td>Diet</td>
<td>Red meat increases risk</td>
<td>Fish reduces risk of stroke. Nut/wholegrain reduce CHD risk Trans fats increase risk</td>
</tr>
</tbody>
</table>

Joshua Naranjo

Sampling Methods in Scientific Studies
Case-control studies select subjects according to disease outcome (cases and controls)
then the investigator looks back to determine exposure or risk factors
necessarily retrospective (there is no waiting for disease outcome)
relative risk is not valid
Example: Effectiveness of Bicycle Safety Helmets

Thompson et al. (1989):

- Cases: 235 persons with bicycling head injuries, who sought emergency care at one of five hospitals
- Controls:
Example: Effectiveness of Bicycle Safety Helmets

Thompson et al. (1989):

- Cases: 235 persons with bicycling head injuries, who sought emergency care at one of five hospitals
- Controls: 433 persons who received emergency care at the same hospitals for bicycling injuries not involving the head
Example: Effectiveness of Bicycle Safety Helmets

Thompson et al. (1989):

- **Cases**: 235 persons with bicycling head injuries, who sought emergency care at one of five hospitals
- **Controls**: 433 persons who received emergency care at the same hospitals for bicycling injuries not involving the head

**Results:**

- Head Injury: 7 percent were wearing helmets
- No head injury: 24 percent were wearing helmets
Example: Effectiveness of Bicycle Safety Helmets

How effective are helmets in preventing head injury?

\[
RR = \frac{.07}{.24} = .29 = \frac{P[\text{Helmet}|\text{Head Inj}]}{P[\text{Helmet}|\text{No Head Inj}]}
\]

“Head injury reduces your risk of wearing a helmet by 71%”
Example: Effectiveness of Bicycle Safety Helmets

How effective are helmets in preventing head injury?

\[ RR = \frac{.07}{.24} = .29 = \frac{P[\text{Helmet}|\text{Head Inj}]}{P[\text{Helmet}|\text{No Head Inj}]} \]

“Head injury reduces your risk of wearing a helmet by 71%”

We want:

\[ RR^* = \frac{P[\text{Head Inj}|\text{Helmet}]}{P[\text{Head Inj}|\text{No Helmet}]} \]

But \( RR^* \neq RR \).
Recall:

\[
\text{Odds}(E \mid D) = \frac{P(E \mid D)}{1 - P(E \mid D)}
\]

It is easy to show

\[
\frac{\text{Odds}(E \mid D)}{\text{Odds}(E \mid \text{not } D)} = \frac{P(E \cap D) \cdot P(E^c \cap D^c)}{P(E^c \cap D) \cdot P(E \cap D^c)} = \frac{\text{Odds}(D \mid E)}{\text{Odds}(D \mid \text{not } E)}
\]
Implication?

\[
\frac{\text{Odds}[\text{Head Inj}|\text{Helmet}]}{\text{Odds}[\text{Head Inj}|\text{No Helmet}]} = \frac{\text{Odds}[\text{Helmet}|\text{Head Inj}]}{\text{Odds}[\text{Helmet}|\text{No Head Inj}]}
\]

\[
= \frac{.07/(1 - .07)}{.24/(1 - .24)} = .25
\]

“Wearing a helmet reduces your odds of head injury by 75%”
Example: Effectiveness of Bicycle Safety Helmets

It is interesting to note the evolution of methodology

- Problem: the event is rare, and randomization is unethical
- Solution: sampling methodology (“Let’s sample the accident cases instead.”)

- Problem: the wrong rates are estimated.
- Solution: statistical theory (risk ratios are wrong, but odds ratios are correct)

“Wearing a helmet reduces your odds of head injury by 75%”
Hormone Replacement Therapy:

Since the 1940’s, when pharmaceutical companies had successfully manufactured estrogen, estrogen was sold as a way to cure the symptoms of menopause (hot flashes, night sweats, irritability, osteoporosis, etc).

Ads targeted the menopausal woman as suffering from ‘estrogen deficiency’, which can be cured by taking estrogen (“remain vital beyond middle age”).

By 1975, Premarin had become the fifth leading prescription drug in the United States
The HRT Story

1975: Published studies linked estrogen use to higher rates of uterine cancer

1976: The FDA required that each package of estrogen contain an insert warning of the risks of estrogen

Progesterone was added to estrogen to offset the risks of uterine cancer
1976: Breast cancer was linked to estrogen therapy in menopausal women

Taking a possible carcinogen for hot flashes was not reason enough and sales dropped.

By 1980, estrogen use had declined by 50% of its 1975 peak.
Early 1980s: several studies showed that estrogen was effective in slowing bone loss

1986: the FDA approved estrogen as a treatment for postmenopausal osteoporosis
1985: Nurses Health Study showed that registered nurses who were currently using estrogen had 70 percent lower risk of developing coronary heart disease.
The HRT Story

1985: Nurses Health Study showed that registered nurses who were currently using estrogen had 70 percent lower risk of developing coronary heart disease.

1985: Framingham Heart Study showed that women who had taken estrogen were 50 percent more likely to develop heart disease.
A Prospective Study of Postmenopausal Estrogen Therapy and Coronary Heart Disease - The Nurses’ Health Study
by Stampfer, et al. (NEJM 313:1044-9, October 24, 1985)

- surveyed 32,317 postmenopausal female nurses, aged 30 to 55 years
- 4 years of follow-up
- RR of CHD in those who had ever used hormones was 0.5 (0.3 and 0.8; P = 0.007)
- RR of CHD in current users was 0.3 (0.2 and 0.6; P = 0.001)
Conclusion:

“The relative risks were similar for fatal and nonfatal disease and were unaltered after adjustment for cigarette smoking, hypertension, diabetes, high cholesterol levels, a parental history of myocardial infarction, past use of oral contraceptives, and obesity. These data support the hypothesis that the postmenopausal use of estrogen reduces the risk of severe coronary heart disease.”
The HRT Story: Framingham Study

Postmenopausal Estrogen Use and Cardiovascular Morbidity in Women over 50 – The Framingham Study
by Wilson et al (NEJM; 313:1038-1043, October 24, 1985)

- surveyed 1234 postmenopausal women, aged 50 to 83 years
- eight years of follow-up
- 50 per cent elevated risk of cardiovascular morbidity ($P<0.01$) among those who had used hormones
- more than a twofold risk for cerebrovascular disease ($P<0.01$)
Conclusion:

“Increased rates for myocardial infarction ($P<0.05$) were observed particularly among the estrogen users who smoked cigarettes. Conversely, among nonsmokers estrogen use was associated only with an increased incidence of stroke ($P<0.05$). No benefits from estrogen use were observed in the study group.”
The HRT Story

Since the Framingham study

1. involved older women (who were thus at greater risk)
2. had received higher doses of estrogen
3. had a smaller sample size (1234 vs 32,317)
4. were not replicated by other studies

the results were largely dismissed by the media and medical community
Subsequent studies were conducted investigating the true effects of HRT on CHD. Most supported Stampfer’s study that HRT was protective against CRD. In Stampfer’s own words (International Journal of Epidemiology, 1990), :

“Of 16 prospective studies, 15 found decreased relative risks, in most instances, statistically significant. The Framingham study alone observed an elevated risk, which was not statistically significant when angina was omitted. Overall, the bulk of the evidence strongly supports a protective effect of estrogens that is unlikely to be explained by confounding factors.”
More researchers kept producing positive studies about hormones preventing heart attacks and bone loss, while not increasing cancer, stroke, or blood clots.

1992: Premarin was the number one prescribed drug in the United States

Major medical professional organizations were recommending long-term use of HRT. E.g., the American of College of Physicians issued guidelines to practicing physicians recommending that “all women. . . should consider preventive hormone therapy,” and that 10 to 20 years of therapy were recommended for “maximum benefit”
The HRT Story

Too good to be true?

Elizabeth Barrett-Connor (UCSD Div. of Epidemiology):
“I thought there were two or three very strong biases

1. women taking estrogen were better educated and wealthier

2. there was compliance bias – that is, people who are compliant in clinical trials, even with a placebo, have less disease.

3. during many of the years covered in these studies, the standard Physicians Desk Reference suggested estrogen should not be prescribed to women with heart disease, hypertension, or diabetes. So women with heart risks were not receiving the drug.

“Healthy Cohort Effect”
The HRT Story

Posthuma et al. (1994): Cardioprotective effect of hormone replacement therapy in post-menopausal women: is the evidence biased?

Vandenbroucke JP (1995): How much of the cardioprotective effect of postmenopausal estrogens is real?

Sturgeon et al. (1995): Evidence of a healthy estrogen user survivor effect.

Matthews et al. (1996): Prior to estrogen replacement therapy, are users healthier than nonusers?
Randomized Study: The Women’s Health Initiative

In the early 1990s, the NIH initiated a large-scale randomized controlled clinical trial on women's health covering heart disease, breast and colon cancer, bone fractures, and the role of hormone therapy, diet, vitamins, and calcium in preventing these diseases.

Between 1993 and 1998, the WHI randomized 16,608 postmenopausal women aged 50-79 years into receiving estrogen plus progestin therapy or placebo.

A second arm of the study involving 10,739 women compared estrogen only against placebo.
Results:

On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo. The test statistic for breast cancer exceeded the stopping boundary, and the global index statistic indicated ‘risks exceeding benefits’.

On February 2, 2004, the data and safety monitoring board recommended stopping the trial of estrogen only vs placebo. Estrogen alone does not appear to affect the risk of heart disease or breast cancer, but it did increase the risk of stroke.
Randomized Study: The Women’s Health Initiative

Risk findings for estrogen plus progestin (cases per 10,000 women):

- Breast cancer: 26% increased risk (38 cases vs 30 on placebo)
- Stroke: 41% increased risk (29 vs 21)
- Heart attack: 29% increased risk (37 vs 30)
- Blood clots (legs, lungs): Doubled rates (34 vs 16)
- Colorectal Cancer: 37% less risk (10 vs 16)
- Fractures: 37% fewer hip fractures (10 vs 15)
Randomized Study: The Women’s Health Initiative

Risk findings for estrogen only (cases per 10,000 women):

- Stroke: 39% increase in strokes (44 cases 32 on placebo)
- Blood clot: 47% higher risk (21 vs 15)
- Coronary heart disease: No significant difference (49 vs 54)
- Colorectal cancer: No significant difference (17 vs 16)
- Breast cancer: No significant difference (26 vs 33)
- Bone fractures: 39% fewer hip fractures (11 vs 17)
Questions:

1. How often do medical studies result in wrong findings?
2. What are the primary causes of wrong findings?
   - Statistical
   - Otherwise


Methods: Authors looked at all original research studies published in 3 major clinical journals (NEJM, JAMA, Lancet) in 1990-2003 and cited more than 1000 times in the literature.
**Results:** Of 49 highly cited original clinical research studies, 45 claimed that the intervention was effective. Of these,

- 7 were contradicted by subsequent studies
- 7 found effects stronger than those of subsequent studies
- 20 found effect confirmed by subsequent studies
- 11 remained largely unchallenged

**Conclusion:** Contradiction and initially stronger effects are not unusual in highly cited research of clinical interventions and their outcomes.
Table 1: Contradicted research and current state of knowledge

<table>
<thead>
<tr>
<th>Highly Cited Study</th>
<th>Current state of knowledge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nurses Health</td>
<td>Estrogen does not protect, but increases CAD risk in postmenopausal women</td>
</tr>
<tr>
<td>2. PEPI</td>
<td></td>
</tr>
<tr>
<td>3. Health Pros</td>
<td>Vit E supplement does not reduce CAD in men</td>
</tr>
<tr>
<td>4. Nurses Health</td>
<td>Vit E supp. does not reduce CAD in women</td>
</tr>
<tr>
<td>5. CHAOS</td>
<td>Vit E supp. does not prevent CAD events</td>
</tr>
<tr>
<td>6. HA-1A Sepsis</td>
<td>HA-1A does not improve survival in sepsis</td>
</tr>
<tr>
<td>7. Rossaint et al</td>
<td>Nitric oxide does not improve survival in respiratory distress</td>
</tr>
</tbody>
</table>
## Contradicted research outcomes

### Table 2: Contradicted research designs

<table>
<thead>
<tr>
<th>Highly Cited Study</th>
<th>Highly cited study design</th>
<th>Contradicting study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nurses Health</td>
<td>Cohort (n=48,470)</td>
<td>RCT (n=16,608)</td>
</tr>
<tr>
<td>2. PEPI</td>
<td>RCT (n=875)</td>
<td>RCT (n=16,608)</td>
</tr>
<tr>
<td>3. Health Pros</td>
<td>Cohort (n=39,910)</td>
<td>RCT (n=6,996)</td>
</tr>
<tr>
<td>4. Nurses Health</td>
<td>Cohort (n=87,245)</td>
<td>RCT (n=2,545)</td>
</tr>
<tr>
<td>5. CHAOS</td>
<td>RCT (n=2,002)</td>
<td>RCT (n=9,541)</td>
</tr>
<tr>
<td>6. HA-1A Sepsis</td>
<td>RCT (n=200)</td>
<td>RCT (n=2,199)</td>
</tr>
<tr>
<td>7. Rossaint et al</td>
<td>Case series (n=9)</td>
<td>MA RCT (n=535)</td>
</tr>
</tbody>
</table>
Recall Women’s Health Initiative: 10,000 women randomized into estrogen or placebo

Toss coin

\[ \begin{array}{c}
0.5 \checkmark \checkmark 0.5
\end{array} \]

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
</table>

Age profile of the two groups? Balanced!
Diet? Exercise? Health attitudes?
Q: Why not do this for all studies?
A: Not always possible.

Ex. "Smoking decreases life span"

| Smokers  | Nonsmokers |

Cannot randomize. Group membership is observed rather than assigned.
Observational vs randomized studies

Observational studies

Apples and Oranges

*Smokers are different from nonsmokers in other ways besides smoking! (e.g. Drink more coffee, exercise less, stand out in the cold more, etc.)*

If estrogen group has lower disease rates than no-estrogen, does this mean that estrogen is protective, or is the estrogen group just fundamentally healthier?

⇒ ”The healthy volunteer effect”
Observational vs randomized studies

Simpson’s Paradox: (Comparing aggregate scores)

**NAEP 1992 8th Grade Math Scores**

<table>
<thead>
<tr>
<th>State</th>
<th>White</th>
<th>Black</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebraska</td>
<td>277</td>
<td>281</td>
<td>236</td>
</tr>
<tr>
<td>New Jersey</td>
<td>271</td>
<td>283</td>
<td>242</td>
</tr>
</tbody>
</table>

Percentage of population

<table>
<thead>
<tr>
<th>State</th>
<th>Nebraska</th>
<th>New Jersey</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>87%</td>
<td>66%</td>
</tr>
<tr>
<td>Black</td>
<td>5%</td>
<td>15%</td>
</tr>
<tr>
<td>Other</td>
<td>8%</td>
<td>19%</td>
</tr>
</tbody>
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Joshua Naranjo
Sampling Methods in Scientific Studies
Observational vs randomized studies

Simpson’s Paradox: (Comparing aggregate scores)

**Basketball**

<table>
<thead>
<tr>
<th>Shot %</th>
<th>FT</th>
<th>3-pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>.540</td>
<td>.600</td>
</tr>
<tr>
<td>You</td>
<td>.460</td>
<td>.700</td>
</tr>
</tbody>
</table>

Percentage of population

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>80%</td>
</tr>
<tr>
<td>You</td>
<td>20%</td>
</tr>
</tbody>
</table>
Observational vs randomized studies

Simpson’s Paradox: (Comparing aggregate scores)

**NAEP Study**

- Race, etc.: Not Balanced

**Driver Leg Injury Study**

- Height: Not Balanced
**Clofibrate Study**
Clofibrate is a cholesterol lowering drug. The study looked at mortality rates of patients with heart disease over a period of 5 years.

<table>
<thead>
<tr>
<th></th>
<th>Clofibrate</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Deaths</td>
</tr>
<tr>
<td>Total</td>
<td>1103</td>
<td>20%</td>
</tr>
<tr>
<td>Adherers</td>
<td>708</td>
<td>15%</td>
</tr>
<tr>
<td>Non-adherers</td>
<td>357</td>
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1. Clofibrate is not effective
2. Adherers are different from non-adherers
Anecdotal Studies

Silicone Breast Implants Story

1960s
The first silicone breast implants

1977
First lawsuit: Cleveland woman claims ruptured implants and subsequent operations had caused pain and suffering. Dow Corning settles, $170,000.

1984
San Francisco woman’s systemic autoimmune disease is found by a jury to be caused by her silicone implants. Jury awards $1.5 million in punitive damages.
June 1988
FDA classifies the implants into Class III. Requires manufacturers to prove their safety in order to keep them on the market.

December 1990
Congressional hearing on safety of silicone implants.

December 1991
A San Francisco woman wins $7.3 million from Dow Corning. Jury concludes her mixed connective-tissue disease is linked to her ruptured silicone implants.
Anecdotal Studies

January 1992
FDA Commissioner David Kessler calls for a voluntary moratorium on the use of silicone implants until the FDA and the advisory panel have an opportunity to consider newly available information. The manufacturers agree.

February 1992
Class action lawsuit is filed in Cincinnati.

December 1993
12,359 lawsuits have been filed against Dow Corning.
Anecdotal Studies

June 1994
Mayo Clinic epidemiologic study finds no increased risk of connective-tissue or other disorders.

December 1994
19,092 lawsuits have been filed against Dow Corning.

May 1995
Dow Corning files for Chapter 11 bankruptcy.

June 1995
Harvard Nurses Epidemiologic Study published in NEJM. Finds no increased risk of connective-tissue disease.
December 1995
By now more than 20 studies in the U.S. and internationally fail to support a causal relationship.

Today
Silicone implants remain off the market. Available only to women who will have breast surgery for a medical condition, and only if they agree to be part of a scientific study.
Anecdotal Studies

The Harvard Nurses Study

New England Journal of Medicine, June 22, 1995

Data: 87,501 nurses followed for other research purposes from 1976 through May 31, 1990. None of the women had connective tissue disease at the start of the study.

During the time frame of the study, 3 women with breast implants developed connective tissue diseases.

Number of women with breast implants who developed disease: 3
Anecdotal Studies

The Harvard Nurses Study

Data is missing!

<table>
<thead>
<tr>
<th></th>
<th>Disease</th>
<th>No Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>No Implant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### The Harvard Nurses Study

Data is missing!

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<td>No Implant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Disease</th>
<th>No Disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant</td>
<td>3</td>
<td>1,180</td>
<td>.0025</td>
</tr>
<tr>
<td>No Implant</td>
<td>513</td>
<td>85,805</td>
<td>.0059</td>
</tr>
</tbody>
</table>

“Don’t ask whether B follows A. Ask whether B follows A more frequently than $A^c$.”
Anecdotal vs Observational vs Randomized studies

Summary:

Show me the study!

IF          THEN          ASK
Anecdotal   No comparisons. Coincidence?
Observational Lurking variables. Similar groups?
Randomized  Best.