Probability (Chapter 3)

Medical statistics Part I
26 august og 2 september 2009
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- What is probability?
- How to calculate with probabilities

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Breast cancer (Example 3.1)

- Incidence of breast cancer the next 5 years for 45-54 years old women
- Group A: First birth before 20 years of age
- Group B: First birth after 30 years of age
- Assume that 4 of 1000 in group A, and 5 of 1000 in group B develop breast cancer. Pure chance or different risk?
- What if the numbers were 40 of 10000 and 50 of 10000? Still chance?

2

Diagnostic test (Example 3.26)

- An automated blood-pressure machine classifies 85% of hypertensive and 23% of normotensive as hypertensive. Assume 20% of the population are hypertensive.
- What is the sensitivity, specificity og positive predictive value?

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Probability of a boy - example 3.2 etc.

Number of live births	Number of boys	Proportion boys
10	8	0.8
100	55	0.55
1000	525	0.525
10000	5139	0.5139
100000	51127	0.51127
3760358	1927054	0.51247
17989361	9219202	0.51248
34832051	17857857	0.51268

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Probability (Def 3.1)

- The sample space, S, is the set of all possible outcomes of an "experiment".
- An experiment is repeated n times. The event A occurs n_A times. The relative frequency n_A/n tends towards a number when n tends towards infinity. This number Pr(A) is the proability of A. (Frequentistic definition of probability)

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How to quantify probability

- Empiric estimation, n_A/n
- Calculated from a theoretical model
- ”Subjective” probability

”Probability has no universally accepted interpretation”

Chatterjee, S. K. *Statistical Thought. A perspective and History.* Oxford University Press, 2003. Page 36.

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Example: Throw a die

- The probability of six is 1/6
- The probability of five or six is 2/6

- These are actually caclulated from the assumption that the die is fair (equal probability for all outcomes) and certain calculation rules.

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(Very) subjective probability:

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Eksempel: (Svært) subjektiv sannsynlighet:

”Det finnes knapt noen vei tilbake, mener FNs klimapanel. Det er 50 prosent sjanse for at nedsmeltingen av polene er uunngåelig, heter det i en rapport som blir publisert i april.”

”FNs klimapanel la frem sin nye rapport i slutten av januar. Her ble det slått fast at det var det var 90 prosent sannsynlig at det var menneskelig aktivitet som er årsaken til den globale oppvarmingen.”

http://www.aftenposten.no/nyheter/miljo/article1650116.ece (19.02.2007)

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http://weather.yahoo.com/ accessed 18 August 2009 at 1100

- Trondheim Tuesday 26 August 2009:
- Chance of precipitation 20%

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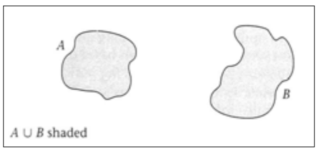
Mutually exclusive (disjoint) events (Def 3.2)

- Two events are A and B are mutually exclusive (disjoint) if they cannot both happen at the same time.



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Eks 3.7

- $A = \{DBP \geq 90\}$
- $B = \{75 \leq DBP \leq 100\}$

- A and B are not mutually exclusive

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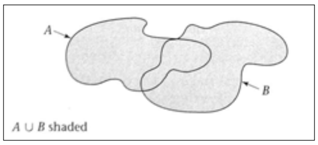
A ∪ B (“A union B”) means that A or B or both occur (Def 3.4).



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example

- A = {DBP ≥ 90}
- B = {75 ≤ DBP ≤ 100}

- A ∪ B = {DBP ≥ 75}

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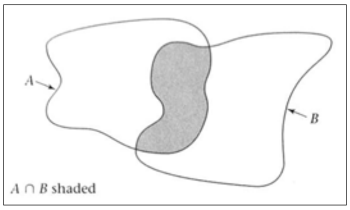
A ∩ B (“the intersection of A and B”) means both A and B occur. (Def. 3.5)



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Example

- A = {DBP ≥ 90}
- B = {75 ≤ DBP ≤ 100}

- A ∩ B = {90 ≤ DBP ≤ 100}

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Basic rules of probability “Kolmogorov’s axioms” (1933) (Equation 3.1 etc)

- The probability of an event E shall always satisfy: 0 ≤ Pr(E) ~~≤ 1~~
- If A and B are mutually exclusive, then Pr(A ∪ B) = Pr(A) + Pr(B). Applies also for more than 2 events.
- The probability of a certain event is 1: Pr(S) = 1

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Example 3.6, diastolic blood pressure, DBP

A means DBP < 90 mmHg (normal). Pr (*A*) = 0.7

B means 90 ≤ DBP < 95 (“borderline”). Pr (*B*) = 0.1

C means DBP < 95

Pr (*C*) = Pr(*A*∪ *B*) = Pr (*A*) + Pr (*B*) = 0.7 + 0.1 = 0.8

Because mutually exclusive

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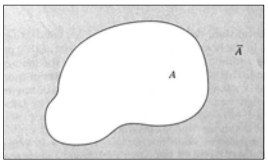
$\overline{A}$ ("The complement of A") means that A does not occur. (Def 3.6)

$Pr(\overline{A}) = 1 - Pr(A)$



Independent events

- "A and B are independent if Pr(B) does not depend on whether A occurs (and vice versa)"
- Def 3.7: A and B are independent if $Pr(A \cap B) = Pr(A)\, Pr(B)$

Example 3.15

Testing for syphilis

A^+ = {Doctor A gives positive diagnose}

B^+ = {Doctor B gives positive diagnose}

Given that

$Pr(A^+) = 0.1 \quad Pr(B^+) = 0.17 \quad Pr(A^+ \cap B^+) = 0.08$

Then

$Pr(A^+ \cap B^+) = 0.08 > Pr(A^+) \times Pr(B^+) = 0.1 \times 0.17 = 0.017$

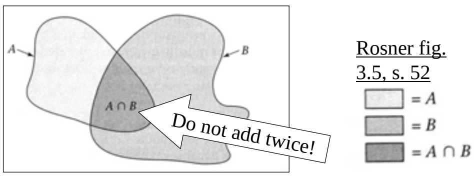
and the events are dependent (as expected)

Multiplication law of probability (Eqn 3.2)

- If $A_1, \ldots, A_k$ are independent events, then $Pr(A_1 \cap A_2 \cap \ldots \cap A_k) = Pr(A_1)Pr(A_2)\ldots Pr(A_k)$

Addition law of probability (Eqn 3.3)

- $Pr(A \cup B) = Pr(A) + Pr(B) - Pr(A \cap B)$



Rosner fig. 3.5, s. 52

Example 3.13 and 3.17

A= {Mother's DBP ≥ 95} B = {Father's DBP ≥ 95}

Pr (A) = 0,1 Pr (B) = 0,2 Assume independence.

What is the probability of a "hypertensive family"?

$Pr(A \cap B) = Pr(A) * Pr(B) = 0,1 * 0,2 = 0,02$

What is the probability of at least one hypentensive parent?

$Pr(A \cup B) = Pr(A) + Pr(B) - Pr(A \cap B)$

$= 0,1 + 0,2 - 0,02 = 0,28$

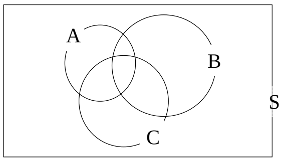
Is independence realistic?

Addition law of probability for 3 events

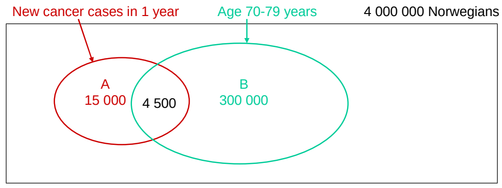
Addition law of probability for 3 events A, B and C

$\Pr(A \cup B \cup C) = \Pr(A) + \Pr(B) + \Pr(C)$

$- \Pr(A \cap B) - \Pr(A \cap C) - \Pr(B \cap C) + \Pr(A \cap B \cap C)$



Conditional probability – from Aalen et al (2006)



A = "Personen får kreft på innen år". $P(A) = \frac{15000}{4000000} = 0.38\%$

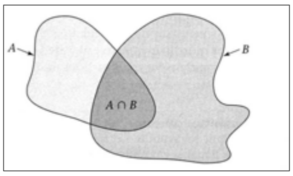
B = "Personen er 70-79 år". $P(B) = \frac{300000}{4000000}$

$P(A \mid B) = \frac{4500}{300000} = 1.5\%$

$P(A \mid B) = \frac{4500/4000000}{300000/4000000} = \frac{P(A \cap B)}{P(B)}$

Conditional probability - def 3.9

- (The conditional) probability for B given A:
- We "redefine" the sample space from S to A.
- $\Pr(B|A) = \Pr(A \cap B)/\Pr(A)$



Conditional probability and independence

A and B are independent if and only if (eqn 3.5 etc)

(1) $\Pr(B|A) = \Pr(B)$

Then, also, $\Pr(B|\bar{A}) = \Pr(B)$, and equivalent for A|B.

(1) could be used as definition of independence!

Example 3.20 (continuation of ex. 3.15)

$\Pr(B^+ \mid A^+) = \Pr(B^+ \cap A^+)/\Pr(A^+) = 0.08/0.1 = 0.8$

$\neq \Pr(B^+) = 0.17$ - the events are dependent

$\Pr(B^+ \mid A^-) = \Pr(B^+ \cap A^-)/\Pr(A^-)$

$\Pr(B^+) = \Pr(B^+ \cap A^+) + \Pr(B^+ \cap A^-)$ because mutually exclusive

hence

$\Pr(B^+ \mid A^-) = (\Pr(B^+) - \Pr(B^+ \cap A^+))/\Pr(A^-) = (0.17 - 0.08)/0.9 = 0.1$

Relative risk

Relative risk (RR) for B given A (def 3.10):

$$RR = \frac{\Pr(B|A)}{\Pr(B|\bar{A})}$$

If A and B are independent, RR=1 (pr def)

Relative risk - example 3.19

A = {Positive mammogram}
B = {Breast cancer within 2 years}

Pr(B|A) = 0.1

$\Pr(B|\bar{A}) = 0.0002$

$$\Pr = \frac{\Pr(B|A)}{\Pr(B|\bar{A})} = \frac{0.1}{0.0002} = 500$$

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Dependent events (example 3.14 etc)

- A = {Mother's DBP ≥ 95},
- B = {First child's DBP ≥ 95}
- Pr(A) = 0.1 Pr(B) = 0.2 Pr(A∩B) = 0.05 (known)
- Pr(A)*Pr(B) = 0.1*0.2 = 0.02 ≠ Pr(A∩B)
  hence: dependent events
- Pr(B|A) = Pr(A∩B)/Pr(A) = 0.05/0.1 = 0.5 ≠ Pr(B)

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The generalized multiplication law (eqn 3.8)

- Fra definisjonen på betinget sannsynlighet får vi:
  - Pr(A∩B) = Pr(A)Pr(B|A)
- og generelt
  - $\Pr(A_1 \cap A_2 \cap ... \cap A_k) = \Pr(A_1)\Pr(A_2|A_1)\Pr(A_3|A_2 \cap A_1)... \Pr(A_k|A_k \cap ... \cap A_2 \cap A_1)$

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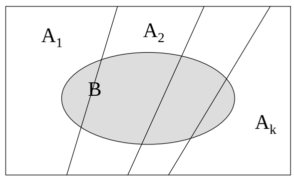
Total probability rule (Eqn 3.7)



$$\Pr(B) = \sum_{i=1}^{k} \Pr(B \mid A_i)\Pr(A_i)$$

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Incidence of cataract - example 3.22

We shall calculate total cumulative incidence of cataract in the population aged ≥ 60 years, the next 5 years. The age specific cumulative incidences are given.

A_1 = {60-64 years}, A_2 = {65-69 years}, A_3 = {70-74 years}, A_4 = {75+ years}, B = {cataract within 5 years}

$\Pr(A_1)$=0,45, $\Pr(A_2)$=0.28, $\Pr(A_3)$=0.20, $\Pr(A_4)$=0.07

$\Pr(B|A_1)$=0.024, $\Pr(B|A_2)$=0.046, $\Pr(B|A_3)$=0.088, $\Pr(B|A_4)$=0.153

$$\Pr(B) = \sum_{i=1}^{k} \Pr(B|A_i)\Pr(A_i)$$
$$= 0.024 \cdot 0.45 + 0.046 \cdot 0.28 + 0.088 \cdot 0.20 + 0.153 \cdot 0.07 = 0.052$$

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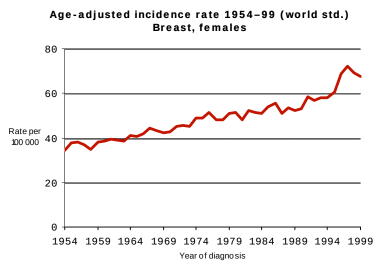
Age adjusted incidence rate of breast cancer, Norway. www.kreftregisteret.no



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Bayes' rule, diagnosis and screening

A = {symptom or positive diagnostic test}

B = {disease}

P(B) = disease prevalence

$P(A|B) =$ sensitivity

$P(A|\bar{B}) =$ " false positive rate"

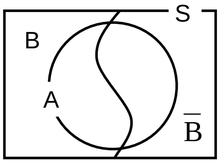
$P(\bar{A}|\bar{B}) =$ specificity

$P(\bar{A}|\bar{B}) + P(A|\bar{B}) = 1$ (why?)

$\Leftrightarrow P(A|\bar{B}) = 1 - P(\bar{A}|\bar{B}) = 1 -$ specificity

$P(B|A) =$ PPV $=$ PV^+ $=$ positive predictive value

$P(\bar{B}|\bar{A}) =$ NPV $=$ PV^- $=$ negative predictive value



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Breast cancer diagnosis (ex 3.23)

A = {pos. mammogram}

B = {breast cancer next 2 years}

$\Pr(B|\bar{A}) = 0{,}0002 \leftrightarrow \Pr(\bar{B}|\bar{A}) = 1 - 0{,}0002 = 0{,}9998$

Dvs. $NPV = PV^- = 0{,}9998$

$\Pr(B|A) = 0{,}1 = PPV = PV^+$

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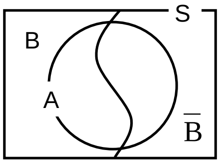
Bayes' rule

Def. (Rosner Eq. 3.9) Bayes' rule (Bayes' theorem)
Combines the conditional probability and total probability:

$$PPV = PV^+ = P(B|A) = \frac{\Pr(B \cap A)}{\Pr(A)} = \frac{\Pr(A|B) \cdot \Pr(B)}{\Pr(A|B) \cdot \Pr(B) + P(A|\bar{B}) \cdot P(\bar{B})}$$



We express a conditional probability in terms of the "opposite" conditional probability!

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Bayes' Rule

Rosner ex. 3.26

Prevalence of hypertension = Pr (B) = 0.2. Auto-BP machine classifies 84 % of hypertensive and 23 % of normotensive as hypertensive. PPV? NPV?

$\Pr(A|B) = 0.84$ (sensitivity)

and $\Pr(A|\bar{B}) = 0.23$ ("false positive rate")

Hence, spesificity $= \Pr(\bar{A}|\bar{B}) = 1 - 0.23 = 0.77$

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From Bayes' rule:

$$PV^+ = \Pr(B|A) = \frac{\Pr(A|B) \cdot \Pr(B)}{\Pr(A|B) \cdot \Pr(B) + \Pr(A|\bar{B}) \cdot \Pr(\bar{B})}$$

$$= \frac{sens \cdot prevalence}{sens \cdot prevalence + (1 - spes) \cdot (1 - prevalence)}$$

$$= \frac{0.84 \cdot 0.2}{0.84 \cdot 0.2 + 0.23 \cdot 0.8} = \frac{0.168}{0.352} = 0.48$$

and analogously

$$PV^- = \Pr(\bar{B}|\bar{A}) = \frac{spes \cdot (1 - prevalence)}{spes \cdot (1 - prevalence) + (1 - sens) \cdot prevalence}$$

$$= \frac{0.77 \cdot 0.8}{0.77 \cdot 0.8 + 0.16 \cdot 0.2} = \frac{0.616}{0.648} = 0.95$$

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Bayes' rule.
Low prevalence – a paradox?

What if the prevalence is low?

Pr(B) = 0.0001

P(A|B) = 0.84 (sensitivity)

$P(\bar{A}|\bar{B}) = 0.77$ (specificity)

Da blir

$$PPV = \frac{0.84 \cdot 0.0001}{0.84 \cdot 0.0001 + (1-0.77)(1-0.0001)} = 0.0037$$

$$NPV = \frac{0.77 \cdot (1 - 0.0001)}{0.77 \cdot (1 - 0.0001) + (1-0.84) \cdot 0.0001} = 0.999998$$

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Bayes' rule, diagnosis and screening

Traditional 2×2 table

		Disease +	Disease –	
Test result	+	a [TP]	b [FP]	a + b
	–	c [FN]	d [TN]	c + d
		a + c	b + d	a + b + c + d

A = {test positiv}, B = {diseased}, TP = true positive, FP = false positive, FN = false negative, TN = true negative

$$\text{Prevalence} = \mathrm{P(B)} = \frac{a+c}{a+b+c+d}$$

$$\textit{Sensitivit} = P(A \mid B) = \frac{a}{a+c}$$

$$\textit{Specificit} = P(\bar{A} \mid \bar{B}) = \frac{d}{b+d}$$

$$PPV = P(B \mid A) = \frac{a}{a+b}$$

$$NPV = P(\bar{B} \mid \bar{A}) = \frac{d}{c+d}$$

$$\left[\textit{Accuracy} = \frac{a+d}{a+b+c+d} \right]$$

Using a 2×2 table, we needed to write down a thought number of patients to compute PPV etc. …!

With Bayes we can compute this straightforward.

Diagnostic tests and ROC curves

Ratings of 109 CT images by a single radiologist

True disease status	Definitely normal (1)	Probably normal (2)	Questionable (3)	Probably abnormal (4)	Definitely abnormal (5)	Total
Normal	33	6	6	11	2	58
Abnormal	3	2	2	11	33	51
Total	36	8	8	22	35	109

Rosner Table 3.2 and 3.3

Criterion "1+": All with rating 1 to 5 are diagnosed as diseased. Identifies all the diseased, but find no non-diseased. Sensitivity = 1, specifisity = 0, false positive rate = 1.

Diagnostic tests and ROC curves

Ratings of 109 CT images by a single radiologist

True disease status	Definitely normal (1)	Probably normal (2)	Questionable (3)	Probably abnormal (4)	Definitely abnormal (5)	Total
Normal	33	6	6	11	2	58
Abnormal	3	2	2	11	33	51
Total	36	8	8	22	35	109

Criterion "2+": All with rating 2 to 5 are diagnosed as diseased. Identifies 48/51 diseased, and 33/58 non-diseased. Sensitivity = 0.94, specifisity = 0.57, false positive rate = 0.43.

Diagnostic tests and ROC curves

Ratings of 109 CT images by a single radiologist

True disease status	Definitely normal (1)	Probably normal (2)	Questionable (3)	Probably abnormal (4)	Definitely abnormal (5)	Total
Normal	33	6	6	11	2	58
Abnormal	3	2	2	11	33	51
Total	36	8	8	22	35	109

Criterion "3+": All with rating 3 to 5 are diagnosed as diseased. Identifies 46/51 diseased, and 39/58 non-diseased. Sensitivity = 0.90, specifisity = 0.67, false positive rate = 0.33.

Diagnostic tests and ROC curves

Ratings of 109 CT images by a single radiologist

True disease status	Definitely normal (1)	Probably normal (2)	Questionable (3)	Probably abnormal (4)	Definitely abnormal (5)	Total
Normal	33	6	6	11	2	58
Abnormal	3	2	2	11	33	51
Total	36	8	8	22	35	109

Criterion "4+": All with rating 4 or 5 are diagnosed as diseased. Identifies 44/51 diseased, and 45/58 non-diseased. Sensitivity = 0.86, specifisity = 0.78, false positive rate = 0.22.

Diagnostic tests and ROC curves

Ratings of 109 CT images by a single radiologist

True disease status	Definitely normal (1)	Probably normal (2)	Questionable (3)	Probably abnormal (4)	Definitely abnormal (5)	Total
	CT rating by radiologist					
Normal	33	6	6	11	2	58
Abnormal	3	2	2	11	33	51
Total	36	8	8	22	35	109

Criterion "5+": All with rating 5 are diagnosed as diseased. Identifies 33/51 diseased, and 56/58 non-diseased. Sensitivity = 0.65, specifisity = 0.97, false positive rate = 0.03.

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Diagnostic tests and ROC curves

Ratings of 109 CT images by a single radiologist

True disease status	Definitely normal (1)	Probably normal (2)	Questionable (3)	Probably abnormal (4)	Definitely abnormal (5)	Total
	CT rating by radiologist					
Normal	33	6	6	11	2	58
Abnormal	3	2	2	11	33	51
Total	36	8	8	22	35	109

Criterion "6+": Only rating > 5 is diagnosed as diseased. Identifies no diseased, classifies all as non-diseased. Sensitivity = 0, specifisity = 1, false positive rate = 0.

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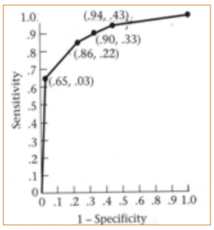
Diagnostic tests and ROC curves

A summary of the results: (Rosner table 3.3)

Test positive criteria	Sensitivity	Specificity	'False pos. rate'
1+	1.0	0	1
2+	.94	.57	0,43
3+	.90	.67	0,33
4+	.86	.78	0,22
5+	.65	.97	0,03
6+	0	1.0	0



… are plotted as an ROC curve. (Rosner fig. 3.7,

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Area under the ROC curve

- A summary of diagnistic accuracy
- Equals the probability that a diseased patient will be classified correctly compared to a non-diseased patient.
- Equals 1 for a perfect test
- Equals 0.5 for a non-informative test
- Equals 0.89 in the example

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Prevalence

- The prevalence of a disease is the proportion of the population who have the disease (def 3.17)
- Example (Aalen, 1998):
  - Per 31/12-1995, 21482 women in Norway had breast cancer.
  - Population: 2 150 000
  - Prevalence: 21482/2150000 = 0.010

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Incidence

- Incidence measures the occurrence of new disease cases.
- Ex (Aalen, 1998):
  - In 1995, a total of 2154 women in Norway got the diagnose breast cancer.
  - Population: 2 150 000
  - Incidence: 2154/2150000 = 0.0010 (pr person year)

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