Learning Objectives

1. Understand different measures of therapeutic benefit, how the measures are related, and which ones are most meaningful in a given context.
Learning Objectives

2. Learn what to consider when deciding whether a given benefit is clinically meaningful.

“When Does a Difference Make a Difference?”
EFFICACY OF BILATERAL PROPHYLACTIC MASTECTOMY IN WOMEN WITH A FAMILY HISTORY OF BREAST CANCER

Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)
Effectiveness of Chemotherapy for Early Stage Breast Cancer
15-Year Breast Cancer Mortality

AGE < 50

P<0.00001

Lancet 2005
Dow-Jones Industrial Average

[Graph showing stock market values over time, with months and years indicated on the x-axis and stock values on the y-axis.]
Temporal changes in patient characteristics or clinical practices other than the insulin protocol could potentially affect in-hospital complications in patients with diabetes.

Temporal changes in patient characteristics or clinical practices other than the insulin protocol could potentially affect in-hospital complications in patients with diabetes.
Effectiveness of Chemotherapy for Early Stage Breast Cancer

15-Year Breast Cancer Mortality

Assume 1000 patients with early breast cancer receive adjuvant chemotherapy

576 patients would not have died in any case
100 patients will thwart death from breast cancer
324 patients will still die within 15 years

Relative Risk Reduction (RRR) = 10.0%/42.4% = 23.6%

Lancet 2005
ABSOLUTE RISK REDUCTION

NUMBER NEEDED TO TREAT
Effectiveness of Chemotherapy for Early Stage Breast Cancer

15-Year Breast Cancer Mortality

Assume 1000 patients with early breast cancer receive adjuvant chemotherapy

- 576 patients would not have died in any case
- 100 patients will thwart death from breast cancer
- 324 patients will still die within 15 years

Relative Risk Reduction (RRR) = 10.0%/42.4% = 23.6%
Absolute Risk Reduction (ARR) = 10.0%
Number Needed to Treat (NNT) = 10

Lancet 2005
PUBLICATION BIAS
Bad Pharma

By

Ben Goldacre
Effectiveness of Chemotherapy for Early Stage Breast Cancer
15-Year Breast Cancer Mortality

Assume 1000 patients with early breast cancer receive adjuvant chemotherapy

496 patients would not have died in any case
30 patients will thwart death from breast cancer
474 patients will still die within 15 years

Relative Risk Reduction (RRR) = 3.0%/50.4% = 6.0%
Absolute Risk Reduction (ARR) = 3.0%
Number Needed to Treat (NNT) = 33

Lancet 2005
"There is a difference between A and B"

"There is a meaningful difference between A and B"
“A difference, to be a difference, must make a difference”

--Gertrude Stein
When Does a Difference Make a Difference?

Biostatistics Lecture Series

April 5, 2017

Donald A. Brand, Ph.D.
<table>
<thead>
<tr>
<th></th>
<th>WOW</th>
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<tbody>
<tr>
<td><strong>Statistical Perspective</strong></td>
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<tr>
<td><strong>Clinical Perspective</strong></td>
<td>WOW</td>
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P<0.01

Statistical Perspective

WOW
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Clinical Perspective

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WOW

Mean BMI dropped from 41 to 30
**Statistical Perspective**
- P<0.01
- WOW
- WOW
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- WOW

**Clinical Perspective**
- WOW
- WOW
- WOW
- WOW

- Mean BMI dropped from 41 to 30
- Mean serum cholesterol dropped from 310 to 230
Statistical Perspective  
- P<0.01  
- P=0.36  
- P<0.01  
- WOW  
- WOW  
- WOW  
- WOW

Clinical Perspective  
- WOW  
- WOW  
- WOW  
- WOW  
- Mean BMI dropped from 41 to 30  
- Mean serum cholesterol dropped from 310 to 230  
- Mean BMI dropped from 39.4 to 39.1
Efficacy of Bilateral Prophylactic Mastectomy in Women with a Family History of Breast Cancer

Lynn C. Hartmann, M.D., Daniel J. Schaid, Ph.D., John E. Woods, M.D., Thomas P. Crotty, M.D., Jeffrey L. Myers, M.D., P.G. Arnold, M.D., Paul M. Petty, M.D., Thomas A. Sellers, Ph.D., Joanne L. Johnson, R.N., Shannon K. McDonnell, M.S., Marlene H. Frost, Ph.D., R.N., and Robert B. Jenkins, M.D., Ph.D.
Bilateral Prophylactic Mastectomy

“91 percent reduction in breast cancer deaths”

Assume 1000 women with a family history of breast cancer undergo prophylactic mastectomy

<table>
<thead>
<tr>
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<th>DEATHS FROM BREAST CANCER*</th>
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<tbody>
<tr>
<td>Expected</td>
<td>21/639 (3.3%)</td>
</tr>
<tr>
<td>Actual</td>
<td>2/639 (0.3%)</td>
</tr>
</tbody>
</table>

*Median length of follow-up = 14 years

Relative Risk Reduction (RRR) = 3%/3.3% = 91%
Absolute Risk Reduction (ARR) = 3%
Number Needed to Treat (NNT) = 33

967 women would not have died from breast cancer in any case

30 women will thwart death from breast cancer
3 women will still die from breast cancer

- Benefit N=30 (3%)
- No Benefit N=970 (97%)

Hartmann, N Engl J Med 1999
MEANINGFUL DIFFERENCE?
“Even in the face of an unprecedented 90 percent reduction in the incidence of breast cancer and of death from breast cancer, the fact remains that this is a study of 639 women who, because of the fear of breast cancer, underwent a disfiguring and potentially psychologically damaging operation. As a result, instead of the 20 deaths related to breast cancer that were expected during the period of observation, there were only 2. The saving of those 18 lives is clearly important, but the 621 women who probably would have survived without prophylactic mastectomy paid a price... “

“It is ironic that data supporting the efficacy of bilateral mastectomy for prevention should appear in an era in which the goal of surgical treatments for breast cancer is breast conservation.”

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“When Does a Difference Make a Difference?”
Comparison of Benefits

Chemotherapy for Breast Cancer
Age<50

Survive without treatment
NNT=10

Survive because of treatment

Die in spite of treatment

Chemotherapy for Breast Cancer
Age 50-69

NNT=33

Prophylactic Mastectomy

NNT=33

NNT=Number Needed to Treat
Prophylactic Prostatectomy

A Policy Analysis

Assume 1000 men undergo prophylactic prostatectomy

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Prostatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIFETIME PROBABILITY OF DEATH FROM PROSTATE CANCER</td>
<td>1/36 (2.8%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Relative Risk Reduction (RRR) = 100%
Absolute Risk Reduction (ARR) = 2.8%
Number Needed to Treat (NNT) = 36

972 men would not have died from prostate cancer in any case

28 men will thwart death from prostate cancer

- Benefit N=28 (2.8%)
- No Benefit N=972 (97.2%)
Assume 1000 women with a family history of breast cancer undergo prophylactic mastectomy

967 women would not have died from breast cancer in any case

30 women will thwart death from breast cancer
3 women will still die from breast cancer

- Benefit N=30 (3%)
- No Benefit N=970 (97%)

Assume 1000 men undergo prophylactic prostatectomy

972 men would not have died from prostate cancer in any case

28 men will thwart death from prostate cancer

- Benefit N=28 (2.8%)
- No Benefit N=972 (97.2%)
INCIDENCE OF POLIOMYELITIS IN THE U.S. IN THE 1950s

50 per 100,000
Effectiveness of the Salk Vaccine for Polio Prevention
1954 Field Trial

Assume 100,000 children receive the Salk vaccine

**POLIO INCIDENCE**

<table>
<thead>
<tr>
<th></th>
<th>Vaccine</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Incidence</td>
<td>33/200,745</td>
<td>115/201,229</td>
</tr>
<tr>
<td>(Incidence per 100,000)</td>
<td>16</td>
<td>57</td>
</tr>
</tbody>
</table>

99,943 children would not have become infected even without vaccination

41 children will resist infection thanks to vaccine
16 children will nevertheless become infected

Relative Risk Reduction (RRR) = 41/57 = 72%

Absolute Risk Reduction (ARR) = 41 per 100,000

Number Needed to Treat (NNT) = 2439

- Benefit N=41 (0.04%)
- No Benefit N=99,959 (99.96%)
MEANINGFUL DIFFERENCE?
“A drug is a substance that, when injected into a rat, will produce a scientific report.” --Matz's Rule
Summary

1. Of the various measures of therapeutic benefit, NNT provides the most transparency.*

   *Stick figures can help a lot, too →

2. How much benefit is enough? (i.e., When does a difference make a difference?)

   There is no formula, but the answer depends on patient preferences and the weighing of harms vs. benefits.