

Statistics in Epidemiology

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Outline

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 - Applications
 - Epidemiology, for example
- 2 Types of studies
 - Descriptive studies
 - Cross sectional studies
 - Cohort studies
 - Case-control studies
- 3 HRT Story
- 4 Lessons

Applications

Statistics - data science (collection, analysis, decision-making)

Applications

Statistics - data science (collection, analysis, decision-making)

- Actuarial science
- Business analytics (finance, sales)
- Census and sample surveys (population stats)
- Government statistics (labor, economy)
- Clinical trials (drug development, therapy assessment)
- Engineering (manufacturing, reliability)
- Economics (health of the market, financial institutions)
- Epidemiology (population health)

Epidemiology

Etymology of “Epidemiology”

<i>epi</i>	<i>demos</i>	<i>logos</i>
⇓	⇓	⇓
Upon	People	Study

literally meaning “the study of what is upon the people”

Epidemiology

From the Centers for Disease Control (CDC)

- “the basic science of public health”

Epidemiology

From the Centers for Disease Control (CDC)

- “the basic science of public health”
- “the study of the distribution and determinants of health-related states in specified populations, and the application of this study to control health problems.”

Epidemiology

Doctors

collect data on a patient and make a diagnosis

Epidemiology

Doctors

collect data on a patient and make a diagnosis

Epidemiologists

collect data on a *population* and make a diagnosis

Epidemiology

Q: Why statistics?

A: Epidemiologists *count* things, and make *hypotheses* about *associations* between disease rates and specific patterns of exposure.

Epidemiological studies may be

- Observational

- Randomized controlled

Epidemiological studies may be

- Observational
 - descriptive
 - inferential

- Randomized controlled

Epidemiological 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: 1854 London cholera outbreak
- Example: Tractor related deaths in Georgia

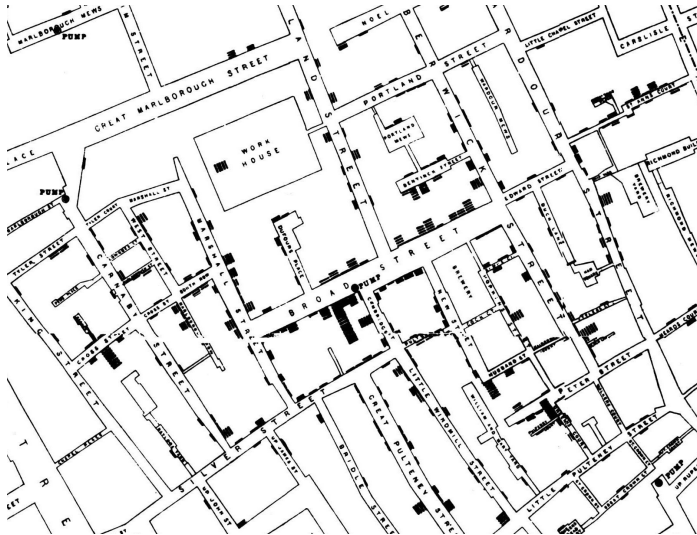
Example: 1854 London cholera outbreak

On 31 August 1854, an outbreak of cholera struck Soho, London. Over the next ten days, 500 people on or near Broad Street died.

John Snow studied the pattern of the disease and made a map showing the clusters of cholera cases.

In Snow's own words:

Nearly all the deaths had taken place within a short distance of the [Broad Street] pump. There were only ten deaths in houses situated decidedly nearer to another street-pump.



Example: 1854 London cholera outbreak

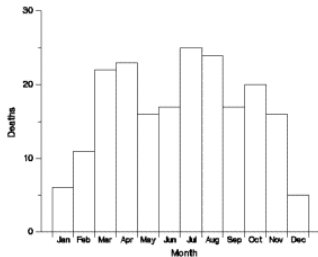
Snow and his map

-persuaded the local council to disable the well pump by removing its handle, effectively ending the outbreak.

-convinced the scientific community that cholera was a waterborne illness, and not transmitted by air.

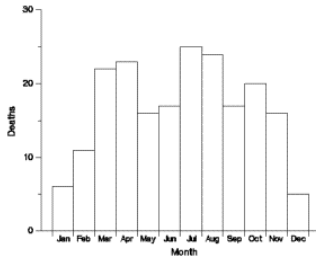
Example: Tractor related deaths in Georgia

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



Example: Tractor related deaths in Georgia

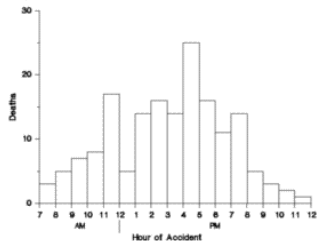
Figure 1: Deaths associated with tractor injuries, by month of death



Peaks during spring and fall. Due to planting and harvest?

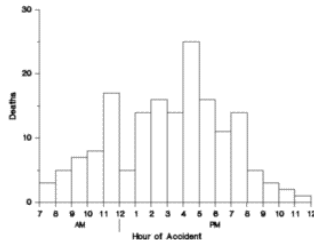
Example: Tractor related deaths in Georgia

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



Example: Tractor related deaths in Georgia

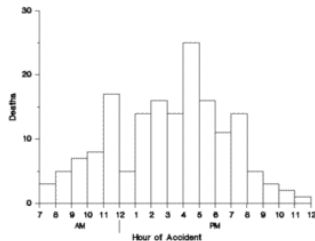
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Increasing before lunch. Fatigue?

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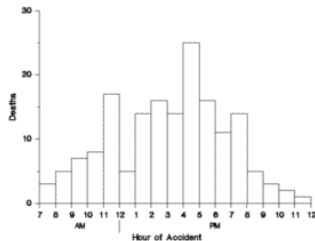


Increasing before lunch. Fatigue?

Peak at 4-5. Fatigue? Hunger? Darkness?

Example: Tractor related deaths in Georgia

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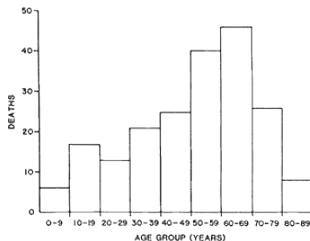
Peak at 4-5. Fatigue? Hunger? Darkness?

Children home from school.

Example: Tractor related deaths in Georgia

Figure 3: Deaths associated with tractor injuries, by age

Fig. 1 FATALITIES ASSOCIATED WITH FARM TRACTOR ACCIDENTS, BY AGE GROUP, GEORGIA, 1971 - 1981



Peak in older age group. Tractor users older? Less likely to survive an accident?

Small peak for school-age group.

Inferential Studies

Inferential epidemiology 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

- 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.

Example: NHANES

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)

Example: NHANES

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 3660
 - premenopausal women in Kalamazoo 20 years and older
 - millennials
 - 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:

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

Case-control 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:

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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

Estimate of the "risk difference" $p_1 - p_2$:

$$p_{\text{sample1}} - p_{\text{sample2}} = .24 - .07 = .17$$

95% confidence interval for $p_1 - p_2$:

$$(.12, .22)$$

Epidemiologists prefer the "risk ratio":

$$RR = \frac{p_{\text{sample1}}}{p_{\text{sample2}}} = \frac{.07}{.24} = .29$$

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%”

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We want:

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

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

But $RR^* \neq RR$.

Recall:

$$\text{Odds}(E|D) = \frac{P(E|D)}{1 - P(E|D)}$$

It is easy to show

$$\frac{\text{Odds}(E|D)}{\text{Odds}(E|\text{not } D)} = \frac{P(E \cap D) \cdot P(E^c \cap D^c)}{P(E^c \cap D) \cdot P(E \cap D^c)} = \frac{\text{Odds}(D|E)}{\text{Odds}(D|\text{not } E)}$$

Example: Effectiveness of Bicycle Safety Helmets

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%”

The HRT Story

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

The HRT Story

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.

The HRT Story

Early 1980s: several studies showed that estrogen was effective in slowing bone loss

1986: the FDA approved estrogen as a treatment for postmenopausal osteoporosis

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

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

The HRT Story: Nurses' Health Study

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; $P = 0.001$)

The HRT Story: Nurses' Health Study

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 ($P < 0.01$)

The HRT Story: Framingham Study

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

The HRT Story

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. "

Table 4 Prospective studies with internal controls

Study	Age at baseline (mean or range)	Number in population	Percentage estrogen users	Follow-up (years) (mean or range)	Endpoint (number of cases)	Relative risk (95% CI)	
						Age-adjusted	Risk factor-adjusted
Potocki (21)	60–70	158	52%	10 ?	MI (4)	0.31 (0.04–2.57) ^a	
Hammond <i>et al.</i> (24)	46.3	619	49%	1.3	CHD (58)	0.33 (0.19–0.56) ^a	
Nachtigall <i>et al.</i> (25)	55	168	50%	10	MI (4)	0.33 (0.04–2.82) ^a	
Lafferty and Helmuth (26)	45–60 (53.7)	124	49%	3–16 (8.6)	MI (7)	0.17 (0.03–1.06) ^a	
Stamper <i>et al.</i> (27)	30–55	32 317	Past 18%	3.3	Nonfatal MI and CHD death (90)	Past 0.7 (0.4–1.2)	0.59 (0.33–1.06)
			Current 35%			Current 0.3 (0.2–0.6)	
			Ever 57%			Ever 0.5 (0.3–0.8)	
Framingham Heart Study ^b							
Wilson <i>et al.</i> (28)	50–84	1234	Past 14%	8	All CVD (194) CVD death (48) MI (51)	1.76 ($P < 0.01$) ^c	
			Current 10%			1.94 ($P > 0.05$) ^c	
						1.87 ($P > 0.05$) ^c	
Eaker and Castelli (29)	50–59	695	15%	10	CHD no angina (35) (51)	0.26 (0.06–1.22) ^{c,d}	0.4 ($P > 0.05$) ^c
	60–69	602	8%			1.68 (0.71–4.00) ^{c,d}	
Bush <i>et al.</i> (30)	40–69	2270	26%	8.5	CVD death (50)	0.34 (0.12–0.81)	0.37 (0.16–0.88)
Petitti <i>et al.</i> (31)	18–54	6093	Ever 44%	10–13	CVD death	0.9 (0.2–3.3)	0.6 (0.3–1.1)
Criqui <i>et al.</i> (32)	50–79	1868	39%	12	CHD death (87)	0.75 (0.45–1.24)	0.99 (0.59–1.67)
Henderson <i>et al.</i> (33)	40–101 (median = 73)	8807	Past 43%	4.6	MI deaths (149)	Past 0.62 (0.43–0.90)	No change
			Current 14%			Current 0.47 (0.20–2.00)	
						Ever 0.59 (0.42–0.82)	
Croft and Hannaford (34)	20–60	Nested	Ever 6.5%	19	MI (9)	0.8	0.8 (0.3–1.8)
Avila <i>et al.</i> (37)	50–64	24 900	Current 14%	5	MI (120)	0.7 (0.4–1.3)	0.7 (0.4–1.4)
Sullivan <i>et al.</i> (38)	?	2268	Ever 10.5%	10	Death		0.16 (0.04–0.66)

^a The crude odds ratio and confidence intervals are derived from data given in the text.

^b The results based on the analysis of Eaker and Castelli (29) are not included in the quantitative overview.

^c This includes high-density lipoprotein cholesterol in the regression analysis.

^d These results are taken as the average of findings using examinations 11 and 12 as baseline.

The HRT Story

Postmenopausal Estrogen Therapy and Cardiovascular Disease – Ten-Year Follow-up from the Nurses' Health Study
by Stampfer et al (NEJM, September 12, 1991)

Abstract: Our earlier report of a benefit from estrogen use in terms of the risk of coronary disease, based on four years of follow-up, was accompanied by a report from the Framingham Study that came to the opposite conclusion. We now report results for both coronary disease and stroke, based on 10 years of follow-up in the Nurses' Health Study, that included 48,470 postmenopausal women with 337,252 person-years of follow-up.

The HRT Story

Results:

After adjustment for age and other risk factors,

- the overall relative risk of major coronary disease in women currently taking estrogen was 0.56 (95% CI, 0.40 to 0.80)
- The relative risk for current and former users of estrogen as compared with those who had never used it was 0.89 (95% CI, 0.78 to 1.00) for total mortality and 0.72 (95% CI, 0.55 to 0.95) for mortality from cardiovascular disease.
- The relative risk of stroke when current users were compared with those who had never used estrogen was 0.97 (95% CI, 0.65 to 1.45)

The HRT Story

Conclusions:

“Current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease, but it is not associated with any change in the risk of stroke.”

The HRT Story

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.

Randomized Study: The Women's Health Initiative

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)

Randomized Study: The Women's Health Initiative

Bottom line? All those studies were wrong!

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- The data: Estrogen group had less coronary disease
- False conclusion: Estrogen decreases risk.

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- Correct:

Randomized Study: The Women's Health Initiative

Bottom line? All those studies were wrong!

- The data: Estrogen group had less coronary disease
- False conclusion: Estrogen decreases risk.
- Correct:
 - Estrogen increases risk.
 - Estrogen group was healthier than non-estrogen group.

The HRT Story

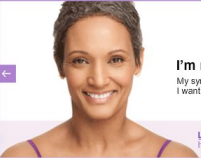
Today:

Estrogen and Estrogen plus Progestin are still on the market.

They are primarily prescribed for short-term treatment of menopausal symptoms and osteoporosis, and long term use is not recommended.

Patient Information, Including Boxed Warning • Important Safety Information • Full Prescribing Information

Looking for relief of hot flashes, night sweats, and vaginal symptoms? Ease these menopausal symptoms with PREMPRO.



I'm ready for relief.
My symptoms sometimes get in the way.
I want to do something about them.

Learn how PREMPRO offers effective hormone therapy with low dose options.

Menopause and you	Low dose options	More resources
Discover what's causing your symptoms and how PREMPRO can help relieve them. Learn more	PREMPRO comes in 4 dosage strengths, including 2 low dose options. Work with your doctor to find the dose that's right for you. Discover your options	Learn more about menopause and hormone therapy from a number of organizations. Get more info

Important Safety Information

What is the most important information I should know about PREMPRO and PREMPHASE (combinations of estrogens and a progestin)?

- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes, or dementia (decline of brain function)
- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women age 65 years or older
- Do not use estrogen-alone to prevent heart disease, heart attacks, or dementia
- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb)
- Using estrogen-alone may increase your chances of getting strokes or blood clots
- Using estrogen-alone may increase your chance of getting dementia, based on a study of women age 65 years or older
- You and your healthcare provider should talk regularly about whether you still need treatment with PREMPRO or PREMPHASE

Litigation

- January 30, 2007:
In *Mary Daniel v. Wyeth*, the jury found that Prempro was responsible for the plaintiff's breast cancer, and awarded \$1.5 million in compensatory damages
- February 21, 2007:
A jury found that Prempro caused the plaintiff's breast cancer and awarded Jennie Nelson \$3 million in compensatory damages
- October 11, 2007:
A Nevada jury awarded \$35 million in compensatory and \$99 million in punitive damages to 3 plaintiffs. Judge reduced verdict to \$23 million in compensatory and \$35 million in punitive damages.

Litigation

- October 27, 2009: The jury awarded Connie Barton of Illinois \$3.7 million in compensatory and \$75 million in punitive damages.
- November 24, 2009: The jury awarded Donna Kendall of Illinois \$6.3 million in compensatory and \$28 million in punitive damages
- About 10,000 similar cases are pending

Lessons

- The physician:
Claims for the use of a drug, whether approved or off-label, should be proven by large, randomized, long-term, placebo-controlled trials with participants from the target population before widely prescribing them for that use.

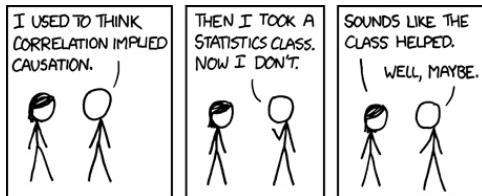
Lessons

- The physician:
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- The consumer:
Make an effort to be informed about the drugs you are taking. Beware of campaigns that make an 'illness' out of normal symptoms of aging:
 - Estrogen deficiency
 - Hair loss
 - Erectile dysfunction
 - Wrinkles

Lessons

- The statistician:
 - Association is not causation (sometimes not even association)
 - Beware of the limitations of 'adjusting for risk factors'
 - covariate adjustment
 - propensity analysis
 - Persistence of the healthy cohort effect
 - systematic selection of subjects that would favor the treatment
 - systematic removal of subjects who show early symptoms

Need a healthy cynicism for results of observational studies.
Without randomized trials, keep thinking “maybe”.



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- Comparing survival curves
 - Log-rank
 - Wilcoxon
- Regression methods
 - Accelerated failure time (AFT)
 - Cox regression
- Categorical data (ignore time-to-event)
 - Relative risk
 - Odds ratio

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 - May be less efficient*

Know your toolbox

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 - Log-rank
 - Wilcoxon
 - Do not adjust for covariates*
- Regression methods
 - Accelerated failure time (AFT) (Proc LIFEREG)
 - Need to specify error distribution*
 - Cox regression (Proc PHREG)
 - Requires proportional hazards*
- Categorical data (ignore time-to-event)
 - Relative risk (Proc FREQ, GENMOD, LOGISTIC)
 - Odds ratio
 - May be less efficient*